Commentary

USP 41–NF 36, Second Supplement

June 16, 2018

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

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

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

General Chapters:
<5> Inhalation and Nasal Drug Products General Information and Product Quality Tests
<467> Residual Solvents
<1099> Limit on Number of Large Deviations When Assessing Content Uniformity In Large Samples
<1168> Compounding for Phase I Investigational Studies
<1211> Sterilization and Sterility Assurance of Compendial Articles
<1222> Terminally Sterilized Pharmaceutical Products--Parametric Release
<1228.4> Depyrogenation by Physical Means
<1467> Residual Solvents—Verification of Compendial Procedures and Validation of Alternative Procedures

Monographs:
Alprazolam Tablets
Amitriptyline Hydrochloride Tablets
Ammonia N 13 Injection
Atropine Sulfate
Bacillus Coagulans
Bacillus Coagulans Capsules
Bendamustine Hydrochloride
Bendamustine Hydrochloride for Injection
Bicalutamide Tablets
Biotin Compounded Oral Suspension
Carbinoxamine Maleate
Carotenes
Castor Oil
Cod Liver Oil
Cortisone Acetate
Cromolyn Sodium
Cyclophosphamide Compounded Oral Suspension
Dextrose Excipient
Escitalopram Tablets
European Elder Berry Dry Extract
Exenatide Injection
Fludarabine Phosphate
Fludeoxyglucose F 18 Injection
Fludrocortisone Acetate Tablets
Fluvastatin Sodium
Fosinopril Sodium
Gemcitabine Hydrochloride
Hydrogenated Vegetable Oil
Hyoscyamine Sulfate
Indomethacin
Isotretinoin Capsules
Krill Oil
Leflunomide Compounded Oral Suspension
Maprotiline Hydrochloride
Methotrexate

Naproxen Sodium and Pseudoephedrine Hydrochloride Extended-Release Tablets
Norethindrone Acetate Tablets
Phytonadione
Prazosin Hydrochloride Compounded Oral Suspension
Primaquine Phosphate
Sotalol Hydrochloride
Travoprost Ophthalmic Solution
Urea Compounded Irrigation
Vigabatrin

No comments were received for the following proposals:

Monographs:
Bacitracin
Candesartan Cilexetil and Hydrochlorothiazide Tablets
Cefazolin Sodium
Captopril Tablets
Carbinoxamine Maleate Tablets
Citalopram Oral Solution
Cod Liver Oil Capsules
Cortisone Acetate Tablets
Cyclobenzaprine Hydrochloride
Dichlorphenamide Tablets
Diethyl Phthalate
Entecavir
Entecavir Oral Solution
Epinephrine Inhalation Aerosol
Epinephrine Bitartrate Inhalation Aerosol
Ergotamine Tartrate Inhalation Aerosol
Flecainide Acetate
Flecainide Acetate Tablets
Gabapentin
Isoetharine Mesylate Inhalation Aerosol
Isoproterenol Hydrochloride Inhalation Aerosol
Isoproterenol Hydrochloride and Phenylephrine Bitartrate Inhalation Aerosol
Ivermectin Compounded Oral Solution, Veterinary
Lansoprazole Delayed-Release Capsules
Loratadine Orally-Disintegrating Tablets
Magnesium Carbonate
Maprotiline Hydrochloride Tablets
Meloxicam Tablets
Mesna
Mesna Tablets
Methscopolamine Bromide
Methscopolamine Bromide Tablets
Methylphenidate Hydrochloride
Mirtazapine Compounded Oral Suspension, Veterinary
Myristic Acid
Naratriptan Tablets
Oxaliplatin for Injection
Palm Oil

Palmitic Acid
Pimobendan
Prilocaine Hydrochloride Injection
Powdered Decaffeinated Green Tea Extract
Propafenone Hydrochloride Tablets
Scaffold Human Amniotic Membrane Allograft
Sennosides
Stavudine Capsules
Sulfiram
Testosterone Topical Solution
Torsemide Tablets
Trichlormethiazide Tablets
Trimethylamine Hydrochloride
Vinblastine Sulfate
Ziprasidone Hydrochloride

General Chapters

General Chapter/Sections:	<5> Inhalation and Nasal Drug Products—General Information and Product Quality Tests/Multiple Sections
Expert Committees:	General Chapters—Dosage Forms
No. of Commenters:	6

General
Comment Summary #1: The commenter indicated that the revision proposal in *Pharmacopeial Forum* (*PF*) 43(4) [Jul.–Aug. 2017] still includes general information to support mostly new monograph development. This therefore represents a guide to create monographs that is best suited in a technical guide or General Chapter numbered above 1000.
Response: Comment not incorporated. The Expert Committee considers the tests to assess the quality and performance attributes of such drug products. Based on a review of data of a given drug product by the regulatory body, the addition and/or removal of a test (if any) may be considered based on data and circumstances.

Introduction
Comment Summary #2: The commenter indicated that the phrase “therapeutically active ingredient(s)” should either be removed from the definitions for *Inhalation Aerosols*, *Inhalation Powders*, and *Nasal Aerosols* or added to the remaining definitions in *Table 1. Established Names and Definitions* because all dosage forms deliver “therapeutically active ingredient(s)”.
Response: Comment incorporated.
Comment Summary #3: The commenter suggested indicating in the definitions for *Inhalation Spray*, *Inhalation Solution*, *Inhalation Suspension*, *Solution for Inhalation*, and *[Drug] for Inhalation Solution* that these are sterile if the associated formulations are aqueous-based, as is most often the case. This would be consistent with current federal regulations (21 Code of Federal Regulations (CFR) 200.51 *Aqueous Based Drug Products for Oral Inhalation*).
Response: Comment incorporated.
Comment Summary #4: The commenter suggested using a consistent description for *Inhalation Spray*” in Table 1 and in Section 2 *General Quality Tests for Inhalation Drug Products*. It is described as “fine droplets” in Table 1, but the term “fine mist” is used later in the General Chapter.
Response: Comment incorporated.

Comment Summary #5: The commenter suggested revising a portion of the definition of *Nasal Powder* to "…with the use of a device that *aerosolizes and delivers* an accurately metered amount…" to be consistent with the other definitions in the table.
Response: Comment incorporated.

Drug Product General Quality Tests and Performance Quality Tests
Comment Summary #6: The commenter suggested revising the last sentence in the first paragraph for to "General quality tests assess the integrity of the dosage form, whereas product performance quality tests assess delivery…" for clarity.
Response: Comment incorporated.
Comment Summary #7: The commenter suggested revising the first sentence in the second paragraph to "Taken together, *general* quality and *product* performance tests ensure…" for clarity.
Response: Comment incorporated.

General Quality Tests for Inhalation Drug Products
Inhalation Aerosol
Comment Summary #8: The commenter suggested revising the second sentence to "The descriptive term aerosol also refers to the fine mist of small droplets and/or solid particles…" because aerosols can contain a combination of small droplets and solid particles.
Response: Comment incorporated.
Comment Summary #9: The commenter recommended including "Valve Delivery" in the list of attributes. Valve delivery is currently recommended for all inhalation aerosol drug products, irrespective of formulation type.
Response: Comment incorporated.

Inhalation Spray
Comment Summary #10: The commenter recommended removing the *Plume Geometry* test from the list of attributes because, according to U.S. Food and Drug Administration (FDA) guidance on metered dose inhalers, plume geometry is a characterization type test, established in development and not routinely performed.
Response: Comment not incorporated. The FDA Guidance "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products" (2002) includes the *Plume Geometry* test as an important attribute for the evaluation of inhalation spray drug products.

Drug for Inhalation Solution
Comment Summary #11: The commenter suggested adding the test for *Reconstitution Time* to the list of attributes.
Response: Comment incorporated.

Inhalation Solution
Comment Summary #12: The commenter suggested revising statements referring to a drug product-specific nebulizer for accuracy because not all inhalation drug products are specified to be used with a particular nebulizer.
Response: Comment not incorporated. It is prudent to consider a specific nebulizer or type of nebulizer following the approved labeling. The performance of a drug product may depend on the nebulizer type, a specific nebulizer for the drug product, and the availability and development of new technologies for the delivery system. If the labeling of a drug product is silent on the type or specific design of a nebulizer, the sponsor may ask the regulatory body for guidance.

Comment Summary #13: The commenter suggested revising "Viscosity, if relevant" to "Viscosity, if formulation contains a viscosity adjusting agent" in the list of attributes to explicitly clarify when the viscosity quality test is relevant. The commenter further recommended updating other attribute list entries of Viscosity in a similar fashion throughout the General Chapter.
Response: Comment not incorporated. The viscosity attribute of a drug product may be affected by other components in the formulation, not only by the addition of a "viscosity adjusting agent". The proposed change may lead to misinterpretation/confusion. The relevance of the test may become clearer as a result of studies and scientific justification to the regulatory body for a given drug product.
Comment Summary #14: The commenter recommended revising the *Osmolality* quality attribute to read "Osmolality, *if formulation contains a tonicity agent or product has a label claim regarding tonicity*" because the test is only necessary under specific circumstances. The commenter further recommended revising other *Osmolality* attribute list entries in a similar fashion throughout the General Chapter.
Response: Comment not incorporated. The osmolality attribute of a drug may be affected by other components in the formulation and not only "if formulation contains a tonicity agent". The proposed change may lead to misinterpretation/confusion. The relevance of the test may become clearer as a result of studies and scientific justification to the regulatory body for a given drug product.

Inhalation Powder
Comment Summary #15: The commenter suggested revising the last sentence of the first paragraph for accuracy because there are several designs which solely rely on the patients' inspiration through the device to create and disperse the aerosol of particles in air.
Response: Comment not incorporated. The current language states, "…all of which rely on various energy sources to create and disperse…". "Patient inspiration" is considered one of the "various energy sources".
Comment Summary #16: The commenter suggested removing the test for *Foreign Particulate Matter* from the list of attributes and changing the description of *Foreign Particulate Matter* in Section *4. Description of Product Quality Tests* from "Particulate matter in inhalation and nasal drug products may originate…" to "Particulate matter in solution formulations of inhalation and nasal drug products may originate …". The *Foreign Particulate Matter* test is not applicable to nasal powder drug formulations because it is well documented that particles in the range typically reported (greater than 10 microns and greater than 25 microns) would not pass through the nasal cavity into the lungs.
Response: Comment not incorporated. Control of *Foreign Particulate Matter* is considered an important quality test from a safety perspective for inhalation and nasal drug products, as well as for production of consistent quality drug product batches, similar to other quality attributes. In addition to foreign particulate matter that is greater than 10 microns, control of foreign particulate matter that is less than 10 microns is equally or more important for such drug products. Thus, a normal profile approach for control of this attribute is recommended.
Comment Summary #17: The commenter suggested revising Volatile and Semivolatile Leachables to "Leachables" in the list of attributes for consistency with other entries throughout the General Chapter.
Response: Comment incorporated.

General Quality Tests for Nasal Drug Products
Nasal Spray
Comment Summary #18: The commenter recommended including "Pump Delivery" in the list of attributes.
Response: Comment incorporated.

