Commentary

USP–NF 2024 Issue 3

June 1, 2024

In accordance with USP's *Rules and Procedures of the Council of Experts ("Rules*"), and except as provided in Section 9.02 *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 (EC) deems appropriate, the proposal may advance to official status or be re-published in *PF* for further notice and comment, in accordance with the Rules. In cases when proposals advance to official status*,* a summary of comments received and the appropriate Expert Committee's responses, as well as Expert Committee-initiated changes, are published in the Proposal Status/Commentary section of USPNF.com at the time the official revision is published.

The *Commentary* is not part of the official text and is not intended to be enforceable by regulatory authorities. Rather, it explains the basis of Expert Committees' responses to public comments on proposed revisions. If there is a difference or conflict between the contents of the *Commentary* and the official text, the official text prevails.

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

General Chapters
<2> Oral Drug Products- Product Quality Tests
<87> Biological Reactivity Tests, In Vitro
<88> Biological Reactivity Tests, In Vivo
<781> Optical Rotation
<1031> The Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants
<1078> Good Manufacturing Practices for Bulk Pharmaceutical Excipients
<1782 >Vibrational Circular Dichroism Spectroscopy – Theory and Practice
<2800> Multi-Ingredient Dietary Supplement Products-Products Quality Tests

Monographs
Bacillus Inaquosorum
Dimethyl Sulfoxide
Dimethyl Sulfoxide Irrigation
Erythromycin
Ethacrynic Acid Tablets
Etodolac
Fenofibric Acid Delayed-Release Capsules
Isosorbide Mononitrate Extended-Release Tablets
Isotretinoin
Ketotifen Fumarate
Mannitol Compounded Injection
Mesalamine Delayed-Release Tablets
Mesalamine Suppositories
Ofloxacin
Ofloxacin Tablets
Polyethylene Glycol 40 Castor Oil
Soybean Phospholipids
Technetium Tc 99m Bicisate Injection
Technetium Tc 99m Mertiatide Injection
Technetium Tc 99m Pentetate Injection
Technetium Tc 99m Tetrofosmin Injection
Tobramycin Inhalation Solution

No comments were received for the following proposals:
General Chapters
<1184> Sensitization Testing

Monographs
Ajowan Fruit
Ajowan Fruit Powder
Ajowan Fruit Dry Extract
Aminopentamide Sulfate
Aminopentamide Sulfate Injection
Aminopentamide Sulfate Tablets
Amitraz
Amitraz Concentrate for Dip

Broccoli Seed Dry Extract
Carbamazepine Extended-Release Capsules
Choline Fenofibrate
Cyclophosphamide Capsules
Gamma Cyclodextrin
Haematococcus pluvialis powder
Lecithin
Lithium Citrate
Pea Protein
Polyoxyl 20 Cetostearyl Ether
Rice Protein
Rimexolone
Rimexolone Ophthalmic Suspension
Sour Jujube Seed
Sour Jujube Seed Powder
Sour Jujube Seed Dry Extract
Soybean Phosphatidylcholine
Ubidecarenone Chewable Gels

General Chapters

General Chapter/Section(s): <2> Oral Drug Products- Product Quality Tests/Multiple Sections
Expert Committee(s): General Chapters-Dosage Forms Expert Committee
No. of Commenters: 2

GENERAL COMMENTS
Comment Summary #1: The commenter suggested adding extra official nitrosamine-related text in the General Chapter.
Response: Comment incorporated.

INTRODUCTION
Comment Summary #2: The commenter recommended revising the second sentence in the first paragraph as follows for clarity: “Through oral delivery, both systemic action and local action…”
Response: Comment incorporated.
Comment Summary #3: The commenter recommended revising a sentence in the second paragraph as follows for clarity: “This chapter only applies to drug products for oral administration.”
Response: Comment incorporated.
Comment Summary #4: The commenter suggested revising the final sentence, for clarity, as follows: “When a validated procedure cannot be recommended, but information is available for a product quality and/or product performance test, it is described in an informational chapter numbered above ⟨1000⟩.”
Response: Comment incorporated.

QUALITY TESTS FOR ORAL DRUG PRODUCTS

Comment Summary #5: The commenter recommended revising the text as follows, for clarity: "Drug product quality tests for oral drug products fall into two categories: 1) universal tests that are applicable to all oral drug products, and 2) specific tests that should be considered for testing of specific types of oral products."
Response: Comment incorporated.

QUALITY TESTS FOR ORAL DRUG PRODUCTS/Universal Tests for Oral Drug Products
Comment Summary #6: The commenter recommended including the following text in the opening of the subsection: "Universal tests should be applied to all oral dosage forms and include Description, Identification, Strength (Assay), and Impurities (organic, inorganic, and residual solvents). Elemental impurities and, when applicable, nitrosamines, and leachables testing should also be applied." to be consistent with current regulatory expectations.
Response: Comment incorporated.
Expert Committee-initiated Change #1: The complete text was changed to "Universal tests should be applied to all oral dosage forms and include Description, Identification, Strength (Assay), and Impurities (organic, inorganic, and residual solvents). Elemental Impurities, Residual Solvents and, when applicable, nitrosamine impurities should also be applied. Extractables and leachables testing is applicable to liquid dosage forms when packaged in specific container/closure systems and may also be applicable to solid oral forms particularly when solvents are utilized in the manufacturing process." for completeness.

QUALITY TESTS FOR ORAL DRUG PRODUCTS/Universal Tests for Oral Drug Products/Identification
Comment Summary #7: The commenter suggested including references and/or information for additional tests applicable to polymorphic drug substances.
Response: Comment incorporated because although rare, a specification for polymorphic form could be considered for drug products manufactured from metastable drug substances. A reference to the applicable FDA guidance was added.

QUALITY TESTS FOR ORAL DRUG PRODUCTS/Universal Tests for Oral Drug Products/Impurities
Comment Summary #8: The commenter recommended the following revision: "The procedures and acceptance criteria should specifically limit toxic materials in the drug product."
Response: Comment incorporated.
Comment Summary #9: The commenter recommended including additional information regarding possible genotoxicity, in alignment with ICH M7.
Response: Comment incorporated.
Comment Summary #10: The commenter suggested revising the bracketed note as follows: "[Note-For additional see Impurities in Drug Substances and Drug Products <1086> and Nitrosamine Impurities <1469>. Please also see Elemental Impurities <232> and <233>, as well as Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems <1664>.]"
Response: Comment partially incorporated. Additional references to the USP *General Notices*, <467>, FDA guidances, and ICH guidelines were added. <1664> was already referenced in the section Extractables and Leachables where it is applicable (the likelihood of Packaging Component-Dosage Form interaction is high or medium). The previous sentence and the bracketed note were changed to: "See specific requirements in *General Notices 5.60, Impurities and Foreign Substances*, including considerations of risk-based analysis for *Elemental Impurities-Limits* <232>, *Elemental Impurities-Procedures* <233>, and *Residual Solvents* <467>. [NOTE—For additional information, see *Impurities in Drug Substances and Drug Products*

⟨1086⟩*, Nitrosamine Impurities* <1469>, the applicable FDA guidance (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs), and ICH M7 guidelines Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk (https://database.ich.org/sites/default/files/M7_R1_Guideline.pdf.]"

QUALITY TESTS FOR ORAL DRUG PRODUCTS/Specific Tests for Uncoated Tablets
Expert Committee-initiated Change #2: The following sentence was added for completeness: "The Universal Tests for Oral Drug Products and Specific Tests for Tablets apply for uncoated tablets."

