Commentary – *USP 35-NF 30*

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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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No comments were received for the following proposals:

General Chapters
<1> Injections
<88> Biological Reactivity Tests, In Vivo
<141> Protein—Biological Adequacy Test
<401> Fats And Fixed Oils
<467> Residual Solvents
<781> Optical Rotation
<1128> Nucleic Acid-Based Techniques—Microarray
<1226> Verification Of Compendial Procedures

No comments were received for the following proposals (continued):

Monographs
Agar
Alpha Lipoic Acid
Ammonio Methacrylate Copolymer
Aztreonam
Bisoprolol Fumarate Tablets
Carmustine For Injection
Cefdinir
Cefdinir Capsules
Cefdinir For Oral Suspension
Chamomile
Clindamycin Hydrochloride
Drospirenone
Estrone Injection
Fish Oil Containing Omega-3 Acids Delayed-Release Capsules
Ginger
Ginger Capsules
Ginger Tincture
Powdered Ginger
Hydrocortisone Acetate
Hydrogenated Starch Hydrolysate
Lactobionic Acid
Lamotrigine Tablets
Levofloxacin Oral Solution
Methyldopa
Phenoxybenzamine Hydrochloride Capsules
Platelets
Polyglyceryl Dioleate
Primaquine Phosphate
Primaquine Phosphate Tablets
Protein Hydrolysate Injection
Red Blood Cells
Rosiglitazone Maleate
Spironolactone
Valsartan And Hydrochlorothiazide Tablets

General Chapters

General Chapter/Section: <3> Topically Applied Drug Products/Product Quality Tests
Expert Committee(s): General Chapters–Dosage Forms
No. of Commenters: 7
Comment Summary #1: The commenter suggested including instructions for the Uniformity in Containers test during accelerated stability studies.

Response: Comment not incorporated. Accelerated stability studies are not covered by this General Chapter.
Comment Summary #2: The commenter suggested that the General Chapter should discuss how the product is treated prior to analysis in the Uniformity in Containers test.
Response: Comment incorporated.
Comment Summary #3: The commenter indicated that the text in *Uniformity in Containers, Products Packaged in Containers Other Than Tubes* implies that the sample taken from the container should be homogenized prior to the final analysis, and could preclude observing variations in the product uniformity.
Response: Comment not incorporated, as the text allows flexibility in the sample treatment.
Comment Summary #4: The commenter indicated that the General Chapter does not address the sampling procedure for the Universal and Specific Tests.
Response: Comment not incorporated. This General Chapter does not address general sampling procedures. These procedures are covered by other appropriate USP standards and guidelines.
Comment Summary #5: The commenter suggested that the acceptance criteria of 90% - 110% of the label claim for Uniformity in Containers is not applicable for all dosage forms.
Response: Comment not incorporated. Products should comply with this acceptance criterion unless specifically exempted by a monograph specification.
Comment Summary #6: The commenter suggested that the additional testing in Uniformity in Containers if the product fails Acceptance Criteria A is not necessary.
Response: Comment not incorporated. The testing of additional samples provides a more accurate evaluation of the uniformity in the containers.
Comment Summary #7: The commenter suggested that the three-location testing is difficult for viscous drug products packaged in small tubes.
Response: Comment incorporated. The text was modified to allow the use of alternative procedures.
Comment Summary #8: The commenter indicated that the text under “Tube (container) content uniformity test acceptance criteria” is not clear regarding the calculation of the relative standard deviation.
Response: Comment not incorporated. The text explains how relative standard deviation is calculated.
Comment Summary #9: Several commenters indicated that the General Chapter should address cold flow.
Response: Comment not incorporated. The Expert Committee will consider the incorporation of tests and information related to cold flow in transdermal systems in a future revision.
Comment Summary #10: The commenter indicated that the texts under Leak Test and under Seal Integrity needs to be clarified regarding the acceptance criteria.
Response: Comment incorporated.
Comment Summary #11: The commenter suggested specifying that the General Chapter only covers passive transdermal systems.
Response: Comment incorporated.

Comment Summary #12: The commenter suggested that acceptance criteria in the item *Description* should not include the labeling information.
Response: Comment incorporated.
Comment Summary #13: The commenter suggested the removal of content or label claim of the article in the item *Description*.
Response: Comment not incorporated. This information is necessary when dealing with different strengths of the same product.
Comment Summary #14: The commenter suggested the inclusion of impurities associated with the adhesive in the *Impurities* subsection of the *Universal Tests* section.
Response: Comment incorporated.
Comment Summary #15: The commenter suggested the inclusion of a requirement for Residual Drug Amount in transdermal systems.
Response: Comment not incorporated. This item is specific for each formulation and any special instructions and precautions should be part of the instructions to the patient or user.
Comment Summary #16: The commenter suggested removal of the word "preservative" in the section *Antioxidant Preservative Content*.
Response: Comment incorporated.
Comment Summary #17: The commenter suggested removal of the entire section *Specific Tests for Ophthalmic Dosage Forms* from the General Chapter.
Response: Comment not incorporated. There is no USP general chapter to which this section could be transferred. The Expert Committee will consider this revision in the future if another more appropriate General Chapter is developed.
Comment Summary #18: The commenter suggested the removal of the sentence that states that apparent viscosity could be used for demonstration of product equivalence before and after post-approval changes because it is contradictory to the FDA SUPAC-SS guidance.
Response: Comment incorporated.
Comment Summary #19: Several commenters suggested the inclusion of the Rolling Ball method in the Tack Test for transdermal systems.
Response: Comment incorporated.
Comment Summary #20: The commenter suggested the inclusion of the Shear or Creep Test for transdermal systems.
Response: Comment not incorporated. The Expert Committee will consider this recommendation for a future revision.
Comment Summary #21: The commenter suggested changing the acceptance criteria for the Leak Test.
Response: Comment incorporated.
Comment Summary #22: The commenter suggested replacing the title of the subsection *Finished Product Testing* in the Leak Test section with *Packaged Product Testing.*
Response: Comment incorporated.
Comment Summary #23: The commenter suggested the deletion of the requirement for two chromatographic procedures in the Identification test.
Response: Comment incorporated.

Comment Summary #24: The commenter suggested removal of cross-references to general chapters that are not official yet.
Response: Comment incorporated.
Comment Summary #25: The commenter suggested the removal of some tests in the sections *Universal Tests* and *Specific Tests*.
Response: Comment not incorporated. The goal of the chapter is to present the quality parameters that may be evaluated for topically applied products. The manufacturer decides which of these parameters are part of the product's specification.
Comment Summary #26: The commenter suggested replacing 1000 g of weight per cm^2 with 13.6 kg in the Seal Integrity test.
Response: Comment incorporated.

General Chapter/Sections: General Chapter <81> Antibiotics/Microbial Assays
Expert Committee: General Chapters—Microbiology
No. of Commenters: 6
Comment Summary #1: The commenter suggested revising the requirement to perform all procedures aseptically because all procedures do not need to be performed in a laminar flow hood.
Response: Comment incorporated. The text will be revised to indicate that all procedures should be performed under conditions designed to avoid extrinsic microbial contamination.
Comment Summary #2: The commenter suggested revising the requirement to use sterile labware for the storage and transfer of test dilutions and microorganisms.
Response: Comment not incorporated. The Expert Committee decided it is necessary to use sterile labware for the specified operations. In addition, the text was revised to indicate that the labware should be sterile and free of interfering residues.
Comment Summary #3: The commenter suggested revising the requirement for fresh working cultures.
Response: Comment not incorporated. Manufacturers should adequately validate alternative procedures.
Comment Summary #4: The commenter suggested revising the requirement for sterile bottles during the preparation of inocula to allow the use of other containers.
Response: Comment incorporated.
Comment Summary #5: The commenter suggested revising the name of one test organism from *Micrococcus luteus* to *Kokuria rhizophila*.
Response: Comment not incorporated. The strain listed in the General Chapter is *Micrococcus luteus* ATCC 10240, which has not been reclassified.
Comment Summary #6: The commenter suggested revising the General Chapter to include the agar cup procedure.
Response: Comment not incorporated. The agar cup procedure has not been evaluated for the antibiotics listed in the General Chapter. The Expert Committee will consider this revision in the future when there is validated data.
Comment Summary #7: The commenter suggested revising the requirement for randomized placement of tubes in the turbidimetric assay.
Response: Comment not incorporated. Programming of the automated system is necessary to ensure randomization.

Comment Summary #8: The commenter suggested revising the requirement for a five-level concentration curve in the cylinder-plate and turbidimetric procedures.
Response: Comment not incorporated. Manufacturers should validate alternative procedures.
Comment Summary #9: The commenter suggested revising the requirement for uninoculated broth as the blank in the turbidimetric procedure.
Response: Comment not incorporated. Manufacturers should validate alternative procedures.
Comment Summary #10: The commenter suggested the correction of the absorbance values for the sample (U_3) in Table 15.
Response: Comment incorporated.
Comment Summary #11: The commenter suggested adding a requirement for relative standard deviation in the cylinder-plate procedure.
Response: Comment not incorporated. Manufacturers should establish acceptance criteria based on verification data for each product.
Comment Summary #12: The commenter suggested adding a procedure to establish uncertainty.
Response: Comment not incorporated. The General Chapter contains guidelines regarding uncertainty measurements but manufacturers should evaluate uncertainty criteria based on verification data for each product.
Expert Committee-initiated Change #1: The cylinder-plate procedure was revised to make the plate dimensions more flexible.
Expert Committee-initiated Change #2: The Calculations section was revised to correct specific calculation formulas in the examples for the cylinder-plate and turbidimetric procedures, the calculations for confidence interval, and the calculation formulas for regression and outlier values.

General Chapter:	General Chapter <610> Alternative Microbiological Sampling Methods for Nonsterile Inhaled and Nasal Products
Expert Committee:	General Chapters—Microbiology
No. of Commenters:	1

Comment Summary #1: The commenter suggested inclusion of reference to General Chapter <1223> *Validation of Alternative Microbiological Methods* to reflect the scope of this chapter.
Response: Comment not incorporated. The *General Notices* section of the *USP-NF* allows the use of validated alternative microbiological methods.
Comment Summary #2: The commenter suggested revising the text for Sampling Size Determination to use number of units that can provide a minimum of 1 gram of product since in some instances 10 units may not provide 1 gram of product.
Response: Comment incorporated.