Comment Summary #19: The commenter suggested revising the third sentence from "…upon activation delivers an accurately metered amount of the formulation delivered as a mist" to "upon activation delivers an accurately metered amount of the formulation as a mist".
Response: Comment incorporated.
Comment Summary #20: The commenter recommended deleting the entry for "Sterility (premetered)" from the list of attributes because *Nasal Spray* formulations are not required to be sterile per FDA *Guidance for Industry: Nasal Spray and Inhalation Solution, Solution, Suspension, and Spray Drug Products–Chemistry, Manufacturing, and Controls Documentation.*
Response: Comment incorporated.

Nasal Powder
Comment Summary #21: The commenter suggested either describing all quality tests within this section or identifying the tests applicable to *Nasal Powders* in the *Inhalation Powder* section
Response: Comment not incorporated. Quality tests for *Inhalation Powder* drug products may apply to *Nasal Powder* drug products, unless demonstrated/justified otherwise for a specific *Nasal Powder* drug product to the regulatory body in a new drug application (NDA).

Description of Product Quality Tests
Comment Summary #22: The commenter recommended adding a test for microbial limits to be consistent with current FDA *Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products–Chemistry, Manufacturing, and Controls Documentation*.
Response: Comment incorporated.

Assay for Antimicrobial Preservative and Stabilizing Excipients (if present)
Comment Summary #23: The commenter recommended revising the last sentence from "The corresponding acceptance criteria normally are based on appropriate preservative effectiveness demonstrated by a microbial challenge test" to "The assay acceptance criteria for antimicrobial preservative normally are based on appropriate preservative effectiveness demonstrated by a microbial challenge test", because this only apply to antimicrobials (not stabilizing excipients).
Response: Comment incorporated.
Comment Summary #24: The commenter recommended deleting "in a multidose container" because stabilizing agents may also be added to drug products packaged in single-unit containers.
Response: Comment incorporated.

Clarity and Color of Solution Upon Dilution
Comment Summary #25: The commenter recommended including the word "quantitative" to distinguish a quantitative assessment from a qualitative observation of color, which can be subjective.
Response: Comment incorporated.

Description
Comment Summary #26: The commenter recommended revising "and the respective labels for the monograph of a drug product" to "and the respective titles for the monographs of a drug product" for clarity.
Response: Comment incorporated.
Comment Summary #27: The commenter recommended revising the paragraph to indicate that a description test plays an important role in assessing container/formulation integrity, as part of a stability program specific to each dosage form, and serves as an indication of drug product integrity, particularly in terms of stability testing. This test involves assessing the

appearance of the contents of the container (i.e., formulation) and the appearance of components of the container closure system for conformance to their respective descriptions.
Response: Comment incorporated.

Elemental Impurities
Comment Summary #28: The commenter suggested revising this subsection to read, "A risk-based evaluation for elemental impurities should be performed per <232>. If testing is determined to be required, analytical procedures should be validated per *Elemental Impurities—Procedures* <233>." The text in the *PF* proposal indicates that testing per General Chapters <232>*Elemental Impurities—Limits* and <233> is required, which is misleading. The International Conference on Harmonization (ICH) Q3D *Guideline for Elemental Impurities* advocates the use of a risk assessment and that testing is not necessarily required.
Response: Comment not incorporated. FDA has issued the following clear statements: "As of January 1, 2018:

- All new and existing NDAs and [abbreviated new drug applications] ANDAs for drug products with an official USP monograph are required to meet the requirements in USP General Chapters <232> and <233> for the control of elemental impurities.
- Applicants submitting NDAs and ANDAs for drug products without a USP monograph are expected to follow the recommendations in the ICH Q3D *Elemental Impurities* guideline."

Thus, any risk-based evaluation, data, and justification should be presented in the drug application for any further action/deviation for a specific drug product.
Comment Summary #29: The commenter suggested deleting the *Elemental Impurities* and *Residual Solvent* tests consistent with the USP *General Notices* application of *Elemental Impurities* and *Residual Solvents* standards.
Response: See above.

Foreign Particulate Matter
Comment Summary #30: The commenter suggested revising the last sentence to include a general statement that the particle size characterization size range should be chosen appropriately for the type of product and route of administration because determining fine particulates, "(e.g., less than 10µm)", is not applicable to all products.
Response: Comment incorporated.
Comment Summary #31: The commenter suggested revising the text to "For toxicological assessment, the type, origin, amount, and size of foreign particulates, including fine particulates (e.g., less than 5 µm), should be …" to harmonize with the *European Pharmacopoeia* (*Ph.Eur.*), which defines fine particles as less than 5 µm.
Response: Comment not incorporated. Alternate language proposed by another commenter was adopted. The language "less than 10 µm", also supported by others, was maintained because of feasibility considerations.

Identification
Comment Summary #32: The commenter recommended revising the third sentence from "A specific identification test for polymorphic forms should be carried out" to "A specific identification test for polymorphic forms should be carried out*,* if applicable", because testing for polymorphs is not necessary for all formulations.
Response: Comment incorporated.

Impurities and Degradation Products

Comment Summary #33: The commenter suggested adding a reference to ICH M7 *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* to encourage the reader to follow this guidance.
Response: Comment incorporated.
Comment Summary #34: The commenter recommended using terminology consistent with ICH Q3B *Impurities in New Drug Products* because "total unspecified" impurities is not a term used in ICH Q3B.
Response: Comment incorporated.

Leachables
Comment Summary #35: The commenter recommended removing a reference to powder formulations because powders cannot leach compounds from container closure systems. While there are situations in which incompatibility of the drug product powder formulation and the container closure system can lead to some degradation, such degradation would not be considered a leachable.
Response: Comment not incorporated. The type of testing may depend on the drug formulation and/or composition of the container closure system components. For example, powder formulations packaged in semi-permeable containers or similar materials need to be evaluated for ingress of semi-volatile or volatile potential leachables. Thus, appropriate data and justification may be provided for a specific drug product in the drug application for exemption. Upon approval, the future USP monograph for that drug product may reflect this.

Leak Rate
Comment Summary #36: The commenter suggested mentioning the performance of a heat stress test prior to the equilibration/quarantine period as part of the leak rate studies.
Response: Comment incorporated.

Microbial Limits
Comment Summary #37: The commenter suggested adding a reference to General Chapter <1111> *Microbiological Examination of Nonsterile Products Acceptance Criteria For Pharmaceutical Preparations and Substances for Pharmaceutical Use* for the acceptance criteria.
Response: Comment incorporated.

Net Fill Weight
Comment Summary #38: The commenter suggested adding a reference to General Chapter <755> *Minimum Fill*, which discusses sprays and aerosols.
Response: Comment incorporated.
Comment Summary #39: The commenter suggested adding a disclaimer "(for multi-use devices only)" after references to *Net Fill Weight* because *Inhalation Solutions* and *Inhalation Suspensions* are typically packaged in single-dose containers, and the test for *Net Fill Weight* should only be applied to multi-use devices. General Chapter <755> requires an excess amount of drug product to be put into each device, and it would not be appropriate to overfill a single-use device to meet that requirement.
Response: Comment not incorporated. The intent of this test is to ensure that each single-dose container is not underweight or overweight as compared to the label claim.

Primary Particle Size Distribution
Comment Summary #40: The commenter suggested replacing the word "can" with "should" in the first sentence to avoid ambiguity and to be consistent with similar text throughout the General Chapter.

Response: Comment incorporated.
Comment Summary #41: The commenter suggested replacing the word “matters” with “matter” in the second sentence to be consistent with similar text in the General Chapter.
Response: Comment not incorporated. The change is not critical and can be adopted at a later time.
Comment Summary #42: The commenter suggested deleting the last sentence because the reference to General Chapter <601> *Inhalation and Nasal Drug Products Aerosols, Sprays, and Powders Performance Quality Tests* may be confusing.
Response: Comment incorporated.
Comment Summary #43: The commenter suggested adding a reference to General Chapter <776> *Optical Microscopy* because that General Chapter discusses particle characterization.
Response: Comment incorporated.

Pump Delivery
Comment Summary #44: The commenter suggested replacing “weight “with “mass” and revising the text to “A test for individual pump spray mass delivery should be performed to …”.
Response: Comment not incorporated. The word “weight” was used as a means of direct measurement. For example, General Chapter <905> *Uniformity of Dosage Units* uses the same concept of *Weight Variation* as a means of measuring uniformity of dosage units.

Viscosity
Comment Summary #45: The commenter suggested adding references to General Chapters <912> *Viscosity—Rotational Methods* and <913> *Viscosity—Rolling Ball Method*. The viscosity of inhalation and nasal drug products may be measured with the rolling ball viscometer method. Rotational rheometer methods may be used to measure the viscosity of Newtonian fluids and apparent viscosity of non-Newtonian fluids.
Response: Comment incorporated.

Water Content
Comment Summary #46: The commenter recommended revising the first sentence by removing the phrase “of the drug product” to avoid redundancy.
Response: Comment incorporated.

General Chapter/Sections: <467> Residual Solvents/Multiple Sections
Expert Committee: General Chapters—Chemical Analysis
No. of Commenters: 13

General
Comment Summary #1: The commenter recommended adding a section on the “Determination of Total Residual Solvents” summarizing all calculations and any applicable *General Notices* affecting testing practices and calculations encompassing several examples of the drugs.
Response: Comment not incorporated. The Expert Committee determined that the section is not needed. The total content of Residual Solvents does not add value because the acceptance limits for individual solvents vary widely, from 2 ppm for a Class 1 Residual Solvent to 5000 ppm for a Class 3 Residual Solvent.
Comment Summary #2: The commenter recommended changing the abbreviation “TCE” to “TCA” throughout the General Chapter.
Response: Comment partially incorporated. The Expert Committee decided to revise the abbreviation to “1,1,1-TCE”.

Introduction

Comment Summary #3: The commenters requested the exclusion of dietary supplements from the scope and text of the General Chapter because ICH Q3C *Impurities: Guideline for Residual Solvents* specifically applies to pharmaceuticals, not dietary supplements or their ingredients. Inclusion of dietary supplements is also inconsistent with the Dietary Supplement Health and Education Act and global food standards (e.g. Codex Alimentarius, Food Chemicals Codex, EU food purity criteria, China GB standards, etc.) that apply to dietary supplement ingredients. Dietary supplements are considered foods in the U.S., not drug products, and as such are regulated differently. The commenters indicated also that U.S. law provides USP with legal authority for drug products and it does not give USP the authority to apply this requirement to dietary supplements.

Response: Comment not incorporated. Dietary supplements that claim compliance with USP specifications must meet the requirements of this General Chapter as mandated by *General Notices* 5.60.20 *Residual Solvents in USP and NF Articles*. The purpose of the revision is not to add new requirements for dietary supplements, but to clarify an apparent inconsistency between the wording in the *Introduction* of the General Chapter and the *General Notices* requirements. Dietary Supplements are official articles as defined in *General Notices* 2.20 *Official Articles*., thus always have been within the scope and specifications of Chapter <467>. Since the requirements for residual solvents are applicable to dietary supplements regardless any rewording in the chapter, incorporation of the comment would only prolong the confusion.

Comment Summary #4: The commenters recommended adding a definition for residual solvents “not likely to be present”.

Response: Comment not incorporated. The Expert Committee determined that the text is suitable because it defines a solvent “likely to be present”.

