Commentary

Second Supplement to USP 37–NF 32

June 2, 2014

In accordance with USP's Rules and Procedures of the 2010-2015 Council of Experts ("Rules") and except as provided in Section 7.02 Accelerated Revision Processes, USP publishes proposed revisions to the *United States Pharmacopeia and the National Formulary* (*USP–NF*) for public review and comment in the *Pharmacopeial Forum* (*PF*), USP's free bimonthly journal for public notice and comment. After comments are considered and incorporated as the Expert Committee deems appropriate, the proposal may advance to official status or be republished in *PF* for further notice and comment, in accordance with the Rules. In cases when proposals advance to official status without republication in *PF*, a summary of comments received and the appropriate Expert Committee's responses are published in the Revisions and Commentary section of the USP Web site at the time the official revision is published.

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

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

General Notices:

Section 5.60.30 Elemental Impurities in USP Drug Products and Dietary Supplements

General Chapters:

<124> Erythropoietin Bioassays
<126> Somatropin Bioidentity Tests
<227> 4-Aminophenol in Acetaminophen-Containing Drug Products
<441> Niacin or Niacinamide Assay
<469> Ethylene Glycol, Diethylene Glycol, and Triethylene Glycol in Ethoxylated Substances
<671> Containers—Performance Testing
<705> Quality Attributes of Tablets Labeled as Having a Functional Score
<736> Mass Spectrometry
<741> Melting Range of Temperature
<781> Optical Rotation
<791> pH
<1111> Bioburden Control of Nonsterile Drug Substances and Products
<1151> Pharmaceutical Dosage Forms
<1181> Scanning Electron Microscopy
<1229.6> Liquid-Phase Sterilization
<1234> Vaccines for Human Use–Polysaccharide and Glycoconjugate Vaccines
<1240> Virus Testing of Human Plasma for Further Manufacture
<1736> Applications of Mass Spectrometry
<2250> Detection of Irradiated Dietary Supplements

Monographs:

L-Alanyl-L-glutamine
Azelastine Hydrochloride
Borage Seed Oil
Brompheniramine Maleate
Carbamapeine Extended-Release Tablets
Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution
Enzacamene
Evening Primrose Oil
Flax Seed Oil
Flunixin Meglumine
Gandoderma Lucidum Fruiting Body
Gandoderma Lucidum Fruiting Body Powder
Glycyl-L-Glutamine
Glycyl-L -Tyrosine
Hydroxyzine Hydrochloride
Imipramine Pamoate
Krill Oil
Krill Oil Capsules
Krill Oil Delayed-Release Capsules
Levobunolol Hydrochloride
Levobunolol Hydrochloride Ophthalmic Solution
Mitomycin
Naphazoline Hydrochloride Ophthalmic Solution
Nicardipine Hydrochloride
Oxymetazoline Hydrochloride Ophthalmic Solution
Paroxetine Extended-Release Tablets
Rhodiola Rosea
Rhodiola Rosea, Powdered
Rhodiola Rosea Extract, Powdered
Rhodiola Rosea Tincture
Risperidone
Salmeterol Inhalation Powder
Sertraline Hydrochloride
Sodium Phenylbutyrate
Trazodone Hydrochloride Tablets

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

General Chapters

- <563> Identification of Articles of Botanical Origin
- <1081> Gel Strength of Gelatin
- <2232> Elemental Contaminants in Dietary Supplements
- <1196> Pharmacopeial Harmonization

Compounded Monographs

- Atenolol Compounded Oral Suspension
- Atenolol Compounded Oral Suspension, Veterinary
- Benazepril Hydrochloride Compounded Oral Suspension, Veterinary
- Clopidogrel Compounded Oral Suspension
- Doxycycline Compounded Oral Suspension, Veterinary
- Enalapril Maleate Compounded Oral Suspension
- Lamotrigine Compounded Oral Suspension
- Lansoprazole Compounded Oral Suspension
- Metronidazole Benzoate Compounded Oral Suspension
- Phenoxybenazmine Hydrochloride Compounded Oral Suspension
- Piroxicam Compounded Oral Suspension
- Prednisolone Compounded Oral Suspension, Veterinary
- Prednisolone Sodium Phosphate Compounded Oral Solution
- Spironolactone Compounded Oral Suspension
- Spironolactone Oral Suspension, Veterinary
- Topiramate Compounded Oral Suspension

Monographs

- Acarbose
- Acetaminophen Capsules
- Acetaminophen Oral Solution
- Acetaminophen for Effervescent Oral Solution
- Acetaminophen Oral Suspension
- Acetaminophen Tablets
- Acetaminophen Extended-Release Tablets
- Acetaminophen and Tramadol Hydrochloride Tablets
- Aspirin Delayed-Release Tablets
- Benazepril Hydrochloride Compounded Oral
- Suspension, Veterinary
- Butylene Glycol
- Carbon Monoxide C11
- Chloramphenicol and Prednisolone Ophthalmic Ointment
- Chloramphenicol, Polymyxin B Sulfate, and Hydrocortisone Acetate Ophthalmic Ointment
- Chloroxylenol
- Chorionic Gonadotropin
- Chorionic Gonadotropin for Injection
- Clopidogrel Compounded Oral Suspension
- Cupric Sulfate
- Cystine
- Dexamethasone Oral Solution
- Dextroamphetamine Sulfate Tablets
- Dextran 40 in Dextrose Injection
- Dextran 70 in Dextrose Injection
- Dextrose Injection
- Felbamate
- Fish Oil Containing Omega-3 Acids Capsules
- Fish Oil Containing Omega-3 Acids Delayed-Release Capsules
- Flumazenil C11 Injection
- Fluphenazine Decanoate Injection
- Fluorodopa F18 Injection
- Gabapentin
- Ginkgo Extract, Powdered
- Guar Gum
- Glyceryl Behenate
- Construct Human Fibroblasts in Polyglactin Scaffold
- Construct Human Fibroblasts in Bilayer Synthetic Scaffold
- Hydralazine Hydrochloride
- Invert Sugar
- Isofluorophate
- Isofluorophate Ophthalmic Ointment
- Isopropyl Myristate
- Isradipine

Monographs, Continued

- Lithium Citrate
- Lithium Oral Solution
- Mandelic Acid
- Mebendazole
- Mephenytoin
- Mephenytoin Tablets
- Mespiperone C11 Injection
- Methionine C11 Injection
- Methylparaben Sodium
- Mexiletine Hydrochloride
- Moricizine Hydrochloride
- Neomycin Sulfate and Hydrocortisone Acetate Ophthalmic Ointment
- Neomycin Sulfate and Prednisolone Acetate Ophthalmic Ointment
- Neomycin Sulfate and Prednisolone Sodium Phosphate Ophthalmic Ointment
- Neomycin Sulfate and Triamcinolone Acetonide Ophthalmic Ointment
- Neomycin Sulfate, Sulfacetamide Sodium, and Prednisolone Acetate Ophthalmic Ointment
- Oleovitamin A and D Capsules
- Oxaprozin
- Pentoxifylline
- Physostigmine
- Physostigmine Sulfate
- Physostigmine Sulfate Ophthalmic Ointment
- Pindolol
- Plicamycin
- Plicamycin for Injection
- Prazosin Hydrochloride
- Proguanil Hydrochloride
- Propranolol Hydrochloride and Hydrochlorothiazide Extended-Release Capsules
- Propylparaben Sodium
- Raclopride C11 Injection
- Ramipril
- Reserpine, Hydralazine Hydrochloride and Hydrochlorthiazide Extended-Release Capsules
- Scopolamine Hydrobromide Ophthalmic Ointment
- Sodium Acetate C11 Injection
- Sodium Picosulfate
- Somatropin
- Somatropin for Injection
- Sucrose
- Tetracaine Ophthalmic Ointment
- Valproic Acid Capsules
- Vidarabine
- Vidarabine Ophthalmic Ointment
- Vinpocetine Capsules
- Vinpocetine Tablets
- Vitamin A
- Vitamin A Capsules
- Water O15 Injection

General Notices Section: 5.60.30 Elemental Impurities in USP Drug Products and Dietary Supplements
No. of Commenters: 32
Comment Summary #1: Several commenters suggested, for various reasons, alternative implementation timing for the application of General Chapters <232> *Elemental Impurities—Limits* and <2232> *Elemental Contaminants in Dietary Supplements* via the General Notices provision, including, but not limited to:

- Alignment with the implementation of the ICH Q3D Guideline
- A tiered approach for established products
- An open-ended moratorium on implementation

Response: During the period of deferral of this General Notices provision, USP formed an Advisory Group to consider implementation issues and specific recommendations for an appropriate implementation time line. Detailed information on the deliberations of the Advisory Group can be found at http://www.usp.org/usp-nf/key-issues/elemental-impurities. The Council of Experts evaluated the input of the Advisory Group and, based on those deliberations, determined the new implementation date to be December 1, 2015. This date reflects the Council's understanding of the requirements for implementation of the standards by industry and the time required to conform, and provides an additional eighteen months beyond the date originally proposed.
Comment Summary #2: Several commenters indicated that the reference to "*official substances* (drug substances and excipients)" extends the scope of General Chapter <232> *Elemental Impurities—Limits* beyond that specified in the General Chapter.
Response: Comment incorporated.
Comment Summary #3: A commenter suggested adding a reference to General Chapter <2232> *Elemental Contaminants in Dietary Supplements*.
Response: Comment incorporated. The inclusion of this General Chapter had been proposed in *Pharmacopeial Forum* 36(1).
Comment Summary #4: A commenter suggested changing the title of the section to "Elemental Impurities in USP Drug Products and Dietary Supplements."
Response: Comment incorporated.

Monograph/Section(s) : <124> EPO Bioassays/Multiple Sections
Expert Committee(s): Monographs—Biologics and Biotechnology 2
No. of Commenters: **2**
Comment Summary #1: The commenter indicated that the use of an *in vivo* assay and the normocythemic mouse reticulocyte assay with an incompletely characterized erythropoietin stimulating agent (ESA) will not give a good understanding of response in humans.
Response: Comment not incorporated. The reference standard used in conjunction with the assay in the General Chapter has been has been calibrated against the *World Health Organization International Standard for EPO* using both the normocythemic mouse bioassay and the exhypoxic polycythemic mouse bioassay. Additionally, the General Chapter does not apply to all ESAs.
Comment Summary #2: The commenter indicated that the timing of reticulocyte collection is a critical parameter of the assay and may be dependent on experimental

conditions and properties of various ESAs, and that the time for reticulocyte collection should be specified.
Response: Comment not incorporated. However ,a statement was added to the introduction to state that the assays and acceptance criteria in this Chapter, and associated RS are not applicable to forms of EPO that have been engineered to prolong their half-life, because the General chapter does not apply to all ESAs,.
Comment Summary #3: The commenter requested adding to the *Introduction* a definition of what a unit of EPO is, and/or the history of how the unit definition has evolved. The EPO unit as currently used cannot be applied to all ESAs, because the unit is based on an *in vivo* assay of short duration.
Response: Comment not incorporated. However ,a statement was added to the introduction to state that the assays and acceptance criteria in this Chapter, and associated RS are not applicable to forms of EPO that have been engineered to prolong their half-life because the General chapter does not apply to all ESAs,.
Comment Summary #4: The commenter suggested the addition of an example to illustrate how process-specific units are assigned to the USP Reference Standard based on the ratio of *in vivo* to *in vivo* activity of the test sample, because measurement of *in vivo* potency alone may not be reflective of the true activity of an EPO test sample. *in vivo in vivo*
Response: Comment incorporated. The text was edited to clarify how the ratio of *in vivo* to *in vivo* activity of the test sample is used to assign a process specific *in vivo* assay unit age for the USP Reference Standard.
Comment Summary #5: The commenter requested providing a description of solution A under assay.
Response: Comment incorporated.
Comment Summary #6: The commenter requested adding a section on Reference Standards to align with USP's Style Guide.
Response: Comment incorporated.

General Chapter/Section(s): <126> Somatropin Bioidentity Tests
Expert Committee(s): General Chapters—Biological Analysis
No. of Commenters: 1
Comment Summary #1: The commenter requested removal of the *in vivo* rat based test as soon as possible and requested a target date for its removal.
Response: Comment not incorporated. The General Chapter contains both the official *in vivo* test as well as the new *in vivo* test to allow manufacturers to verify the new procedure. USP cannot provide a firm date for the removal of the *in vivo* test at this time, but intends to do so as soon as possible.