QUALITY TESTS FOR ORAL DRUG PRODUCTS/Specific Tests for Uncoated Tablets/Tablets for Oral Solution and Tablets for Oral Suspension
Expert Committee-initiated Change #3: The following sentence was added for completeness: "Development of tests to be performed after reconstitution must be undertaken using the reconstitution process which will be described on the product label."
QUALITY TESTS FOR ORAL DRUG PRODUCTS/Specific Tests for Coated Tablets
Expert Committee-initiated Change #4: The following sentence was added for completeness: "The Universal Tests for Oral Drug Products and Specific Tests for Tablets apply for coated tablets."

QUALITY TESTS FOR ORAL DRUG PRODUCTS/Specific Tests for Granules
Expert Committee-initiated Change #5: The following sentence was added for completeness: "Development of tests to be performed after reconstitution must be undertaken using the reconstitution process which will be described on the product label."

QUALITY TESTS FOR ORAL DRUG PRODUCTS/Specific Tests for Powders
Expert Committee-initiated Change #6: The following sentence was added for completeness: "Development of tests to be performed after reconstitution must be undertaken using the reconstitution process which will be described on the product label." **QUALITY TESTS FOR ORAL DRUG PRODUCTS/Specific Tests for Liquids**
Comment Summary #11: The commenter recommended clearly stating within the subsection that testing on solids for solution/suspension should be executed on the prepared liquid as labeled.
Response: Comment incorporated in previous subsections of the chapter, as noted in Expert-Committee-initiated Changes #3, #5, and #6.

QUALITY TESTS FOR ORAL DRUG PRODUCTS/Specific Tests for Liquids/Extractable and Leachables
Comment Summary #12: The commenter noted the following statement is misleading: "Where development and stability data show no significant evidence of extractables and leachables, elimination of this test may be proposed." The commenter stated that extractable and leachable data is required for liquid formulations stored in non-glass containers and/or those with rubber stoppers, regardless of the development and stability data. For clarity, the commenter proposed the following for the Expert Committee's consideration: "Where development studies that include extractable studies, leachable assessment through shelf life, and stability data show no significant evidence of extractables or leachables, elimination of testing for specific leachables may be proposed."
Response: Comment incorporated.

Comment Summary #13: The commenter suggested including some text to inform the reader that other oral dosage forms (e.g., powders/granules which utilize solvents during manufacturing process) may also be affected by extractables and leachables. Alternatively, acknowledgment of extractable/leachables within these dosage forms' subsections may make the text clearer to the reader.
Response: Comment incorporated.

General Chapter/Sections: <87> Biological Reactivity Tests, In Vitro
Expert Committee(s): General Chapters—Packaging and Distribution
No. of Commenters: 5

General
Comment Summary #1: The commenter suggested clarifying that there is no need to perform chemical characterization and toxicological assessment for elastomeric materials when material fails <87>.
Response: Comment incorporated. Guidance on how to select the appropriate tests and how to apply this chapter to materials and components for packaging and delivery systems was added.
Comment Summary #2: The commenter recommends making the chapter out of scope for combination products.
Response: Comment incorporated.

Scope
Comment Summary #3: The commenter suggests clarifying that the combination product and medical devices are out of scope.
Response: Comment incorporated.

Skin Irritation, 4.4 Test Controls
Comment Summary #4: The commenter suggests that a combination of 1% sodium dodecyl sulfate (SDS) containing Y-4 polymer should be used as a positive control. However, both materials could be used as a positive control, and this should be reflected in the text.
Response: Comment incorporated

5.3.1 Chromosomal Aberration Test
Comment Summary #5: The commenter suggests the positive criteria be added to this section as it currently includes negative criteria under a positive "header." The Commentor recommended reviewing the section and including the appropriate criteria.
Response: Comment incorporated.

5.3.3 Micronucleus (MNvit) Test
Comment Summary #6: The commenter recommends deletion of *Step 4* as it is a duplicate of *Step 3*.
Response: Comment incorporated.

Reference
Comment Summary #5: The commenter recommends making the correct ISO reference.
Response: Comment incorporated.

General Chapter/Sections: <88> Biological Reactivity Tests, In Vivo
Expert Committee(s): General Chapters—Packaging and Distribution
No. of Commenters: 3

General
Comment Summary #1: The commenter recommended keeping the intracutaneous (irritation) test section in for the time being, with the disclaimer that in vitro testing should be performed preferentially.
Response: Comment not incorporated. The Expert Committee no longer sees the value in keeping such a test in the USP General Chapter, especially because USP is working to reduce all non-value animal testing.

Scope
Comment Summary #2: The commenter recommended adding a definitive statement(s) within <88> that if comparable testing is performed per ISO standards it does not need to be repeated for the component to be classified “pharmaceutical grade polymeric materials.”
Response: Comment not incorporated. It is the responsibility of the user to confirm that the testing meets the applicable standards at the time that the testing is performed.
Comment Summary #3: The commenter suggests clarifying that the combination product and medical devices are out of scope.
Response: Comment incorporated.

2.3 Extraction Solvents and Extraction Procedure, Extraction procedure
Comment Summary #4: The commenter suggests that, because the cell cultures are not listed as extraction solvents for <88> tests, the extractions in serum should be deleted.
Response: Comment incorporated.

Reference
Comment Summary #5: The commenter recommends making the correct ISO reference.
Response: Comment incorporated.

General Chapter/Section(s): <781> Optical Rotation / Multiple Sections
Expert Committee(s): General Chapters-Physical Analysis Expert Committee
No. of Commenters: 3

Comment Summary #1: The commenter requested more clarity on the requirement in the section *Wavelength Accuracy and Bandwidth*: "It is recommended to record attributes of the wavelength and the bandwidth".
Response: Comment incorporated. The text in the chapter was revised for clarity as follows: "It is recommended to record attributes of the wavelength and the bandwidth (i.e., the wavelength characteristics of the bandpass filter used in the instrument)."
Comment Summary #2: The commenter suggested to revise the sentence "Calculate the variability of the replicates, typically expressed as the standard deviation” in the *Repeatability* section and replace it with the following: "Calculate the variability of the replicates, typically expressed as either the standard deviation or the relative standard deviation."
Response: Comment not incorporated. The variability is more commonly expressed as standard deviation. The current wording is intentionally kept flexible by stating “typically expressed as …” so that the user can use whatever calculation is necessary for comparing the results with the manufacturer’s specifications.

General Chapter/Sections: <1031>The Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants (title published in *PF*)

	<1031> The Biocompatability of Pharmaceutical Packaging Systems and their Materials of Construction (new title)
Expert Committee(s):	General Chapters—Packaging and Distribution
No. of Commenters:	12

General
Comment Summary #1: The commenter suggested providing guidance on materials upstream of the final packaging (e.g. single-use bioprocessing components).
Response: Comment not incorporated. This information is beyond the scope of this General Chapter.
Comment Summary #2: The commenter suggested clarifying that <1031> can be applied to the material constituents in a drug-device combination product.
Response: Comment not incorporated. This information is beyond the scope of this General Chapter.
Comment Summary #3: The commenter suggested adding more content in the chapter discussing the link between USP <1031> and <661.1>.
Response: Comment not incorporated. This information is beyond the scope of this General Chapter.
Comment Summary #4: The commenter suggested changing “plastic packaging” to “polymeric packaging” as the latter term is more inclusive.
Response: Comment incorporated.
Comment Summary #5: The commenter suggested that USP publish the legacy methods and/or change the history document with the dates the methods were in place to enable comparison.
Response: Comment not incorporated. *USP-NF* currently has this capability.
Comment Summary #6: The commenter recommended that clarification be made to discuss whether all previously classified Class VI plastics are going to automatically receive the new pharmaceutical grade designation, or whether gap analysis/additional testing will be required to gain this designation.
Response: Comment not incorporated. An internal gap analysis is recommended to determine if additional testing is needed.