Comment Summary #5: The commenters suggested using the text from the introduction of the current General Chapter.

Response: Comment not incorporated. The Expert Committee determined that the text is suitable.

Comment Summary #6: The commenter recommended that USP develop residual solvent requirements for dietary supplements in a separate General Chapter numbered above 2000, following the approach that the USP took for elemental impurities.

Response: Comment not incorporated. The Expert Committee determined that the text is suitable.

Classification of Residual Solvents by Risk Assessment

Comment Summary #7: The commenter requested that USP clarify the testing requirement for benzene, specifically regarding the statement, “potential sources of benzene may include its presence as an impurity in a solvent used in the manufacturing process”, and clarify if this update would require companies to start obtaining specific benzene waivers.

Response: Comment not incorporated. The Expert Committee determined that the request is beyond the scope of this General Chapter.

Comment Summary #8: The commenters recommended that USP adopt the changes in ICH Q3C (R6).

Response: Comment incorporated. USP will incorporate the changes when the Reference Standards are available as required by *General Notices* 5.80. *USP Reference Standards*.

Control Strategy

Comment Summary #9: The commenter indicated that the intent and difference between control strategy options 2a and 2b are not clear.

Response: Comment incorporated. The Expert Committee revised the text.

Comment Summary #10: The commenters requested clarification of this section.
Response: Comment incorporated. The Expert Committee revised the text.
Comment Summary #11: The commenters recommended clarifying this section by using the terms “drug product” and “ingredients” instead of “official product” and “official substances.”
Response: Comment not incorporated. The Expert Committee determined that the text is suitable and reflects the definition provided in *General Notices* 2. *Official Status and Legal Recognition*.
Comment Summary #12: The commenter indicated that the need for testing should be left up to the manufacturer because the decision depends on many factors.
Response: Comment not incorporated. The Expert Committee determined that the text is suitable. There is a difference between testing and analyzing.

Identification, Control, and Quantification of Residual Solvents
Comment Summary #13: The commenter recommended revising “...in a manner that prevents the loss of volatile solvents” to “...in a manner that minimized the loss of volatile solvents” in the first paragraph.
Response: Comment incorporated.
Comment Summary #14: The commenter recommended including units for pressurization time in *Table 9. Headspace Operating Parameters*.
Response: Comment incorporated.

Analytical Procedures for Class 1 and Class 2 Residual Solvents
Comment Summary # 15: The commenter suggested adding to *Figure 4* a description of the treatment of the actual sample to quantify/limit residual solvents for clarity.
Response: Comment partially incorporated. The Expert Committee changed “Water Articles” to “Water Soluble Articles” in the diamond box in *Figure 4*.

Screening of Water-Insoluble Articles, Standard Solutions
Comment Summary #16: The commenter requested revision of the text to state, “Transfer 1.0 mL of Class 2 mixture A standard stock solution to an appropriate headspace vial containing 4.0 mL of water and 1.0mL of dimethyl sulfoxide, apply the stopper, cap and mix”.
Response: Comment partially incorporated. The Expert Committee removed “and 1 mL of dimethyl sulfoxide” from the sentence.

Quantification for Water-Soluble Articles
Comment Summary #17: The commenter requested, under Spiked Sample Solution, replacing “The use of a vial containing the sample spiked with multiple standards is permitted, provided that the procedure is validated” with “The use of a vial containing the sample spiked with multiple standards is permitted provided that the procedure verification is successful”.
Response: Comment partially incorporated. The Expert Committee revised the text to state, “The use of a vial containing the sample spiked with multiple standards is permitted, provided that the procedure is validated accordingly”.
Comment Summary #18: The commenter indicated that the system suitability requirements conflict with those in *Figure 4* and the text does not mention any difference in requirements between *Procedure A* and *Procedure B*.
Response: Comment incorporated. The text was revised to include the same requirements for *Procedure B* as in Sections *8.2 Screening of Water-Soluble Articles* and *8.3 Screening of Water-Insoluble Articles*, and revised requirements for the targeted test.

Other

Comment Summary #19: The commenter asked why USP removed the *Other Residual Solvents* table.
Response: Comment not incorporated. The Expert Committee determined that the removal of the *Other Residual Solvents* table is appropriate because there is no toxicological data.

General Chapter/Sections:	<1168> Compounding For Phase I Investigational Studies/Multiple Sections
Expert Committees:	Compounding
No. of Commenters:	11

General
Comment Summary #1: The commenter suggested revising the General Chapter to be more compounding-focused and to remove language similar to those used in good manufacturing practices (GMP).
Response: Comment incorporated. The General Chapter was revised to be more specific for compounders, and to clarify the roles of the sponsor and compounder.
Comment Summary #2: The commenter suggested adding a definition for "qualified person" and specifying whether the person is a quality assurance person or the pharmacist-in-charge.
Response: Comment partially incorporated. "Qualified person" was removed and replaced with "designated person", and the responsibilities of the designated person were described. The term will be defined in future revisions of General Chapters <795> *Pharmaceutical Compounding–Nonsterile Preparations* and <797> *Pharmaceutical Compounding–Sterile Preparations*.
Comment Summary #3: The commenters requested clarification on whether certain provisions of the General Chapter are "must" requirements or "should" recommendations.
Response: Comment incorporated. The intent of this General Information Chapter is to provide recommendations for compounding Phase I investigational studies. The requirements in current official General Chapters (e.g., <795> and <797>) are maintained as "must" requirements. Other provisions in the General Chapter are included as "should" recommendations.

Introduction
Comment Summary #4: The commenter indicated that the definition of Phase I studies is too limited and may include patients as well as healthy volunteers.
Response: Comment incorporated.
Comment Summary #5: The commenter requested clarification on how the sponsor should evaluate the compounder to ensure that effective quality control functions are in place.
Response: Comment not incorporated. The sponsor's evaluation plan should be specific to their products and procedures.
Comment Summary #6: The commenter requested clarification for differentiating compounded preparations used for treating patients and for investigational Phase I studies.
Response: Comment partially incorporated. Text was eliminated.
Comment Summary #7: The commenters requested clarification on the federal requirements for compounding investigational agents.
Response: Comment partially incorporated. The Expert Committee removed the information specific to federal, state, local, and international regulations, and added text to state that applicable regulatory requirements must be followed.
Comment Summary #8: The commenter suggested differentiating the considerations between compounders and manufacturers under subsection 1.4 *Best Practices*.
Response: Comment partially incorporated. The title of subsection 1.4 was revised to "Additional Considerations" to clarify that these are example questions that compounders should consider prior to preparing an investigational agent.

Comment Summary #9: The commenter suggested revising the numbered list of considerations from questions to statements to remove uncertainty on what compounders should consider when preparing investigational preparations.
Response: Comment not incorporated. The Expert Committee determined that the compounder should consider and answer these questions prior to preparing an investigational agent.
Comment Summary #10: The commenters requested clarification on the criteria to determine when GMPs would apply.
Response: Comment incorporated. The Expert Committee determined that this is not a consideration that is specific to the compounder and may be determined by the sponsor. The consideration was removed from the list.
Comment Summary #11: The commenter requested clarification on specific "checks and balances" that are to be followed.
Response: Comment incorporated. The Expert Committee added text to clarify that the "checks and balances" refer to those described in the General Chapter and added a parenthetical example.
Comment Summary #12: The commenters requested clarification on when the investigational preparation would require additional release testing.
Response: Comment incorporated. The question was revised to clarify that the compounder should consider whether release testing is required and parenthetical examples of release testing were added.

Personnel Training
Comment Summary #13: The commenters suggested requiring compounders to be knowledgeable of the mandatory standards in General Chapters <795>, <797>, and <800> *Hazardous Drugs–Handling in Healthcare Settings*. They also suggested recommending that compounders be knowledgeable of information in General Chapter <1163> *Quality Assurance in Pharmaceutical Compounding*.
Response: Comment incorporated.
Comment Summary #14: The commenter suggested recommending that training be documented.
Response: Comment incorporated.

Buildings and Facilities
Comment Summary #15: The commenter requested clarification of special controls for the design of facilities.
Response: Comment incorporated. A parenthetical example was added to clarify the intent of special controls in a facility design.

Equipment and Components
Comment Summary #16: The commenter requested clarification on what additional standards in <1163> would be applicable for components. The commenter suggested that <1163> is applicable to final compounded preparations.
Response: Comment incorporated. The Expert Committee removed the reference to <1163> because <1163> does not address component selection.
Comment Summary #17: The commenter suggested changing "must" to "should" in the sentence, "Any materials not supplied by the sponsor must be appropriate for human use as determined by the study sponsor".
Response: Comment incorporated. General Chapter <1168> is intended to be a General Information Chapter. Information that is not a requirement in other enforceable chapters (e.g., <795> and <797>) was changed to "should" recommendations. Compounders must still follow

applicable regulatory requirements as described in subsection 1.3 Applicable Regulatory Requirements.
Comment Summary #18: The commenters indicated that not all materials used in the compounded preparation may be traceable to the individual patient.
Response: Comment incorporated. The recommendation was revised to specify that active substances and excipients should be traceable to the individual patient.
Comment Summary #19: The commenter suggested that investigational materials in Phase 1 clinical trials will not likely be compendial, but excipients may be compendial.
Response: Comment partially incorporated. The section was revised to state that bulk drug substances and excipients preferably should be official compendial articles.
Comment Summary #20: The commenter suggested that all bulk investigational agents and other ingredients should be "visually inspected" instead of "examined" prior to release for use, because most Phase I facilities do not have the capability to conduct analytical examinations.
Response: Comment incorporated.
Comment Summary #21: The commenter suggested removing "approved" from "Conventionally manufactured approved drug dosage forms (e.g., tablets, capsules, injectables, or liquids) may be used…". .
Response: Comment incorporated.

Standard Operating Procedures
Comment Summary #22: The commenter suggested clarifying that the Standard Operating Procedure (SOP) should facilitate the compounding process and must follow the applicable requirements in <795> and <797>.
Response: Comment incorporated.
Comment Summary #23: The commenter indicated that the statement on risk assessment of the material to be prepared may cause confusion with the risk assessment for hazardous drugs as described in <800>.
Response: Comment incorporated.
Comment Summary #24: The commenter suggested changing "batch" to "preparation" in "A record of changes in procedures and processes used for subsequent batches…", because "batch" is GMP terminology.
Response: Comment not incorporated. The Expert Committee determined that "batch" is commonly used by compounders and in compounding facilities.
Comment Summary #25: The commenter suggested that a record of microbiological controls is typically not contained in written procedures.
Response: Comment incorporated. Requirements for environmental monitoring for sterile compounding facilities are required as described in <797>.

Preparation Activities
Comment Summary #26: The commenter suggested that a trial run may be unnecessary in some situations and suggested that a risk assessment may be performed instead.
Response: Comment not incorporated. A trial run is a recommendation, not a requirement.
Comment Summary #27: The commenter suggested that performing a trial run allows the compounder to become more proficient, make revisions to the processes, and reduce risks of error.
Response: Comment partially incorporated. The proposed General Chapter suggested that the trial run helps ensure that a quality preparation is produced. However, the Expert Committee recognized several other advantages of performing a trial run. Instead of listing all of the advantages, the General Chapter recommends conducting a trial run.
Comment Summary #28: The commenter suggested that compounders are not given extra material to perform a trial run.