General Chapter/Sections: <227> 4-Aminophenol in Acetaminophen—Containing Drug Products/Multiple Sections
Expert Committee (s): Monographs—Small Molecules 2
No. of Commenters: 9
Comment Summary #1: The commenters recommended widening the limit of 4-aminophenol for solid oral dosage forms and suppositories from NMT 0.01% to NMT 0.15% to reflect current regulatory requirements.

Response: Comment incorporated. The acceptance criteria, the *Standard solution* and the *System suitability section* were revised to reflect this change.
Comment Summary #2: The commenter requested including information about other columns that are suitable for this procedure.
Response: Comment not incorporated. Chromatographic column brand information is not part of the public standard; it is provided for information only. Additional brands can be included in the list in the future when supporting data becomes available.
Comment Summary #3: The commenter indicated that the procedure may not be adequately robust.
Response: Comment not incorporated. The procedure was evaluated by five laboratories that participated in a collaborative study and was found to be robust.
Comment Summary #4: The commenter requested adding detailed instructions for pH adjustment in the *Buffer* section.
Response: Comment not incorporated. The statement about pH adjustment was deleted. Mixing the proposed concentrations of sodium citrate and citric acid results in the required pH; no additional pH adjustment is needed.
Comment Summary #5: The commenter requested adding detailed instructions for the duration of stirring for *Solution A*.
Response: Comment partially incorporated. The instructions were reworded for clarity.
Comment Summary #6: The commenter recommended revising the *Standard stock solution* and *Sample stock solution* to provide details of the weights and volumes used.
Response: Comment not incorporated. The proposed text is consistent with current USP format, which allows flexibility in terms of weights and volumes.
Comment Summary #7: The commenter recommended tightening the *Relative standard deviation* limit in the *Chromatographic Method* section.
Response: Comment incorporated. The relative standard deviation was revised to be 5.0% for all dosage forms.
Comment Summary #8: The commenter requested including solution stability profiles for the *Standard solution* and *Sample solution*.
Response: Comment not incorporated. The four-hour storage time for the *Standard stock solution* is based on data acquired in multiple laboratories. General Chapter <227> allows for this timeframe to be extended based on solution stability data acquired by individual laboratories.
Comment Summary #9: The commenter requested eliminating the need for evaluating spiked samples to allow multiple lots and products to be evaluated in the same chromatographic run.
Response: Comment not incorporated**.** The Expert Committee specifically selected the single-point standard-addition approach to address the diversity of dosage formulations. Because of the fragile nature of 4-aminophenol, both in terms of being formed by hydrolysis of acetaminophen and in terms of degrading and disappearing from solution, a single-point standard-additions approach is preferred. When the *Sample solution* and *Standard solution* are prepared at about the same time and injected one after the other, the potential for bias due to matrix affects, kinetics, or other factors is minimized.
Expert Committee-Initiated change #1: Additional changes were made to correct the text to revise spelling, grammar, and style.

Expert Committee-Initiated change #2: The concentration of the *System suitability solution* was revised from 0.5 µg/mL to 2.5 µg/mL based on the recommendation of the Acetaminophen Expert Panel.

General Chapter/Section(s): <441> Niacin or Niacinamide Assay
Expert Committee(s): General Chapters—Dietary Supplements
No. of Commenters: 1
Expert Committee-Initiated Change #1: The applicability of each procedure in the General Chapter was clarified using bullet points.

General Chapter/Section: <469> Ethylene Glycol, Diethylene Glycol, and Triethylene Glycol in Ethoxylated Substances/ Impurities
Expert Committee(s): General Chapters—Chemical Analysis
No. of Commenters: 1
Comment Summary #1: The commenter recommended broadening the tailing factor range to 0.8-2.0 in the *System suitability* section.
Response: Comment partially incorporated. Based on the data submitted, the Expert Committee determined that the tailing factor range of 0.8-1.8 is appropriate.
Comment Summary #2: The commenter suggested widening the relative standard deviation specification in the *System suitability section*.
Response: Comments not incorporated. The Expert Committee determined that the submitted data do not support the suggestion, but will consider future revisions upon receipt of additional supporting data.

General Chapter/Sections: <671>Containers—Performance Testing
Expert Committee(s): General Chapters—Packaging, Storage and Distribution
No. of Commenters: 1

General
Comment Summary #1: The commenter suggested that the testing condition of 40°/75%RH is not appropriate for all situations and that testing conditions should be determined by the end-user.
Response: Comment not incorporated. Alternate testing methods and procedures can be used if deemed equivalent or better.
Comment Summary #2: The commenter recommended including Dynamic Vapor Sorption technology.
Response: Comment not incorporated. Alternate testing methods and procedures can be used if deemed equivalent or better.
Comment Summary #3: The commenter recommended the inclusion of a water-filled blister permeation (by weight loss) method.
Response: Comment not incorporated. Alternate testing methods and procedures can be used if deemed equivalent or better.

Comment Summary #4: The commenter recommended that other procedures for handling aberrant data and should allow end-user the flexibility to choose be recognized.
Response: Comment incorporated. The Expert Committee agreed that all data should be reviewed for anomalies and these methods should follow any established standard procedures for analysis.
Comment Summary #5: The commenter recommended revising the classification (tight and well-closed) of the currently official methods.
Response: Comment not incorporated. However, the Expert Committee agreed that classification system needs to be revised and an Expert Panel has been formed to address the deficiencies in the current classification system.
Comment Summary #6: The commenter recommended removal of any requirement for pharmaceutical manufacturers to classify their container closure systems, e.g., bottle systems as tight container or blisters as Class A.
Response: Comment not incorporated. However, the Expert Committee agreed that the classification system needs to be revised and an Expert Panel has been formed to address the deficiencies in the current classification system.

Definitions
Comment Summary #7: The commenter suggested adding definitions for low/high barrier bottle systems.
Response: Comment not incorporated. The definitions for unit-dose containers is meant to define the duration and MVTR expected for a package system, which can be applied to low or high barrier multi-unit containers.
Comment Summary #8: The commenter requested the deletion of the definition for "Test Unit," because the term "Sample" is more universally understood and accepted.
Response: Comment not incorporated. The Expert Committee decided current terminology was appropriate.
Comment Summary #9: The commenter recommended deleting the reference to *ASTM E-96,* because the reference document does not discuss the advantages of weighing more units, as stated in the General Chapter.
Response: Comment incorporated.

Barrier Protection Determination for Packaging Systems for Solid Oral Dosage Forms
Comment Summary #10: The commenter suggested that instead of the reference to *ASTM D7709*, a more general reference would be more appropriate to avoid future divergence between USP and ASTM.
Response: Comment incorporated. The sentence was revised to clarify that the method is based on the *ASTM D7709.*

Barrier Protection Determination for Packaging Systems for Solid Oral Dosage Forms—Desiccants
Comment Summary #11: The commenter recommended drying desiccant for two hours instead of seven hours.

Response: Comment not incorporated Based on data presented at the USP Moisture Permeation Workshop in 2013, water activity of the desiccant is also dependent on the sample size being dried. If there is a large quantity, more than four hours is required.

Barrier Protection Determination for Packaging Systems for Solid Oral Dosage Forms—Procedure

Comment Summary #12: The commenter suggested a test sample set of six instead of 15.

Response: Comment not incorporated. The sample number proposed in General Chapter was based on statistical analysis.

Comment Summary #13: The commenter recommended allowing the end-user the option of removing the outer closure of an induction sealed bottle, because leaving the closure in place can increase variability

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

Comment Summary #14: The commenter suggested controlling the temperature and humidity during the equilibration step at ± 5° and ± 5% RH.

Response: Comment not incorporated. The suggested temperature and humidity tolerance is too stringent and could be difficult to implement for some stakeholders.

Comment Summary #15: The commenter suggested that minimum fill of the container can be determined on the sample and thus the reference to ASTM is not necessary and can be deleted.

Response: Comment incorporated.

Comment Summary #16: The commenter suggested that the pre-storage weighing instruction is not necessary and should be omitted.

Response: Comment not incorporated. The instructions are intended to limit the amount of time that samples are outside the test conditions.

Comment Summary #17: The commenter recommended providing information on the control of temperature and RH for the equilibration step, which can increase variability.

Response: Comment incorporated.

Comment Summary #18: The commenter requested replacing the term “specimen” with the term “sample,” because it is more universally understood and accepted.

Response: Comment not incorporated. The Expert Committee decided that the current terminology was suitable.

Barrier Protection Determination for Packaging Systems for Solid Oral Dosage Forms—Calculations

Comment Summary #19: The commenter suggested an alternate moisture vapor transmission rate calculation.

Response: Comment not incorporated. The General Chapter does not restrict the use of alternate calculations and analysis of the data.

Comment Summary #20: The commenter recommended deleting the requirement for sample weighing at time zero.

Response: Comment not incorporated. The day zero time point is used for the low barrier calculations. The intent is to clarify that it is not used for the regression calculation.

Comment Summary #21: The commenter suggested that Method 3 be optional with a provision for testing low barrier blisters according to Method 2 at 25°/60%RH or other temperatures.
Response: Comment not incorporated. It is recognized that there is some sacrifice in accuracy for low barrier blisters using the two day method at 40°/75%. The primary purpose of the method is to allow comparison across container closure systems
Comment Summary #23: The commenter recommended not having a fixed number of samples and indicated that six should be a minimum.
Response: Comment not incorporated. The accuracy of the method was developed and is supported by a sample size of 10. If an alternate sample size is used this will need to be described and justified in the reporting of the results.

General Chapter/Section(s): <705> Quality Attributes of Tablets Labeled as Having a Functional Score/Multiple Sections
Expert Committee: General Chapters—Dosage Forms
No. of Commenters: 5
Comment Summary #1: The commenter requested clarifying that the General Chapter covers tablets with approved labeling indicating that the tablets can be split into multiple portions that have corresponding fractional doses.
Response: Comment incorporated.
Comment Summary #2: The commenter requested that the sentence, “Disintegration testing is required only when approved as a surrogate for dissolution and specified in the monograph” be removed from the *Purpose* section as it is repeated under the *Disintegration* section.
Response: Comment incorporated.
Comment Summary #3: The commenter requested removal of the sentence, “The dose of the split tablet portions should be stated on the product labeling” from the *Purpose* section.
Response: Comment incorporated.
Comment Summary #4: The commenter requested removing the instructions for the testing to be performed promptly after splitting the tablets.
Response: Comment incorporated.
Comment Summary #5: The commenter requested that the procedure allow other justified tablet splitting methods instead of splitting by hand.
Response: Comment not incorporated. The Expert Committee determined that hand splitting is representative of rudimentary practice by patients and is preferable than allowing the multitude of available splitting devices for this procedure.
Comment Summary #6: The commenter indicated that the test for Splitting Tablets with Functional Scoring should be brought into alignment with the *FDA Guidance for Industry—Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*. There are specific differences between the General Chapter and FDA’s Guidance in sample size, additional confirmation of the ability of split portions to meet *USP <1216> Tablet Friability*, and the metric of comparing the weight of the split portion to the expected fractional weight based on the weight of the intact tablet.
Response: Comment not incorporated. The Expert Committee determined that this test applies to tablets reviewed for scoring functionality based on the expectations for content uniformity, friability, and loss of mass detailed in the FDA Guidance document.

The Expert Committee finds that the Splitting Tablets with Functional Scoring test incorporates elements of uniformity and loss of mass and provides a simplified demonstration that tablets having approved labeling can be split with the resulting split portions approaching the expected weight.
Comment Summary #7: The commenter requested that only one of the split portions resulting from an intact tablet should be used for the dissolution test sample.
Response: Comment not incorporated. The Expert Committee found that the selection of a single split portion from an intact tablet can also be a source of bias for subsequent test results.

General Chapter/Section(s): <736> Mass Spectrometry/Multiple Sections
Expert Committee(s): General Chapters—Chemical Analysis
No. of Commenters: 8

Introduction
Comment Summary #1: The commenter indicated that the term "molecular weight" should be avoided when referring to the determination by mass spectrometry and "molecular mass" should be used instead.
Response: Comment incorporated. Weight changed to "molecular mass or m/z" throughout General Chapter.
Comment Summary #2: The commenter suggested use of the word "technique" instead of "method."
Response: Comment incorporated. "Method" was changed to "technique" or "procedure" as appropriate throughout the General Chapter.