General Chapter/Sections:	<659> Packaging and Storage Requirements Multiple Sections
Expert Committee(s):	General Chapters–Packaging, Storage and Distribution

No. of Commenters: 6

General

Comment Summary #1: The commenter suggested revising the classification system to encompass more forms and levels of protection, beyond “well-closed” and “tight.”
Response: Comment Incorporated. The Expert Committee agreed with the comment and plans to address this issue with the revision of General Chapter <671> *Containers—Performance Testing.*
Comment Summary #2: The commenter indicated that the terms “article,” “preparation,” and “contents” appear to be used interchangeably throughout the General Chapter, and suggested that one term should be used.
Response: Comment Incorporated. The term “preparation” is now used consistently throughout the text.
Comment Summary #3: The commenter suggested that the use of “active pharmaceutical ingredients” or “API” and “drug substances” adds confusion.
Response: Comment incorporated. The term “active pharmaceutical ingredient” is now used consistently throughout the text.
Comment Summary #4: The commenter suggested emphasizing that the definitions for performance testing (Tight, Well-Closed, and light-resistant) do not address container compatibility.
Response: Comment not incorporated. This topic is not within the scope of the General Chapter.

Introduction

Comment Summary #5: The commenter suggested that the specific packaging and storage requirements for monographs be deleted from the *Storage* section.
Response: Comment not incorporated. The default statement is required since not all USP monographs state packaging and storage requirements.

General Definitions

Comment Summary #6: The commenter suggested changing “Pharmacy Bulk Package” to “Injectable Pharmacy Bulk Package.”
Response: Comment not incorporated. The current term is widely accepted by industry.
Comment Summary #7: The commenter suggested including the Code of Federal Regulations (CFR) reference to the Child Resistant definition.
Response: Comment incorporated.
Comment Summary #8: The commenter suggested including the CFR reference to the Senior Friendly definition.
Response: Comment incorporated.

Associated Components

Comment Summary #9: The commenter suggested a more comprehensive introductory paragraph for the *Associated Components* section.
Response: Comment incorporated.
Comment Summary #10: The commenter suggested including language that clarifies dosing cups can be sold or purchased separately.

Response: Comment incorporated.
Comment Summary #11: The commenter suggested including language that clarifies a dosing spoon can be sold or purchased separately.
Response: Comment incorporated.
Comment Summary #12: The commenter suggested including a general statement about materials of construction to the *Medicine Dropper* definition.
Response: Comment incorporated.
Comment Summary #13: The commenter suggested that the definition in the *Oral Syringe* section be worded consistently to avoid confusion and unintentional alterations that imply a different meaning than intended.
Response: Comment incorporated.
Comment Summary #14: The commenter suggested that the *Oral Syringe* definition allow for the indirect expulsion of the measured amount into the patient's mouth.
Response: Comment not incorporated. The Expert Committee does not agree that this should be allowed due to loss of volume by the indirect expulsion
Comment Summary #15: The commenter suggested adding a note to the *Teaspoon* section that states a household spoon is not an acceptable alternative to a graduated component described in this section.
Response: Comment incorporated.

Storage Conditions
Comment Summary #16: The commenter suggested changing the *Freezer* definition to "A place in which the temperature is actively or passively maintained between below -18."
Response: Comment not incorporated. The current definition is widely accepted by industry.
Comment Summary #17: The commenter suggested including shipping under allowable excursions under the *Controlled Room Temperature* definition.
Response: Comment incorporated.
Comment Summary #18: The commenter suggested replacing the text "remains in the allowed range" with "does not exceed 25°" in the *Controlled Room Temperature* definition.
Response: Comment incorporated.
Comment Summary #19: The commenter suggested that the statement "mean kinetic temperature shall not exceed 25°" should be changed, as many products are labeled up to 86°F (and some allow to 104°F on the label for excursion ranges).
Response: Comment incorporated. Text was added to the introduction paragraph of the Storage section to clarify this issue.
Comment Summary #20: The commenter suggested including the following storage option: Controlled Room Temperature: Store between 2°C and 25°C (36°F-77°F).
Response: Comment not incorporated. The current storage range is appropriate. If justification is provided for the proposed change, the Expert Committee will consider an alternative range as part of a future revision.
Comment Summary #21: The commenter suggested expanding the temperatures range for Controlled Room Temperature from 20°C to 25°C to 15°C to 25°C.

Response: Comment not incorporated. The current storage range is appropriate. If justification is provided for the proposed change, the Expert Committee will consider an alternative range as part of a future revision.
Comment Summary #22: The commenter suggested adding the term Protection to Excessive Heat.
Response: Comment incorporated

General Chapter:	<823> Positron Emission Tomography Drugs for Compounding , Investigational and Research Uses/ Multiple Sections
Expert Committee:	General Chapters—Physical Analysis
No. of Commenters:	10

General
Comment Summary #1: The commenters indicated that the revision of the General Chapter adds unnecessary requirements and could prevent the progress of the PET drug product development efforts.
Response: Comment not incorporated. The revision of the General Chapter is necessary to clarify the requirements for the development of PET drugs. The revisions also reflect changes that have occurred over the past two decades since the original publication of the General Chapter.
Comment Summary #2: The commenter suggested the replacement of the word "should" with "shall" throughout the chapter.
Response: Comment not incorporated. In order to maintain flexibility, which is a key element for the development of investigational and research PET drugs, most instances of "should" must be maintained in the proposed revision.
Comment Summary #3: The commenters indicated that revised text uses both PET Drug and PET Drug product interchangeably while the General Chapter is intended for PET Drug Products. The commenters suggested the term "PET Drug Product" be used throughout the General Chapter.
Response: Comment incorporated.
Expert Committee-initiated Change #1: The PET drug industry uses the phrases "media simulation" and "aseptic simulation" interchangeably. The text was revised by replacing the phrase "media simulation" with "aseptic simulation" to maintain consistency.

Introduction
Comment Summary #4: The commenter suggested adding other PET isotopes that are used in PET imaging procedures (e.g., Cu-62, I-124 and Rb-82).
Response: Comment incorporated.
Comment Summary #5: The commenter suggested cross-referencing USP General Chapter <797> *Pharmaceutical Compounding—Sterile Preparations* wherever the term "compounding" occurs.
Response : Comment not incorporated because General Chapter <797> includes a reference to <823>. General Chapter <823> applies to the production of PET drug products, whereas General Chapter <797> applies to the dispensing of PET drug

products after the completion of compounding or production. Once the compounding or production is complete, the dispensing would be covered under <797>.

Definitions

Comment Summary #6: The commenter suggested that the definition of the term *Active Pharmaceutical Ingredient* does not apply to PET because the radioactive substance is not isolated, purified, and characterized before it is included in the PET drug product.

Response: Comment incorporated.

Comment Summary #7: The commenter suggested that the definition of *Batch* be revised to read as: "— a quantity of PET drug that is intended to have uniform character and quality, within specified limits, and that is produced in single production order during the same cycle of production."

Response: Comment incorporated with minor modification. The revised text reads as: "—a quantity of PET drug product that is intended to have uniform character and quality, within specified limits, and that is produced according to one or more production order(s)."

Comment Summary #8: The commenter suggested removing the word "Final" from "Conditional Final Release" and revising its definition.

Response: Comment not incorporated. The original text in the proposed revision is clear and understood by industry.

Comment Summary #9: The commenters suggested revising the term *PET Drug* to be consistent with the definition in 21 CFR 212.

Response: Comment incorporated with modifications. The revised definition reads as: "PET Drug—a radioactive drug that exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and is used for the purpose of providing dual photon positron emission tomographic diagnostic images."

Comment Summary #10: The commenters suggested the revising the term *PET Drug Product* to read as: "finished dosage form of a PET Drug, whether or not it is in association with one or more ingredients."

Response: Comment incorporated.

Comment Summary #11: The commenter suggested the deletion of the definitions for *PET Drug* and *PET Drug Product* because they are redundant.

Response: Comment not incorporated. The text in the proposal is widely understood by industry.

Comment Summary #12: The commenter suggested that the definition of the term *Compounding* be changed to be consistent with the Food Drug and Cosmetic Act, Chapter II.

Response: Comment incorporated with modifications by including as a bullet point a portion of the definition of "compounded PET drug" from Section 201(ii) of the Federal Food, Drug and Cosmetic Act. Inclusion of the entire definition was not necessary considering the scope of this general chapter.

Comment Summary #13: The commenters suggested the addition of the term *Line Clearance* in the definition section.

Response: Comment incorporated.

Comment Summary #14: The commenter suggested including the definition of the phrase *Manufacturer's certification* and replacing the term COA in the General Chapter with the word "*Manufacturer's certification*."
Response: Comment incorporated.
Comment Summary #15: The commenter suggested the term *Out of Specification (OOS)* to be included in the *Definitions* section.
Response: Comment incorporated.
Comment Summary #16: The commenter suggested revising the definition of *Production* as " –all operations involved in the synthesis of a PET drug and all operations involved in the preparation and formulation of a PET drug product, and includes processing, packaging, labeling, reprocessing, repacking, relabeling and testing of PET drug or a PET drug product for investigational or research use."
Response: Comment incorporated with modification "— the process of synthesis or formulation of a PET drug or PET drug product including processing, packaging, labeling, reprocessing and testing for investigational or research use."
Comment Summary #17: The commenter suggested the definition of the term *Quality Assurance (QA)* be consistent with 21 CFR 212.
Response: Comment incorporated.
Comment Summary #18: The commenter suggested the deletion of the definition for *Quality Assurance* since the quality of PET Drug Products is ensured through equivalent means.
Response: Comment not incorporated because the definition of *Quality Assurance* is essential for the completeness of the General Chapter.
Comment Summary #19: The commenter suggested the definition of the term *Quality Control (QC)* be revised to: "— a system for determining quality including testing of components, intermediates, materials, supplies, and PET drug products by procedures, tests, analytical methods and acceptance criteria."
Response: Comment incorporated with the modification: "— a system for determining the quality of components, materials, supplies, and PET drugs products by procedures, tests, analytical methods, and acceptance criteria."
Comment Summary #20: The commenter suggested the revision of the term *Quality Control* to read "a system for releasing components and materials."
Response: Comment not incorporated because the definition in the proposal, as amended in the response above (*Definitions* - Comment #14), is clear and well understood.
Comment Summary #21: The commenter suggested the definition of the term *Sub-batch* be changed from "Sub-batches are required for PET drugs with very short lived radionuclides" to "Sub-batches may be needed for PET drugs with very short lived radionuclides."
Response: Comment incorporated.
Comment Summary #22: The commenter suggested the definition of the term *Sub-batch* include the possibility of using "succession of multiple irradiations using a given synthesis or purification operation" for the production of the PET drug product.
Response: Comment incorporated.
Comment Summary #23: The commenter suggested the deletion of the definitions for the terms *Validation* and *Verification* since neither is required for clinical trials.

Response: Comment not incorporated because *Validation* and *Verification* are relevant aspects of the General Chapter.