Response: Comment not incorporated. A trial run is a recommendation, not a requirement.
Comment Summary #29: The commenters requested clarification of the definition of "high-quality finished preparation".
Response: Comment incorporated. The section was revised to remove qualifiers such as "high" to describe preparations.
Comment Summary #30: The commenter suggested that the quality assurance measures to ensure that the actual yield matches the theoretical yield should not be applicable to liquid preparations and should be applied only to solid preparations.
Response: Comment not incorporated. The Expert Committee determined that ensuring quality assurance through matching the actual and theoretical yield should apply regardless of whether the dosage form is a solid or liquid.
Comment Summary #31: The commenters suggested revising the retention requirements for samples from "at least two years" to the requirements set forth in the sponsor's clinical study documentation.
Response: Comment incorporated
Comment Summary #32: The commenters indicated that the retention of samples is a requirement for pivotal studies and not all studies. Many preparations have limited stability and facilities may not have the storage capacity.
Response: Comment incorporated. The retention and storage of samples should be determined by the sponsor's clinical study documentation.
Comment Summary #33: The commenter suggested that individually prepared suspensions or tablets may not be retained.
Response: Comment incorporated. The retention samples should be determined by the sponsor's clinical study documentation.
Comment Summary #34: The commenter requested clarification on the extent of "access" that sponsors should have to compounding records and retained components.
Response: Comment not incorporated. The policies and procedures of each facility should be specific for that facility, the study performed, and the sponsor-compounder relationship. The sponsor should be able to make a request to review all pertinent compounding records and documentation.
Comment Summary #35: The commenter noted that it is not feasible to retain twice the quantity of components required to perform a release test at a later date.
Response: Comment incorporated. The recommendation for retaining components was changed to reflect those of the clinical study documentation.
Comment Summary #36: The commenter suggested that the sample retention recommendations would require final review/approval of the finished preparation. The commenter suggested adding that final approval of the preparation instructions is required.
Response: Comment not incorporated. The section is relevant to the retention of samples and not related to final review of the preparation procedures.
Comment Summary #37: The commenter suggested specifying who is responsible for retention of the samples.
Response: Comment not incorporated. Samples should be retained as described in the clinical study documentation and should be part of the agreement between the sponsor and compounder.
Comment Summary #38: The commenter requested clarification on how to determine when a sample is unstable and may be considered for an alternative sample retention approach.
Response: Comment incorporated. Sample storage and retention should be determined by the sponsor, who would have more information on the stability of the samples.
Comment Summary #39: The commenter suggested adding a distinction on whether the materials were supplied by the sponsor or compounding facility when accounting for all used and unused supplies of the investigational agent.

Response: Comment not incorporated. Materials used for the investigational study should be accounted for regardless of whether they are supplied by the sponsor or compounding facility.

Release of Investigational Agent/Preparation

Comment Summary #40: The commenter recommended using the term "approval" instead of "release" because "release" is used in GMP.

Response: Comment not incorporated. The Expert Committee determined that use of the term "approval" may be more misleading. The term "release" is currently used in <797> and use of the term in this General Chapter is consistent. The use of the term does not necessarily imply GMP requirements.

Comment Summary #41: The commenter suggested referencing specific release requirements.

Response: Comment not incorporated. Release testing should be specified by the sponsor and may vary based on the sponsor and the study.

Comment Summary #42: The commenter requested details on how to delegate the responsibilities for approving the final investigational preparation.

Response: Comment not incorporated. The requirements of the study should be described in the clinical study documentation and agreed upon by the sponsor and study site. Additionally, most studies have a delegation log.

Comment Summary #43: The commenter indicated that approval responsibility is described in the study protocol in one section of the General Chapter and also described in the contractual documentation in another section.

Response: Comment incorporated. The responsibilities should be described in the clinical study documentation, which include but are not limited to the study protocol, study manual, compounding logs, investigator brochure, and consent forms.

Comment Summary #44: The commenter suggested that the proposal limits responsibility for the testing program to the qualified personnel designated by the sponsor or sponsor-investigator and recommended recognizing that the compounder could be qualified to be responsible for implementing the testing or working with a contract laboratory.

Response: Comment incorporated.

Labeling

Comment Summary #45: The commenter requested clarification on labeling control and the intent of recommending only the "exact number of labels" to be printed.

Response: Comment incorporated. The Expert Committee determined that labeling reconciliation is important and revised the section to indicate that only the required quantity of labels should be printed and all labels should be accounted for.

Comment Summary #46: The commenter suggested that an example label may be maintained electronically and may not necessarily be affixed to the compounding record.

Response: Comment incorporated.

Establishing Beyond-Use Dates

Comment Summary #47: The commenter suggested adding language that the beyond-use date (BUD) is established by the sponsor and the compounder may assign the actual BUD after mixing.

Response: Comment incorporated.

Quality Assurance and Quality Control

Comment Summary #48: The commenter requested information on how the quality assurance (QA) program should be documented.

Response: Comment not incorporated. Documentation practices should be determined by the facility.
Comment Summary #49: The commenter requested revision of the annual assessment of the QA program to a frequency that is determined by the quality system requirements. The industry standard is to set up quality system requirements, and sites are assessed via an audit program on a risk-based approach.
Response: Comment incorporated. Regular assessment of the QA program should be performed per the facility's SOPs.
Comment Summary #50: The commenter suggested changing "qualified" person to "designated" person to be consistent with other compounding General Chapters.
Response: Comment incorporated.
Comment Summary #51: The commenter requested clarification on whether the qualified person is one person or multiple people.
Response: Comment incorporated. The term "qualified personnel" was revised to "designated person" to be consistent with other compounding General Chapters. The designated person may be one person or multiple people.
Comment Summary #52: The commenter suggested that the recommendation for the QA program to include testing is a GMP requirement and recommended only visual inspection prior to dosing.
Response: Comment partially incorporated. The QA program was revised to state that it may include testing. The Expert Committee did not incorporate visual inspections because other types of tests may be performed by compounders.
Comment Summary #53: The commenter suggested that inspection of the QA program should be performed by an external party and should not be performed internally.
Response: Comment partially incorporated. The QA program should be reviewed with the study sponsor.

Storage, Handling, Packaging, and Transport
Comment Summary #54: The commenter suggested that a Safety Data Sheet (SDS) may not be available for new drugs that are being studied and recommended adding SDS when available.
Response: Comment incorporated.

Documentation
Comment Summary #55: The commenter requested clarification on whether packaging would be considered an ingredient which would require a certificate of analysis (COA).
Response: Comment incorporated. The compounding facility should maintain a COA specifically for active pharmaceutical ingredient(s) [API(s)] and excipient(s).
Comment Summary #56: The commenter indicated that a COA is not available for conventionally manufactured products.
Response: Comment incorporated. The compounding facility should maintain a COA specifically for API(s) and excipient(s).
Comment Summary #57: The commenter requested clarification on whether electronic records are required to be compliant with 21 CFR Part 11 *Electronic Records; Electronic Signatures—Scope and Application*.
Response: Comment not incorporated. Compounders must follow applicable regulatory requirements as described in subsection 1.3 *Applicable Regulatory Requirements*.

General Chapter/Sections:	<1099> *Limit on Number of Large Deviations When Assessing Content Uniformity in Large Samples*
Expert Committees:	General Chapters—Statistics

No. of Commenters: 4

Comment Summary #1: The commenter requested inclusion of operating characteristic curves comparing risk outcomes with those in General Chapter <905> to justify the parameters selected.
Response: Comment not incorporated. <1099> is intended only to provide criteria corresponding to the zero tolerance criterion in <905> when a sample size larger than that called for in <905> is collected.
Comment Summary #2: The commenter suggested that the General Chapter include additional values of the parameters "P" and "f" to calculate c2 values for different sample sizes.
Response: Comment not incorporated. The General Chapter intends to provide the same level of control (not a tighter level of control) as the zero tolerance part of <905> provides when a large sample is collected. Further, the choice of the parameters "P" and "f" is harmonized with the corresponding criterion in *Ph.Eur.* 2.9.47. *Demonstration of Uniformity of Dosage Units Using Large Sample Sizes*.
Comment Summary #3: The commenter suggested that the General Chapter include a limit on the deviation of individual values.
Response: Comment not incorporated. The criterion in <1099> is intended to be used together with other criteria that may be selected when companies collect large samples for purposes such as batch release.
Comment Summary #4: The commenter recommended that <1099> include a clarification that the General Chapter is intended to apply to drug products that are manufactured using process analytical technology methodology.
Response: Comment not incorporated. The General Chapter applies whenever large samples are collected without regard to the manufacturing control methodology.
Comment Summary #5: The commenter recommended that <1099> state that it is not intended as a batch release test and that it does not provide a reason to go beyond the sample size of 30 established in <905>.
Response: Comment incorporated.

General Chapter/Sections: <1211> *Sterility Assurance*
Expert Committee: General Chapters—Microbiology
No. of Commenters: 5
Comment Summary #1: The commenter suggested changing the term "impact" to "influence" regarding factors that contribute to sterility assurance.
Response: Comment incorporated.
Comment Summary #2: The commenter recommended clarifying the purpose of Figure 2 and its relationship to the overall text.
Response: Comment incorporated.
Comment Summary #3: The commenter recommended changing the title of the "Post-Aseptic Fill Terminal Sterilization"sub-section to be consistent with the content of the sub-section.
Response: Comment incorporated.
Comment Summary #4: The commenter indicated that while there is a block in Figure 1 for Materials, there is no section discussing materials within the document.
Response: Comment incorporated. The change was made to the title of the sub-section that discusses materials.
Comment Summary #5: The commenter suggested adding information on whether International Organization for Standardization (ISO) Class 5 Cleanroom conditions are essential in an isolator system and whether unidirectional airflow, air velocities, space pressurization, and particulate levels are the same in an isolator as in a cleanroom.

Response: Comment not incorporated. The suggestion is outside the scope of this General Chapter.
Comment Summary #6: The commenter suggested changing the statement "reducing the need for in-process environmental monitoring" to "reducing the level of in-process environmental monitoring required" as an advantage of Post Aseptic Processing Terminal Sterilization.
Response: Comment incorporated.
Comment Summary #7: The commenter suggested changing the statement, "Terminal sterilization can be applicable at lower lethality levels where bioburden is controlled through aseptic processing" to "Where bioburden is controlled through aseptic processing, terminal sterilization can be applicable at lower lethality levels based on a risk assessment".
Response: Comment incorporated.
Comment Summary #8: The commenter suggested adding clarity and/or references on the sterilization validation requirements and acceptance criteria.
Response: Comment incorporated.
Comment Summary #9: The commenter suggested the addition of ease of administration of the product to the patient as a consideration for the selection of containers and closures.
Response: Comment incorporated.
Comment Summary #10: The commenter suggested including a discussion on the parameters that contribute to effective decontamination.
Response: Comment not incorporated. This suggestion is outside the scope of this General Chapter.
Comment Summary #11: The commenter suggested that manufacturing equipment should be designed to limit exposure of the product to the manufacturing environment.
Response: Comment incorporated.
Comment Summary #12: The commenter suggested including discussion on the use of single-use product contact equipment.
Response: Comment incorporated.
Comment Summary #13: The commenter suggested including clarification and emphasizing the rationale for occasional use of sporicidal agents.
Response: Comment incorporated.
Comment Summary #14: The commenter suggested including a definition for "Controlled non-classified environment" in Table 1.
Response: Comment incorporated.
Comment Summary #15: The commenter suggested providing criteria for how "closed systems" (to be located in a Controlled non-Classified environment) can be distinguished from "isolators" (to be located in an ISO Class 8 Cleanroom).
Response: Comment incorporated.
Comment Summary #16: The commenter indicated that the term "aide" refers to a person. "Aides" should be changed to "aids" in the header.
Response: Comment incorporated.
Comment Summary #17: The commenter recommended adding a sentence indicating that laboratory results/data should not be used to rationalize a poorly designed process.
Response: Comment incorporated.
Comment Summary #18: The commenter recommended emphasizing that process simulations during media fills should be representative of actual processing conditions using equipment that is utilized during routine production.
Response: Comment incorporated.
Comment Summary #19: The commenter recommended clarifying that written procedures are documents that define, not fix, the operations as indicated.
Response: Comment incorporated.