Qualitative Analysis
Comment Summary #3: The commenter indicated that high resolution mass spectrometers (HRMS) do not preclude accurate mass. The commenter suggested adding the sentence, "Tighter tolerances on mass accuracy are also afforded using HRMS"
Response: Comment incorporated. The following sentence was added, "Also, tighter tolerances on mass accuracy are also afforded using high-resolution mass spectrometry (HRMS)."

Qualitative Analysis, Experimental Parameters
Comment Summary #4: The commenter recommended providing a description of a "large biomolecule" that includes minimum molecular size (for example; mass in Daltons), because it is not clear if the term "large biomolecules" refers only to large macromolecules such as proteins and nucleic acids.
Response: Comment incorporated. The prefix "bio" was deleted and a mass lower limit of 2000 m/z was added to the description.
Comment Summary #5: The commenter suggesting revising the Mass Resolution section to read "A demonstration… of the instrument's established performance qualification (PQ) procedure if run daily or prior to the time of use," because not all PQ tests are method specific, and System Suitability needs to be performed prior to testing

of samples. If this test is listed under System Suitability and is performed as part of PQ there would be a discrepancy.
Response: Comment incorporated. The Expert Committee revised the last sentence of the section to state, "A demonstration of the appropriate resolution is included in the system suitability tests for a procedure. The performance test in the instrument's established PQ executed daily or prior to the time of use may suffice."

Qualitative Analysis, Interpretation Directions
Comment Summary #6: The commenter suggested changing the phrase, "The definitive and most certain identification…" to "identification…"
Response: Comment incorporated.
Comment Summary #7: The commenter indicated that both MS/MS and accurate mass capabilities are accessible and that a minimum of three ions may be overly restrictive. The commenter suggested the addition of the text, "the spectrum of the standard should closely resemble that of the sample and a minimum of three structurally relevant ions, one of which is an ion representing the molecular mass of the analyte, should be used for the comparison. In the case where only the ion representing the intact molecule is produced, the accurate mass or MS/MS spectrum of the molecular ion may be used to strengthen the identification**."**
Response: Comment incorporated.

Quantitative Analysis
Comment Summary #8: The commenter indicated that MS is not specified only for "organic" analytes.
Response: Comment incorporated. The Expert Committee removed the word "organic."

Quantitative Analysis, System Suitability
Comment Summary #9: The commenter suggested adding information to indicate that the parameters precision, linearity, accuracy, and quantitation limit can be shown once for system suitability in the scope of the validation. Otherwise the General Chapter might be interpreted as a requirement for each release testing. Regarding the practical performance of analytical release testing, it is not possible to include these parameters in each system suitability testing.
Response: Comment partially incorporated. The Expert Committee added the caveat "as appropriate."
Comment Summary #10: The commenter indicated that ±0.50 m/z mass accuracy may not be adequate, because ±0.50 is not sufficient for quantitation and recommend a value of ±0.20.
Response: Comment not incorporated. The Expert Committee determined that while tighter criteria can be achieved on many instruments, it is not necessary for quantitative analysis when a modest deviation from ideal mass accuracy can be taken into account by using a known reference standard–the exact target analyte–to set up the method.
Comment Summary #11: The commenter suggested including one or two examples in the accuracy section for when quality control (or check) samples may also be appropriate for inclusion in the procedure.

Response: Comment not incorporated. The Expert Committee determined that it was not essential to add an example. The wording is only meant to highlight the option that it may be appropriate to include quality control samples.
Comment Summary #12: The commenter indicated that the *Quantitative Limit* section should focus on limits of validated range (demonstrated by accuracy and precision) rather than discussion on limit tests and signal-to-noise ratio requirements.
Response: Comment not incorporated. The Expert Committee determined that accuracy and precision criteria were adequately described in the *System suitability* section.

Qualification of Mass Spectrometry Instruments, Operational Qualification
Comment Summary #13: The commenter suggested revising the following phrase to state, "MS instruments should be qualified against target specification for the intended application ***or manufacturer specifications if suitable***," instead of "not simply the specifications supplied by the manufacturer."
Response: Comment not incorporated. The Expert Committee determined that while manufacturer specifications may work in some cases, the intended purpose is always the driver.

Qualification of Mass Spectrometry Instruments, Performance Qualification
Comment Summary #14: The commenter indicated that the sentence, "Method-specific PQ tests, also known as system suitability tests, may be used in lieu of PQ requirements for validated procedures" implies that PQ is used to prove the instrument functions properly after certain intervals, and that system suitability is used to prove that a specific instrument, at a specific time point, is capable of correctly analyzing a specific product. Therefore, it appears that the statement would only be true when both sets of tests were the same, which appears to conflict the purpose of each test, PQ for the instrument, and, SS for the product). Validation of the procedure typically is different from PQ's proving that an instrument is working properly at different intervals in time (e.g., every 6 months). If a PQ and SS test were exactly the same, then the results could be used to show that the instrument is running properly and is capable on that day to run a specific product. Assuming the PQ and SS were the same, SS results might be utilized as a part of a validation; however, one would hope a method was validated well in advance of running actual samples with released results.
Response: Comment not incorporated. The system suitability test is not positioned as a test to be performed on the same frequency as a separate PQ test (e.g. 6 months). The system suitability test would be performed prior to use, each time the validated method were executed.
Comment Summary #15: The commenter recommend revising the text as follows for clarity, "Periodic PQ calibration or verification should include a subset of the OQ...Depending on typical use, ~~the specifications for PQ~~ specification criteria may be ~~higher or lower than the manufacturer's installation specifications~~ more or less stringent depending on end user needs
Response: Comment not incorporated. "PQ" is the standard language utilized in USP General Chapters. The Expert Committee determined that these changes were not necessary.

Comment Summary #16: The commenter recommended revising the section to clarify the intent of “Periodic PQ” as compared to “system suitability.” As currently presented, the “Periodic PQ” definition and intent are lost and intertwined with the term “system suitability” intent. Periodic PQ is intended for general system qualification activities, and “system suitability” is used to show that the system is acceptable for a particular defined test/analysis.”
Response: Comment not incorporated. The system suitability test is not positioned as a test to be performed on the same frequency as a separate PQ test (e.g. 6 months). The system suitability would be performed prior to use, each time the validated method were executed.
Comment Summary #17: The commenter indicated that PQ in the sentence, “For qualitative applications, the PQ experiment includes a check of the mass accuracy of the instrumentation,” would be identical to a daily mass accuracy check of the instrument or what is sometimes called a “check tune.” The commenter suggested discussing this as part of the PQ assessment, because if this “check tune” does not meet prescribed mass accuracy the instrument parameters are typically “re-tuned” to meet the mass accuracy needed.
Response: Comment not incorporated. Each instrument manufacturer may call the PQ experiment something different. The Expert Committee determined that the sentence as written is appropriate.

VALIDATION AND VERIFICATION OF MASS SPECTROMETRY ANALYTICAL PROCEDURES
Expert Committee-Initiated Change #2: The sentence, “The required validation performance characteristics of an MS analytical procedure are listed in Table 1,” was replaced with the following sentences, “The required validation performance characteristics of an MS analytical procedure, assuming the typical Category 1 USP specifications of 98.0-102.0% for drug substance and 95.0-105.0% for drug product, are listed in Table 1. The actual validation performance characteristics would be dependent upon the specifications in place and should provide sufficient evidence that the measurement capability is sufficient for those specifications.” The Expert Committee determined that the criteria presented in Table 1, particularly those for accuracy and precision, are designed to provide assurance of minimum procedure capability for the various monograph acceptance criteria. The criteria presented in Table 1 are consistent with the criteria used for the validation of chromatographic procedures. Procedures applying mass spectrometry may not be capable of meeting these criteria (Table 1). Public comments on previously published spectroscopy general chapters have raised similar issues. Although certain spectroscopic method limitations (by comparison with the proposed acceptance criteria) undoubtedly exist, the absolute need for appropriate procedure capability has been given precedence in the establishment of the criteria. From a practical viewpoint, these limitations may preclude the use of a given spectroscopic method for a specific application. In rare instances, only one spectroscopic method can be used for a given quality attribute, and the criteria (Table 1) cannot be met; however, these instances are indeed the exception rather than the rule and will be managed accordingly.

Comment Summary #18: The commenter indicated that it is unclear how the proposed General Chapter should be applied to MS used as detection system for GC and HPLC. In those cases they indicated that the ICH documents on "Validation of Analytical Procedures" and General Chapter<1225> should be applied and should prevail.
Response: Comment not incorporated. The Expert Committee determined that the use of MS as a detection system is included in the scope of this General Chapter.
Comment Summary #19: The commenter indicated that for “quantitative determination of impurities (Category II)”, mass spectrometry tests may be an additional test for genotoxic impurities at the trace (ppb to ppm) level based on new guidance by *EMEA/CHMP/QWP/251344/2006.*
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data.

Table 1. Analytical Measurement Requirements
Comment Summary #21: The commenter recommended revising Table 1 to reflect limit tests, because mass spectrometry methods are often used to achieve specificity and or sensitivity when more conventional techniques cannot and these are often limit tests. The table currently reflects routine quantitative analyses, which are not typical.
Response: Comments not incorporated. The Expert Committee determined that the limits proposed are appropriate. See Expert Committee-Initiated Change #2.
Comment Summary #22: The commenter asked for clarification of the term rNLT
Response: Comment incorporated. The phrase “correlation coefficient (R) must not be less than (NLT)…” was added.
Comment Summary #23: The commenter recommended changing the range requirement for Category I to +/- 20% to be consistent with 100% centered, because often 85% to 115% is acceptable.
Response: Comment not incorporated. The Expert Committee determined that the limits are appropriate. See Expert Committee-Initiated Change #2.
Comment Summary #24: The commenter requested to change the range requirement for Category II tests to 50-150%, because impurity levels often vary with a larger range.
Response: Comment not incorporated. The Expert Committee determined that the limits are appropriate. See Expert Committee-Initiated Change #2.
Comment Summary #25: The commenter suggested that the Range criteria under Category II be clarified, because it is not clear what this range refers, only that it relates to impurities.
Response: Comment not incorporated. The range is relative to Category II tests as stated in General Chapter <1225>. See Expert Committee-Initiated Change #2.
Comment Summary #26: The commenter indicated that the accuracy criteria for Category I tests are too tight for MS quantitation, because accuracy will depend on MS response and may still have poor response, even if it is the main component, and suggested a +/- 10% for drug substance and drug product.
Response: Comment not incorporated. The Expert Committee determined that the limits are appropriate and noted that if these criteria cannot be met, then MS is not the appropriate technique to employ.

Comment Summary #27: The commenter suggested that the repeatability criteria for Category I tests are too tight for MS response and suggested a NMT 10% for drug substance and drug product.
Response: Comment not incorporated. The Expert Committee determined that the limits are appropriate. See Expert Committee-Initiated Change #2.
Comment Summary #28: The commenter indicated that the intermediate precision criteria for Category I tests are too tight for MS response and suggested a NMT 15% for drug substance and drug product.
Response: Comment not incorporated. The Expert Committee determined that the limits are appropriate. See Expert Committee-Initiated Change #2.
Comment Summary #29: The commenter indicated that the intermediate precision criteria for Category II tests are too tight.
Response: Comment not incorporated. The Expert Committee determined that the limits are appropriate. See Expert Committee-Initiated Change #2.
Comment Summary #30: The commenter suggested including criteria on limit and Category IV tests.
Response: Comment partially incorporated. See Expert Committee-Initiated Change #2
Comment Summary #31: The commenter suggested that the column headers could be clearer.
Response: Comment not incorporated. The definitions are made clear for the intended purpose in General Chapter <1225>.
Comment Summary #32: The commenter recommend adding a separate table, similar to Table 1, specifically for biologics, or eliminating Table 1 altogether and instead make specific reference to other USP General Chapters for small molecules and biologics requirements, because Table 1 makes no reference to possible differences between small molecules and biologics and does not reflect the wider acceptance criteria of biologics.
Response: Comment not incorporated. The Expert Committee determined that large molecules will have to be addressed on a case-by-case basis, making it difficult to provide a meaningful table. The submitter can make their justifications in their monograph submissions on a case by case basis. The Expert Committee will take the comment under consideration for future updates to the General Chapter.
Comment Summary #33: The commenter suggested changing the linearity requirement for Category II test to correlation coefficient NLT 0.98.
Response: Comment not incorporated. The Expert Committee determined that the criterion is appropriate. See Expert Committee-Initiated Change #2
Comment Summary #34: The commenter indicated that Table 1 should include stability requirements as a category, because there is a section at the end of this General Chapter that mentions solution stability.
Response: Comment not incorporated. The Expert Committee determined that the stated criteria are appropriate. See Expert Committee Change #2.
Comment Summary #35: The commenter indicated that the acceptance criteria listed in Table 1 are very strict for mass spectrometry, because they are stricter than HPLC-UV methods and will be difficult to meet them all for all Category I.