Scope
Comment Summary #7: The commenter suggested clarifying that the combination product and medical devices are out of scope.
Response: Comment incorporated.

Overview of Biocompatibility Evaluation
Comment Summary #8: The commenter suggested clarifying the point in the text that some materials are designed for medical industries and the supplier performs the grading evaluation against the medical regulations.
Response: Comment incorporated.

3.1 Pharmaceutical Grade Plastic Packaging Materials
Comment Summary #9: The commenter suggested that *Table 1* should have a clear path established between successful in vitro test results and ‘Pharmaceutical Grade Packaging Materials’.
Response: Comment incorporated.
Comment Summary #10: The commenter suggested clarifying the meaning of “manufacturing components.”

Response: Comment incorporated.
Comment Summary #11: The commenter indicated that in *Figure 1*, the box following "No" for *Compounds of toxicological concern* is used for the *Sensitization Test*. However, this test is being removed from <87> or <88>, and <1184>. The commenter recommended that the *Figure 1* should be revised to reflect this point.
Response: Comment incorporated.
Comment Summary #12: The commenter suggested adding *Figure 1* to <87> and <88>.
Response: Comment not incorporated. *Figure 1* is meant for informational purposes and would not be appropriate in a >1000 chapter.
Comment Summary #13: The commenter suggested clarifying the kind of information required to conduct a toxicological assessment.
Response: Comment not incorporated. This comment is already addressed in an earlier section of the General Chapter.

4.0 Risk-based Approach to Biocompatibility Evaluation, Gather Relevant Available Data
Comment Summary #14: The commenter suggested removing additives from information to be gathered from materials' suppliers, as this information is proprietary.
Response: Comment not incorporated. Adding additives to the list of information that could be gathered is not a requirement, just a recommendation.
Comment Summary #15: The commenter suggested that for *Figure 3* when the intended use is unknown, a conservative approach that considers all potential intended uses should be appropriate.
Response: Comment incorporated.
Comment Summary #16: The commenter suggested clarifying the kind of information that is required to conduct a toxicological assessment.
Response: Comment not incorporated. This comment is already addressed in an earlier section of the General Chapter.
Comment Summary #17: The commenter suggested removing additives from information to be gathered from materials' suppliers, as this information is proprietary.
Response: Comment not incorporated. Adding additives to the list of information that could be gathered is not a requirement, just a recommendation.
Comment Summary #18: The commenter suggested that for *Figure 3* when the intended use is unknown, a conservative approach that considers all potential intended uses should be appropriate.
Response: Comment incorporated.
Comment Summary #19: The commenter suggested that in *Figure 3*, chemical composition and/or extractable profile with toxicological assessment is only done when appropriate.
Response: Comment incorporated.
Comment Summary #20: The commenter suggested removing additives from information to be gathered from materials' suppliers, as this information is proprietary.
Response: Comment not incorporated. Adding additives to the list of information that could be gathered is not a requirement, just a recommendation.
Comment Summary #21: The commenter suggested that for *Figure 3* when the intended use is unknown, a conservative approach that considers all potential intended uses should be appropriate.
Response: Comment incorporated.
Comment Summary #22: The commenter suggested removing additives from information to be gathered from materials' suppliers, as this information is proprietary.
Response: Comment not incorporated. Adding additives to the list of information that could be gathered is not a requirement, just a recommendation.

Comment Summary #23: The commenter suggested that for *Figure 3* when the intended use is unknown, a conservative approach that considers all potential intended uses should be appropriate.
Response: Comment incorporated.

5.2 In Vitro Test Selection
Comment Summary #24: The commenter suggested updating references 7 to (7), "Russell, WMS and Burch, RL, (1959). The Principles of Humane Experimental Technique, Methuen, London," which is applicable to this statement.
Response: Comment incorporated.

5.3 Illustrative Examples Cytotoxicity Reactive Grades
Comment Summary #25: The commenter suggested adding 2 sets of pictures which are not currently included, to the General Chapter.
Response: Comment incorporated.

General Chapter/Section(s):	<1078> Good Manufacturing Practices for Bulk Pharmaceutical Excipients/Multiple
Expert Committee(s):	Excipients Test Methods
No. of Commenters:	7

General

Comment Summary #1: The commenter suggested that the general chapter address how manufacturers collaborate with agents and brokers, specifically, including guidance on roles, responsibilities, and quality agreements.
Response: Comment not incorporated. Other general chapters such as *Good Distribution Practices for Bulk Pharmaceutical Excipients <1197>* and *Supplier Qualification <1083>* may contain relevant information.
Comment Summary #2: The commenter suggested enhancing the general chapter to include a discussion of GPS tracking devices, geo-location, and geo-fencing for materials in transit, as well as expanding SOPs and training, calibration, quality management, and risk assessment systems to ensure supply chain security.
Response: Comment not incorporated. The comment is beyond the scope of the General Chapter. Ordinarily, excipients are shipped to the customer via less-than-truckload (LTL) by common carriers. Oftentimes, the load is cross-docked enroute. The user must rely on proper verification of the arrival of the excipient without any indication of damage or tampering. Tamper-evident seals information can be found in *6.6.3 Excipient Packaging Systems*.
Comment Summary #3: The commenter requested harmonizing with the recently updated "IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients" (2022 version).
Response: Comment not incorporated. The work on the general chapter revision started before the new version of the "IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients" became available.
Comment Summary #4: The commenter recommended that the general **c**hapter explain the two-way communication needed between the excipient manufacturer and its customer to determine the suitability of the excipient for its intended use in drug products, clarify how Quality Risk Management incorporates a full understanding of the potential intended use(s) of the excipient and how the excipient manufacturer communicates the grade of the excipient to be provided to its customers. Additionally, the commenter emphasized that excipient manufacturers should identify on the label or Certificate of Analysis (CoA) whether the excipient is suitable for

parenteral use or not. Furthermore, the customer's quality requirements (e.g., acceptance criteria, quality attributes) should be communicated to the excipient manufacturer based on the excipient's intended use(s) and the significance of identified risks.
Response: Comment not incorporated. Section 1.2 *Risk-Based Principles* recommends using suitable risk assessment approaches and tools that the manufacturer may utilize as suited to their circumstances. The methodologies detailed in The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q9—Quality Risk Management are applicable to pharmaceutical manufacture. Therefore, the specific communication details requested by the commenter are not explicitly addressed in the current general chapter.
Comment Summary #5: The commenter recommended using harmonized terminology or providing a definition in the *Glossary* to clarify the terms "interested party" and "Customer", which were used interchangeably.
Response: Comment not incorporated. The *Glossary* already contains a definition of "Customer", which defines it as the organization that purchases the excipient.
Additionally, section 3.2 *Understanding the Needs and Expectations of Interested Parties*, specifies that the organization should determine the interested parties relevant to the Quality Management System (QMS).
Comment Summary #6: The commenter recommended defining the differences between "responsible officials" and the "quality unit" in the *Glossary*.
Response: Comment incorporated. A definition of Quality Control Unit was added to the Glossary. Additionally, there is already a definition of Top Management (formerly referred to as "responsible officials") in the *Glossary*.
Comment Summary #7: The commenter recommended replacing "purity" with "consistent composition", which is a more accurate description of the desired attribute for excipients.
Response: Comment incorporated. In the *Introduction* section, excipient purity was defined as "consistent composition". This is applicable to all instances of "purity" throughout the general chapter.
Comment Summary #8: The commenter recommended using "top management" to replace "responsible officials" as defined in ANSI 363 standard.
Response: Comment incorporated.
Comment Summary #9: The commenter recommended the use of "the excipient manufacturer's intended use (e.g., route of delivery)" to replace "intended use".
Response: Comment incorporated. In section 1.1 *Purpose and Scope*, "the excipient manufacturer's intended use" was introduced as an equivalent to "intended use" that is being used throughout the chapter.