Comment Summary #20: The commenter suggested using more precise language in the *Summary* section, replacing "important characteristics" and "satisfied" with a phrase such as "their critical product quality attributes consistently meet specifications."
Response: Comment incorporated.

General Chapter/Sections: <1222> *Terminally Sterilized Pharmaceutical Products—Parametric Release*/Multiple Sections
Expert Committee: General Chapters—Microbiology
No. of Commenters: 4

Introduction
Comment Summary #1: The commenter indicated that the probability of failing a sterility test is dependent on the batch size, and failure numbers should reflect this dependence.
Response: Comment not incorporated. The probability of failing a sterility test is dependent on the sample size, not the batch size.
Comment Summary #2: The commenter recommended revising the text to indicate that parametric release is the default mode of product release and should be used instead of sterility testing unless parametric release is not feasible.
Response: Comment incorporated.
Comment Summary #3: The commenter suggest replacing "at least" in reference to Probability of a Non-sterile Unit (PNSU) with the technically correct expression "less than or equal to".
Response: Comment incorporated. The change was made throughout the text wherever PNSU was discussed.

User Requirements
Comment Summary #4: The commenter suggested adding a recommendation that firms should have experience with terminal sterilization at a given facility with a given set of equipment before implementing parametric release.
Response: Comment not incorporated. This change could contradict the established technical and statistical fallibility of the sterility test.
Comment Summary #5: The commenter suggested discussing bioburden and pyroburden separately in this section because materials can have high bioburden but low pyroburden (or vice versa).
Response: Comment incorporated.
Comment Summary #6: The commenter suggested considering minimum time durations (e.g., Exposure Phase) in the context of sterilization efficacy because they are critical to product sterility, while maximum time durations are most critical to product stability.
Response: Comment incorporated.
Comment Summary #7: The commenter recommended indicating that repeat sterilization prior to the release of products that failed to meet critical process parameters would require regulatory approval.
Response: Comment incorporated.

Risk Assessment
Comment Summary #8: The commenter recommended changing "loss of integrity resulting in non-sterility" to "loss of integrity which could potentially allow microbial ingress" because of the potential for non-sterility regardless of whether or not the unit becomes nonsterile.
Response: Comment incorporated.

General Chapter/Sections: <1228.4> Depyrogenation by Rinsing
Expert Committee: General Chapters—Microbiology

No. of Commenters: 3

Comment Summary #1: The commenter suggested using either “levels” or “activity” to indicate the amount of endotoxin throughout the General Chapter.

Response: Comment partially incorporated. “Activity” and “levels” are not synonymous, but clarification is provided wherever the term “level” is used.

Comment Summary #2: The commenter expressed concern about the use of the use of “naturally occurring endotoxins” (NOEs) for validation of depyrogenation because NOEs are unpurified, uncharacterized, and are obtained from crude culture preparations of gram-negative bacteria.

Response: Comment not incorporated. NOEs should be prepared using a standard procedure, calibrated against the USP Endotoxin Reference Standard (RS), and characterized as indicated in General Chapter <1228.5> *Depyrogenation*.

Comment Summary #3: The commenter recommended clarifying the term “analyte”.

Response: Comment incorporated. Examples were added.

Comment Summary #4: The commenter recommended including a minimum concentration or challenge level for depyrogenation.

Response: Comment incorporated. A recommendation on challenge levels was added.

General Chapter/Sections: <1467> *Residual Solvents—Verification of Compendial Procedures and Validation of Alternative Procedures*/ Multiple Sections

Expert Committee: General Chapters—Chemical Analysis

No. of Commenters: 10

Expert Committee-initiated Change #1: The following sentence was incorporated in the last paragraph of the introductory text: “A risk-based approach may be appropriate to determine the degree and extent of the verification or validation process to assure the fitness for purpose of the procedure”.

General

Comment Summary #1: The commenter suggested that, rather than creating this new General Chapter, USP consider adjusting the residual solvents verbiage within General Chapter <1225> *Validation of Compendial Procedures*.

Response: Comment not incorporated. The Expert Committee determined that this General Chapter is needed. Validation characteristics may vary from one instrumental method to another, so the General Chapter includes separate *Validation* sections for several instrumental techniques (e.g., Raman, Near Infrared).

Table 1. Summary of Verification and Validation Requirements

Comment Summary #2: The commenter suggested that robustness is not feasible for limit tests based on a possible requirement for S/N of Not Less Than (NLT) 3.

Response: Comment not incorporated. The Expert Committee determined that the robustness is feasible and should be demonstrated before implementation.

Comment Summary #3: The commenter suggested replacing “..of assessing the robustness of the procedure before the implementation” with “… of assessing the robustness of the procedure either during development or in the verification study” in footnote “e”.

Response: Comment not incorporated. The Expert Committee determined that the existing text was suitable. The suggestion is already addressed in footnote “d”.

Comment Summary #4: The commenter requested removal of “Solution stability” from its list of requirements for Verification and Validation in Table 1, or change the entries to “no” and provide

further instruction to users, such as, “to determine the solution stability if the solutions are not tested within 24 hours or are not used freshly prepared”.
Response: Comment not incorporated. The Expert Committee determined that the existing text was suitable. Many solutions may not be stable for testing for 24 hours. The real stability can be determined only experimentally.

Verification of Compendial Procedures
Limit Procedures: Procedure A and Procedure B
Verification When Solvents Likely To Be Present (LTBP) Are Not Known
Comment Summary #5: The commenters recommended adding acceptance criteria based on S/N or percent change to be considered significant to clarify “significant interference” under *Specificity*.
Response: Comment partially incorporated. The Expert Committee decided to revise the first sentence to state, “Recommended acceptance criteria: An appropriate blank should be injected to assure lack of a significant interference. A significant interference is one producing a deviation in the fitness for purpose of the procedure, affecting precision and/or accuracy.”.

Verification When Solvents Likely To Be Present (LTBP) Are Known
Comment Summary #6: The commenter requested clarification on why the resolution requirement for any pair of peaks is NLT 1.5 when the resolution requirement in the *Standard Solution* and *Spiked Sample Solution* is NLT 1.0.
Response: Comment not incorporated. The Expert Committee determined that the existing text was suitable and that Figure 4 provides clarity. The current procedure includes pairs of peaks with resolution of about 1.0. In other cases the resolution should be at least 1.5. In all cases, verification should demonstrate fitness for purpose.
Comment Summary #7: The commenter requested the definition of a “fresh solution”.
Response: Comment not incorporated. The Expert Committee determined that this is common knowledge. A fresh solution is prepared at the time of use.

Verification of Compendial Procedures
Quantitative Procedures: Procedure C
Comment Summary #8: The commenter requested clarification on why the resolution requirement for any pair of peaks is NLT 1.5 when the resolution requirement in the *Standard Solution* and *Spiked Sample Solution* is NLT 1.0.
Response: Comment not incorporated. The Expert Committee determined that the existing text was suitable and that Figure 4 provides clarity. The Expert Committee does not know which solvents are present in real samples. The current procedure includes pairs of peaks with resolution of about 1.0. In other cases the resolution should be at least 1.5. In all cases, verification should demonstrate fitness for purpose.
Comment Summary #9: The commenter recommended changing “.. or Quantitation Limit may be demonstrated by Accuracy” to “..or the Quantitation Limit may be demonstrated by both Accuracy and Repeatability Precision” because the phrase was misleading and implied that Accuracy was sufficient.
Response: Comment incorporated.
Comment Summary #10: The commenter suggested changing the text under *Quantitation Limit* to state that “the QL be verified at a concentration of NMT 50% of the specification”.
Response: Comment not incorporated. The Expert Committee determined that the existing text was suitable. There is a curve proposed at 50%, 100%, and 150% of the specification. Because the requirement states “after correction for native (original) solvent”, it inherently includes verification at a concentration of NMT 50% of specification.

Comment Summary #11: The commenter recommended changing the *Accuracy* acceptance criteria to “Acceptance criteria recommended is 80%–120% for mean recovery value; criteria for individual recovery value are not recommended”.
Response: Comment not incorporated. The Expert Committee determined that the existing text was suitable. Accuracy at 100% is acceptable for pure substances, and three levels are generally requested for products or cases where a range is expected.
Comment Summary #12: The commenter requested a widening of the recovery criteria to 70%–130% for residual solvents with acceptance limits less than 100 ppm.
Response: Comment not incorporated. The Expert Committee determined that the existing text was suitable. Good science may promote the use of alternative approaches when necessary, but justification is needed.
Comment Summary #13: The commenter suggested clarifying how to evaluate the data under *Accuracy* and *Precision/Repeatability* when the level of residual solvents is lower than the detection limit, and suggested that the relative standard deviation (RSD) for recovery could be used instead.
Response: Comment not incorporated. The Expert Committee determined that the existing text was suitable. Spiked solutions provide responses NLT the limit of detection.
Comment Summary #14: The commenter suggested clarifying the need to prepare six sample solutions for *Precision/Repeatability*.
Response: Comment not incorporated. The Expert Committee determined that the existing text was suitable. This General Chapter is a guideline for verification and validation, not for routine testing.
Comment Summary #15: The commenter requested confirmation of the need to demonstrate precision with spiking, even in cases where analyzed samples show the presence of residual solvents.
Response: Comment not incorporated. The Expert Committee determined that the existing text was suitable. This is a standard for every possible matrix, and matrix effect cannot be excluded.
Comment Summary #16: The commenter suggested changing the *Solution Stability* acceptance criteria from “% variation” to “% RSD”.
Response: Comment partially incorporated. The Expert Committee revised the text to state, “NMT 20% change in solvent(s) content compared to the initial time point”.