Response: Comment not incorporated. The Expert Committee determined that the criteria are driven by the general validation criteria and not by the technique. See Expert Committee-Initiated Change #2.

Section: Analytical Procedure Validation
Comment Summary #36: The commenter indicated that the statement "These (Robustness tests) can include measuring the stability of the analyte under specified storage or ionization conditions" should also include appropriate chromatographic conditions, such as flow rate, mobile phase composition, etc.
Response: Comment incorporated.

General
Comment Summary #37: The commenter requested combining this General Chapter with General Chapter <1736> Applications of Mass Spectrometry as the information in both General Chapters is applicable to the Mass Spectrometry.
Response: Comment not incorporated. The Expert Committee followed the strategy developed and published in a Stimuli Article "An Alignment of Concepts and Content across the Spectroscopy General Chapters in the United States Pharmacopeia–National Formulary (USP–NF)"; *Pharmacopeia Forum* 40(1) [Jan.–Feb. 2013].
Comment Summary #38: The commenter indicated that the General Chapter titles for <1736> and <736> appear to be mismatched, because more general MS information is provided in the applications General Chapter <1736> than in General Chapter <736>, and the qualitative and quantitative analysis and expected system suitability and criteria in <736> should be included in <1736>
Response: Comment not incorporated. The Expert Committee determined that the content and concepts are aligned with the strategy discussed in the Stimuli Article "An Alignment of Concepts and Content across the Spectroscopy General Chapters in the United States Pharmacopeia–National Formulary (USP–NF)"; *Pharmacopeia Forum* 40(1) [Jan.–Feb. 2013].

General Chapter/Section(s): <741> Melting Range or Temperature/Procedures
Expert Committee(s): General Chapters—Physical Analysis
No. of Commenters: 2

Comment Summary #1: The commenters proposed removing the sample height requirement for tests performed with Apparatus II and replacing it with a statement indicating that the vendor recommendations for sample height should be followed, based on differences in the design of the heating block and optical (or other) detection system, and in order to avoid impact in the accuracy of the measurement.
Response: Comment incorporated. A nominal height of 3 mm is now prescribed, and a new statement is incorporated stating that, "Due to the instrument design, alternative sample sizes may be instructed by the instrument manufacturer."

General Chapter/Section(s): <781> Optical Rotation/Multiple Sections
Expert Committee(s): General Chapters—Physical Analysis
No. of Commenters: 1

Introduction

Expert Committee-Initiated Change #1: The definitions of dextrorotatory and levorotatory (optical isomers) were updated for clarity.

General

Comment Summary #1: The commenter requested the usage of the suffix "^{0}C" for all references to temperature, because the use of "^{0}" is also used to reference optical rotation and may cause confusion.
Response: Comment incorporated.
Comment Summary #2: The commenter recommended adding a footnote clarifying that all references of wavelengths are in vacuum. The sodium D line is 589.44 in vacuum and 589.3 in air.
Response: Comment incorporated.

Introduction

Comment Summary #3: The commenter suggested replacing the reference to the wavelength of 578 nm, because there are no monographs that have this optical rotation and it is very close to 589 nm, the standard wavelength used by most monographs. In lieu of 578 nm, the commenter recommended mentioning 325 nm, because some monographs make reference to this wavelength.
Response: Comment incorporated.
Comment Summary #4: The commenter requested keeping the contact data of the unique supplier of NIST traceable quartz calibration standards.
Response: Comment incorporated. A revised footnote was reintroduced.

Procedures

Comment Summary #5: The commenter recommended the removal of the requirement of a 1.0-dm tube, because there are monographs that use other lengths.
Response: Comment not incorporated. The General Chapters states "unless otherwise directed" to accommodate exceptions. The majority of monographs use a 1.0-dm tube.
Comment Summary #6: The commenter recommended removing the temperature requirement of 25^{0}C, because there are monographs stating different temperatures for measurement.
Response: Comment not incorporated. The General Chapter states "unless otherwise directed" to accommodate exceptions. The standard temperature for both optical rotation and specific rotation measurements is 25^{0}C.

General Chapter/Section(s): <791> pH/Multiple Sections
Expert Committee(s): General Chapters—Chemical Analysis
No. of Commenters: 7

General

Comment Summary #1: The commenter recommended using the international terminology outlined in *ISO Guide 99 International Vocabulary of Metrology*.
Response: Comment not incorporated. This recommendation requires a thoughtful evaluation and, if it is accepted would require change in all of the USP standards for consistency. The Expert Committee will consider it in future revisions to the general chapters.

Instrument Requirements

Comment Summary #2: The commenter requested clarifying the requirement for the accuracy of the temperature measurement system from "at least 1^0C" to "$\pm1^0$C."
Response: Comment incorporated.
Comment Summary #3: The commenter requested clarifying the requirement of the resolution of the temperature measurement system from "at least 0.1^0C" to "not more than 0.1^0C."
Response: Comment not incorporated. The Expert Committee finds the current wording of this statement to be sufficient.

Comment Summary #4: The commenter suggested harmonizing the temperature for measurements with the *Eur.Ph.* to be 20-25^0C instead of the current 25 ± 2^0C.
Response: Comment not incorporated. This is not a fully harmonized document. The calibration requirements are harmonized within Table 2. However, the current text is more flexible than *Eur.Ph.* regarding temperature by stating that"… temperatures outside this range are acceptable…" For example, a testing criteria defined by the user to be 25 ± 2^0C satisfies both USP and *Eur.Ph.* specifications.
Comment Summary #5: The commenter suggested revising the note on challenges in applying non-aqueous systems to pH measurements based on systems standardized to aqueous buffers from "… nonaqueous solutions or (any) suspensions…" to "… nonaqueous systems…" to generalize the application.
Response: Comment incorporated.

Measurement System

Expert Committee-Initiated Change #1: The title of the section was changed to: "Buffer Solutions for Standardization of the pH Measurement System," to describe the content of the section more accurately.

Comment Summary #6: The commenter requested that a wider labeled accuracy, than ±0.02 pH units, be considered for buffer solutions greater than pH 12, because there are no such buffer solutions commercially available.
Response: Comment not incorporated. There are several commercially available buffer solutions greater than pH 12 in compliance with the specification of ±0.02 pH units.
Comment Summary #7: The commenter suggested stating that for buffer solutions lower than pH 11, only prepared buffers and not commercially available buffers can be used.
Response: Comment not incorporated. The Expert Committee did not find it necessary to dictate whether the pH buffer solutions shall be self-prepared or commercially supplied.
Comment Summary #8: The commenter suggested the addition of a pH 7.01 buffer solution in Table 2, because it is one of the most common pH buffer solutions used for standardization.
Response: Comment not incorporated. There is potential difficulty in the traceability of the precise weight of sodium hydroxide into a phosphate salt during the preparation of the pH 7 buffer, due to the hygroscopic nature of the sodium hydroxide. pH 7.01 buffer solution has not been listed in *USP* or *Eur.Ph*. pH buffer solutions. NIST offers many pH buffer Certified Reference Materials, but they do not offer one at 7.0 pH.

Calibration
Comment Summary #9: The commenter recommended clarifying whether the temperature at which the calibration is performed should be concordant with the temperature of subsequent sample measurements.
Response: Comment not incorporated. The sample should be prepared according to the specific monograph instructions, if any. There is no requirement in <791> to assure that the temperatures of the calibration buffer solutions and the sample(s) need to be the same (or close). The user shall determine the sample temperature.
Comment Summary #10: The commenter requested adding the provision “preferably” in the selection of buffer solutions for standardization in order to provide more flexibility, and consistency with the footnote for the use of other buffers. This change is also consistent with the language in the *Eur.Ph.*
Response: Comment incorporated.
Comment Summary #11: The commenter requested clarifying that pH values should be linearly interpolated as a function of temperature, according to Table 2, where the calibration temperature falls at values intermediate of the 5^0C data intervals provided.
Response: Comment incorporated. A new sentence was added in the Calibration section, item 4 for temperatures not included in Table 2.

Comment Summary #12: The commenter requested clarifying that automatic temperature compensation is a feature that only applies to calibration.
Response: Comment partially incorporated. The temperature compensation (for Nernst equation) can be performed manually or automated during the calibration and operation. A new sentence was added in the introduction of the Operation section.
Comment Summary #13: The commenter recommended clarifying the text to perform offset verification after the first calibration point to allow application to more pH meters within the scope.
Response: Comment not incorporated. The offset and slope can only be measured after the 2-point calibration process is completed.
Comment Summary #14: The commenter requested reviewing the acceptable requirement of the range for slope of the two point calibration of 95-105% to 90-100%.
Response: Comment partially incorporated. The acceptable slope range was changed to 90-105%.
Comment Summary #15: The commenter suggested changing the slope and offset to be defined by the user of the pH meter, because the acceptable range depends on the use of the pH meter.
Response: Comment not incorporated. Reasonable acceptance criteria for the pH sensor are necessary. The Expert Committee determined that the values for the slope (90-105%) and offset (0.5 pH units) represent highly tolerant criteria.

Operation
Comment Summary #16: The commenter requested stating to record both the pH and the temperature of the sample in situations where it is not practical to measure at 25^0C.
Response: Comment incorporated.

General Chapter/Sections: <1115> Bioburden Control in Nonsterile Drug Substances and Products
Expert Committee: General Chapters—Microbiology
No. of Commenters: 9
Comment Summary #1: The commenter suggested adding prevention of microbial ingress as an additional consideration for product quality.
Response: Comment incorporated.

Comment Summary #2: The commenter suggested revising the text relating bioburden levels lower than those recommended in <1111> to microbial toxins, as they are unlikely to pose a risk from microbial toxins or infections.
Response: Comment incorporated.
Comment Summary #3: The commenter suggested revising or deleting the sentence, “The products themselves are sterile or harbor a low population of microorganisms.” This is misleading as sterile products by definition should harbor no living organisms.
Response: Comment incorporated.

Comment Summary #4: The commenter suggested adding a statement about applicability to biotech drug substances, which although nonsterile, in almost all cases, are used to manufacture sterile products.
Response: Comment not incorporated. The statement is already included within the scope of the General Chapter; therefore, explicit mention is not needed.
Comment Summary #5: The commenter suggested removing the term “frank” to qualify pathogenicity.
Response: Comment incorporated.
Comment Summary #6: The commenter suggested changing the term “microbial hazard” to “microbial contamination risk” in the context of susceptibility of nonsterile pharmaceutical products.
Response: Comment incorporated.
Comment Summary #7: The commenter indicated that the General Chapter should also include processing steps and hold periods that could result in changes in the bioburden in the context of susceptibility of nonsterile pharmaceutical products.
Response: Comment incorporated.
Comment Summary #8: The commenter suggested that the General Chapter should also indicate that risk can arise where microorganism are able to proliferate to sufficient numbers and that this is an objectionable condition.
Response: Comment incorporated.
Comment Summary #9: The commenter suggested revising the sentences that relate to proliferation of microorganisms and the associated risks to both patient (from toxins) and product (therapeutic properties).
Response: Comment incorporated.
Comment Summary #10: The commenter suggested including all relevant sections in the *Code of Federal Regulations* relative to objectionable microorganisms/conditions.
Response: Comment incorporated.
Comment Summary #11: The commenter suggested including microbiological attributes of in-process intermediates to the list of points to be considered to assess the potential risk associated with nonsterile drug product manufacturing.
Response: Comment incorporated.
Comment Summary #12: The commenter suggested modifying the bullet point “age and probable general health of intended recipients of the drug product,” to state “main target population to which the product is delivered (e.g. Neonates, immune compromised patients, etc.)," because it is almost impossible to track precisely for products which are given to a high variety of patients (e.g. Ibuprofen, Aspirin).
Response: Comment incorporated. The statement was changed to, “population to which the product is delivered.”
Comment Summary #13: The commenter suggested revising objectionable facility conditions to include conditions that favor microbial ingress and proliferation.
Response: Comment incorporated.
Comment Summary #14: The commenter suggested deleting reference to product recalls as it relates to factors contributing to microbial contamination and revising the term “risk factors” to “factors,” because this does not relate to risk assessment
Response: Comment incorporated.