Section 1
Comment Summary #10: The commenter recommended that excipient manufacturing, re-packaging, re-labeling, QC testing, and QA functions be included within the scope of the General Chapter.
Response: Comment not incorporated because manufacturing, QC testing and QA functions are covered in the chapter, and "re-packaging, re-labeling" is beyond the scope of the chapter. However, the sentence "Good Distribution Practices (GDP) are covered in *Good Distribution Practices for Bulk Pharmaceutical Excipients ⟨1197⟩*" has been changed to read "Good distribution practices (GDP) including packaging from bulk, re-packaging and re-labeling are covered in *Good Distribution Practices for Bulk Pharmaceutical Excipients ⟨1197⟩.*"
Comment Summary #11: The commenter requested that, in section 1.1 *Purpose and Scope*, the sentence "Monographs or appropriate specifications provide for safe excipients of acceptable quality." be replaced with "Monographs or appropriate specifications assure that the quality of the excipient is acceptable for use in a drug product." because specifications

themselves do not assure that the excipient is safe for use in drug products, but rather they assure that the quality of the excipient is suitable for pharmaceutical usage.

Response: Comment incorporated.
Comment Summary #12: The commenter requested, in section 1.3 *Principles Adopted*, to revise the sentence “Pharmaceutical excipients often have uses other than pharmaceutical applications” to “Materials used as pharmaceutical excipients often have uses other than pharmaceutical applications.”
Response: Comment incorporated.

Section 2
Comment Summary #13: The commenter requested, in section 2.2 *Excipient GMP Implementation,* adding “earliest” in front of “point” into the sentence describing the synthetic process and add the sentence “However, based on process knowledge and risk assessment, later points in the process are often justified (e.g., distillation, crystallization, etc.).”
Response: Comment partially incorporated. The word “earliest’ was not added to the sentence “For a synthetic process, this can be the point at which excipient raw material is added to the process to produce the excipient structural fragment” because it was used in the previous sentence to identify the point “at which full compliance with the expectations of this General Chapter might apply”. The above sentence is used as an example of the earliest point of full GMP compliance for the synthetic process. Additionally, “final purification” instead of “distillation, crystallization” was proposed as an example of the latest point at which full compliance can apply. The proposed sentence reads “However, based on process knowledge and risk assessment, later points in the process may be justified i.e., final purification.”
Section 3
Comment Summary #14 (in both Sections 3&7): The commenter recommended, in sections 3.6.4 *Change Management* and 7.2.1 *Change Control,* including the situation where the manufacturer discontinues the production of an excipient.
Response: Comment incorporated. The following statements were added: “Discontinuation of manufacture of an excipient.” was added to section 3.6.4. “This also applies to discontinuation of manufacture of an excipient.” was added to section 7.2.1.

Comment Summary #15: The commenter requested, in the sentence related to electronic records in section 3.6.3 *Control of documented information,* removal of the reference to 21 CFR 11 and inclusion of the reference to the need to follow principles of ALOCA.
Response: Comment incorporated.

Section 4
Comment Summary #16: The commenter requested in section 4.2 *Quality Policy,* that customer evaluation of the effectiveness of the company’s QMS not be part of the quality policy.
Response: Comment not incorporated because the company should allow its QMS to be assessed and indicate this in the quality policy.

Section 5
Comment Summary #17: The commenter suggested, in section 5.3.1 *Buildings and Facilities,* to incorporate the information about cross-contamination control. Specifically, it highlights the need for techniques to mitigate cross-contamination risk for personnel handling highly sensitizing or toxic products and emphasizes the importance of dedicated facilities for this purpose. Additionally, it suggests that other techniques, such as equipment separation, may be appropriate for facilities dealing with non-sensitizing, non-toxic products.

Response: Comment not incorporated. The Expert Committee believes that section 5.3.1 *Buildings and Facilities* sufficiently covers contamination prevention and cross-contamination control. For personnel involved in the manufacture of highly sensitizing or toxic materials, the Expert Committee recommended adding "the following text: "Movement of personnel between areas used in the manufacture or control of highly sensitizing or toxic materials and other areas is strongly discouraged. If it is required, full decontamination procedures should be followed" to section 5.2.3 *Personnel Hygiene.*

Comment Summary #18: The commenter recommended changing the sentence in Section 5.2.2 *Competence, awareness, and training*, "Continuous training based on risk management should be planned." to "A training plan should be developed based on risk management and on-going training frequency should be established." The commenter found the term "continues training" confusing and not defined.

Response: Comment not incorporated. The term "continuous training" has been used by companies for employee development programs.

Comment Summary #19: The commenter requested, in Section 5.2.3 *Personal Hygiene,* to replace the requirement to limit the storage and use of food, drink, personal medication, tobacco products, or similar items to designated locations separate from manufacturing areas to designated locations where the excipient is not exposed to risk of contamination.".

Response: Comment incorporated.

Comment Summary #20: The commenter requested, in Section 5.3.5 *Computer Systems,* to change term "classify" to "identify"*.*

Response: Comment incorporated with minor wording changes. The updated sentence reads: "The organization should identify those computer systems that may impact QMS and those that may impact excipient quality."

Comment Summary #21: The commenter requested, in Section 5.3.5 *Computer Systems,* to reference ALCOA principles, instead of FDA guidance because the referenced FDA guidance is applicable to drug products, not to excipients.

Response: Comment incorporated.

Comment Summary #22: The commenter requested to clarify in Section 5.3.7 *Water*, that purification of water is not always necessary or used.

Response: Comment not incorporated. *Purified Water* is an official article in the *USP-NF*. It is prepared from potable or drinking water by a suitable process. As it is stated in the chapter, water used in the production of excipients should, at a minimum, meet the requirements for drinking or potable water. This water can be obtained by treating (purifying) water from springs, hyporheic zones and aquifers (groundwater), rainwater collection, surface water (rivers, streams, glaciers) or desalinated sea water.

Comment Summary #23: The commenter requested, under Section 5.4.9 *Monitoring and Measuring Resources,* to change "computerized systems" to "electronic measuring devices" in the sentence relating to calibration and maintenance.

Response: Comment not incorporated. This requirement applies to all measuring and testing devices, including those controlled by computers. Only these measuring and test devices are called computerized systems in the context of this subsection, not LIMS and SAP.