Validation of Alternative Procedures
Linearity and Range
Comment Summary #17: The commenter suggested that linearity is usually performed on the results of the dilution of a standard stock solution at five different levels consistent with ICH guidelines.
Response: Comment not incorporated. The Expert Committee determined that the existing text was suitable. This method is highly matrix dependent, and the matrix may influence recovery and linearity. This is consistent with ICH.
Comment Summary #18: The commenter suggested changing the linearity requirement to five points covering the range, not the sample matrix, and tightening the correlation coefficient to NLT 0.95.
Response: Comment not incorporated. The Expert Committee determined that the existing text was suitable. The matrix cannot be taken apart. The matrix is a fundamental part of the sample and in many cases is “alive”. The existing recommended acceptance criterion of NLT 0.90 is suitable, and consistent with the 80%–120% criteria for recovery and the 20% RSD for precision.
Comment Summary #19: The commenter recommended tightening the correlation coefficient requirement from NLT 0.90 to NLT 0.98.

Response: Comment not incorporated. The Expert Committee determined that the existing recommended acceptance criterion of NLT 0.90 is suitable. This is consistent with the 80%–120% criteria for recovery and the 20% RSD for precision.
Comment Summary #20: The commenter suggested clarifying the spiking because a 100% spike in a sample containing residual solvents at specification limits would result in a 200% level.
Response: Comment not incorporated. The Expert Committee determined that the existing text was suitable. It is expected that the matrix used for spiking is as clean as possible. If not, the base level should be calculated through the standard addition method to evaluate recovery.

Quantitation Limit
Comment Summary #21: The commenter suggested changing "…from at least three determinations is NLT 10. The Quantitation Limit may also be demonstrated by Accuracy" to "…from at least six determinations from a single preparation is NLT 10. The Quantitation Limit may also demonstrated by Accuracy and Repeatability Precision".
Response: Comment partially incorporated. The Expert Committee determined that the existing text was suitable for the number of determinations and changed "Accuracy" to "Accuracy and Precision".
Comment Summary #22: The commenter requested clarification on how the native solvent correction is accomplished in evaluating the S/N ratio.
Response: Comment not incorporated. The Expert Committee determined that the existing text was suitable and is consistent with General Chapter <621> *Chromatography*.
Comment Summary #23: The commenter requested clarification on why the limit of quantitation is determined using a spiked sample solution in addition to dilutions of the standard solution, which is not consistent with ICH.
Response: Comment not incorporated. The Expert Committee determined that the existing text was suitable and is consistent with ICH Q2 *Validation of Analytical Procedures: Text and Methodology*.

Accuracy
Comment Summary #24: The commenter requested clarification on whether the percent recovery is to be calculated versus a standard solution of mid-range spiked solution.
Response: Comment not incorporated. The Expert Committee determined that the existing text was suitable. Accuracy at mid-range (100% level) is acceptable for pure substances, and three levels are generally requested for products or cases where a range is expected.
Comment Summary #25: The commenter suggested suggest updating the General Chapter to allow the assessment of NLT three accuracy levels (lowest level, mid-level, and highest level covering the range of interest), to align with ICH and General Chapter <1225>.
Response: Comment not incorporated. The Expert Committee determined that the existing text was suitable. The text covers three levels and is aligned with ICH.
Comment Summary #26: The commenter requested the allowance of a provision to calculate recovery by compensating with a recovery factor.
Response: Comment not incorporated. The Expert Committee determined that the existing text was suitable. The text does not preclude using an alternative method.

Solution Stability
Comment Summary #27: The commenter suggested that the *Solution Stability* recommendation is not feasible for a headspace General Chapter because single solution vials are used for analysis and these vials cannot be reinjected.

Response: Comment not incorporated. The Expert Committee determined that the existing text was suitable. The test requires the use of multiple vials. This is a section on validation and verification, not a routine test.

Comment Summary #28: The commenter suggested listing robustness under *Validation of Alternative Procedures* and including suggested method changes recommended for evaluation.
Response: Comment not incorporated. The Expert Committee determined that the existing text was suitable. The robustness test implies a risk assessment from the user.

Monographs

Monograph/Sections: Alprazolam Tablets/Organic Impurities
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 2
Comment Summary #1: The commenters requested revision of the acceptance criteria for one or more impurities and individual unspecified degradation products for consistency with FDA-approved specifications.
Response: Comment incorporated.
Expert Committee-initiated Change #1: The references to "chromatographic acetonitrile" in the *Assay* were replaced with references to "acetonitrile" because the proposal to add an entry to the reagent section for "chromatographic acetonitrile" was cancelled.
Expert Committee-initiated Change #2: The statement to disregard peaks less than 0.1% was replaced with, "The reporting threshold is 0.1%" for consistency with *USP* style.

Monograph/Sections: Amitriptyline Hydrochloride Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 2
Comment Summary #1: The commenter requested revising the *Sample solution* preparation in the *Assay* and *Organic Impurities* test to include crushing the tablets or another procedure because of the extensive time needed to disintegrate the tablets completely using shaking alone.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of the necessary supporting data.
Comment Summary #2: The commenter requested improvement of the resolution between the two enantiomers and amitriptyline related compound A in the *Organic Impurities* test.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of the necessary supporting data.
Comment Summary #3: The commenters requested identification of amitriptyline related compound A, amitriptyline related compound B, nortriptyline, and cyclobenzaprine as process impurities in the *Organic Impurities* test.
Response: Comment incorporated. The references to cyclobenzaprine and USP Cyclobenzaprine Hydrochloride RS were removed from the *Standard solution* preparation, the *Analysis* section, and Table 1 in the *Organic Impurities* test as well as from the *USP Reference Standards* section. The acceptance criteria for amitriptyline related compound A, amitriptyline related compound B, and nortriptyline were retained based on data demonstrating that these compounds are degradation products.
Comment Summary #4: The commenter requested the addition of a molecular weight correction to the calculation of nortriptyline or modification of the acceptance criteria to refer to nortriptyline hydrochloride.
Response: Comment not incorporated. The text as written is consistent with the drug substance monograph and with FDA-approved requirements.

Comment Summary #5: The commenter requested replacement of the use of external reference standards for all known impurities to the use of relative response factors (RRFs).
Response: Comment not incorporated. The text as written is appropriate for use as the public standard.
Comment Summary #6: The commenter requested a widening of the limit for total degradation products to NMT 2.0%.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of the necessary supporting data.

Monograph/Sections: Ammonia N13 Injection/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 5
Comment Summary #1: The commenter requested revising the tests for *Radiochemical Identity* and *Radiochemical Purity* to include alternate procedures for counting radioactivity on the thin-layer chromatography (TLC) plate.
Response: Comment not incorporated. The use of alternative methods and procedures are discussed in *General Notices 6.30 Alternative and Harmonized Methods and Procedures*.
Comment Summary #2: The commenter requested revision of the test for *Radiochemical Identity* to allow the user to spray or stain the TLC plate.
Response: Comment incorporated.
Comment Summary #3: The commenter indicated that the cellulose diethylamino ethyl strips used in the tests for *Radiochemical Identity* and *Radiochemical Purity* are not widely available and requested the inclusion of alternative strips.
Response: Comment not incorporated. The use of alternative methods and procedures are discussed in *General Notices 6.30*.
Comment Summary #4: The commenter requested inclusion of a note regarding the sub-batch concept because of the short half-life of this article.
Response: Comment not incorporated. The text as written is appropriate for use as the public standard.
Comment Summary #5: The commenter requested inclusion of a note in the test for *Radionuclidic Impurities* to provide the option of using the periodic quality indicator test concept that is included in the *Fludeoxyglucose F 18 Injection* monograph proposal.
Response: Comment incorporated.
Comment Summary #6: The commenter requested replacement of the specific volume of “25 µL” with “suitable volume” in the pH test to be consistent with the *Fludeoxyglucose F 18 Injection* monograph proposal.
Response: Comment incorporated.
Comment Summary #7: The commenter requested retention of the high-performance liquid chromatographic procedures in the tests for *Radiochemical Identity* and *Radiochemical Purity.*
Response: Comment not incorporated. The text as written is suitable for inclusion in the public standard. The use of alternative methods and procedures is discussed in *General Notices, 6.30*.
Comment Summary #8: The commenter requested revision of the definition to include a statement indicating that N13 is a positron emitting radionuclide.
Response: Comment not incorporated. It is well known in the positron emission tomography (PET) industry N13 is a positron emitter.

Monograph/Sections: Atropine Sulfate/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 3

Comment Summary #1: The commenters requested retention of the existing *Relative standard deviation* requirement in the *Assay* or replacement of the requirement with a reference to a table within General Chapter <621>.
Response: Comment not incorporated. The text as written is suitable for inclusion in the public standard.
Comment Summary #2: The commenter requested the addition of a storage temperature requirement in the *Packaging and Storage* section.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of the necessary supporting data.

Monograph/Sections: *Bacillus coagulans*/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 0
Expert Committee-initiated Change #1: The title of the monograph was changed from strain level ("*Bacillus coagulans*, GBI-30, 6086") to species level ("*Bacillus coagulans*") so that multiple strains of *Bacillus coagulans* could be included in one species-level monograph. The *Definition* and *Labeling* sections were also revised to reflect the title change.
Expert Committee-initiated Change #2: Sample preparation procedures for the *Identification* and *Enumeration* tests were changed to be consistent with those of the *Food Chemicals Codex (FCC)* monograph, *Bacillus coagulans* GBI-30, 6086
Expert Committee-initiated Change #3: Requirements for contaminants were changed to be consistent with those of the *FCC* monograph, *Bacillus coagulans* GBI-30, 6086

Monograph/Sections: *Bacillus coagulans* Capsules/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 0
Expert Committee-initiated Change #1: The title of the monograph was changed from strain level ("*Bacillus coagulans*, GBI-30, 6086 Capsules") to species level ("*Bacillus coagulans* Capsules"), so that multiple strains of *Bacillus coagulans* could be included in one species-level monograph. The *Definition* and *Labeling* sections were also revised to reflect the title change.
Expert Committee-initiated Change #2: Sample preparation procedures for the *Identification* and *Enumeration* tests were changed to be consistent with those of the *FCC* monograph, *Bacillus coagulans* GBI-30, 6086.
Expert Committee-initiated Change #3: Requirements for contaminants were changed to be consistent with those of the *FCC* monograph, *Bacillus coagulans* GBI-30, 6086.

Monograph/Sections: Bendamustine Hydrochloride/Multiple Sections
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 3
Comment Summary #1: The commenter requested the addition of the bendamustine hydrochloride monohydrate form and revision of the acceptance criteria for the *Assay* and *Water Determination*.
Response: Comment incorporated. The bendamustine hydrochloride monohydrate form was added to the *Definition* and *Chemical Information* sections. Flexible acceptance criteria for *Assay* and *Water Determination* were also added.
Comment Summary #2: The commenter recommended revising the limit for Bendamustine Related Compound D in the *Organic Impurit*ies test.
Response: Comment not incorporated. The proposed limits are based on FDA-approved acceptance criteria. The Expert Committee will consider future revisions to the monograph upon receipt of the necessary supporting data.
Comment Summary #3: The commenter recommended revising the bacterial endotoxins limit.