Comment Summary #16: The commenter suggested revising the term “process water” to “water used in active ingredient manufacturing, formulation, cleaning and housekeeping” under *Water Systems and Use*.
Response: Comment incorporated.
Comment Summary #17: The commenter indicated molds generally do not grow in purified water.
Response: Comment incorporated. The sentence revised to indicate some molds can grow.
Comment Summary #18: The commenter recommended revising or deleting the phrase "stand in pools or puddles," because it is not clear.
Response: Comment incorporated.
Comment Summary #19: The commenter suggested inclusion of assessment for likely contamination or proliferation risk of ingredients and excipient as important in the reduction of microbial risk associated with these materials
Response: Comment incorporated.
Comment Summary #20: The commenter suggested including a reference to those processes at higher risk of contamination, i.e., synthetic processes with aqueous isolation steps or open processing, and biological processes with no downstream chemistry or defined microbial removal step.
Response: Comment incorporated.
Comment Summary #21: The commenter suggested clarifying the term “compounding” in the context of its use.
Response: Comment incorporated.
Comment Summary #22: The commenter suggested clarifying the phrase "labeled with respect to microbiological status."
Response: Comment incorporated.
Comment Summary #23: The commenter indicated that the sentence that refers to method suitability is confusing and should be deleted.
Response: Comment incorporated
Comment Summary #24: The commenter suggested defining or replacing the less commonly term “Modern Microbiological Methods” with a more commonly used terminology.
Response: Comment incorporated. The term was replaced with the term “Alternate Microbiological Methods.”
Comment Summary #25: The commenter indicated that the sentence that refers to the quality of gowns is unclear and needs clarification
Response: Comment incorporated.
Comment Summary #26: The commenter indicated that while equivalence may be of little relevance in the context of usage of alternate methods, it is important that test methods deliver valid and meaningful results.
Response: Comment incorporated.
Comment Summary #27: The commenter suggested revising the term “intensity” with “frequency” in the context of sampling sites for monitoring.
Response: Comment incorporated.
Comment Summary #28: The commenter suggested replacing the phrase microbiological “contamination potential” with microbiological “contamination risk.”

Response: Comment incorporated.
Comment Summary #29: The commenter suggested inclusion of facility design in risk analysis.
Response: Comment incorporated.

General Chapter/Section(s): <1151> Pharmaceutical Dosage Forms/ Multiple Sections
Expert Committee: General Chapters—Dosage Forms
No. of Commenters: 2
Comment Summary #1: The commenter indicated that dose uniformity can be demonstrated by other appropriate assays in addition to a chemical assay.
Response: Comment incorporated.
Comment Summary #2: The commenter requested deletion of the proposed change to the definition of a capsule as possibly having drug coating on the capsule shell.
Response: Comment not incorporated. The Expert Committee found that a capsule may have a drug as a coating.
Expert Committee-Initiated Change #1: The subsection under specific dosage forms giving typical information on preparation or manufacture will be uniformly named as Preparation. The Expert Committee finds the term preparation to be more general than manufacture and will use it for the title of these subsections. Changes were made under Lozenges and Ointments, both of which can be produced (prepared) by a pharmacist.

General Chapter/Section(s): <1181> Scanning Electron Microscopy
Expert Committee: General Chapters—Physical Analysis
No. of Commenters: 2
Comment # 1: The commenter requested adding a recommendation to use traceable reference standards as a verification that the system is functioning properly in the X-Ray Generation and Elemental Compositional Analysis section.
Response: Comment incorporated.
Comment # 2: The commenter indicated that Figure 4. Decision Tree for SEM Sample Preparation would be easier to read if it was clearer and larger.
Response: Comment incorporated.
Comment # 3: The commenter suggested that in Figure 2. Interaction Diagram, the letter “X” be used instead of “XRE,” which is the abbreviation used in the table prior to this diagram. In addition, the commenter suggested defining the abbreviation “PE” used in the diagram and labeling the greyed out areas under the surface of the sample.
Response: Comment incorporated.
Comment # 4: The commenter indicated that the statement “Crystalline particles can be transparent to the electron beam” in the *Shape analysis* sub-section is problematic, because many things are transparent and transparency may be increased if the molecular weight is very similar to the background stub.
Response: Comment incorporated.
Comment # 5: The commenter indicated that the reference to Figure 1 under *Sample Preparation* is incorrect, because there is no example of a sample stub in this version of the General Chapter.
Response: Comment incorporated. The reference was deleted.

General Chapter/Sections: <1229.6> Liquid Phase Sterilization
Expert Committee: General Chapters—Microbiology
No. of Commenters: 6

Comment Summary #1: The commenter suggested clarifying the scope of the General Chapter and providing examples to indicate if this chapter is about liquid chemical sterilants, equipment for processing, or something else.
Response: Comment not incorporated. This General Chapter is part of a series of chapters on sterilization processes using different technologies. There is no need for a specific scope for this General Chapter.
Comment Summary #2: The commenter suggested deleting the sentence that indicates that chemical agents are capable of destroying bacteria and fungi, including both vegetative cells and spores in a quantitative fashion.
Response: Comment not incorporated. References were added from literature to support the statement.
Comment Summary #3: The commenter suggested simplifying the statement which indicates that in chemical sterilization it is customary to include the agent's removal in the overall process and also avoid recontamination.
Response: Comment incorporated.
Comment Summary #4: The commenter suggested revising the statement on the sterilizing property of liquid chemicals to indicate or emphasize that this occurs in aqueous solutions.
Response: Comment incorporated.
Comment Summary #5: The commenter suggested removing the examples of both glutaraldhyde and formaldehyde, because these are not appropriate for use in the pharmaceutical industry.
Response: Comment not incorporated. The Expert Committee indicated that these agents are still used. This document only addresses the scientific aspects of sterilization and the majority of these agents are highly toxic to humans.
Comment Summary #6: The commenter suggested deleting the statement that indicates adequate humidity in sterilization is assured by use in aqueous solution, since this is obvious.
Response: Comment incorporated.
Comment Summary #7: The commenter suggested revising the statement about other factors that affect sporicidal activity by replacing the term "sporicidal" with "antibacterial."
Response: Comment incorporated.
Comment Summary #8: The commenter stated that the statement about the choice of biological indicators is too broad and suggested providing references from literature.
Response: Comment not incorporated. The document identifies two different Bacilli as possible biological indicators.
Comment Summary #9: The commenter suggested adding contact time to the list of variables for liquid chemical sterilants.
Response: Comment incorporated.
Comment Summary #10: The commenter suggested adding container closure integrity to the list of factors to be considered by the manufacturer when selecting the appropriate liquid chemical sterilant.

Response: Comment incorporated.
Comment Summary #11: The commenter suggested revising wording to indicate that the half cycle approach supports a theoretical reduction of the biological indicators to at least 10^{-6}.
Response: Comment incorporated.
Comment Summary #12: The commenter suggested deleting Figure 2, because it I unclear/confusing.
Response: Comment incorporated.
Comment Summary #13: The commenter suggested clarifying that penetration of sterilant into needle lumens, closely fitted parts, and porous materials should be confirmed.
Response: Comment incorporated.
Comment Summary #14: The commenter suggested revising the section on *Biological Indicators* to suggest that manufacturers place indicators within loads at locations based on risk assessment, rather than visual examination.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the General Chapter upon the receipt of the necessary supporting data.
Comment Summary #15: The commenter suggested clarifying which of the criteria in routine process control applies to liquid chemical sterilization, because there is no FDA guideline on this topic.
Response: Comment not incorporated. The routine process controls are universal for all methods.

General Chapter/Section(s): <1240> Virus Testing of Human Plasma for Further Manufacture/Multiple Sections
Expert Committee(s): General Chapters—Biological Analysis
No. of Commenters: 1
Comment Summary #1: The commenter requested that the General Chapter also include testing for Syphilis, Chagas, Dengue, and similar categories of diseases caused by bacteria, spirochetes, or parasites on plasma for further manufacture.
Response: Comment not incorporated. This General Chapter focuses on virus testing and the Expert Committee determined that the requested additions were beyond the scope.

Introduction
Comment Summary #2: The commenter requested adding a reference to General Chapter <1180> after the bulleted list item describing manufacturers' strategies to minimize the risk of virus transmission by plasma-derived products.
Response: Comment incorporated.
Comment Summary #3: The commenter requested adding the underlined text to the sentence: "Virus transmission is a major public safety concern, because infections with these highly pathogenic viruses typically progress to chronicity."
Response: Comment incorporated.
Comment Summary #4: The commenter requested modifying the sentence with the underlined text: "Other permanent or temporary donor-deferral criteria are in place to avoid donations from potentially infected donors based on the epidemiological

surveillance of a country, or region or donor population for transfusion-transmissible infections relevant to the safety of blood components."
Response: Comment incorporated.
Comment Summary #5: The commenter requested clarifying the sentence that states, "such as anti-HCV or anti-HIV antibodies" to specify that anti-HIV testing is for both HIV-1 and HIV-2.
Response: Comment incorporated.
Comment Summary #6: The commenter requested adding the underlined text to the sentence: "There is a finite time period, known as the window period, between the infection of a donor and the time at..."
Response: Comment incorporated.
Comment Summary #7: The commenter requested adding the sentence: "The recommended limit for viral load of B19V DNA in the manufacturing plasma pool should not exceed 10^4 IU/mL (see FDA Guidance for industry cited in the Appendix)."
Response: Comment not incorporated. This information is already discussed earlier in the text.
Comment Summary #8: The commenter requested adding the underlined text to the sentence, "Testing of the plasma donations, at the individual or minipool level, and the fractionation pools are two of the elements that manufacturers put into place to maintain the safety margins of these products."
Response: Comment incorporated.
Comment Summary #9: The commenter requested adding the underlined text to the sentence, "The high sensitivity of NAT tests also allows earlier virus detection compared to an antigen- or antibody-based test, thereby reducing the average length of the window period donations."
Response: Comment incorporated.
Comment Summary #10: The commenter requested adding the underlined text to the sentence, "Nevertheless, manufacturing of plasma-derived products also includes dedicated steps designed solely to inactivate (e.g., by solvent-detergent treatment) or remove (e.g., by virus filtration) potential viral contaminants"
Response: Comment incorporated.

Introduction and Appendix
Comment Summary #11: The commenter requested adding the reference "Adherence to Good Manufacturing Practices at all levels of the production process as a strategy to reduce risk of virus transmission (see *GAO-HEHS-98-205, 21 CFR Part 606*, and *WHO Technical Report Series 941* cited in the Appendix)" to the bulleted list in the Introduction and adding these new references to the *Appendix.*
Response: Comment incorporated.

Rationale for Virus Testing Of Plasma for Further Manufacture
Comment Summary #12: The commenter requested adding the underlined text and a new reference to the *Appendix* in the sentence, "Instead, in-process NAT testing is performed ~~done~~ to interdict high-titer donations and thereby limit the B19V load in the manufacturing pool (see *EMEA/CPMP/BWP/5180/03* cited in the Appendix)."

Response: Comment partially incorporated. The term “NAT" was added, but the Expert Committee did not think the underlined text benefited the General Chapter and the requested reference is sufficiently covered in other parts of the General Chapter.
Comment Summary #13: The commenter requested adding the underlined text to the sentence, "The B19V neutralizing antibodies present in a plasma pool and the validated virus reduction steps included in the manufacturing process ensure..."
Response: Comment incorporated.
Comment Summary #14: The commenter requested adding the underlined text to the sentence, "However, in the United States, the Food and Drug Administration (FDA) recommends WNV NAT testing for blood and blood components for transfusion because of the epidemiological situation and the risk of WNV transmission by blood components (see FDA Guidance for industry cited in the Appendix).” and the new reference to the Appendix: “*FDA Guidance for industry*: use of nucleic acid tests to reduce the risk of transmission of West Nile Virus from donors of whole blood and blood components intended for transfusion.”
Response: Comment incorporated.