Comment Summary #24: The commenter requested, in Section 5.4.10 *Organization Knowledge,* to change the sentence "The organization should have knowledge of the regulations concerning the use of the excipients supplied." to "The organization should have knowledge of the laws and regulations concerning the intended use of their excipients as marketed."

Response: Comment incorporated.

Section 6

Comment Summary #25: The commenter suggested that, in Section 6.4.5 *Blending or Mixing,* the chapter include a statement stating that the blending or mixing of out-of-specification batches with an in-specification batch to achieve an in-specification batch is not allowed.
Response: Comment not incorporated because section 7.2.8 *Reworking* contains the requested text. A reference to 7.2.8 *Reworking* was added.
Comment Summary #26: The commenter suggested, in Section 6.2.1 *Determination of Requirements Related to the Product,* adding Nitrosamine assessment as an additional requirement.
Response: Comment not incorporated. However, a general statement was added to the section - "Potentially reactive, mutagenic and/or toxic impurities (for example, ethylene glycol (EG), diethylene glycol (DEG), nitrites, peroxides, aldehydes, etc.) statements."
Comment Summary #27: The commenter requested, under section 6.2.1 *Determination of Requirements Related to the Product,* describing the elemental impurities statement as an "Assessment Report" rather than a "Statement." Additionally, they suggested adding a Nitrosamine impurities potential occurrence assessment report within the Additional requirements.
Response: Comment not incorporated. See comment response #26.
Comment Summary #28: The commenter suggested, in Section 6.2.1 *Determination of Requirements Related to the Product,* adding a Nitrosamine impurities potential occurrence assessment report within the Additional requirements.
Response: Comment not incorporated. See comment response #26.
Comment Summary #29: The commenter recommended removing Section 6.2 *Customer Related Processes,* and include a section aligned with customer focus as described in the newly revised IPEC GMP guide.
Response: Comment not incorporated. Some of this information is taken from ANSI 363 standard. Additionally, the revision of the chapter began before the new revised IPEC GMP manual became available.
Comment Summary #30: The commenter recommended, in Section 6.3.1 *General,* changing the sentence for auditing to "There should be a procedure to periodically assess excipient raw material suppliers. Records of these activities should be maintained."
Response: Comment partially incorporated. The sentence has been changed to "There should be a procedure that describes the assessment of suppliers to ensure they meet the expectations of the excipient manufacturer. The procedure should require periodic reassessment to confirm continued supplier conformance."
Comment Summary #31: The commenter recommended, in Section 6.3.1 *General,* specifying only "quality-critical raw materials" specifications should be purchased against a mutually agreed-upon specifications.
Response: Comment not incorporated. A different sentence was added: "For those materials that are identified as quality-critical, excipient manufacturers should have an agreement with the supplier for a change notification. In the absence of such agreement, a risk assessment should be undertaken to demonstrate that a change by the material supplier won't impact excipient quality."
Comment Summary #32: The commenter recommended removing Section 6.3.2 *Purchasing Information* as it is not relevant to GMPs.
Response: Comment not incorporated. It is important to retain this section because it states what information is critical to excipient quality.
Comment Summary #33: The commenter recommended, in Section 6.4.2 *Production Instructions and Records,* changing the sentence related to statement of the percentage of theoretical yield as "The quantity produced for the defined batch and a statement of the percentage of theoretical yield, where applicable."

Response: Comment not incorporated because the original sentence was deleted. The sentence was changed to “A statement of theoretical yield and allowable range (deviations should be investigated):

- For excipients produced using batch processing, the quantity as a percentage of theoretical yield, unless otherwise justified.
- For excipients produced using continuous processing, yields should be monitored to ensure they fall within the established range”.

Comment Summary #34: The commenter recommended, in Section 6.4.4 *Equipment Cleaning,* rewriting the sentence on cleaning and sanitization documentation to “Records of cleaning and sanitization should be available to indicate the cleanliness or sanitization status.” because cleaning and sanitization procedures do not show the status of equipment.
Response: Comment incorporated.
Comment Summary #35: The commenter recommended changing “system” to “process” under Section 6.4.7 *Packaging and Labeling* in the sentence about documentation of the proper labeling.
Response: Comment incorporated.
Comment Summary #36: The commenter recommended, under Section 6.5.2 *Inspection and Test Status,* changing “test status” to “release status” *in* the sentence as “Although storing materials in identified locations is preferred, any means that clearly identifies the release status is satisfactory.”
Response: Comment incorporated.
Comment Summary #37: The commenter recommended, in Section 6.5.3 *Labeling,* removing reference to codes in alignment with FDA’s recent warning letters.
Response: Comment incorporated.
Comment Summary #38: The commenter recommended, under Section 6.6.3 *Labeling,* modifying the sentence on tamper-evident seals because excipient manufacturers typically do not reconcile tamper evident seals.
Response: Comment incorporated. The sentence was changed to “Tamper-evident seals should be traceable to the excipient manufacturer and should not be reusable once the seal is broken.”
Expert Committee-Initiated Change #1: In Section 6.3.2 *Purchasing Information*, removed the sentence “Drawings, process requirements, inspection instructions, and other relevant technical data, including requirements for approval or qualification of the material or service provided.” in purchasing agreement requirements.
Expert Committee-initiated Change #2: In Section 6.4.4 *Equipment Cleaning*, deleted the sentence: ”They should contain sufficient detail to allow operators to clean each type of equipment in a reproducible and effective manner.”

Section 7
Comment Summary #39: The commenter suggested, in Section 7.3.9 *Certification of Analysis,* the requirement for a Certificate of Analysis (CoA) containing an electronic signature statement should be elaborated.
Response: Comment not incorporated. However, a sentence was added stating “Note that it is a responsibility of the excipient purchaser to satisfy their expectation if an electronic signature is used.”
Comment Summary #40: The commenter requested, in Section 7.3.9 *Certification of Analysis,* adding storage conditions in the Certificate of Analysis (CoA).
Response: Comment incorporated.
Comment Summary #41: The commenter requested, in Section 7.3.11 *Impurities,* adding a risk assessment on nitrosaminesin addition to the residual solvents and elemental impurities.