Adequate Personnel and Resources
Comment Summary #24: The commenters suggested the deletion of the words "*Adequate*" and "*Resources*" from the title of the section since they are redundant of the content described in this section.
Response: Comment incorporated.
Comment Summary #25: The commenters suggested the section be divided into two subsections, one describing the training requirements and the other description of the specific training involved in aseptic operations.
Response: Comment incorporated.
Comment Summary #26: The commenters suggested the phrase "Personnel should pass written assessments" to be replaced with "Training should be documented."
Response: Comment incorporated.
Comment Summary #27: The commenter suggested revising the sentence "Media simulations should include all manipulations required for the assembly of the PET drug vial" with the addition of the following parenthetical phrase to clarify the meaning of "assembly": "(vial, filter and syringe assembly)."
Response: Comment incorporated.
Expert Committee-initiated Change #2: Based on an Expert Panel recommendation, the various aspects of aseptic operations training were changed from paragraph form to a bulleted list to improve clarity.

Quality Assurance
Comment Summary #28: The commenter suggested adding the term *Quality Control* to the section title.
Response: Comment not incorporated because Quality Control is a part of Quality Assurance
Comment Summary #29: The commenter suggested the replacement of the word "important" with "required" in the first sentence of the section
Response: Comment incorporated.
Comment Summary #30: The commenter suggested the deletion of the phrase "QC is a subset of QA."
Response: Comment not incorporated. Quality Control is inherently a part of Quality Assurance.
Comment Summary #31: The commenter suggested the deletion of sentence "The QA function typically consists of oversight activities, and the QC function consists of execution activities."
Response: Comment not incorporated. Although the sentence may be redundant, it emphasizes the differences between QA and QC functions.
Comment Summary #32: The commenter suggested the replacement of the phrase "QC functions include the following" with "Quality Control requirements are."
Response: Comment not incorporated because the suggested replacement may not provide the intended flexibility.

Comment Summary #33: The commenter suggested the deletion of the word "rejection" from the second bullet point of the QC functions since it is not necessary.
Response: Comment incorporated.
Comment Summary #34: The commenter suggested the replacement of the phrase "The oversight functions associated with QA include the following:" with "Quality Assurance requirements are."
Response: Comment not incorporated because the suggested replacement may not provide the intended flexibility.
Comment Summary #35: The commenter suggested the deletion of the bullet point that reads "Review completed batch records for accuracy and completeness" because QA does not review batch records.
Response: Comment not incorporated because QA can choose to review batch records as needed.
Comment Summary #36: The commenters suggested the deletion of the word "validate" from the bullet point that reads "Validate and approve...."
Response: Comment incorporated.
Comment Summary #37: The commenter suggested the addition of the following phrase to the QA function list: "Ensure that changes to component quality, suppliers, changes to production procedures, changes to testing procedures and specifications are appropriate and implemented properly."
Response: Comment incorporated.
Comment Summary #38: The commenter suggested the addition of the word "preventive" to the bullet point: "Investigate errors and ensure that appropriate corrective actions are taken to prevent their recurrence."
Response: Comment incorporated.
Comment Summary #39: The commenter suggested the revision of the bullet point "Ensure that the PET drugs are distributed according to the established procedures and practices for PET drugs" to "Ensure that the PET drugs are produced, tested, labeled, released and distributed according to the facility's established procedures and practices for PET drug products."
Response: Comment incorporated.
Comment Summary #40: The commenter suggested the deletion of the bullet point that reads "Conduct periodic audits…" because auditing needs to be an independent function.
Response: Comment not incorporated because auditing is a part of QA even though it functions independently.

Facilities and Equipment
Comment Summary #41: The commenter suggested inclusion of a system of change control in the introductory paragraph of this section.
Response: Comment not incorporated because the addition of a new bullet point to QA functions is not necessary. (See Comment summary #10 under *Quality Assurance* section).

Environmental Controls for Parenteral PET Drugs

Comment Summary #42: The commenter suggested the exclusion of laboratory sinks near *Aseptic Workstation*.
Response: Comment not incorporated because Aseptic workstations are not generally located near sinks.
Comment Summary #43: The commenter suggested the inclusion of sporicidal agent in the Aseptic workstation cleaning.
Response: Comment not incorporated because the current text allows flexibility to use "appropriate disinfectants."
Comment Summary #44: The commenter suggested the title of the subsection *Microbiological Testing* be changed to Environmental testing.
Response: Comment not incorporated because Microbial testing includes environmental testing.
Comment Summary #45: The commenter suggested revising the sentence in the subsection *Microbiological testing* that begins "Microbiological testing of aseptic workstation…" to read: "For microbial testing of the aseptic workstation, the air should be tested as part of the workstation qualification (e.g. semi-annually) and the surface (contact plate) should be assessed after use, each day of use."
Response: Comment incorporated.
Comment Summary #46: The commenter suggested the addition of the phrase "of the aseptic areas" at the end of the sentence: "Microbiological testing of the environment should be performed to assess air quality and surface disinfection."
Response: Comment incorporated.
Comment Summary #47: The commenter suggested adding "at least quarterly" to the sentence starting: "Nonviable particle counts may be determined…"
Response: Comment not incorporated in order to retain the flexibility of the proposed text.
Comment Summary #48: The commenter suggested deleting the sentence starting with "Action and alert limits…." since they are not defined.
Response: Comment not incorporated in order to retain the flexibility of the proposed text.
Expert Committee-initiated Change #3: Per the recommendation of a USP Expert Panel and its discussions with the facilities involved, the following statement has been included: "These requirements supersede those in other USP general chapters (e.g., General Chapter <1116> *Microbiological Evaluation of Clean Rooms and Other Controlled Environments*") in the subsection *Aseptic Workstation* because those requirements are not intended for PET drug facilities.

Equipment
Comment Summary #49: The commenter suggested the deletion of the references to IQ/OQ/PQ, as this is not required for clinical studies.
Response: Comment not incorporated. IQ, OQ and PQ are inherent to laboratory practices.
Comment Summary #50: The commenter suggested the *Installation of Equipment* section allow for the complexity of the instrument.
Response: Comment incorporated.

Comment Summary #51: The commenter suggested the inclusion of the use of disposable equipment to improve efficiency.
Response: Comment not incorporated because the section does not exclude the use of disposable equipment.
Comment Summary #52: The commenter suggested revising the first section of the subsection Calibration of Equipment to read as: “Analytical equipment calibration should be performed before use, as appropriate.”
Response: Comment incorporated.
Comment Summary #53: The commenter suggested replacing the sentence that begins with “System suitability tests should be performed according...” with “System suitability tests should be performed prior to using the equipment according to the established procedures.”
Response: Comment incorporated.
Comment Summary #54: The commenter suggested replacing the sentence “Use the calibration curve over an extended period of time (e.g., six months)” with ”The calibration curve should be used over a suitably specified period of time after which time a new one should be established. A new calibration curve should be created each time an update is made to the chromatographic system.”
Response: Comment incorporated with modification: “The calibration curve should be used over a suitably specified period of time (e.g., six months), after which time a new one should be created. A new calibration curve should be created each time an alteration is made to the chromatographic system.”
Comment Summary #55: The commenter suggested the referencing of USP General Chapter <621> *Chromatography for System Suitability* testing and appropriate acceptance criteria.
Response: Comment not incorporated because some of the system suitability parameters in <621> Chromatography may not be applicable to the type of samples (e.g., PET drugs with short half life).
Comment Summary #56: The commenter suggested including restrictions on the concentration of the standard solution when single point calibration is used.
Response: Comment not incorporated because analytical chemistry methodology requires that the standard concentration be chosen so that it is in the middle of the linear range of the calibration curve.
Comment Summary #57: The commenter suggested checking the TLC Scanner sensitivity.
Response: Comment not incorporated because the verification of detector linearity accomplishes this.

Control of Components, Materials and Supplies
Comment Summary #58: The commenter suggested deleting the phrase “documented evidence of” at the end of bullet point number 6.
Response: Comment incorporated.
Comment Summary #59: The commenter suggested the addition of the sentence “Reference standards used in chromatographic procedures should have suitable documentation of identity and purity of the lot” in bullet point number 7.
Response: Comment incorporated.

Comment Summary #60: The commenter suggested revising the sentence in bullet point number 9 from “Media used in the sterility testing of PET drugs should be commercially available” to “Media used in the sterility testing of PET drugs may be commercially obtained.” Related, the commenter also suggested the deletion of everything in the proposed text after the sentence and replacement with the following: “Growth Promotion testing sterility test commercially prepared (ready to use) media should be done on initial qualification and periodically (e.g., quarterly).”
Response: Comment incorporated.
Comment Summary #61: The commenter suggested the expansion of bullet point number 7 to include the criteria for accepting the material based on manufacturer’s certification.
Response: Comment not incorporated to maintain the desired flexibility.
Comment Summary #62: The commenter suggested replacement of bullet point number 9 with the following text: “Media used for sterility testing shall be sourced from approved suppliers that perform internal growth promotion testing as a condition of release. Sterility media shall be shipped overnight in refrigerated containers, and received and stored at the PET facility in a timely manner to ensure the ability of the media to support growth.”
Response: Comment not incorporated in order to retain the intended flexibility of the proposed revision.

Process Controls
Comment Summary #63: The commenter suggested revising a portion of bullet point number 1 that begins with “For PET drugs intended for parenteral...” to read “For PET drugs intended for parenteral administration, specifications should include criteria for sterility and bacterial endotoxins. If a USP monograph exists, or if there are specifications that have been previously accepted by FDA, then these standards, if applicable to your method of manufacture, may be applied as the minimum acceptance criteria.”
Response: Comment incorporated with modification: “For PET drugs intended for parenteral administration, specifications should include criteria for sterility and bacterial endotoxins. If a USP monograph exists, or if there are specifications that have been previously accepted by FDA, then these standards, if applicable, may be applied as the minimum acceptance criteria.”
Comment Summary #64: The commenter suggested the inclusion of the phrase “and post-integrity testing” at the end of bullet point number 2.
Response: Comment not incorporated in order to retain the intended flexibility of the proposed revision.
Comment Summary #65: The commenter suggested the inclusion of “steam sterilization” in the bullet point number 2.
Response: Comment incorporated.
Comment Summary #66: The commenter suggested the addition of a bullet point with the text “Include lot (batch) number of components, materials, and supplies used to make PET drugs, including precursors, standards, reagents, stock solutions, and related items.”
Response: Comment incorporated.