Regulatory Environment
Comment Summary #15: The commenter requested adding the underlined text to the sentence, "For HIV and HCV, the procedure includes not only the quarantine and destruction of unused, previously donated units from an infected donor, but also the further testing of the donor and notification of the recipients of the blood and blood components (*21 CFR 610.47-48*).”
Response: Comment incorporated.
Comment Summary #16: The commenter requested revising the text as shown, "Additional tests and specifications for plasma for further manufacture have been developed as a ~~voluntary industrial standard by~~ part of the Plasma Pro~~duc~~tein Therapeutics Association (PPTA) Voluntary Standards Program. The PPTA Quality Standards of ~~or~~ Excellence, Assurance, and Leadership (QSEAL) includes requirements for additional routine testing of blood and plasma donations or plasma pools for HCV RNA, HIV RNA, HBV DNA, HAV RNA, and B19V DNA.”
Response: Comment incorporated.

Table 3
Comment Summary #17: The commenter requested adding the underlined text to the second column of the table, "Required with a manufacturing pool limit of ≤ 10^4 IU/mL B19V DNA” and in column 3 for B19V: “Required for specific products (anti-D immunoglobulin and pooled S/D-treated plasma); a manufacturing pool limit of B19V DNA ≤ 10^4 IU/mL is required. This limit is voluntarily implemented by most plasma fractionators for all products.”
Response: Comment incorporated.

Conclusions
Comment Summary #17: The commenter requested adding the underlined text to the second column of the table, "Both manufacturers and regulators face continuing

challenges, because of the emergence of new blood-borne viruses, mutants, and variants of existing viruses not detected by current serological/NAT technology."
Response: Comment incorporated.

General Chapter/Section(s): <1234> Vaccines for Human Use-- Polysaccharide and Glycoconjugate Vaccines/Multiple Sections
Expert Committee(s): General Chapters—Biological Analysis
No. of Commenters: 1

Key Quality Parameters for Activated Intermediates, Degree of Activation of Activated Polysaccharides subsection
Comment Summary #1: The commenter requested a correction to the sentence, "Residual unconjugated linker that could interfere with subsequent steps should be controlled via measurement or process validation," because the testing is not appropriate for this intermediate prior to conjugation.
Response: Comment incorporated. The sentence was omitted and replaced with the sentence, "In cases where the activated polysaccharide is conjugated without isolation, consistency in the degree of polysaccharide activation may also be demonstrated as part of process validation or reflected by characteristics of the final conjugate bulk."

Key Quality Parameters for Activated Intermediates, Degree of Activation of Activated Carrier Protein subsection
Comment Summary #2: The commenter requested a correction to the sentence, "In a validated process where production consistency has been established, and depending on the conjugation chemistry used and the results of clinical trials, testing may be used as an in-process control." because the testing is not appropriate for this intermediate prior to conjugation.
Response: Comment incorporated. The sentence was omitted and replaced with the sentence, "Depending on the conjugation chemistry used (i.e., immediate conjugation after activation), consistency in degree of carrier protein activation may also be demonstrated as part of process validation or reflected by characteristics of the final conjugate bulk.
Expert Committee-Initiated Change #1: Table 1 was corrected by removing the X's in the hexosamine column for Men A, Y, and W, and removing the X's in the total sugar column for Men C.
Expert Committee-Initiated Change #2: Table 2's glycosylation nomenclature was updated from NeuNAc to Neu5Ac for consistency and to harmonize with General Chapter <1084>'s terminology.

General Chapter/Section(s): <1736> Applications of Mass Spectrometry/Multiple Sections
Expert Committee(s): General Chapters—Chemical Analysis
No. of Commenters: 7

Section 1. Introduction
Comment Summary #1: The commenter indicated that mass spectrometers measure mass and not weight.
Response: Comment incorporated
Comment Summary #2: The commenter suggested replacing "(Identification test)" with structural elucidation.
Response: Comment not incorporated. The Expert Committee will consider further revisions to the monograph upon the receipt of supporting data.
Comment Summary #3: The commenter suggested that comparison of a mass spectrometer to an analytical balance is misleading.
Response: Comment incorporated. The sentence was removed.
Comment Summary #4: The commenter suggested that the sentence "Molecular weight thus can become a surrogate for confirmation…" does not deliver adequate certainty unless minimally accurate mass is employed.
Response: Comment not incorporated. The Expert Committee determined that the passage does not specify that molecular mass is the only identification criteria.

Section 2. Mass Spectrometers
Comment Summary #5: The commenter suggested revising the sentence**:** **"…**represented in a graphic representation of mass-to-charge ratio (m/z) versus intensity" to change the order of intensity and mass-to-charge ratio.
Response: Comment not incorporated. The Expert Committee determined that the change would not enhance the meaning and understanding of the General Chapter**.**
Comment Summary #6: The commenter suggested deletion of "from low mass ions to high" in the sentence: "Regardless of type, the mass analyzer separates ions according to the m/z, from low mass ions to high."
Response: Comment incorporated.
Comment Summary #7: The commenter suggested deletion of the phrase, " … a survey of ions generated in the ion source" from the sentence "The mass analyzer continuously acquires data across a predefined range of masses to generate the resulting mass spectra, a survey of ions generated in the ion source."
Response: Comment incorporated.
Comment Summary #8: The commenter suggested deleting sample preparation and chromatography from the processes typical of MS measurements as they are specific to liquid or gas chromatographic procedures and not mass spectrometry procedures.
Response: Comment partially incorporated. The Expert Committee determined that this statement is appropriate in the *Overview* section and that the edits made to the *Layout* section were sufficient to address this comment.
Comment Summary #9: The commenter suggested that fragmentation ions generated during an MS/MS experiment be included as a source of ions in the *Overview.*

Response: Comment not incorporated. The Expert Committee determined that sufficient explanation of ion fragmentation is contained in the *General Layout* sections.
Comment Summary #10: The commenter suggested editing the following sentence ".mass (molecular weight assignment) of each of the 10 components" to indicate that if the components have different molecular weights, then chromatographic separation is not necessary.
Response: Comment incorporated. The sentence was changed to read, "… mass-to-charge of each of the 10 components"
Comment Summary #11: The commenter indicated that all mass spectrometers need a sample introduction technique.
Response: Comment incorporated. Sample introduction technique bullet was added to the *General Layout* section.
Comment Summary #12: The commenter suggested editing the sentence to "and is represented in a graphic representation of intensity versus mass-to-charge ratio (m/z)." instead of "…mass-to-charge (m/z) versus intensity."
Response: Comment not incorporated. Because?
Comment Summary #13: The commenter suggested that the word "measure" be used in place of "count" in the phrase: "A detector to count the ions."
Response: Comment incorporated.
Comment Summary #14: The commenter suggested that Figure 1 be amended to remove Autosampler segment, by replacing "Collection" with "Detection" over the UV spectrum, "fractionation" with "separation" over HPLC, and "Spectroscopic Analysis" with "detection (and fragmention)."
Response: Comment incorporated. The Expert Committee also replaced "Spectroscopic Analysis" with "Mass Spectrometric Analysis."
Comment Summary #15: The commenters indicated that mass spectrometers measure mass-to-charge and not molecule weight.
Response: Comments incorporated. The use of the term molecular weight was replaced in several places in the chapter with mass-to-charge or molecular mass as appropriate.
Comment Summary #16: The commenter suggested that the statement "A system with two mass analyzers in sequence" does not allow for tandem in time (ion traps).
Response: Comment incorporated. The sentence was edited to state, "A system capable of carrying out two sequential m/z analysis events."
Comment Summary #17: The commenter suggested broadening the definition of tandem mass spectrometers in *Section 2.2.2*
Response: Comment incorporated.
Comment Summary #18: The commenter suggested that section *Direct Introduction* include descriptions of the many ambient ionization techniques.
Response: Comment not incorporated. The Expert Committee may consider including this suggestion in future revisions of the General Chapter.
Comment Summary #19: The commenter indicated that the section title contains the improper case for the letter n, in the abbreviation $MS^{n.}$
Response: Comment incorporated.

Comment Summary #20: The commenter suggested revising the definition in the HPLC chromatographic introduction technique section to allow for non-volatile components to be analyzed.
Response: Comment incorporated. The Expert Committee edited the sentence to more broadly describe analytes capable of HPLC analysis. “HPLC procedures are preferred for non-volatile and thermally labile analytes, but are suitable for use with any analyte that is readily ionizable in a solution environment with the appropriate chemical modifiers.”
Comment Summary #21: The commenter indicated that *Section 2.4.1* should be revised, because proteins and peptides are typically protonated with more than one proton.
Response: Comment incorporated.
Comment Summary #22: The commenter suggested adding the sentence, “Additionally, fragmentation patterns have been extensively studied for electron ionization and can help determine structure of unknown compounds.” to *Section 2.5.1*.
Response: Comment incorporated.
Comment Summary #23: The commenter suggested adding the sentence, “CI is very useful for reactive and unstable compounds where a molecular mass determination is desired” to *Section 2.5.2*.
Response: Comment incorporated.
Comment Summary #24: The commenter indicated that chemical ionization is dependent on both analyte and reagent gas.
Response: Comment not incorporated. The Expert Committee determined that this Section does not contradict this comment.
Comment Summary #25: The commenter indicated that the term “protonated molecule” should be used instead of “protonated molecular ion” throughout the General Chapter.
Response: Comment incorporated.
Comment Summary #26: The commenter requested that the schemes in *Section 2.5.2* be corrected to have a consistent format.
Response: Comment incorporated. The schemes were formatted to be consistent.
Comment Summary #27: The commenter requested that the sub-section *Electrospray Ionization* be moved to a subsection under *Section 2.5.3 Atmospheric Pressure Ionization.*
Response: Comment incorporated.
Comment Summary #28: The commenter suggested moving Table 1 out of the paragraph and placing it at the end of the document or another unobtrusive location.
Response: Comment not incorporated. Table 1 is located in a location close to the first reference, as is conventional.
Comment Summary #29: The commenter suggested splitting *Section 3.3 Ion Traps and Ion Cyclotron Resonance* into two sections.
Response: Comment not incorporated. The Expert Committee determined that the change would not enhance understanding of the General Chapter.
Expert Committee-Initiated Change #1: The Section titled *Atmospheric Pressure Chemical Ionization* was moved to become a subsection under *Section 2.5.3 Atmospheric Pressure Ionization.*

Section 4. MS/MS and MS^n Spectrometers

Comment Summary #30: The commenter suggested changing the nomenclature to MS/MS and/or MS^n in the section titles and text.

Response: Comment incorporated.

Comment Summary #31: The commenter suggested revising the caption for Figure 4C to read "The scan results in a spectrum that contains all ions…" instead of "molecular ion."

Response: Comment incorporated. The Expert Committee modified this proposal to read "precursor ions."

Comment Summary #32: The commenter suggested removing the explanation of SWIFT in *Section 4.1.5 Fourier-Transform Ion Cyclotron Resonance*, because the proposed explanation is inadequate.

Response: Comment incorporated.

Comment Summary #33: The commenter suggested that the General Chapter cover Orbitrap™ technology.

Response: Comment partially incorporated. Orbital trapping mass spectrometers have been included in the list of some possible configurations, but trademarked brand names were avoided.

Comment Summary #34: The commenter suggested changing the phrase "scan mode" to "acquisition mode" in *Section 4.2.2.4 MS^n*, because FT-ICR spectrometers are not scanning instruments.

Response: Comment incorporated.

Section 5. Qualitative Analysis

Comment Summary #35: The commenter indicated that it was unclear whether sub-section *5.1.1 Resolution* defined resolution or mass resolving power.

Response: Comment partially incorporated. The sub-section title was changed to *5.1.1 Mass Resolution*. The Expert Committee determined that a more detailed definition of resolution and mass resolving power was not necessary to give the reader an adequate perspective.

Comment Summary #36: The commenter suggested clarifying the sentence, "HRMS can be performed with a number of different technologies, including TOF–MS, as well as orbital-trapping MS and ion cyclotron resonance MS use Fourier transformation to process the raw data,' in section *5.1.1.2 High resolution*, to reflect that the latter two techniques use Fourier transformation and not TOF-MS.