Response: Comment incorporated. The numerical limit was deleted and a reference to General Chapter <85> *Bacterial Endotoxins Test* was added.
Comment Summary #4: The commenter recommended revising the *Residue on Ignition* limit.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of the necessary supporting data.
Comment Summary #5: The commenter recommended changing "Store at room temperature" to "Store at controlled room temperature" under *Packaging and Storage.*
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of the necessary supporting data.
Comment Summary #6: The commenter recommended including chemical structures for all specified impurities in the monograph.
Response: Comment not incorporated. Inclusion of structures for impurities will be considered in a future revision.
Comment Summary #7: The commenter requested revision of the *Infrared Absorption* test for *Identification A* to accommodate the differences in spectra because of the presence of different polymorphic forms.
Response: Comment not incorporated. The Expert Committee determined that the differences observed in the spectra attributed to the presence of polymorphs are addressed by General Chapter <197> *Spectrophotometric Identification Tests*.
Expert Committee-initiated Change #1: The phrase "Disregard any peak less than 0.05%" in the *Organic Impurities* test was replaced with "The reporting threshold is 0.05%", consistent with *USP* style.

Monograph/Sections: Bendamustine Hydrochloride for Injection/Multiple Sections
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 3
Comment Summary #1: The commenter requested revision of the analysis time from 25 minutes to 45 minutes to be consistent with the run time listed in Table 1 in the *Assay*.
Response: Comment not incorporated. The Expert Committee reviewed the supporting data and determined that the analysis time is correct in the monograph.
Comment Summary #2: The commenter recommended deleting the reference to the General Chapter <905> *Weight Variation* from the *Uniformity of Dosage Units* test to provide flexibility.
Response: Comment incorporated.
Comment Summary #3: The commenter indicated that 254 nm may not be the appropriate analytical wavelength for the *Organic Impurities* test.
Response: Comment not incorporated. The Expert Committee determined that the procedure is consistent with supporting validation data and suitable for the intended use.
Comment Summary #4: The commenter requested revision of the *Bacterial Endotoxins* limit from NMT 0.5 to NMT 0.8 USP Endotoxin Units/mg of bendamustine hydrochloride.
Response: Comment incorporated. The numerical limit was deleted and a reference to General Chapter <85> was added.
Expert Committee-initiated Change #1: The phrase "Disregard any peak less than 0.05%" in the *Organic Impurities* test was replaced with "The reporting threshold is 0.05%", consistent with *USP* style.

Monograph/Sections: Bicalutamide Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 1
Comment Summary #1: The commenter recommended revising the acceptance criteria for total impurities in the *Organic Impurities* test.

Response: Comment not incorporated. The proposed limits are based on FDA-approved acceptance criteria. The Expert Committee will consider a future revision to the monograph upon receipt of supporting data.
Comment Summary #2: The commenter recommended updating the parameters and tolerances in the *Dissolution* test to include those of all FDA-approved manufacturers.
Response: Comment not incorporated. The Expert Committee will consider a future revision to the monograph upon receipt of supporting data.

Monograph/Section: Biotin Compounded Oral Suspension
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested clarifying whether the biotin used in the formulation was the API or another product.
Response: Comment incorporated.

Monograph/Sections: Carbinoxamine Maleate/Multiple Sections
Expert Committee: Chemical Medicines Monographs 5
No. of Commenters: 1
Comment Summary # 1: The commenter suggested revising the acceptance limit for an individual impurity.
Response: Comment not incorporated. The Expert Committee will consider a future revision to the monograph upon receipt of supporting data.
Comment Summary # 2: The commenter suggested adding a storage temperature requirement.
Response: Comment not incorporated. The Expert Committee will consider a future revision to the monograph upon receipt of supporting data.

Monograph/Sections: Carotenes/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter recommended replacing "dilute with cyclohexane" with "dilute with tetrahydrofuran" for the *Sample stock solution* in the *Content of Total Carotenes* test because tetrahydrofuran is a more effective dissolving solvent.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested adding a note to Table 2 to indicate that the RRFs of carotene components are determined at a 445 nm wavelength.
Response: Comment incorporated.
Comment Summary #3: The commenter suggested adding the content of all-*trans*-beta carotene to the *Labeling* section.
Response: Comment not incorporated. The content of all-*trans*-beta carotene is not available because the test procedure is designed to determine the total beta carotene content, not individual isomers.
Expert Committee-initiated Change #1: "Tetrahydrofuran" was changed to "cyclohexane" as a diluent for the *System suitability solution* (for the second dilution step only), *Standard solution A*, and the *Sample solution* in the *Content of Alpha and Beta Carotene* test to improve the peak shape of the targeted carotene components.

Monograph/Sections: Castor Oil/Multiple Sections
Expert Committee: Excipients Monographs 1
No. of Commenters: 3

Comment Summary #1: The commenter requested removal of the *Bacterial Endotoxins Test* <85> and clarification on the need for the requirement. For a parenteral product, endotoxins will form part of the specification and will be tested after further processing of the castor oil. Castor oil has been demonstrated to have low bioburden and endotoxin levels.
Response: Comment not incorporated. The Expert Committee determined that control of this quality attribute is necessary for castor oil that is subjected to further processing during the preparation of injectable dosage forms.
Comment Summary #2: The commenter recommended moving the specification of *Saponification Value* to *Other Requirements* as an additional requirement when intended for parenteral use. In the last case, which would apply to refined oil, the specific test limits would supersede those for *Nonaqueous Vehicles* (185 to 200) established in General Chapter <1> *Injections and Implanted Drug Products (Parenterals)—Product Quality Tests*, which are not appropriate for Castor Oil (176 to 182). The commenter provided data to support their recommendation.
Response: Comment incorporated.

Monograph/Sections: Cod Liver Oil/Identification
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: **0**
Expert Committee-initiated Change #1: The quartz tube used for the *Standard solution* in the *Fatty Acid profile* test was replaced with an equivalent glass tube (made from borosilicate glass), because it is difficult to obtain the quartz tube commercially.

Monograph/Section: Cortisone Acetate/Organic Impurities
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 2
Comment Summary #1: The commenter indicated that the acceptance criterion for *Total impurities* is inconsistent with the FDA-approved requirements.
Response: Comment not incorporated. The Expert Committee will consider a future revision to the monograph upon receipt of supporting data.
Comment Summary #2: The commenter requested inclusion of their impurity profile, acceptance criteria, and RRF values.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.

Monograph/Sections: Cromolyn Sodium/ Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1
Comment Summary #1: The commenter requested revision of the acceptance criteria in the *Organic Impurities* test for consistency with FDA-approved requirements.
Response: Comment not incorporated. The acceptance criteria are consistent with an FDA-approved application.
Comment Summary #2: The commenter requested revision of the format of the acceptance criteria in the *Limit of Oxalate* test.
Response: Comment not incorporated. The text as written is appropriate for use as the public standard.
Comment Summary #3: The commenter requested addition of a temperature requirement in the *Packaging and Storage* section.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of the necessary supporting data.

Expert Committee-initiated Change #1: The *Resolution* requirement in the *Organic Impurities* test was revised to NLT 2.5 based on supporting data.

Monograph/Sections: Cyclophosphamide Compounded Oral Suspension
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that use of Cyclophosphamide for Injection may be preferable to use of Cyclophosphamide Capsules. The labeling for FDA-approved Cyclophosphamide for Injection states that Cyclophosphamide for Injection may be used to prepare "liquid preparations of cyclophosphamide for oral administration may be prepared by dissolving cyclophosphamide for injection in Aromatic Elixir, National Formulary (NF)."
Response: Comment not incorporated. A validated stability-indicating study was performed on the formulation described in the monograph to establish a BUD that is specific for that formulation. Compounders may still use the formulation described in the FDA-approved labeling for Cyclophosphamide for Injection.
Comment Summary #2: The commenter suggested incorporating language that the preparation is cytotoxic and that gloves should be worn when handling Cyclophosphamide Capsules.
Response: Comment not incorporated. Cyclophosphamide is a hazardous drug as defined by the National Institute for Occupational Safety and Health and users must follow applicable chapter such as <795> and <800> (when it becomes official).

Monograph/Sections: Dextrose Excipient/Multiple Sections
Expert Committee: Excipient Monographs 1
No. of Commenters: 0
Expert Committee-initiated Change #1: In the *Water Determination* test, a requirement to dry under vacuum was added because it was missing from the *PF* proposal. The data supporting the change in the drying temperature were collected under vacuum.
Expert Committee-initiated Change #2: In *Identification A* and *Identification C,* replace the reference "*Water Determination <921>, Method III*" with a reference to the *Water Determination* test in the monograph.
Expert Committee-initiated Change #3: In *Related Substances,* under *Analysis,* replace "Disregard any peak with an area less than the principal peak from Standard solution C (0.05%)" with "The reporting threshold is 0.05%. Disregard any peak with an area less than the principal peak from *Standard solution C"* to align with *USP* style.
Expert Committee-initiated Change #4: In *Assay,* under *Analysis,* define C_U as a concentration of the Dextrose Excipient in the *Sample solution. "*Dextrose Excipient" was missing from the C_U definition in the *PF* proposal.

Monograph/Section: Escitalopram Tablets/Organic Impurities
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 0
Expert Committee-initiated Change #1: The references to "3-oxocitalopram", "citalopram *N*-oxide", and "3-hydroxycitalopram" in Table 1 were removed because the chemical names provided in Table 1 and in the *USP Reference Standards <11>* section are sufficient.

Monograph/Sections: European Elder Berry Dry Extract/Multiple Sections
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 2

Comment Summary #1: The commenter indicated that the water content specification should be on the anhydrous basis because water content is determined by Karl Fischer, not Loss on Drying, in the monograph.
Response: Comment incorporated.
Expert Committee-initiated Change #1: USP Lab project test results showed that on the high-performance-thin-layer chromatography plate, a weak blue band was observed that was partially co-eluted with chlorogenic acid, between chlorogenic acid and the yellow band above. "A weak blue band that is partially overlapped with chlorogenic acid appears between chlorogenic acid and the yellow band above" was added.

Monograph/Section: Exenatide Injection/Packaging and Storage
Expert Committee: Biologics Monographs 1—-Peptides
No. of Commenters: 1
Comment Summary #1: The commenter recommended deleting the *Packaging and Storage* requirements because they are specific to formulation and stability.
Response: Comment partially incorporated. The Expert Committee deleted the packaging requirements, but maintained the storage requirements.

Monograph/Sections: Fludarabine Phosphate/Multiple Sections
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 4
Comment Summary #1: The commenter requested the addition of footnotes for impurity chemical names in Table 1 and Table 2 in the *Organic impurities* test.
Response: Comment incorporated.
Comment Summary #2: The commenter recommended removing the RSD requirement from the *Assay* system suitability requirement to allow flexibility in the number of injections as described in General Chapter <621>.
Response: Comment not incorporated. The request will be considered in the future as an overarching issue across all monographs. The revision of the RSD for the *Assay* system suitability requirement was canceled.

Monograph/Sections: Fludeoxyglucose F 18 Injection/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 2
Comment Summary #1: The commenter requested revision of the tests for *Radiochemical Identity* and *Radiochemical Purity* to include alternate procedures for counting radioactivity on the TLC plate.
Response: Comment not incorporated. The use of alternative methods and procedures is discussed in *General Notices 6.30*.
Comment Summary #2: The commenter requested removal of the *Radionuclidic Impurities* test.
Response: Comment not incorporated. The test is not new. The test may be a periodic quality indicator test and is appropriate for inclusion in the public standard.
Comment Summary #3: The commenter requested retention of the existing test for *Organic Impurities*.
Response: Comment not incorporated. The text as written is suitable for inclusion in the public standard. The use of alternative methods and procedures is discussed in *General Notices 6.30*.
Comment Summary #4: The commenter requested removal of the *Limit of Fludeoxyglucose Related Compound B* test.
Response: Comment not incorporated. The text as written is suitable for inclusion in the public standard.