Comment Summary #67: The commenter suggested revising the bullet point that reads “Describe the calculations…” to read as “Describe the calculations performed for quantitative parameters associated with making and QC testing the PET drug (e.g., radiochemical yield, radiochemical purity, specific activity, solvent amounts, etc.).”
Response: Comment incorporated.
Comment Summary #68: The commenter suggested formulae for calculations to be included in the bullet point that begins with, “Describe the calculations....”
Response: Comment not incorporated in order to retain the flexibility in the proposed text.
Comment Summary #69: The commenter suggested revision of the bullet point, “Demonstrate a consistent process that is suitable for the intended use of the PET drug” to read as “Demonstrate a consistent process that is suitable for the intended production of the PET drug.”
Response: Comment incorporated with modifications: “Demonstrate a consistent process that is suitable for the intended preparation of the PET drug.” The word “preparation” was substituted for “production” since it is more applicable to the scope of <823>.
Comment Summary #70: The commenter suggested insertion of the phrase “at least” in the bullet point that reads: “Be completed on three batches made according to the master formula, and all three batches should meet all acceptance criteria.”
Response: Comment not incorporated since the phrase does not bring any additional value.
Comment Summary #71: The commenter suggested the insertion of the word “consecutive” in the bullet point that reads: “Be completed on three batches made according to the master formula, and all three batches should meet all acceptance criteria.”
Response: Comment not incorporated since the phrase removes the desired flexibility.
Comment Summary #72: The commenter suggested the addition of the statement “Prior to the implementation of updates, appropriate validation and/or verification should be approved by QA” to the bullet point that reads: “The processes and steps described in the master formula should be updated as needed and should be reviewed annually to ensure they are current.”
Response: Comment incorporated with modification. Revised statement reads: “Prior to the implementation of updates, appropriate validation and/or verification should be approved and performed.”
Comment Summary #73: The commenter suggested the word “annually” be changed to “biennially” to be consistent with industry standards in the following statement: “The processes and steps described in the master formula should be updated as needed and should be reviewed annually to ensure they are current.”
Response: Comment not incorporated because two years is too long of a period.
Comment Summary #74: The commenter suggested the inclusion of a software standard to validate the automated equipment software.
Response: Comment not incorporated because of the potential changing nature of a standard for software validation.

Operational Controls

Comment Summary #75: The commenter suggested rearranging the bullet points so that Line Clearance is the first operation listed.

Response: Comment incorporated.

Comment Summary #76: The commenter suggested the inclusion of the version number of the software, as well as the post release test information a part of the batch record.

Response: Comment not incorporated since the existing list covers relevant items.

Aseptic Operations for Parenteral Drug Products

Comment Summary #77: The commenter suggested changing the sentence beginning "Although the chemical synthesis of a parenteral PET drug…." with "Although the chemical synthesis of a parenteral PET drug may take place in an open or closed apparatus, the membrane filtration of the PET drug should be closed system downstream from filter."

Response: Comment incorporated with modifications: "Although the chemical synthesis of a parenteral PET drug product may take place in an open or closed apparatus, the membrane filtration of the PET drug should be a closed system downstream of the membrane filter. This system should be aseptically assembled from presterilized, commercially available components."

Comment Summary #78: The commenter suggested the deletion of the last sentence in the *Components* subsection.

Response: Comment not incorporated because the sentence provides clarification to the meaning of the paragraph. .

Comment Summary #79: The commenter suggested adding the following text to the *PET Drug Vial Assembly* section: "Once assembled, the PET drug vial assembly shall be inspected for particulates and defects. Assemblies that pass visual inspection shall be kept in a sterile bag to keep it free from any additional particulate matter."

Response: Comment not incorporated because the proposed text serves as a sufficient public standard for the intended purpose.

Comment Summary #80: The commenter suggested revising the following sentence to include storage conditions: "The storage time for assembled vials should be based on data from aseptic media fills."

Response: Comment incorporated by revising the sentence as follows:
"The storage conditions and time for assembled vials should be based on data from aseptic simulations."

Stability

Comment Summary 81: The commenter suggested revising the sentence, "In addition, the PET drug should meet acceptance criteria for radiochemical purity, appearance, pH, and stabilizer or preservative effectiveness (as appropriate) at expiry" to read "In addition, the PET drug should meet acceptance criteria for radiochemical purity, appearance (color and clarity), pH, and stabilizer effectiveness (as appropriate), and chemical purity at expiry."

Response: Comment incorporated.

Comment Summary #82: The commenter suggested the clarification of the term "strength."
Response: Comment incorporated by the defining the term "strength" in the *Definitions* section.

Controls and Acceptance Criteria for Finished Pet Drug Products
Comment Summary #83: The commenter indicated that the numbered lists in on QC tests subsection should be combined into one to clarify which QC tests must be performed on all batches prior to release for administration.
Response: Comment incorporated.
Comment Summary #84: The commenter suggested that bullet point number 6 in the section that deals with the correction of equipment malfunction be expanded to state: "Promptly correct the malfunction of the testing equipment, complete the omitted test with a reserved sample, after the malfunction is corrected, and make efforts to prevent the occurrence of malfunction. If OOS results when retesting, immediately notify the receiving facility. You may not release another PET drug product until you have corrected the problem concerning the malfunction and completed the omitted finished product."
Response: Comment incorporated by expanding the bulleted list in the Conditional Final Release tests which captures the multiple steps highlighted by the commenter.
Comment Summary #85: The commenter suggested deleting the text "Visually inspect parenteral dosage forms" because the dosage form will be labeled at this point.
Response: Comment not incorporated because visual inspection is an important QC test.
Comment Summary #86: The commenter suggested deleting the following sentence in the bullet point pertaining to bubble point test: "Although it is not strictly a QC test on the final PET drug, this test is important to ensure the preparation of a sterile solution."
Response: Comment incorporated.
Comment Summary #87: The commenters suggested the removal of the text "(e.g., *E. Coli*)" from the sentence "It is acceptable to exceed the 30-hour period because of weekends or holidays provided it is shown that the extended period does not significantly reduce the viability of a *USP* indicator organism (e.g., *E. coli*) in the sample" since it is not a sufficient indicator of the typical flora found in the aseptic operations of this kind.
Response: Comment incorporated.
Comment Summary #88: The commenter indicated that it should be explicitly stated that the Bacterial Endotoxin test should be completed before release whenever possible.
Response: Comment not incorporated because it is implied in the current text.
Comment Summary #89: The commenter indicated there is no support for the statement: "After a record of successful sterility tests is established for a particular PET drug product, it is only necessary to test the first batch prepared each day for that PET drug product," and therefore, it should be replaced with the following: statement: "all batches should be tested for sterility."
Response: Comment not incorporated because such a requirement can be too restrictive in a research environment.

If a Pet Drug Does Not Conform to Specifications

Comment Summary #90: The commenter suggested that the title of the section be revised to "*If a Pet Drug Product Does Not Conform to Specifications*" because this section deals with only the PET drug product.

Response: Comment incorporated.

Comment Summary #91: The commenters suggested revising the sentence that begins "If the outcome of the investigation concludes that the OOS result was a true failure…" to read "If a PET drug product fails to meet a criterion for sterility, you must immediately notify all facilities that received the product of the test result and provide any appropriate recommendations. Upon completion of an investigation into the failure to meet a criterion for sterility, you must notify all facilities that received product of the microbiological findings from the investigation."

Response: Comment incorporated with modifications: "Upon completion of the investigation, immediately notify all receiving facilities if the product fails to meet the criterion for sterility, including the microbiological findings from the investigation."

Labeling and Packaging

Comment Summary #92: The commenter suggested the title of this section to be changed to *Labeling and Shipping*.

Response: Comment not incorporated. However, the title of the section has been changed to *Labeling* as the section only deals with the labeling of the PET drug and/ or PET drug product.

Comment Summary #93: The commenter suggested the revision of the bulleted list in the section to include the following:

- Replace the "the name of the PET drug" with "the name of the PET drug, including dosage form."
- Include the following caution statement as a bullet point: "Statement for Investigational use- Caution: New Drug- Limited by Federal (or United States) law to investigational use."
- Revise the statement, "Added substances(s) (e.g., stabilizer or preservative)" to "Added substance(s) (e.g., stabilizer and inactive ingredients)."
- Include the following statement as an additional bullet point: "Name of the Producer of the PET drug product."

Response: Comment incorporated.

General Chapter/Sections: General Chapter <1113> Microbial Identification/ Characterization and Strain Typing
Expert Committee: General Chapters - Microbiology
No. of Commenters: 6

Comment Summary #1: The commenter suggested revising the statement on the scope of the chapter to include all applications of microbiology by deleting the term Pharmaceutical.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested replacing the references to "codon" in Table 2 to: "gene," "operon," or "sequence."

Response: Comment incorporated.
Comment Summary #3: The commenter suggested revising the title of the section "*Preliminary Screening of Microbial Isolates*" to "*Primary Screening and Characterization*" to be consistent with the discussion on degrees of microbial identification.
Response: Comment incorporated.
Comment Summary #4: The commenter suggested revising the Gram-positive organism reaction from "blue" to either "purple" or "blue violet."
Response: Comment incorporated.
Comment Summary #5: The commenter suggested inclusion of methods other than Gram Staining for determining cell wall characteristics (Gram positive or Gram negative, such as KOH test).
Response: Comment not incorporated. Gram Staining is the method that is most commonly used.
Comment Summary #6: The commenter suggested revising the statement "…genotypic methods are technically challenging to pharmaceutical microbiologists" to "…genotypic methods can be technically challenging to microbiologists."
Response: Comment incorporated.
Comment Summary #7: The commenter suggested that the clinical microbiology laboratory example is not appropriate for an informational chapter. Therefore, it is suggested to remove the example of Neisseria gonorrhoeae and use the ICH table and EP as guidance
Response: Comment not incorporated since this is a General Information chapter that applies to all areas of microbiology, including a clinical microbiology laboratory.
Comment Summary #8: The commenter suggested revising the sentence discussing relatedness of organisms and indicated that the text in the proposal is incorrect. It should be: "In general, organisms with > 97% Relatedness are considered the same genus and those with >99% relatedness are considered the same species."
Response: Comment incorporated.
Comment Summary #9: The commenter suggested that the reference to Clarridge be restored as a reference relevant to the relatedness statement above.
Response: Comment incorporated.
Comment Summary #10: The commenter indicated that in the paragraph describing the renaming of "A.niger" to "A.braslliensis" that the new name includes only some strains, including ATCC 16404. There are other strains that were not transferred to the new species and "A. niger" should be retained since it is still a valid species name.
Response: Comment incorporated.
Comment Summary #11: The commenter suggested adding the terms *Microbial Characterization* and *Strain Typing* to the glossary section.
Response: Comment incorporated.

General Chapter/Sections:	General Chapter <1116> Microbiological Control and Monitoring of Aseptic Processing Environments/Sections
Expert Committee:	General Chapters - Microbiology
No. of Commenters:	6

Introduction
Comment Summary #1: The commenter suggested revising the definition of *Advanced Aseptic Processing* to accurately reflect the process.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested adding a statement providing guidance about the determination of monitoring locations.
Response: Comment incorporated.
Comment Summary #3: The commenter suggested clarifying the contamination recovery rate criteria.
Response: Comment incorporated.