Response: Comment incorporated. The sentence was changed to state, "HRMS can be performed with a number of different technologies, including TOF–MS, as well as orbital-trapping MS and ion cyclotron resonance MS, where the latter two approaches utilize Fourier transformation to process the raw data."

Comment Summary #37: The commenter indicated that the sentence, "The mass of a compound often is represented by the peak observed at highest m/z in the spectrum." in sub-section *5.2 Interpretation of Mass Spectra* is not true in many instances.

Response: Comment incorporated. The sentence was deleted.

Comment Summary #38: The commenter indicated that the statement "M+H and M-H often appear most prominent" is too general and not always true. The ions that appear are chemistry and ion source condition dependent.
Response: Comment incorporated. The sentence is revised to state that the M+H and M-H often appear as a prominent peak.
Comment Summary #39: The commenter suggested that the acronym mMRA be defined in the phrase "With the development of complete databases of many genes, mMRA, and proteins…"
Response: Comment partially incorporated. The acronym mMRA was a misspelling of mRNA. The Expert Committee determined that the acronym should be replaced with the word "transcripts," which makes the context of the sentence more broadly applicable and clear.
Comment Summary #40: The commenter indicated that there is no need for multiple protease digestions if one enzyme digest covers all sequence.
Response: Comment not incorporated. The Expert Committee determined that the section does not contradict the comment.
Expert Committee-Initiated Change #2: The sub-script 1 on 12C and 34S was removed, because it was not necessary. When a single heavy isotope is present, the sentence may read, "The major contributor to the A + 1 peak results from the occurrence of versions of the molecule containing ^{13}C, and the major contributor to the A + 2 peak, is naturally occurring ^{34}S.
Expert Committee-Initiated Change #3: Figure 6A. peptide fragmentation nomenclature was replaced, but there were no other changes.

Section 6. Quantitative Analysis
Comment Summary #41: The commenter suggested including a discussion regarding the use of quantitative analysis of potential genotoxic impurities.
Response: Comment not incorporated. Potential genotoxic impurities are a case study within the broader context of this section. The Expert Committee determined that specific attention to such analysis was not necessary.

Section 7. Drug Product Authentication and Contamination Detection
Comment Summary #42: The commenter indicated the standard MS experiment described in sub-section *7.1.1 Identification* was inadequate to provide certainty and that accurate mass and MS/MS experiments were both needed.
Response: Comment partially incorporated. The sub-section title was changed to *Identification* and/or *Verification of the Active Ingredient*. The Expert Committee determined that a more thorough explanation of the types of experiments needed for certainty were beyond the scope of this document, because many scenarios are possible and are case dependent.
Expert Committee-Initiated Change #4: Figure 9 was converted to black and white, because some symbols do not appear in the color version in the *Pharmacopeial Forum*. No changes were made to the data or caption.

General

Comment Summary #43: The commenter requested that General Chapter <736> *Mass Spectrometry* (instrument qualification and method validation) be combined with General Chapter <1736> *Applications of Mass Spectrometry* (theory, instrumentation, and practices), because the information in both chapters is applicable to the Mass Spectrometry.

Response: Comment not incorporated. The Expert Committee followed the strategy developed and published in a Stimuli Article "An Alignment of Concepts and Content across the Spectroscopy General Chapters in the United States Pharmacopeia–National Formulary (USP–NF)" *Pharmacopeia Forum* 40(1) [Jan.–Feb. 2013].

Comment Summary #44: The commenter indicated that General Chapter <1736> Applications of Mass Spectrometry is very detailed and proposed several different approaches for organization of the information.

Response: Comment not incorporated. The Expert Committee followed the current USP format for a general information chapter.

Comment Summary #45: The commenter indicated that with the advent of higher resolution accurate mass instruments, potential structural formulas can now be generated for molecular ions and fragments.

Response: Comment not incorporated. The Expert Committee determined that the contents of the General Chapter do not contradict this comment.

Comment Summary #46: The commenter indicated that the General Chapter is specific to small molecule drugs and does not cover biologics. The commenter proposed options for handling the interpretation of spectra for these two very different classes.

Response: Comment not incorporated. The Expert Committee determined that the current scope is sufficient but will reconsider the comment with future revisions.

Comment Summary #47: The commenter indicated that the placement of *Table 1* in the text was a distraction and did not add value to the immediate discussion.

Response: Comment not incorporated. The placement of Table 1 was not presented well due to the *Pharmacopeial Forum* format. In the *USP–NF* format, the Table placement is appropriate.

General Chapter/Section(s): <2250> Detection of Irradiated Dietary Supplements/ Multiple Sections
Expert Committee: General Chapters—Chemical Analysis
No. of Commenters: 2

Comment Summary # 1: The commenter requested that the phrase "except for disinfestation of arthropods using 1 kGy (*21 CFR 179.26*)," be deleted from the *Introduction*.

Response: Comment incorporated.

Comment Summary # 2: The commenter mentioned that some products like soy isoflavones have high photostimulated luminescence (PSL) signal which might be misinterpreted as positive.

Response: Comment not incorporated. This situation is covered in the General Chapter by stating that (1) PSL is a simple preliminary screening method to detect irradiation and (2) samples classified as intermediate based on PSL signals will require further

investigation by the TL method to determine their irradiation status. The Expert Committee will consider future revisions to the General Chapter upon the receipt of necessary supporting data.

Monograph/Section(s): L-Alanyl-L-Glutamine/Multiple Sections
Expert Committee: Monographs—Dietary Supplements
Expert Committee-Initiated Change #1: The *Identification C* test was removed, because it was not suitable for identification purposes.

Monograph/ Section(s): Azelastine Hydrochloride/Multiple sections
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 3
Comment Summary #1: The commenter requested revising the *Assay* to include additional instructions to prevent overheating in the reaction medium.
Response: Comment incorporated.
Comment Summary #2: The commenter requested widening the limit for the test for *Residue on Ignition* from NMT 0.1% to NMT 0.2% to reflect approved acceptance criteria.
Response: Comment incorporated.
Comment Summary #3: The commenter requested widening the limit in the test for *Heavy Metals* from NMT 10 ppm to NMT 20 ppm to reflect approved acceptance criteria.
Response: Comment incorporated.
Comment Summary #4: The commenter requested revising the names of "benzohydrazide" and "chlorophenylacetyl benzoic acid" to "Azelastine Related Compound A" and "Azelastine Related Compound C," respectively, to make them consistent with the labels used in the *Ph.Eur.* monograph.
Response: Comment not incorporated. The proposed names are consistent with current USP format; the use of the term "Related Compound" is reserved for materials that are available as USP Reference Standards.
Comment Summary #5: The commenter requested widening the limit in the test for Loss on Drying from NMT 0.5% to NMT 1.0% to reflect approved acceptance criteria.
Response: Comment incorporated.
Comment Summary #6: The commenter requested eliminating the test for *Acidity or Alkalinity,* because the *Organic Impurities* test quantifies acidic and alkaline impurities.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.

Monograph/Section(s): Borage Seed Oil/ Multiple Sections
Expert Committee: Monographs—Dietary Supplements
Expert Committee-Initiated Change #1: The monograph title was changed from "Borage Oil" to "Borage Seed Oil" to specify the plant part from which the oil is obtained.
Expert Committee-Initiated Change #2: The Identification B test was removed, because the cross-referenced new General Chapter <202> Identification of Fixed Oils by Thin Layer Chromatography is still in development.

Expert Committee-Initiated Change #3: The USP Borage Seed Oil RS requirement was removed, because it is associated with the removed Identification B test.

Monograph/ Section(s): Brompheniramine Maleate/Organic impurities
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested tightening the total impurity limits in the test for *Organic Impurities* to reflect approved acceptance criteria.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.

Monograph/Sections: Carbamazepine Extended-Release Tablets/Assay
Expert Committee: Monographs—Small Molecules 4
Expert Committee-Initiated change: The preparation of *Sample stock solution B* is corrected to refer to *Sample stock solution A* rather than to *Standard stock solution*.

Monograph/Section: Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution/ Multiple Sections
Expert Committee: Monographs—Small Molecules 3
No. of Commenters: 2
Comment Summary #1: The commenter requested widening the limits in the test for pH to reflect approved acceptance criteria.
Response: Comment incorporated. The pH range was widened from 5.5-5.8 to 5.4-5.9.
Comment Summary #2: The commenter requested widening the limit for timolol impurity B from NMT 0.5% to NMT 1.0%, and the limit for unspecified impurities from NMT 0.5% to NMT 0.6% in the test for *Organic impurities: Timolol Maleate* based on approved acceptance criteria.
Response: Comment incorporated.
Comment Summary #3: The commenter requested revising the *Organic impurities* procedure to include the limits for two additional impurities.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.
Comment Summary #4: Commenter requested revising the dorzolamide concentration of the *Standard solution* in the test for *Organic impurities: Dorzolamide Hydrochloride* to facilitate the determination of unspecified impurities.
Response: Comment not incorporated. The unspecified impurities are calculated by area normalization, and the concentration of the *Standard solution* does not affect their quantitation.
Comment Summary #5: The commenter requested revising the test for *Organic impurities: Dorzolamide Hydrochloride* to include relative response factors for the calculation of dorzolamide related compounds B and D*.*
Response: Comment not incorporated. The procedure does not require a relative response factors for these impurities because USP Dorzolamide Related Compounds B and D are used quantitatively in the proposed procedure.
Comment Summary #6: The commenter suggested adding the relative retention time of timolol in *Table 2* in the test for *Organic impurities: Dorzolamide Hydrochloride.*

Response: Comment not incorporated. The Expert Committee determined that timolol peak is not observed in the procedure.

Monograph/Section: Enzacamene /Identification B
Expert Committee: Monographs—Small Molecules 3
Expert Committee-Initiated Change #1: The acceptance criterion for the ratio of absorptivities was deleted. The Expert Committee determined that the maxima and minima agreements between *Standard solution* and *Sample solution* provide sufficient information to identify enzacamene.

Monograph/Section(s): Evening Primrose Oil/Multiple Sections
Expert Committee: Monographs—Dietary Supplements
Expert Committee-Initiated Change #1: The Identification B test was removed, because the cross-referenced new General Chapter <202> Identification of Fixed Oils by Thin Layer Chromatography is still in development.
Expert Committee-Initiated Change #2: The USP Evening Primrose Oil RS requirement was removed, because it is associated with the removed Identification B test.

Monograph/Section(s): Flax Seed Oil/Multiple Sections
Expert Committee: Monographs—Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter suggested increasing the upper limit of Iodine Value from 165 to 200.
Response: Comment not incorporated. The Expert Committee will consider further revisions to the monograph upon receipt of supporting data.
Expert Committee-Initiated Change #1: The monograph title was changed from Flax Oil to Flax Seed Oil to specify the plant part from which the oil is obtained.

Monograph/Section(s): Flunixin Meglumine/Multiple sections
Expert Committee: Monographs—Small Molecules 3
No. of Commenters: 1
Comment Summary #1: The commenter requested aligning the concentration of flunixin related compound C in the test for *Organic Impurities* with that of impurity C in the test for *Related substances* in the corresponding *Ph.Eur.* monograph.
Response: Comment not incorporated. The Expert Committee determined that the concentration of related compound C in the *PF 39(4)* proposal is appropriate for its intended application.
Comment Summary #2: The commenter requested adding a relative response factor for the quantitation of related compound C in the test for *Organic impurities*.
Response: Comment not incorporated. The procedure does not require a relative response factor for related compound C, because USP Related Compound C RS is used quantitatively in the proposed procedure.
Comment Summary #3: The commenter requested aligning the resolution requirement with that in the test for *Related substances* in the corresponding *Ph.Eur.* monograph.

Response: Comment not incorporated. The Expert Committee determined the resolution limit in the *PF 39(4)* proposal, which is supported by validation data, is appropriate for its intended use.
Comment Summary #4: The commenter requested alignment of the sample concentration and temperature used in the test for *Specific Rotation* with that in *Specific Optical Rotation* test in the corresponding *Ph.Eur.* monograph.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.
Comment Summary #5: The commenter requested tightening the limit in the test for *Residue on Ignition* from NMT 0.2% to NMT 0.1% to align with the *Sulfated Ash* limit in the corresponding *Ph.Eur.* monograph.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.