Response: Comment not incorporated. See comment response #26. In addition, the paragraph outlining requirements for risk assessment for residual solvents and elemental impurities, and the last sentence in the next paragraph was rewritten.
Comment Summary #42: The commenter requested removing the sentence from Section 7.3.12 *Stability and Expiry/Retest Periods*: "Although many excipient products are stable and may not require extensive testing to ensure stability."
Response: Comment incorporated. The sentence was deleted. Additionally, a new sentence was added: "Where a stability study is used to demonstrate excipient shelf life, the details of the study should be documented and periodically confirmed."
Comment Summary #43: The commenter recommended including a separate section on post-release non-conformances or cross-referencing to Sections 7.2.5 and 7.2.6 within the appropriate sections (e.g., 6.2.4 and 6.6.5) to cover investigation and disposition decisions.
Response: Comment incorporated. The following statement was added to Section 7.2.5: "These investigative principles apply to customer complaints. (See section 6.2.4 Customer Complaints.)" With cross-references to Sections 6.2.4, 7.2.5, and 7.2.6, other recommendations are addressed.
Comment Summary #44: The commenter recommended clarifying that disposition and market action (e.g., recall) decisions should be made for any potentially impacted batches, including other impacted excipients, based on investigation outcomes.
Response: Comment incorporated. See comment response #43 above.
Comment Summary #45: The commenter recommended the general chapter should state that investigations, corrective actions, and customer notification of issues detected after delivery of the excipient should be performed in a timely manner.
Response: Comment incorporated. See comment response #43 above.
Comment Summary #46: The commenter recommended including the following in Section 7.3 *Performance Evaluation*: Establishing scientifically sound and appropriate specifications, standards (e.g., compendial standards, if relevant), sampling plans, and test procedures. Verification and validation, as appropriate, of test procedures for the intended use. Evaluation of excipient risk related to nitrosamine, azide, and other impurity formation in drug products.
Response: Comment not incorporated. Assessing excipient risk for "other impurity formation" may not be feasible due to the complex nature of excipients, typically being mixtures of materials resulting from manufacture. Instead, the expectation is that the excipient manufacturer should know how to meet the needs of interested parties and monitor the market for threats such as nitrosamine contamination and melamine Economically Motivated Contamination.
Comment Summary #47: The commenter recommended adding "sampling methods" into the text in Section 7.3.12 *Stability and Expiry/Retest Periods* as "The results of stability testing and/or evaluation should be documented with the following: The number of batches, sample sizes and sampling methods, and test intervals."
Response: Comment not incorporated. The relevant text was deleted due to comment #59.
Comment Summary #48: The commenter recommended adding reference to general chapter <1195> in Section 7.2.1 *Change Control*.
Response: Comment incorporated.
Comment Summary #49: The commenter recommended in Section 7.2.2 *Finished Excipient Testing and Release,* making the sentence of excipients conforming to specifications universal, and not just for excipients produced by continuous process.
Response: Comment incorporated.
Comment Summary #50: The commenter recommended, in Section 7.2.6 *Disposition of Non-conforming Finished Excipients,* adding a bullet allowing customer to accept a deviated product. To prevent drug shortages, a customer may choose to accept material that deviates from an agreed upon specifications when the parameter is corrected in the manufacturing process.
Response: Comment incorporated.

Comment Summary #51: The commenter recommended, in Section 7.2.8 *Reworking,* changing the last bullet as “Need to notify the customer of reworked excipient and documentation that the customer has agreed to accept the material.” for consideration when performing the risk assessment.
Response: Comment incorporated.
Comment Summary #52: The commenter recommended deleting from Section 7.3.9 *Certification of Analysis* “to the required specification” in the first sentence, replacing “specific identity of the test procedure” with “name of parameter being tested” in bullet 4 and adding references to IPEC, ANSI and EXCiPACT in bullet 8.
Response: Comment partially incorporated. “The specific identity of the test procedure” was changed to “Reference to the test procedure”. Other recommendations were not incorporated. From <1080>: “For the excipients listed in *USP–NF*, the product specifications are set by the supplier to include all attributes listed in the monograph. For excipients that are not included in *USP–NF*, specifications should be set by the supplier to ensure that the quality of the material is maintained on a continuing basis and reflects both the inherent properties of the excipient and its manufacturing process.” In both cases, these are required specifications. Because requirements for information included in certificates of analysis and statements of compliance to GMP in IPEC, ANSI and EXCiPACT documents can be updated without USP’s knowledge, references to these sources as requested by the commenter cannot be added to the chapter.
Comment Summary #53: The commenter recommended deleting text from Section 7.3.10 *Excipient Composition* related to the excipient manufacturer setting limits as this practice is not typical.
Response: Comment incorporated.
Comment Summary #54: The commenter recommended, in Section 7.3.10 *Excipient Composition,* adding “when necessary” to clarify that limits for excipient composition are not typically required, but when they are, they should be based on an understanding of safety considerations, regulatory requirements, official compendia, and customer requirements.
Response: Comment not incorporated. Impurities are part of the excipient composition therefore limits for excipient composition are required.
Comment Summary #55: The commenter recommended, in Section 7.3.11 *Impurities,* not specifying risk assessments made for specific tests.
Response: Comment partially incorporated. The relevant sentences were changed to “Excipient manufacturers should conduct documented risk assessments to determine whether the excipient specifications should include tests and limits for impurities, based on safety or the expectations of interested parties (see 3.2 *Understanding the Needs and Expectations of Interested Parties*). Where needed, limits and methods should be established such as required for *Residual Solvents ⟨467⟩*, elemental impurities (*Elemental Impurities—Limits ⟨232⟩)*, and other in the *USP-NF*.”
Comment Summary #56: The commenter recommended deleting text related to microbiological bioburden of the material from Section 7.3.11 *Impurities* and referencing general chapter <1111>.
Response: Comment incorporated.
Comment Summary #57: The commenter recommended, in Section 7.3.11 *Impurities,* changing “de minimis” to “technically unavoidable particles based on the manufacturers processing equipment and current technical capability of processes,” for clarity.
Response: Comment incorporated.
Comment Summary #58: The commenter recommended, from Section 7.3.11 *Impurities,* deleting reference to general chapters <788> and <790> as they are not applicable to excipients and most excipients are not for parenteral and injectables.
Response: Comment incorporated. A reference to IPEC Technically Unavoidable Particle Profile (TUPP) Guide was added.

Comment Summary #59: The commenter recommended, in Section 7.3.12 *Stability and Expiry/Retest Periods,* removing the details on the stability study because This level of detail exceeds that needed for this subject in this General Chapter.
Response: Comment incorporated.
Expert Committee-initiated Change #3: In Section 7.3.10 *Excipient Composition*, the Expert Committee added a reference to <1195> that describes impact of changes in the manufacturing process, raw materials or their sources, etc. on excipient composition profile and quality.
Expert Committee-initiated Change #4: In Section 7.3.12 *Stability and Expiry/Retest Periods*, "Although many excipient products are stable and may not require extensive testing to ensure stability," was deleted.

Glossary
Comment Summary #60: The commenter recommended, in the definition of the term "Batch (Lot)", explaining the homogenous and aligning the definition with the definition from ANSI 363 standard.
Response: Comment partially incorporated with minor wording changes. The definition was changed to: "A specific quantity of material produced in a process or series of processes so that it can be expected to be uniform in attributes and quality within specified limits."
Comment Summary #61: The commenter recommended not stating "conforming grades" in the definition of the term "Blending (Mixing)".
Response: Comment not incorporated. According to section *6.4.5 Blending and Mixing,* batches of the same excipient, but not just materials, can be blended (mixed) for several reasons to produce a homogeneous batch/lot. The chapter prohibits the blending batches that do not meet specifications. Thus, the Expert Committee decided to retain the proposed definition, but replace "grades" with "batches". The word "grades" describes different types of the same excipient that may have different physical and chemical characteristics and usually are not blended.
Comment Summary #62: The commenter recommended including the result of in-process data, in the definition of the term "Certificate of analysis".
Response: Comment incorporated. The definition was changed to "A document listing the test methods, specification, and test results from samples representative of the batch or in-process data from the material to be delivered."
Comment Summary #63: The commenter recommended using the IPEC definition for the definition of the term "Commissioning".
Response: Comment incorporated. It was changed to the IPEC definition without referencing ISPE because the source could not be confirmed.
Comment Summary #64: The commenter recommended including process equipment in the list, in the definition of the term "Critical".
Response: Comment not incorporated. This term and its definition were deleted because another term "Quality-Critical" defines critical relevant parameters that directly influence the quality attributes of the excipient and is used throughout the general chapter.
Comment Summary #65: The commenter recommended defining as customers only parties that take physical possession of the excipient, such as users and distributors and remove brokers and agents in the definition of the term "Customer".
Response: Comment not incorporated. Because an organization that purchases the excipient takes possession of it, the definition of Customer was changed to "Customer: The organization that purchases the excipient."
Comment Summary #66: The commenter recommended deleting the term "immediate" in the definition of "Drug Product".