Monograph/Sections: Fludrocortisone Acetate Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 5
No. of Commenters: 2

Comment Summary #1: The commenter requested revision of the acceptance criteria for fludrocortisone and for total degradation products in the *Organic Impurities* test for consistency with FDA-approved requirements.
Response: Comment incorporated.
Comment Summary #2: The commenter requested postponement of the *Organic Impurities* test and the *Packaging and Storage* section revision to allow additional time to evaluate the suitability of the proposed revisions.
Response: Comment incorporated. The proposal was postponed from two ballots. In the absence of specific issues supported by data, the Expert Committee decided to proceed with the revisions.
Comment Summary #3: The commenter requested replacement of the proposed *Organic Impurities* test with their in-house procedure or addition of their in-house procedure as an alternative test.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of the necessary supporting data.

Monograph/Sections: Fluvastatin Sodium/Assay
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 1
Comment Summary #1: The commenter recommended retaining the percent RSD requirement of NMT 1.0% in the *System Suitability* for the *Assay* to be consistent with the method validation.
Response: Comment not incorporated. The Expert Committee determined that the proposed percent RSD of NMT 0.73% is supported by the validation data and will consider a future revision upon receipt of supporting data.
Expert Committee-initiated Change #1: The Expert Committee deleted "Fluvastatin t-butyl ester" from the *Organic Impurities Table 2*, and revised the impurity chemical names in the *Table 2* footnotes to be consistent with *USP* style and naming conventions.
Expert Committee-initiated Change #2: The Expert Committee included the chemical name for USP Fluvastatin Related Compound B RS under the *USP Reference Standards <11>* section, "*tert*-Butyl (3*RS*,5*SR*,*E*)-7-[3-(4-fluorophenyl)-1-isopropyl-1*H*-indol-2-yl]-3,5-dihydroxyhept-6-enoate along with [*R**,*S**-*E*]-(±)-7-[3-(4-Fluorophenyl)-1-methylethyl-1*H*indol-2-yl]-3,5-dihydroxy-6-heptenoic acid 1,1-dimethylethyl ester", to be consistent with the chemical name on the Reference Standard label.

Monograph/Sections: Fosinopril Sodium/Assay
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 1
Comment Summary #1: The commenter recommended retaining the percent RSD requirement of NMT 2.0% under *Assay, System Suitability,* because the proposed percent RSD requirement is not aligned with the *Assay* content/range specified in the General Chapter <621>.
Response: Comment not incorporated. The Expert Committee determined that the validation data supports the proposed percent RSD of NMT 0.73% and will consider a future revision upon receipt of the supporting data.

Monograph/Sections: Gemcitabine Hydrochloride/Multiple Sections
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 1

Comment Summary #1: The commenter recommended including a temperature requirement in the *Packaging and Storage* section.
Response: Comment not incorporated. The Expert Committee will consider a future revision to the monograph upon receipt of supporting data.
Comment Summary #2: The commenter recommended correcting the chemical name for the USP Cytosine RS in Table 2 in the *Organic Impurities* test and the *Reference Standard <11>* section.
Response: Comment incorporated. The chemical name was changed from "4-Amino-1-(2-deoxy-2,2-difluoro-α-d-erythro-pentofuranosyl)pyrimidin-2(1H)-one" to "2(1H)-Pyrimidinone, 4-amino-".
Comment Summary #3: The commenter recommended adding a third name for Gemcitabine Hydrochloride to distinguish it from the α-anomer impurity in the *Definition* section.
Response: Comment not incorporated. The Expert Committee determined that the chemical name for Gemcitabine Hydrochloride, "2'-Deoxy-2',2'-difluorocytidine monohydrochloride (β-isomer)", distinguishes it from the α-anomer impurity.

Monograph/Sections: Hydrogenated Vegetable Oil/Multiple Sections
Expert Committee: Excipient Monographs 1
No. of Commenters: 3
Comment Summary #1: The commenters recommended removing "cottonseed" and "Hydrogenated Cottonseed Oil NF" from the following sentence: "If the botanical source is identified as cottonseed, or soybean and the type as Type I, compliance with Hydrogenated Cottonseed Oil NF, Hydrogenated Palm Oil NF, or Hydrogenated Soybean Oil NF is required". They provided supporting data.
Response: Comment incorporated.

Monograph/Section: Hyoscyamine Sulfate/Packaging and Storage
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 1
Comment Summary #1: The commenter recommended revising *Packaging and Storage* to include "store at controlled room temperature" instead of "room temperature".
Response: Comment not incorporated. The Expert Committee will consider a future revision to the monograph upon receipt of supporting data.

Monograph/Sections: Indomethacin/Multiple Sections
Expert Committee: Chemical Medicine Monographs 2
No. of Commenters: 1
Comment Summary #1*: The commenter recommended revising the acceptance criterion for indomethacin related compound B under *Organic Impurities* to be consistent with the FDA-approved limit.
Response: Comment incorporated. The Expert Committee retained the current requirement of NMT 0.5% for indomethacin related compound B.
Comment Summary #2*: The commenter recommended adding a storage temperature requirement under the *Packaging and Storage* section.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.

Monograph/Sections: Isotretinoin Capsules/Multiple Sections
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 2

Comment Summary #1: The commenter recommended retaining the *Assay* RSD requirement of NMT 2.0% that is in the current monograph.
Response: Comment incorporated.
Comment Summary #2: The commenter recommended deleting the RSD requirement for the isotretinoin peak and retaining the requirement for the tretinoin peak only in the *Organic impurities* test, because all impurities are calculated against the tretinoin peak.
Response: Comment incorporated.
Expert Committee-initiated Change #1: The diode array detector ultraviolet range for *Identification B* test in the *Assay* was changed from "200 nm–400 nm" to "230 nm–400 nm" because the noise generated by 200 nm to 230 nm makes this range unsuitable for identification.

Monograph/Section: Krill Oil/Composition
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter suggested changing the acceptance criteria in the *Content of Total Phospholipids* test from "Phosphatidylcholine: 60%-96% (w/w) of the *Total phospholipids* content" to "Phosphatidylcholine, 1-lysophosphatidylcholine, and 2-lysophosphatidylcholine: 60%–96% (w/w) of the *Total phospholipids* content" to be consistent with the *Definition*.
Response: Comment incorporated.

Monograph/Section: Leflunomide Compounded Oral Suspension
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested clarifying whether the leflunomide used in the formulation was the API or another product.
Response: Comment incorporated.

Monograph/Section: Methotrexate/Packaging and Storage
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 1
Comment Summary #1: The commenter requested the addition of a storage temperature requirement.
Response: Comment not incorporated. The Expert Committee will consider a future revision to the monograph upon receipt of supporting data.

Monograph/Section: Naproxen Sodium and Pseudoephedrine Hydrochloride Extended-Release Tablets/Packaging and Storage
Expert Committee: Chemical Medicines Monographs 6
No. of Commenters: 1
Comment Summary #1*: The commenter recommended adding a "tight container" requirement to *Packaging and Storage*.
Response: Comment not incorporated. The Expert Committee determined that the proposed *Packaging and Storage* conditions are consistent with the supporting data. The Expert Committee will consider a future revision to the monograph upon receipt of the necessary supporting data.

Monograph/Section: Maprotiline Hydrochloride/Packaging and Storage
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1

Comment Summary # 1: The commenter requested the addition of a storage temperature requirement.
Response: Comment not incorporated. The Expert Committee determined that the proposal as written is consistent with the validation data and is suitable for the intended purpose.

Monograph/Section: Norethindrone Acetate Tablets/Organic Impurities
Expert Committee: Chemical Medicines Monographs 5
No. of Commenters: 2
Comment Summary #1: The commenter requested revision of the *Total impurities* acceptance criteria for consistency with FDA-approved requirements.
Response: Comment incorporated.
Comment Summary #2: The commenter requested the addition of their acceptance criteria (NMT 0.5%) for impurity 6β-Hydroxynorethindrone acetate in the *Organic Impurities* section.
Response: Comment not incorporated. 6β-Hydroxynorethindrone acetate was not listed as a specified degradation product in the proposal. The acceptance criterion for an individual degradation product (NMT 0.5%) will apply. The Expert Committee will consider revising this monograph in the future upon receipt of the necessary supporting data.
Comment Summary #3: The commenter requested revision of the *Total impurities* acceptance criteria for consistency with FDA-approved requirements.
Response: Comment incorporated.
Expert Committee-initiated Change #1: The Expert Committee replaced the statement "Disregard any impurity peak less than 0.1%" with "The reporting threshold is 0.1%", in the *Organic Impurities* test for consistency with the *USP* style.

Monograph/Section: Phytonadione/Packaging and Storage
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter suggested adding a temperature requirement to the *Packaging and Storage* section.
Response: Comment incorporated.

Monograph/Section: Primaquine Phosphate/Packaging and Storage
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 1
Comment Summary #1: The commenter recommended adding a storage temperature requirement.
Response: Comment not incorporated. The Expert Committee will consider a future revision to the monograph upon receipt of supporting data.

Monograph/Section: Prazosin Hydrochloride Compounded Oral Suspension
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested adding a cautionary statement that "Care should be taken to prevent inhaling particles of Prazosin Hydrochloride and to prevent its contacting any part of the body".
Response: Comment not incorporated. Precautions must be taken for all powdered drug substances used during compounding procedures. Additionally, compounders must follow the requirements in General Chapter <795>.

Monograph/Section: Sotalol Hydrochloride/Assay
Expert Committee: Chemical Medicines Monographs 2

No. of Commenters: 1
Comment Summary #1: The commenter recommended including additional RSD values of 0.5%, 1.0%, and 1.5% for allowed upper limit B in *Table 1* because the rationale for revising the percent RSD from NMT 2.0% to NMT 0.55% in the *Assay* was not clear.
Response: Comment not incorporated. The Expert Committee determined that the validation data supports the proposed percent RSD and will consider a future revision upon receipt of supporting data.

Monograph/Section: Travoprost Ophthalmic Solution/pH
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 1
Comment Summary #1: The commenter recommended revising the pH range to include a different specification for products containing zinc.
Response: Comment not incorporated. The Expert Committee will consider a future revision to the monograph upon receipt of supporting data.

Monograph/Sections: Urea Compounded Irrigation/Multiple Sections
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the bacterial endotoxin limit to eliminate the trailing zero.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested rephrasing the BUD section to specify that sterility and endotoxin testing are within acceptable limits instead of indicating “successful completion”.
Response: Comment incorporated.

Monograph/Section: Vigabatrin/Organic Impurities
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 2
Comment Summary #1: The commenter indicated that the acceptance criteria for *Vigabatrin related compound A* and *Vigabatrin related compound B* are inconsistent with the FDA-approved requirements.
Response: Comment not incorporated. The Expert Committee will consider a future revision to the monograph upon receipt of supporting data.
Comment Summary #2: The commenter requested inclusion of their impurity profile, acceptance criteria, and RRF values.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.