General Considerations
Comment Summary #4: The commenter suggested deleting the discussion on monitoring in nonsterile environments since the current chapter is devoted to Aseptic Processing
Response: Comment incorporated.
Comment Summary #5: The commenter suggested adding the term RABS globally throughout the text in conjunction with the term Isolators.
Response: Comment incorporated.

Advanced Aseptic Technologies
Comment Summary #6: The commenter suggested revising the last sentence in the this section by replacing the word “similar” with “comparable.”
Response: Comment incorporated.

Clean Room Classification for Aseptic Processing Environments
Comment Summary #7: The commenter suggested inclusion of current reference to ISO 14644 rather than referencing the standard from 1999.
Response: Comment not incorporated. Current version is not yet official.

Establishment of Clean Room Classifications
Comment Summary #8: The commenter indicated that Table 1 incorrectly lists the clean room classification associated with ISO 8
Response: Comment incorporated.
Comment Summary #9: The commenter suggested adding FED-STD 209 in each of the classes mentioned in Table 1.
Response: Comment not incorporated. A footnote clarifies this.

Physical Evaluation of Contamination Control Effectiveness
Comment Summary #10: The commenter suggested including additional information on particulate matter generated for the challenge test.
Response: Comment not incorporated. The Expert Committee may consider addressing this recommendation in a future revision.

Comment Summary #11: The commenter suggested modifying the recommendation on the use of sterilized gowns with the qualifier “well fitted.”
Response: Comment not incorporated. The recommendation is appropriate as written for a general information chapter. ***Training of Personnel***
Comment Summary #12: The commenter suggested adding a specific note that people with open lesions not be allowed to enter an aseptic processing environment.
Response: Comment not incorporated. Current text includes a general reference concerning persons with illnesses..

Selection of Growth Media
Comment Summary #13: The commenter suggested either deleting or clarifying the statement regarding “bacterial over growth” on SCDM medium.
Response: Comment incorporated.

Selection of Culture Conditions
Comment Summary #14: The commenter suggested specifying the actual range of temperature as 20º– 35º instead of approximately 20º.
Response: Comment incorporated.
Comment Summary #15: The commenter suggested revising the statement on aseptically prepared media to include 100% preincubation and visual inspection of all sampling media should be performed before entry into the clean room.
Response: Comment incorporated.

Establishment Of Sampling Plan And Sites
Comment Summary #16: The commenter suggested including a note to specifically indicate that open product can be contaminated even if an operator's gloved hands moves across the top of the product with no contact.
Response: Comment not incorporated because the current text is general enough to cover this situation.
Comment Summary #17: The commenter suggested replacing the term “operator” with the term “clean room personnel.”
Response: Comment incorporated.
Comment Summary #18: The commenter suggested harmonizing Frequency of Sampling in Table 2: with current EU and FDA regulatory documents.
Response: Comment not incorporated. The stated frequency of sampling is appropriate.
Comment Summary #19: The commenter suggested revising Table 2 to include recommendations for Isolators.
Response: Comment incorporated.

Microbiological Control Parameters in Aseptic Processing Areas, Clean Rooms, Isolators And Rabs
Comment Summary #20: The commenter indicated that the suggested initial contamination recovery rates in ISO 7 and 8 areas (Table 3) are too stringent for those classifications of manufacturing areas.

Response: Comment incorporated.
Comment Summary #21: The commenter suggested that the use of % recovery rates should be recommended only for trend analyses and maintaining the maximum recovery limit of cfu for every grade as a guidance value.
Response: Comment not incorporated. Limitations on use of cfu values are discussed in the text.
Comment Summary #22: The commenter suggested clarification of the statement which indicates that any excursion > 15 cfu should prompt a careful and thorough investigation.
Response: Comment incorporated.

Further Considerations About Data Interpretation
Comment Summary #23: The commenter suggested revising the paragraph on accomplishing sterility assurance to clarify various modes of contamination.
Response: Comment incorporated.

Glossary
Comment Summary #24: The commenter suggested adding the definition of clean rooms and adding definitions for Isolators and Contamination Recovery Rates.
Response: Comment incorporated.

General Chapter/Sections: <1151> Pharmaceutical Dosage Forms/Multiple Sections
Expert Committee: General Chapters—Dosage Forms
No. of Commenters: 4

General Considerations
Comment Summary #1: The commenter suggested that a dosage form need not have excipients and that the following sentence should be amended to indicate this: “A dosage form is a combination of API and excipients to facilitate dosing, administration, and delivery of the medicine to the patient.”
Response: Comment incorporated.
Comment Summary #2: The commenter suggested that the packaging, storage, and labeling information in the various sections of the chapter is variable in approach. Furthermore, the *General Notices* allow the instructions on the manufacturer’s label to supersede monograph instructions. The removal of the packaging and storage information from the individual dosage forms sections in the chapter was suggested. As an alternative method of presentation, the General Considerations section of the chapter could include a general statement on packaging and storage.
Response: Comment not incorporated. The comment is under consideration by the Expert Committee and may be part of a future proposed revision.
Expert Committee-initiated Change #1: Under *Dose Uniformity*, the Expert Committee determined that the discussion of the conditions for tablets and capsules where the *Weight Variation* procedure may be substituted for *Content Uniformity* was unnecessary and therefore the sentence was deleted.

Expert Committee-initiated Change #2: Under *Stability*, the Expert Committee added examples of measures of continuing dosage form performance over time, which for tablets and capsules includes dissolution and disintegration.
Expert Committee-initiated Change #3: Under *Bioavailability*, the Expert Committee determined that disintegration and dissolution may "sometimes be" rather than "commonly are" used as surrogates to demonstrate consistent availability of the API from the formulated dosage form and only with proper justification. The text was updated to reflect this.
Expert Committee-initiated Change #4: Under *Routes of Administration*, the Expert Committee found that tests for particulate matter may be required for certain dosage forms rather than the narrower wording in *PF* that only mentioned solution dosage forms. The text was updated to reflect this.
Expert Committee-initiated Change #5: Under *General Product Quality Tests, Antioxidant Preservative Content*, the Expert Committee determined that the addition of the word "preservative" was inaccurate and deleted it from the subsection heading as well as the text. A rationale for such testing to maintain the product's quality at all stages throughout its proposed usage and shelf life was also added to the text.
Expert Committee-initiated Change #6: The Expert Committee found that the general test, *Extractables* was more correctly termed, *Leachables*. The corresponding title and wording within the text were changed to reflect this.

Aerosols
Expert Committee-initiated Change #7: The Expert Committee determined that the primary function of metal containers for aerosols was to withstand the pressure produced by the propellant. The text was changed to reflect that determination.
Expert Committee-initiated Change #8: The Expert Committee determined that with each actuation, nasal aerosols release a measured mass and appropriate API quality rather than one dose. The text was changed to reflect that determination.
Expert Committee-initiated Change #9: The Expert Committee determined that topical aerosols may be designed to deliver a metered amount on valve actuation, or alternatively, to provide a continuous release while the valve is depressed.

Capsules
Comment Summary #3: The commenter suggested that the section, *Two-Piece Capsules*, be modified to note that pigments other than iron oxides and also plasticizers are important components of capsule shell material. Additionally, the commenter noted that a locking joint between the cap and body is an alternative to sealing with a band.
Response: Comments incorporated.
Expert Committee-initiated Change #10: The Expert Committee revised the subsections dealing with modified release capsules to indicate that two subcategories of modified release products are available, extended release, and delayed release.

Dry Powder Inhalers
Comment Summary #4: The commenter indicated that a powder does not form a mist because a mist is a colloidal suspension of a liquid in a gas. The commenter suggested that the word, "mist" could be replaced by "dispersion" in the sentence: "The dose is

released from the packaging by an appropriate mechanism and is mobilized into a fine mist only upon oral inhalation by the patient."
Response: Comment incorporated.
Expert Committee-initiated Change #11: The Expert Committee revised the name of this dosage form from "Dry Powder Inhalers" to "Inhalation Powders." An inhaler is a device and the committee found that the dosage form is a powder. Acknowledgement is given that inhalation powders are commonly known as dry powder inhalers. The Expert Committee intends that subsequent revisions of the General Chapter will place this dosage form within the Powders section.
Expert Committee-initiated Change #12: The Expert Committee found that inhalation powders are delivered not only as pre-metered units, but also as device metered dry powder inhalers. This finding is acknowledged in the text under *Typical Components*.

Feed Additives
Comment Summary #5: The commenter suggested that "feed additives" is an inappropriate title for these articles. The commenter suggested that these articles are medicated animal feeds or in the case of Type A medicated articles, drugs with at most excipients as a carrier.
Response: Comment incorporated.

Medical Gases (Inhalation Materials)
Comment Summary #6: The commenter suggested that medical gases are administered to more than the pulmonary route or via extracorporeal methods. The commenter enumerated many additional routes and uses.
Response: Comment incorporated.

Gels
Comment Summary #7: The commenter suggested that gels are not often used to treat mastitis but rather are a therapeutic option.
Response: Comment incorporated.

Granules
Comment Summary #8: The commenter suggested that granules are used both as granules (solids) as well as suspensions in facilitating flexible dosing regimens
Response: Comment incorporated.
Comment Summary #9: The commenter suggested that in the manufacture of granules, wetting to promote agglomeration can be effected by an appropriate pharmaceutical binding solution in addition to solvents or blends of solvents.
Response: Comment incorporated.
Comment Summary #10: The commenter suggested that when reconstituted as suspensions, granules should be thoroughly mixed or shaken before use to suspend the dispersed particulates.
Response: Comment incorporated.

Inserts

Comment Summary #11: The commenter suggested that inserts are only placed in naturally occurring body cavities other than the mouth or rectum. The revised wording would distinguish inserts from implants that are placed in surgically created body cavities and from tablets and capsules that are administered through the mouth.
Response: Comment incorporated.

Liquids
Comment Summary #12: The commenter suggested removing the sentence discussing veterinary liquids since no veterinary dosage forms are pure chemical liquids.
Response: Comment incorporated.

Pellets
Comment Summary #13: The commenter suggested that depending on the size of the animal, multiple pellets rather than a set number may be implanted in the ears of cattle in veterinary practice.
Response: Comment incorporated.
Comment Summary #14: The commenter suggested that the upper limit of pellets for oral administration should be 2.0 mm as given in the draft “FDA Guidance for Industry: Size of Beads in Drug Products labeled for Sprinkle.”
Response: Comment not incorporated. The discussion of the upper limit of such pellets is ongoing and awaits resolution. The size range currently given in the chapter reflects the range 8 to 25 of US Sieves as presented in General Chapter <786> *Particle Size Distribution Estimation by Analytical Sieving*.