Response: Comment not incorporated because the revised definition no longer contains the relevant text. The definition was changed to “Drug product: The dosage form intended for use by a patient.”

Comment Summary #67: The commenter recommended, in the definition of the term "Expiry (Expiration) date", specifying “while in the original, unopened container” because stability studies are conducted on material stored in unopened containers.

Response: Comment incorporated.

Comment Summary #68: The commenter recommended using the IPEC definition of the term "Impurity" which includes a statement that an impurity is undesirable.

Response: Comment partially incorporated. The word “undesirable” was replaced with the word “unintended”. Impurity was also described as a component of the excipient and not a material.

Comment Summary #69: The commenter recommended using the term “in-process” instead of “intermediate” and use the following definition for it: “In-process materials that undergo further manufacturing steps.” The commenter explained that chemical companies typically use the term “in-process” when referring to intermediates.

Response: Comment not incorporated. The term “intermediate” is defined in the glossary of the International Pharmaceutical Excipients Council – Federation (IPEC-Federation). The Expert Committee prefers to use terminology that is generally accepted in the excipient industry. The Expert Committee also proposed a simplified, clearer version of this definition: “Intermediate: Material that must undergo further processing to become the excipient.”

Comment Summary #70: The commenter recommended, in the definition of the term "Manufacturer/Manufacturing Process", replacing “All operations of” to “All operations from”.

Response: Comment incorporated. However, the definition of manufacturing process was changed to “Manufacturing process: All steps necessary to produce an excipient from raw materials.”

Comment Summary #71: The commenter recommended removing “bulk pharmaceutical” from the definition of “Reevaluation Date (Retest Date)".

Response: Comment not incorporated. The definition was changed to “Reevaluation date (Retest date): The date when a specific batch of excipient must be re-examined to ensure it is still suitable for its intended use.”

Comment Summary #72: The commenter recommended using the IPEC definition of the term "Reprocessing".

Response: Comment incorporated.

Comment Summary #73: The commenter recommended using the IPEC definition of the term "Reworking".

Response: Comment incorporated.

Comment Summary #74: The commenter recommended adding “and/or accept risk in order to reduce risk” to the definition of "Risk Control" for clarity.

Response: Comment not incorporated. The term was removed from the Glossary because it was not used in the General Chapter.

Comment Summary #75: The commenter recommended removing the term "Service Provision" because it was only used in section headings.

Response: Comment not incorporated. It is important for stakeholders to understand what this term means.

Comment Summary #76: The commenter recommended, in the definition of "Supplier", changing “pharmaceutical starting materials” to “materials” because pharmaceutical starting materials were not applicable to excipients.

Response: Comment incorporated.

Expert Committee-initiated Change #5: The term “Manufacturer/ Manufacturing process” was split into two separate terms: “Manufacturer” and “Manufacturing process”. The Expert Committee defined “Manufacturer” as “The organization that performs final production steps and release of the excipient.”
Expert Committee-initiated Change #6: The subsection title 7.2 was changed from “Monitoring and Measurement of Product” to “Monitoring and Measurement of Excipient”.
Expert Committee-initiated Change #7: In the last paragraph of 7.2.1 *Change Control*, “product” was replaced with “excipient”.

Appendix
Comment Summary #77: The commenter requested, in the Appendix *Auditing Considerations Documentation and Record Review,* adding a phrase indicating communication of stability data to the customer upon request and specifying the stability-indicating tests to be monitored after the re-test date.
Response: Comment incorporated. A sentence has been added: “For those that degrade under storage, stability-indicating methods should be developed and used. Data and the stability test program should be made available during an audit (customer or certification).”

General Chapter/Section(s):	<1782 >Vibrational Circular Dichroism Spectroscopy – Theory and Practice/Measurement OF VCD Spectra
Expert Committee(s):	General Chapters-Chemical Analysis Expert Committee
No. of Commenters:	1

Comment Summary #1: The commenter suggested adding “*and less toxic”* in the following statement: “*Besides hydrogen-free solvents, such as carbon tetrachloride (CCl4), other commonly used **and less toxic** solvents for VCD are deuterated chloroform (CDCl3) and deuterated dimethyl sulfoxide (DMSO-d6).”* to convey that highly hazardous reagents can be replaced with less toxic solvents.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested adding the word “cell” in the following sentence: “*The spectrum of this sample of neat (−) -(S)-α-pinene was collected for a period of 1 h at 4 cm^{-1} spectral resolution in a barium fluoride (BaF2) **cell** with a path length of 75 µm.”*
Response: Comment incorporated.

General chapter/Section(s):	<2800> Multi-Ingredient Dietary Supplement Products-Products Quality Tests
Expert Committee(s):	Non-Botanical Dietary Supplements
No. of Commenters:	2

Comments Summary # 1: The commenter recommended excluding specifications for water activity and pH, which are established for chewable gel products covered by existing *USP* monographs, as a general recommendation for all chewable gel products.
Response: Comment incorporated. The references to the chewable gels monograph’s specifications for water activity and pH were removed from the *Water Activity* and *pH* sections of the general chapter.
Comments Summary #2: The commenter suggested adding the term "Nutritional(s)" to align with other related USP chapters (<2021>, <2022>, <2023>, etc.).
Response: Comment not incorporated. Based on a review of relevant FDA documents and USP general chapters, no justification was found for including the term "Nutritional(s)" in the general chapter.

Monographs

Monograph/Sections: Bacillus Inaquosorum / Multiple sections
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 0

Definition
Expert Committee-initiated Change #1: The statement "Note—The nucleic acid-based identification method detailed in *Identification B* applies only to *Bacillus inaquosorum* DE111" was moved from the *definition* to *Identification B, Nucleic-Acid Based Identification*.

Identification
Expert Committee-initiated Change #2: The sentence "Proceed as directed in the *Assay* and follow the procedures in *Microbial Characterization, Identification, and Strain Typing ⟨1113⟩, Primary Screening and Characterization, Gram Straining and Spore Straining*." was changed to "Proceed as directed in the *Assay* and perform microscopic examination," because the chapters above 1000 are never applicable to standards according to *General Notices*. Development of Chapters below 1000 or above 2000 for microscopic evaluation of microbial articles, inclusion for the microscopic evaluation in <64>, and reference in the monograph will be considered in future revisions.