Monograph/Section(s): Ganoderma Lucidum Fruiting Body/*Identification*
Expert Committee: Monographs—Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter indicated that in the Identification B by HPLC, Ganoderenic acid A was listed within the acceptance criteria, although absent from Table 3 listing Relative Retention Times and Relative Response Factors.
Response: Comment incorporated. The reference to Ganoderenic acid A was removed from the Acceptance Criteria.

Monograph/Section(s): Ganoderma Lucidum Fruiting Body Powder/ *Identification*
Expert Committee: Monographs—Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter noted that in the Identification B by HPLC, Ganoderenic acid A was listed within the acceptance criteria, although absent from Table 3 listing Relative Retention Times and Relative Response Factors.
Response: Comment incorporated. The reference to Ganoderenic acid A was removed from the Acceptance Criteria.

Monograph/Section(s): Glycyl-L-Glutamine/Multiple Sections
Expert Committee: Monographs—Dietary Supplements
Expert Committee-Initiated Change #1: The *Identification C* test was removed, because it was not suitable for identification purposes.

Monograph/Section(s): Glycyl-L-Tyrosine/Multiple Sections
Expert Committee: Monographs—Dietary Supplements
Expert Committee-Initiated Change #1: The *Identification C* test was removed, because it was not suitable for identification purposes.

Monograph/Sections: Hydroxyzine Hydrochloride/Multiple sections
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 2
Comment Summary #1: The commenter requested retaining the test for *Loss on Drying* but with the drying conditions from the corresponding *European Pharmacopeia* monograph.
Response: Comment not incorporated. The Expert Committee had previously considered the requested change and determined that the test for *Water Content* is appropriate for inclusion in this monograph.
Comment Summary #2: The commenter requested adding the specified impurity 4-chlorobenzophenone to the monograph based on FDA approved limits.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.

Monograph/Sections: Imipramine Pamoate/Multiple sections
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested including a test for chloride based on FDA approved limits.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.
Comment Summary #2: The commenter requested including a test for pamoic acid content based on FDA approved limits.
Response: Comment not incorporated. The Expert Committee finds the current content requirement for the active moiety and identification test for the pamoic acid to be sufficient.

Monograph/Section(s): Krill Oil/Multiple Sections
Expert Committee: Monographs—Dietary Supplements
No. of Commenters: 2

Identification A
Comment Summary #1: The commenter requested the specifications of the Fatty Acid Profile in Table 1 be modified to reflect a wider range of sources from which the krill oil is obtained.
Response: Comment incorporated.

Content of Total Phospholipids
Comment Summary #2: The commenter requested that the purity specification of NLT 99.0% for triphenyl phosphate, the internal standard, be added to clarify the reagent grade requirement.
Response: Comment incorporated.
Comment Summary #3: The commenter requested adding '^{1}H frequency' to the specification of magnetic field strength to clarify the type of isotopes frequency used.
Response: Comment incorporated.

Monograph/Section(s): Krill Oil Capsules/Multiple Sections
Expert Committee: Monographs—Dietary Supplements
No. of Commenters: 2

Identification A
Comment Summary #1: The commenter requested the specifications of the Fatty Acid Profile in Table 1 be modified to reflect a wider range of sources from which the krill oil is obtained.
Response: Comment incorporated. The specifications for the fatty acid profile were modified based on the additional data received.

Content of Total Phospholipids
Comment Summary #2: The commenter requested that additional clarifications be provided for the purity of the triphenyl phosphate used for Internal standard preparation.
Response: Comment incorporated. Additional clarifications were provided.
Comment Summary #3: The commenter requested adding '^{1}H frequency' to the specification of magnetic field strength to clarify the type of isotopes frequency used
Response: Comment incorporated. Additional clarifications were provided.

Monograph/Section(s): Krill Oil Delayed-Release Capsules/Multiple Sections
Expert Committee: Monographs—Dietary Supplements
Expert Committee-Initiated Change #1: Expert Committee incorporated the comments received for Krill Oil Capsules monograph into the Krill Oil Delayed-Release Capsules monograph.

Monograph/Section: Levobunolol Hydrochloride / Multiple Sections
Expert Committee: Monographs—Small Molecules 3
Expert Committee-Initiated Change #1: The *Resolution* requirement in the test for *Organic Impurities* was revised to indicate that the resolution is between the levobunolol and atenolol peaks.
Expert Committee-Initiated Change #2: In *Packaging and Storage* the requirement for storage at "controlled room temperature" is changed to "room temperature."

Monograph/Section: Levobunolol Hydrochloride Ophthalmic Solution /Assay
Expert Committee: Monographs—Small Molecules 3
Expert Committee-Initiated Change #1: The Relative Standard Deviation under System suitability is widened from NMT 0.73% to NMT 1.5%.

Monograph/Sections: Mitomycin/Organic Impurities
Expert Committee: Monographs—Small Molecules 1
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the relative response factors for the impurities based on laboratory data.

Response: Comment not incorporated. The requested change is not consistent with the validated procedure and the proposed acceptance criteria.

Monograph/Section: Naphazoline Hydrochloride Ophthalmic Solution /Assay
Expert Committee: Monographs—Small Molecules 3
Expert Committee-Initiated Change #1: The *Chromatographic system* in the *Assay* is revised to add a reference to the diode array detector to accommodate the proposed test for *Identification B*. A note is added to indicate that the diode array detector should be used to perform *Identification B*.

Monograph/Section(s): Nicardipine Hydrochloride/Organic Impurities
Expert Committee(s): Monographs—Small Molecules 2
No. of Commenters: 1
Comment Summary # 1: The commenter requested widening of the reporting threshold in the test for *Organic Impurities*.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.

Monograph/Section: Oxymetazoline Hydrochloride Ophthalmic Solution /Assay
Expert Committee: Monographs—Small Molecules 3
Expert Committee-Initiated Change #1: The *Chromatographic system* in the *Assay* is revised to add a reference to the diode array detector to accommodate the proposed test for *Identification B*. A note was added to indicate that the diode array detector should be used to perform *Identification B*.

Monograph/Section(s): Paroxetine Extended-Release Tablets/ Multiple Sections
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 2
Comment Summary #1: The commenter requested aligning the concentrations of the *Sample solution* and *Standard solution* in the Assay.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.
Comment Summary #2: The commenter requested including stereochemical information in the chemical name for ethoxyparoxetine.
Response: Comment incorporated.
Comment Summary #3: The commenter requested including a *Dissolution* procedure and acceptance criteria.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.
Comment Summary #4: The commenter requested including a test for the limit of enantiomer.

Response: Comment not incorporated. The stability data provided by the sponsor shows no evidence of racemization.

General Chapter/Section(s): Polysorbate 80/Assay
Expert Committee(s): Monographs—Excipients
No. of Commenters: 1
Comment Summary #1: The commenter indicated that in Table 3 in *Assay*, the acceptance criteria for Oleic Acid should be NLT 58.0% instead of NMT 58.0%.
Response: Comment incorporated.

Monograph/Section(s): Rhodiola rosea /Multiple Sections
Expert Committee: Monographs—Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter noted that the volume of acetone was not specified in the preparation of Derivatization reagent of Thin-Layer Chromatography Test A of the *Identification* section.
Response: Comment incorporated. The volume of acetone, 40 mL, was included.
Expert Committee-Initiated Change #1: The USP Powdered Rhodiola rosea Extract RS under *USP Reference Standards* in the *Additional Requirements* section was renamed to USP Rhodiola rosea Root and Rhizome Dry Extract RS to reflect the updated nomenclature conventions.
Monograph/Section(s): Powdered Rhodiola rosea/Multiple Sections
Expert Committee: Monographs—Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter noted that the volume of acetone was not specified in the preparation of Derivatization reagent of Thin-Layer Chromatography Test A of the *Identification* section.
Response: Comment incorporated. The volume of acetone, 40 mL, was included.
Expert Committee-Initiated Change #1: The USP Powdered Rhodiola rosea Extract RS under *USP Reference Standards* in the *Additional Requirements* section was renamed to USP Rhodiola rosea Root and Rhizome Dry Extract RS to reflect the updated nomenclature conventions.

Monograph/Section(s): Powdered Rhodiola rosea Extract/Multiple Sections
Expert Committee: Monographs—Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter indicated that the volume of acetone was not specified in the preparation of Derivatization reagent of Thin-Layer Chromatography Test A of the *Identification* section.
Response: Comment incorporated. The volume of acetone, 40 mL, was included.
Expert Committee-Initiated Change #1: The USP Powdered Rhodiola rosea Extract RS under *USP Reference Standards* in the *Additional Requirements* section was renamed to USP Rhodiola rosea Root and Rhizome Dry Extract RS to reflect the updated nomenclature conventions.

Monograph/Section(s): Rhodiola rosea Tincture/Multiple Sections
Expert Committee: Monographs—Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter indicated that the volume of acetone was not specified in the preparation of Derivatization reagent of Thin-Layer Chromatography Test A of the *Identification* section.
Response: Comment incorporated. The volume of acetone, 40 mL, was included.
Expert Committee-Initiated Change #1: The USP Powdered Rhodiola rosea Extract RS under *USP Reference Standards* in the *Additional Requirements* section was renamed to USP Rhodiola rosea Root and Rhizome Dry Extract RS to reflect the updated nomenclature conventions.

Monograph/Section: Risperidone /Organic Impurities
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 2
Comment Summary #1: The commenter requested including the chemical name of risperidone related compound G in Table 2 in the test for *Organic Impurities*.
Response: Comment not incorporated. The chemical name is available in the *USP Reference Standards section* of the monograph.
Comment Summary #2: The commenter requested revising the test for *Organic Impurities* to address a compound that is observed in the commenter's product and which co-elutes with 5-fluororisperidone.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.
Comment Summary #3: The commenter requested revising the test for Organic Impurities to include acceptance criteria for additional compounds.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.

Monograph/Section: Salmeterol Inhalation Powder/Multiple sections
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 2
Comment Summary #1: The commenter requested including specific details of the procedure use for Microbial Enumeration<61>.
Response: Comment not incorporated. The existing text allows the flexibility of choosing the most appropriate procedure included in General Chapter <61>.
Comment Summary #2: The commenter requested clarifying the variables W_n and W_u in the test for *Organic Impurities*.
Response: Comment incorporated.

Monograph/Section: Sertraline Hydrochloride /Multiple sections
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 5
Comment Summary #1: The commenter requested revising the limit for *Total Impurities* in the test for *Organic Impurities*.

Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data.
Comment summary #2: The commenter requested widening the *Tailing Factor* requirement in the *Assay* from NMT 1.6 to NMT 2.0 based on supporting data.
Response: Comment incorporated.
Comment summary #3: The commenter requested increasing the concentration of the *Sample solution* in the test for *Organic Impurities* to allow more accurate quantification of the impurities.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.
Comment summary #4: The commenter requested revising *Organic Impurities Procedure 2* to improve recovery.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.
Comment summary #5: The commenter requested including an additional identification test.
Response: Comment not incorporated. The Expert Committee finds the current three identification procedures to be sufficient.
Comment summary #6: The commenter requested including their procedures for *Organic impurities*.
Response: Comment not incorporated. The Expert Committee determined that the commenter's procedures do not offer significant advantages over the proposed procedures.

Monograph/ Sections: Sodium Phenylbutyrate/Multiple Sections
Expert Committee: Monographs—Small Molecules 3
Expert Committee-Initiated Change #1: The names of USP Sodium Phenylbutyrate Related Compounds A, B, and C RS were changed to USP Phenylbutyrate Related Compounds A, B, and C RS, respectively.
Expert Committee-Initiated Change #2: The name of the test for *Limit of Sodium Phenylbutyrate Related Compound C* was revised to *Limit of Phenylbutyrate Related Compound C.*

Monograph/Section: Succinic Acid/Assay
Expert Committee(s): Monographs—Excipients
No. of Commenters: 1
Comment Summary #1: In the *Assay*, the commenter recommended providing detailed information for preparation of *Diluent*.
Response: Comment incorporated.

Monograph/Section: Trazodone Hydrochloride Tablets/Organic Impurities
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the trazodone concentrations of the *System suitability solution* and *Standard solution* in the test for *Organic Impurities* to align with each other.

Response: Comment not incorporated. The proposed concentrations of trazodone in the *System suitability solution* and *Sample solution* reflect supporting validation data.
Comment summary #2: The commenter requested tightening the limit for any individual unspecified degradation product.
Response: Comment not incorporated. The proposed acceptance criteria are consistent with the sponsor's FDA approved limit.