Pills
Comment Summary #15: The commenter suggested that pills are not necessarily prepared by a wet massing technique and that tablets are not always manufactured by compression.
Response: Comment incorporated.

Powders
Comment Summary #16: The commenter suggested that the statement under labeling regarding the need for powders intended for veterinary use be revised to indicate that they are only for veterinary use applies to any veterinary product and thus should be part of a general statement on labeling.
Response: Comment incorporated.

Sprays
Expert Committee-initiated Change #13: The wording of the section on sprays was changed to conform to the Expert Committee determination that a spray dosage form is assumed to deliver a metered amount through the delivery system and that alternatively, non-metered sprays are available.

Tablets

Comment Summary #17: The commenter suggested that there is no necessity to distinguish between hard and soft chewable tablets. Additionally, the instructions that chewable tablets must or alternatively may be chewed are confusing, and in the case of veterinary products, there is no certainty that the product will be chewed. Furthermore, in the case of patients who are unable to chew, the section should allow that in lieu of chewing, the tablets should be crushed before administration.
Response: Comments incorporated.
Expert Committee-initiated Change #14: The subsections dealing with modified release tablets were revised to indicate that two subcategories of modified release products are available, extended release and delayed release.

Glossary
Comment Summary #18: The commenter suggested that the definition of *Chewable* allow that the intention is that the solid dosage form may also be crushed where the patient is unable to chew.
Response: Comment incorporated.
Comment Summary #19: The commenter suggested that the definition of *Cream* be revised to conform to the CDER Data Standards Manual. A cream is an emulsion often containing more than 20% water and volatiles and/or containing less than 50% hydrocarbons, waxes, or polyols.
Response: Comment incorporated.
Comment Summary #20: The commenter suggested that an additional statement be added to the definition of *Excipient* in recognition that the term is synonymous with inactive ingredient.
Response: Comment incorporated.
Comment Summary #21: The commenter suggested that the definition of *Feed Additive* is incorrect and should be removed from the Glossary.
Response: Comment incorporated.
Comment Summary #22: The commenter suggested that the Expert Committee review the definition of *Oral* not only as a result of its use as a specific location within the body, but also as a route for delivering dosage forms to the gastro-intestinal tract.
Response: Comment not incorporated. The definition was removed from the Glossary and discussions within the Expert Committee regarding its elaboration are ongoing.
Comment Summary #23: The commenter suggested that the definition of *Oro-Pharyngeal* should contain the wording oral cavity rather than buccal cavity. The buccal cavity comprises a portion of the oral cavity.
Response: Comment incorporated.
Expert Committee-initiated Change #15: The definition of *Delayed-Release* was revised to explain that enteric-coated products are not the only example of this modified release category.
Expert Committee-initiated Change #16: The definition for *Patch* was revised to note that while not preferred, the term is frequently and not incorrectly used in reference to a Transdermal System.

General Chapter/Sections: <1224> Transfer of Analytical Procedures/Multiple Sections

Expert Committees: General Chapters - Physical analysis
No. of Commenters: 5

General Considerations
Expert Committee-initiated Change #1: Under *Comparative Testing*, the final sentence was reworded to reflect that the purpose of the transfer is to qualify the receiving unit.
Expert Committee-initiated Change #2: Under *Elements recommended for the Transfer of Analytical Procedures*, information on comparative testing was removed.
Expert Committee-initiated Change #3: Under *Preapproved Protocol*, second paragraph, the justification of a waiver is removed since it is mentioned elsewhere in the chapter.

Introduction
Comment Summary #1: The commenter suggested using only the term “transferring unit,” eliminating the reference to “sending unit.”
Response: Comment incorporated.
Comment Summary #2: The commenter suggested eliminating the reference to “verification” under the *Introduction* section.
Response: Comment incorporated.

Types of Transfers of Analytical Procedures
Comment Summary #3: The commenter suggested the inclusion of confirmation testing as an acceptable type of method transfer: There may be circumstances when the risks assessed are considered to be low, but not low enough to consider a transfer waiver.
Response: Comment not incorporated. This is a very specific case that does not need to be included, as the chapter supports a risk-based transfer process.
Comment Summary #4: The commenter suggested that TAP can be waived if the transferring unit and the receiving unit are part of the same laboratory setup, follow the same SOPs, and have same Quality Assurance authority.
Response: Comment not incorporated. If the developing lab and QC lab are distinct units, some level of transfer is appropriate.
Comment Summary #5: The commenter suggested adding “at the transferring unit” after “…validation team…” in the second sentence under *Co-validation Between Two or More Laboratories*.
Response: Comment incorporated.
Comment Summary #6: The commenter suggested removing the last three sentences under *Types of Transfers of Analytical Procedures* since it is not critical for the purpose of this chapter.
Response: Comment incorporated.
Comment summary #7: The commenter suggested removing the phrase “is the most common method for TAP” under *Comparative Testing*.
Response: Comment incorporated.

Comment Summary #8: The commenter suggested better describing the parties involved in co-validation.
Response: Comment incorporated.
Comment Summary #9: The commenter suggested, changing the word “incidences” to “scenarios” in the third sentence under *Transfer Waiver*.
Response: Comment incorporated
Comment Summary #10: The commenter suggested that the reason for the transfer waiver should be documented.
Response: Comment incorporated.
Comment Summary #11: The commenter suggested under *Transfer Waiver* adding a statement that indicates in the case of compendial procedures a transfer may be waived.
Response: Comment incorporated.
Comment Summary #12: The commenter suggested better defining of “comparable composition” under *Transfer Waiver* because, for example, if excipients are different, specificity may be affected.
Response: Comment not incorporated. The success of the transfer is not related to the specificity of the procedure because the new procedure has already been validated.
Comment Summary #13: The transfer waiver should state validation as a prerequisite.
Response: Comment not incorporated. The Expert Committee believes that it is a common understanding that new analytical procedures need to be validated.

Elements Recommended for the Transfer of Analytical Procedures
Comment Summary #14: The commenter suggested that clarification should be provided regarding documentation of data generated during training or pre-transfer activities.
Response: Comment not incorporated. This general information chapter does not cover this level of detail.
Comment Summary #15: The commenter suggested the deletion of the statement “…or the receiving unit should run the procedures and identify any issues that may need to be resolved before the transfer protocol is signed.” The suggestion is based on the idea that this could be quite difficult to do in practice if one had no or little experience with the product or the analytical method.
Response: Comment not incorporated. The activities described in the paragraph are recommendations, not requirements.
Comment Summary #16: The commenter suggested removing special reference to “contract research organization.”
Response: Comment not incorporated. Contract research organizations are very common entities involved in this activity.
Comment Summary #17: The commenter suggested deleting the last sentence in the section. In other sections of the General Chapter, the use of one lot it is recommended.
Response: Comment incorporated.

Preapproved Protocol

Comment Summary #18: The commenter indicated that, if the TAP is planned across overseas sites and travel for training is a problem, the pre-approved transfer protocol across two sites should be sufficient to cover the training requirement.
Response: Comment not incorporated. The transferring lab should determine when training is appropriate. However, if training overseas is difficult and deemed not required, then that should be documented.
Comment Summary #19: The commenter suggested incorporating a reference to General Chapter <1226> *Verification of Compendia Produces* immediately after the reference to <1225>.
Response: Comment incorporated.
Comment Summary #20: The commenter suggested clarifying the way the acceptance criteria may be derived.
Response: Comment incorporated.

The Analytical Procedure
Comment Summary #21: The commenter suggested removing the word “batches” in the last sentence. In other sections of the General Chapter the use of “one lot” is recommended.
Response: Comment incorporated.

Transfer Report
Comment Summary #22: The commenter suggested changing “analyst” to “receiving unit” in the first sentence.
Response: Comment incorporated.
Comment Summary #23: The commenter suggested changing “may be” to “is” in the third sentence starting with “If the acceptance criteria are met…”
Response: Comment incorporated.

Monographs

Monograph/ Section: Alprazolam Orally-Disintegrating Tablets/Organic Impurities
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested the addition of several degradation products with appropriate limits to the impurity profile.
Response: Comment not incorporated. One of the degradation products listed by the commenter, 2-amino-5-chloro-benzophenone, is already included in the monograph. The Expert Committee may consider this revision in the future upon receipt of the necessary supporting data.

Monograph/ Section: Candesartan Cilexetil/Organic Impurities
Expert Committee: Monographs—Small Molecules 2
No. of Commenters: 5
Comment Summary #1: The commenter requested changing the resolution criterion from NLT 5.0 to NLT 2.5.

Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of the necessary supporting data.
Comment Summary #2: The commenters requested revising the chemical names for the impurities as follows: change “ethyl candesartan cilexetil” to “ethyl candesartan”, and change “candesartan cilexetil-9a-*N*-ethyl” to “N^2-ethyl candesartan cilexetil.” The commenter also requested revising the chemical names in the footnotes 2 and 3 from “1- (cyclohexyloxycarbonyloxy)ethyl 1-{[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}oxobenzimidazole-7-carboxylate” to “(±)-1-(cyclohexyloxycarbonyloxy)ethyl 1-{[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}-2-oxobenzimidazole-7-carboxylate” and “1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-{[2'-(N-ethyl-tetrazol-5-yl) biphenyl-4-yl]methyl}benzimidazole-7-carboxylate to “(±)1-(Cyclohexyloxycarbonyloxy) ethyl 2-ethoxy-1-{[2'-(N-ethyltetrazol-5-yl) biphenyl-4-yl]methyl}benzimidazole-7-carboxylate.”
Response: Comments incorporated.
Comment Summary #3: The commenter indicated that the proposed method for related compounds does not detect some of their process impurities.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of the necessary supporting data.
Comment Summary #4: The commenter requested adding a Note under the gradient table to indicate that a 10 min equilibration may be necessary between runs.
Response: Comment incorporated.
Comment Summary #5: The commenter requested adding acceptance criteria for total impurities to meet the general quality requirement as per ICH Q3B guideline.
Response: Comment not incorporated. The current proposal includes a specification for total impurities which is consistent with FDA-approved specifications.

Monograph: Cranberry Liquid Preparation
Expert Committee: Monographs—Dietary Supplements
No. of Commenters: 1
Expert Committee-initiated Change #1: *Identification test B* was renamed as “*B. HPLC Identification Test.*”

Monograph/Section: Diethylene Glycol Monoethyl Ether/Labeling
Expert Committee: Monographs—Excipients
No. of Commenters: 1
Expert Committee-initiated Change #1: The Labeling section was revised to state the route of administration as seen in the FDA’s Inactive Ingredient Database (IIG). The statement was changed from, “Label it to indicate that it is intended for topical use only and it is stored under an atmosphere of an inert gas” to “Label it to indicate that it is intended for topical or transdermal use only and it is stored under an atmosphere of an inert gas. The material is not intended for parenteral use.”

Monograph/Sections: Docetaxel Injection/Multiple Sections
Expert Committee: Monographs—Small Molecules 3
No. of Commenters: 7

Comment Summary #1: The commenter requested that the monograph title “Docetaxel Injection” be used for the one-vial formulation only, and that a separate monograph titled “Docetaxel Injection Concentrate” be developed for the two-vial formulation.
Response: Comment not incorporated. USP monographs for injectable dosage forms are developed to cover multiple strengths and concentrations of the active ingredient in a single monograph, including both diluted and concentrated solutions. This approach is consistent with the General Chapter <1121> *Nomenclature* which states: “For products intended for parenteral administration, the use of the word “Concentrate” in the monograph title is restricted to one specific monograph, Potassium Chloride for Injection Concentrate. The word “Concentrate” should not appear in the monograph title for any other parenteral product; rather, this issue is to be addressed in the product labeling.”
Comment Summary #2: The commenter requested revising the *Definition* to state “It contains suitable amounts of polysorbate 80 and/or solubilizing agents,” in order to accommodate different formulations.
Response: Comment incorporated.
Comment Summary #3: The commenter requested that the *Assay* acceptance criteria be changed from “90.0%-105.0%” to “90.0%-110.0%” to be consistent with FDA-approved specifications.
Response: Comment incorporated.
Comment Summary #4: The commenter requested that the *Standard solution* preparation in the *Assay* be revised to omit the polysorbate 80, to accommodate different formulations.
Response: Comment incorporated.
Comment Summary #5: The commenter indicated that the Docetaxel Injection is viscous, and requested adding a weighing procedure in the *Sample solution* to replace the term “transfer.”
Response: Comment not incorporated because the term “transfer” is defined as a quantitative manipulation in the *General Notices*, Section 8.200.*Transfer*.
Comment Summary #6: The commenter requested that the limit for unspecified impurities be changed from NMT 0.20% to NMT 0.2% to be consistent with FDA-approved specifications.
Response: Comment incorporated.
Comment Summary #7: The commenter requested that the limit of bacterial endotoxins should be changed from NMT 1.75 USP Endotoxin Units/mg of Docetaxel (anhydrous) to 1.94 USP EndotoxinUnits/mg of Docetaxel (anhydrous), to be consistent with FDA-approved specifications.
Response: Comment incorporated.
Comment Summary #8: The commenter requested that the test for *pH* be deleted to accommodate different formulations.
Response: Comment incorporated.
Comment Summary #9: The commenter requested that multi-dose containers be added in the *Packaging and Storage* to accommodate different products.
Response: Comment incorporated.
Comment Summary #10: The commenter requested that the disregard limit in *Organic impurities* be changed from 0.10% to 0.1% to be consistent with the ICH guideline.
Response: Comment incorporated.

Comment Summary #11: The commenter requested that chemical names for the organic impurities be harmonized with those in the *European Pharmacopoeia* monograph for Docetaxel.
Response: Comment incorporated.
Comment Summary #12: The commenter requested tightening the limits for organic impurities**.**
Response: Comment not incorporated because the limits for organic impurities in the monograph are consistent with the specifications approved by FDA.
Comment Summary #13: The commenter requested that the resolution requirement in the tests for *Assay and Organic impurities* be changed from 3.5 to 2.0 because a resolution of 2.0 is commonly accepted and is suitable to ensure the baseline separation.
Response: Comment not incorporated. The resolution requirement of NLT 3.5 is supported by the validation data and is suitable for the analysis.
Comment Summary #14: The commenter requested correcting the definition of r_S under *Organic impurities* from "peak area of docetaxel from the *Standard solution*" to "sum of all of the peak areas from the *Sample solution*."
Response: Comment incorporated.
Comment Summary #15: The commenter requested that the concentration of the *Sensitivity solution* be changed from 1.0 µg/mL (0.5%) to 0.2 µg/mL (0.1%) to be consistent with the disregard limit.
Response: Comment incorporated.

Monographs/Sections: Eleuthero, Powdered Eleuthero, Powdered Eleuthero Extract
Expert Committee: Monographs—Dietary Supplements
No. of Commenters: 2
Expert Committee-initiated Change #1: The HPTLC plate in the Identification test was changed to indicate that it should be developed over a path of 6 cm.
Expert Committee-initiated Change #2: The *Identification test B* was renamed as "*B. HPLC Identification Test*."

Monograph/Section: Ethylcellulose Dispersion Type B/Content of Medium-Chain Triglycerides
Expert Committee: Monographs—Excipients
No. of Commenters: 1
Comment Summary #1: The commenter suggested replacing USP Oleic Acid RS in the *Standard solution* with oleic acid, because in this test oleic acid is included to assist with consistent integration between the *Standard* and *Sample solutions*.
Response: Comments incorporated.

Monograph/Section(s): Fluconazole Injection**/**Organic Impurities, Procedure 4
Expert Committee: Monographs— Small Molecules 1
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the limit for "any other individual impurity" according to ICH Q3B guideline, based on the maximum daily dose for the drug product.

Response: Comment not incorporated. The limit in the proposed monograph is consistent with FDA-approved specifications.

Monographs/Section(s): Ginkgo, Powdered Ginkgo Extract, Ginkgo Capsules, and Ginkgo Tablets
Expert Committee(s): Monographs—Dietary Supplements
No. of Commenters: 3
Expert Committee-initiated Change #1: For the *Ginkgo*, and *Powdered Ginkgo Extract* monographs, the HPTLC plate in the ID tests was changed to indicate that it should be developed over a path of 6 cm.
Expert Committee-initiated Change #2: For *Powdered Ginkgo Extract*, "*Identification test B*" was renamed as "*B. HPLC Identification Test*."
Expert Committee-initiated Change #3: For *Ginkgo Capsules* and *Ginkgo Tablets*, "*Identification tests*" was renamed as "*HPLC Identification Test A & B*."

Monograph/Section: Glycopyrrolate/Limit of Erythro Isomer
Expert Committee: Monographs—Small Molecules 3
No. of Commenters: 1
Comment Summary #1: The commenter requested changing the relative response factor for the erythro isomer from 0.86 to 1.0, to be consistent with the *European Pharmacopoeia* monograph.
Response: Comment incorporated.

Monograph/Sections: Glycopyrrolate Tablets/Multiple sections
Expert Committee: Monographs—Small Molecules 3
Expert Committee-initiated Change #1: The preparations of the *Sample solution* under *Assay*, *Organic impurities*, and *Dissolution* are revised to state "discard a few mL of the filtrate," rather than to specify an exact volume of the solution to be discarded.

Monograph/Sections: Hydromorphone Hydrochloride/Multiple Sections
Expert Committee: Monographs— Small Molecules 2
No. of Commenters: 4
Comment Summary #1: The commenter requested correcting the percentage of *Solution B* at 70 minutes from 20% to 80% in the gradient table under *Organic impurities.*
Response: Comment incorporated
Comment Summary #2: The commenter requested tightening the limits for dihydromorphine and for individual unspecified impurities to be consistent with the ICH Q3A guideline.
Response: Comment not incorporated because the limits for organic impurities in the monograph are consistent with the specifications approved by FDA.
Comment Summary #3: The commenter requested that two additional process impurities, 8,14-dihydrooripavine and 6-beta-tetrahydrooripavine, be included in the *Impurity Table 1* under *Organic impurities* to accommodate the impurity profile of their product.
Response: Comment incorporated.

Comment Summary #4: The commenter requested that a second *Organic impurities* procedure be added to the monograph using a flexible approach to accommodate the impurity profile generated by their manufacturing process.
Response: Comment incorporated.

Monograph/Section: Lansoprazole/Organic Impurities
Expert Committee: Monographs—Small Molecules 3
No. of Commenters: 3
Comment Summary #1: The commenter requested that USP not adopt the introduction of the new USP Lansoprazole Related Compound B RS, and instead, retains the relative response factor of 0.79 to quantitate this impurity.
Response: Comment not incorporated. The introduction of USP Reference Standards for impurities helps manufacturers and users to identify and quantify the impurities.
Comment Summary #2: The commenter requested that USP not adopt the introduction of the new USP Lansoprazole Related Compound B RS, and instead, changes the relative response factor for this impurity from 0.79 to 1.0.
Response: Comment not incorporated. When the value of a response factor for an impurity is being questioned, the best approach is to introduce a quantitative standard for this impurity.
Comment Summary #3: The commenter indicated that the disregard limit of 0.05% has been inadvertently deleted from the monograph, and requested to add this limit under the *Acceptance criteria*.
Response: Comment incorporated

Monograph/Sections: Loratadine Orally Disintegrating Tablets/Multiple Sections
Expert Committee: Monographs—Small Molecules 4
Expert Committee-initiated Change #1: The TLC *Identification* test was deleted from the monograph because the Expert Committee considers a single identification test based on HPLC retention time agreement to be adequate for this drug product monograph.
Expert Committee-initiated Change #2: The column efficiency system suitability requirement is maintained in *Assay Procedure 1* and in *Organic Impurities Procedure 1* because the Expert Committee determined it was necessary to ensure adequate chromatographic performance.

Monographs: Malabar-Nut-Tree, Leaf, Powdered Malabar-Nut-Tree, and Powdered Malabar-Nut-Tree Extract
Expert Committee: Monographs—Dietary Supplements
No. of Commenters: 5
Expert Committee-initiated Change #1: These monographs now include a new *Identification test A: the article meets the requirements under Botanical Characteristics*. Other identification tests are renumbered accordingly.
Expert Committee-initiated Change #2: *Identification test B* was renamed as "*B. HPLC Identification Test*"
Expert Committee-initiated Change #3: Development distance in the *TLC analysis* section was changed from about 90% to about three-fourths of the plate.

Expert Committee-initiated Change #4: The TLC detection was limited to examining under UV light at 254 nm and the use of Dragendorff's reagent was deleted.
Expert Committee-initiated Change #5: The formula to calculate *Content of vasicine* was changed to the classical monograph format similar to those in *USP 32–NF 27* for plant monographs.

Monograph/Sections: Mercaptopurine/Multiple Sections
Expert Committee: Monographs—Small Molecules 3
No. of Commenters: 2
Comment Summary #1: The commenter requested specifying that salicylic acid should be added to the solvent used for the *Water Determination*.
Response: Comment not incorporated because this may limit the options available to the analysts performing the test.
Comment Summary #2: The commenter indicated that mercaptopurine may degrade to form mercaptopurine disulfide in the *Sample solution* under *Organic impurities*, and requested adding a Note that the *Sample solution* should be injected within 1 hour of preparation.
Response: Comment incorporated.
Comment Summary #3: The commenter indicated that potential process impurities from their material may coelute with the mercaptopurine peak in the *Organic impurities* test.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of the necessary supporting data.

Monograph/Section: Mercaptopurine Tablets/Dissolution Test 1
Expert Committee: Monographs—Small Molecules 3
Expert Committee-initiated Change #1: The chemical formula of mercaptopurine under *Tolerances* is corrected, to be consistent with the *Definition*.

Monograph/Section: Methacrylic Acid Copolymer Dispersion (new name: Methacrylic Acid and Ethyl Acrylate Copolymer Dispersion)/Limit of Monomers
Expert Committee: Monographs—Excipients
No. of Commenters: 1
Comment Summary #1: The commenter indicated that the recovery for the monomer ethyl acrylate is unsatisfactory and suggested that an alternative method be used.
Response: Comments not incorporated. The revision sponsor was contacted regarding the report. The sponsor performed tests in their labs and demonstrated that the results were within the validation ranges. Additional tests are in the process. The Expert Committee is willing to consider future changes to the monograph upon receipt of the necessary supporting data.

Monograph/Section: Morphine Sulfate Extended-Release Capsules/Dissolution
Expert Committee: Monographs—Small Molecules 2
No. of Commenters: 1

Comment Summary #1: The commenter requested adding a reference to the General Chapter <711> Dissolution where *Acceptance Table 3* is specified under *Tolerances*.
Response: Comment incorporated.

Monograph/Sections: Orlistat/Multiple Sections
Expert Committee: Monographs—Small Molecules 2
No. of Commenters: 5
Comment Summary #1: The commenter requested adding a test for residual solvents to the monograph.
Response: Comment not incorporated. The USP approach to testing for residual solvents is addressed in the *General Notices*, Section 5.60.20.*Residual Solvents in USP and NF Articles*.
Comment Summary #2: The commenter requested increasing the concentration of orlistat in the *Standard* and *Sample solutions* under *Assay*, and increasing the concentration of USP Orlistat Related Compound A RS in the *Standard solution* under *Organic impurities, Procedure 1* to improve the detector response.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of the necessary supporting data.
Comment Summary #3: The commenter requested removal of USP Orlistat Related Compound D RS from the *System suitability solution* under *Organic Impurities, Procedure 3* since this impurity is controlled in *Procedure 4*.
Response: Comment not incorporated. The system suitability requirement in *Procedure 3* includes a S/N ratio for the Orlistat Related Compound D peak.
Comment Summary #4: The commenter requested tightening the requirement for the relative standard deviation under *Organic impurities, Procedures 3* and *4*.
Response: Comment not incorporated. The current requirement is consistent with the submission received from the FDA-approved sponsor.
Comment Summary #5: The commenter requested correcting the gradient table under *Organic impurities, Procedure 5*: *Limit of Orlistat Related Compound E* to indicate that the system runs in an isocratic mode with 100% of Solvent B between 24 and 38 minutes.
Response: Comment incorporated.
Comment Summary #6: The commenter requested revising the preparation of the *Standard stock solution*, *Standard solution* and *Sample solution* under *Organic impurities, Procedure 5*: *Limit of Orlistat Related Compound E*, to include the derivatization procedure.
Response: Comment incorporated.
Comment Summary #7: The commenter requested including an additional procedure for *Organic Impurities* using a flexible monograph approach to accommodate impurities observed during their fermentation process.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of the necessary supporting data.
Comment Summary #8: The commenter requested inclusion of test for *Melting Range* to the monograph.

Response: Comment not incorporated. The inclusion of this test will not add value to the monograph.
Comment Summary #9: The commenter requested revising the *Optical Rotation* test by replacing the solvent dehydrated alcohol with chloroform.
Response: Comment not incorporated because chlorinated solvents present a safety concern and should not be included in the monograph if an alternative solvent is suitable for the test.
Comment Summary #10: The commenter requested changing the storage condition in the *Packaging and Storage* statement to “between 2° and 8°” in lieu of controlled room temperature**.**
Response: Comment incorporated.
Comment Summary #11: The commenter requested a correction to the chemical name for the orlistat open ring amide from **“***N*-formyl-*L*-leucine (*S*)-1-[(2*S* ,3*S*)-2-hydroxy-3-[1-phenyl-*R*-ethylcarbomoyl]nonyl]-dodecyl ester” to “*N*-formyl-*L*-leucine (*S*)-1-[(2*S* ,3*S*)-2-hydroxy-3-[1-phenyl-*R*-ethylcarbamoyl]nonyl]-dodecyl ester” in the *Organic impurities Procedure 4*.
Response: Comment incorporated.
Comment Summary #12: Commenter requested specifying the time period for which the *Standard* and *Sample solutions* in the *Assay* and *Organic Impurities, Procedure 3* can be stored at the prescribed temperature of 5°.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of the necessary supporting data.

Monograph/Sections: Orlistat Capsules/Multiple Sections
Expert Committee: Monographs—Small Molecules 2
No. of Commenters: 2
Comment Summary #1: The commenter requested using acetonitrile instead of *Mobile phase* as a diluent for the *Standard* and *Sample solutions* in the *Assay* and *Organic Impurities.*
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of the necessary supporting data.
Comment Summary #2: The commenter indicated that their correction factors for the impurities with relative retention times of 2.0 (hexyl undecyl pyranone) and 4.7 (henicosenyl leucinate) are 0.88 and 0.43, respectively, and requested correcting relative response factors in the *Impurity Table 1* under *Organic impurities*.
Response: Comment incorporated.
Comment Summary #3: The commenter requested the removal of the phosphoric acid modifier from the *Mobile phase* under *Dissolution* test.
Response: Comment incorporated.
Expert Committee-initiated Change #1: The *Apparatus* to be used for the *Dissolution* test is specified as “Apparatus 2.”

Monographs: Phyllanthus amarus and Powdered Phyllanthus amarus
Expert Committee: Monographs—Dietary Supplements
No. of Commenters: 4

Expert Committee-initiated Change #1: A new *Identification test A: the article meets the requirements under Botanical Characteristics* was added, and other identification tests were renumbered accordingly.
Expert Committee-initiated Change #2: *Identification test B* was changed to "*B. HPLC Identification Test*"
Expert Committee-initiated Change #3: The development distance in the TLC analysis section was changed from about 90% to about three-fourths of the plate.
Expert Committee-initiated Change #4: The formula to calculate *Content of Lignans* was changed to the classical monograph format similar to that in *USP 32–NF 27* for plant monographs.

Monograph/Section: Risperidone Orally Disintegrating Tablets/Dissolution
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter suggested inclusion of the *Dissolution* test for their product.
Response: Comment not incorporated. The Expert Committee will consider adding this *Dissolution* test once the commenter's product receives full FDA approval.

Monograph/Section: Temazepam/Organic Impurities
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested canceling the proposal to replace the TLC procedure with two *Organic impurities* HPLC methods, and instead replace it with a new single HPLC method which is able to monitor all impurities.
Response: Comment incorporated. The commenter's proposal will be presented in a future issue of *PF*.

Monograph/ Section: Telmisartan/Heavy Metals
Expert Committee: Monographs— Small Molecules 2
No. of Commenters: 1
Comment Summary #1: The commenter requested adding a reference to the <231> *Heavy Metals, Method II* and deleting the published procedure, to be consistent with their current procedure for heavy metals testing.
Response: Comment incorporated.

Monograph/Section: Temozolomide/Assay
Expert Committee: Monographs—Small Molecules 3
No. of Commenters: 1
Comment Summary #1: The commenter requested specifying the column temperature in the *Chromatographic System* under *Assay*.
Response: Comment not incorporated. The validation was performed with the column maintained at an ambient temperature (about 25°), which is considered a default parameter as per *USP General Notices*, Section 8.180.*Temperatures*.

Monograph/Section: Tramadol Hydrochloride Tablets/Organic Impurities

Expert Committee: Monographs— Small Molecules 2
Expert Committee-initiated Change #1: The relative response factors for the peaks with relative retention times of 0.85 and 5.27 and for any unspecified impurity peak are changed from 1.00 to 1.0 in *Impurity Table 1*.

Monograph/Sections: Tramadol Hydrochloride Extended-Release Tablets/Multiple Sections
Expert Committee: Monographs— Small Molecules 2
No. of Commenters: 2
Comment Summary #1: The commenter requested a moisture content specification be added to the monograph.
Response: Comment not incorporated. The tests for moisture content are generally not included in the dosage form monographs, as these specifications are formulation-specific. However, if this specification is required to address a known stability issue for this drug product, the Expert Committee will consider adding this test in the future upon receipt of the necessary supporting data.
Comment Summary #2: The commenter indicated that the *Organic Impurities* test method calls for the use of a UHPLC system, and that while most companies have started using this technology, it is fairly new and requires specialized equipment.
Response: This proposal reflects USP's attempt to introduce new technologies into compendial standards. The use of UHPLC systems helps in reducing solvent consumption and the time of the analysis, which is consistent with current laboratory practices. To address industry's requests to incorporate UHPLC approach into *USP-NF* monographs, a recently proposed revision to General Chapter <621> *Chromatography* will allow the analyst to convert a UHPLC to a conventional chromatographic procedure, and to achieve separation power equivalent to that obtained using the prescribed column. In addition, the Expert Committee is willing to consider a submission of an alternative procedure employing a conventional HPLC technique.
Comment Summary #3: The commenter requested adding their validated procedure as an alternate method for *Organic Impurities*
Response: Comment not incorporated. The Expert Committee may consider this proposal in the future if the sponsor provides the necessary supporting data to confirm that the current procedure does not separate the impurities generated by their manufacturing process.
Expert Committee-initiated Change #1: The relative response factor for the peak with relative retention time of 0.84 is changed from 1.00 to 1.0 in *Impurity Table 2* under *Organic Impurities*.

Monograph/ Section: Trandolapril/Organic Impurities
Expert Committee: Monographs— Small Molecules 2
No. of Commenters: 1
Comment Summary #1: The commenter indicated having difficulty in meeting the system suitability requirement for the relative standard deviation, and requested to widen it.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of the necessary supporting data.

Monograph/Sections: Vinorelbine Tartrate/Multiple Sections
Expert Committee: Monographs—Small Molecules 3
No. of Commenters: 1
Comment Summary #1: The commenter requested adding a requirement for tailing factor under the *System suitability requirements* under *Assay* and *Organic impurities*.
Response: Comment incorporated.

Monograph/Section: Zein/Identification C. SDS-Polyacrylamide Gel Electrophoresis
Expert Committee(s): Monographs—Excipients
No. of Commenters: 1
Comment Summary #1: The commenter suggested holding this revision until their small molecular lab has finished evaluation studies for Identification C. SDS-Polyacrylamide Gel Electrophoresis.
Response: Comment not incorporated. The Expert Committee will consider a future revision when validated data is presented.