Monograph/Section(s): Dimethyl Sulfoxide / Organic Impurities
Expert Committee: Small Molecules 3
No. of Commenters: 2

Comment Summary #1: The commenter requested to add nitrogen as the carrier gas in the test for *Organic Impurities* indicating that nitrogen is safer than hydrogen.
Response: Comment not incorporated. The Expert Committee indicated that hydrogen is a common carrier gas and is safe to use with modern equipment and proper precautions. In addition, use of hydrogen is consistent with the validated procedure. The Expert Committee will consider future revision to the monograph upon the receipt of supporting data.
Comment Summary #2: The commenter recommended removing the reporting threshold in the test for *Organic Impurities* as it will vary based on product-specific factors.
Response: Comment not incorporated. A new USP general chapter, ⟨477⟩ *User-Determined Reporting Thresholds* supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

Monograph/Section(s): Dimethyl Sulfoxide Irrigation / Assay
Expert Committee: Small Molecules 3
No. of Commenters: 1

Comment Summary #1: The commenter indicated issues meeting the peak symmetry requirements outlined in <621> for the currently official Dimethyl Sulfoxide Irrigation *Assay* procedure due to excessive fronting. The commenter is concerned if the *PF* 49(4) proposal was evaluated against, and considers, the <621> peak symmetry requirements of 0.8-1.8.
Response: Comment not incorporated. The proposed *Assay* procedure includes a tailing (peak symmetry) requirement of NMT 1.5 for dimethyl sulfoxide and addresses the fronting issue experienced by the commenter using the current *Assay* procedure.

Monograph/Section(s): Erythromycin / Multiple sections
Expert Committee(s): Biologics Monographs 4– Antibiotics
No. of Commenters: 1

Comment Summary #1: The commenter asked if it is acceptable to confirm system suitability using the EP CRS and requested to share the chromatogram of Erythromycin System Suitability Mixture RS in the *Assay* and the *Organic Impurities* test.
Response: Comment not incorporated. USP Erythromycin System Suitability Mixture RS is available, and the example chromatogram is provided in the certificate.
Comment Summary #2: The commenter requested to extend the time for re-equilibrium in *Table 1* to a minimum of 3-4 minutes to have better chromatography without any changes in the existing elution gradient in the *Assay* and the *Organic Impurities* test.
Response: Comment partially incorporated. The re-equilibrium step is deleted.
Expert Committee-initiated Change #1: The volume of the solvent used in the *Water Determination* test (20 mL) is removed since the volume does not need to be specified.

Monograph/Section(s): Ethacrynic Acid Tablets / Multiple sections
Expert Committee: Small Molecules 2
No. of Commenters: 4

Comment summary #1 The commenter indicated that they use the currently official UV identification procedure along with retention time agreement based on the *Assay*. The commentor asked if they need to update their approved UV identification to match the proposed UV identification based on the PDA HPLC *Assay* procedure.
Response: Comment not incorporated. Identification tests are discussed in *General Notices 5.40. Identification*.
Comment summary #2: The commenter recommended removing the reporting threshold in the test for Organic Impurities as it will vary based on product-specific factors.
Response: Comment not incorporated. A new USP general chapter, ⟨477⟩ *User-Determined Reporting Thresholds*, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.
Expert Committee-initiated change #1: To add additional clarity and provide consistency with the drug substance monograph, the name “Ethacrynic acid pyrane dimer” is added as a footnote to Ethacrynic acid related compound C in *Table 2* in the test for *Organic Impurities*.

Monograph/Section(s): Etodolac / Multiple sections
Expert Committee: Small Molecules 2
No. of Commenters: 2

Comment summary #1: The commenter indicated that in the *Assay* the % RSD requirement of NMT 0.73% for the *Standard solution* could not be achieved consistently.

Response: Comment not incorporated. The Expert Committee determined that based on the validation data, the *Assay* procedure is suitable for the intended use.
Comment summary #2: The commenter stated in the test for *Organic Impurities* that the proposed method differs from the *European Pharmacopoeia* (EP) monograph with respect to the gradient program and requested USP to keep the gradient program in line with the EP monograph.
Response: Comment not incorporated. The proposed *Organic Impurities* procedure is consistent with the sponsor's validated test method and is suitable for the intended use. Use of alternate procedures is discussed in *General Notices 6.30. Alternative and Harmonized Methods and Procedures*.
Comment summary #3: The commenter requested in the test for *Organic Impurities* to keep the *Standard solution* concentration at 0.4 ppm, in line with EP monograph.
Response: Comment not incorporated. The proposed *Organic Impurities* procedure is consistent with the sponsor's validated test method and is suitable for the intended use. Use of alternate procedures is discussed in *General Notices 6.30. Alternative and Harmonized Methods and Procedures*.
Comment summary #4: The commenter recommended using an autosampler temperature of 15°C per their validated method for the test for *Organic Impurities.*
Response: Comment not incorporated. The Expert Committee determined that autosampler temperature of 5° is consistent with the sponsor's validation and is suitable for the intended use. If necessary, the Expert Committee will consider future revisions to the monograph upon the receipt of supporting data. Use of alternate procedures is discussed in *General Notices 6.30. Alternative and Harmonized Methods and Procedures.*
Comment summary #5: The commenter recommends in the test for *Organic Impurities* that relative response factors be removed for the known impurities to be consistent with the EP monograph, and as the RRFs are close to 1.
Response: Comment not incorporated. The Expert Committee determined that the relative response factors are consistent with the sponsor's validation and are suitable for the intended use.
Comment summary #6: The commenter requested USP to consider the user perspective where a single harmonized testing method could have a huge impact on resources utilized for batch testing, batch data review, and batch release timelines across the globe.
Response: Comment not incorporated. The Expert Committee determined the proposed method is consistent with the sponsor's validation and is suitable for the intended use. Use of alternate procedures is discussed in *General Notices 6.30. Alternative and Harmonized Methods and Procedures* Future revisions to align with EP, can be considered upon the receipt of approved specifications and supporting data.
Comment summary #7: The commenter recommended removing the "reporting thresholds" in the test for *Organic Impurities* as they will vary based on product-specific factors.
Response: Comment not incorporated. A new USP general chapter, ⟨477⟩ *User-Determined Reporting Thresholds*, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

Monograph/Section(s): Fenofibric Acid Delayed-Release Capsules / Organic Impurities
Expert Committee: Small Molecules 2
No. of Commenters: 1

Comment summary #1: The commenter recommended removing the "reporting threshold" in the test for *Organic Impurities* as it will vary based on product-specific factors.

Response: Comment not incorporated. A new USP general chapter, ⟨477⟩ *User-Determined Reporting Thresholds*, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

Monograph/Section(s): Isosorbide Mononitrate Extended-Release Tablets / Organic Impurities
Expert Committee: Small Molecules 2
No. of Commenters: 1

Comment Summary #1: The commentor recommended adding a decimal point to the acceptance criteria for the "Isosorbide" impurity from "NMT 1%" to "NMT 1.0%" in the test for *Organic Impurities.*
Response: Comment not incorporated. The proposed limit of 1% for the Isosorbide impurity is consistent with the limits in the current official monograph. The Expert Committee can consider a future revision upon the receipt of approved specifications and supporting data.
Comment Summary #2: The commenter recommended removing the "reporting threshold" in the test for *Organic Impurities* as it will vary based on product-specific factors.
Response: Comment not incorporated. A new USP general chapter, ⟨477⟩ *User-Determined Reporting Thresholds*, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

Monograph/Section(s): Isotretinoin / Multiple sections
Expert Committee: Small Molecules 3
No. of Commenters: 4

Comment summary #1: The commenter indicated that peak area count of standard injections in the *Assay* decreased for each subsequent injection for three separate runs. The 0.73% RSD requirements of the method was met, but due to the decreasing area count bracketing standard injections did not comply with the RSD requirement. The commentor recommends to further optimize the method or retain the currently official assay titration method.
Response: Comment not incorporated. The Expert Committee determined that the procedure is consistent with the sponsor's validation and is suitable for the intended use.
Comment summary #2: The commenter recommended removing the "reporting threshold" in the test for *Organic Impurities* as it will vary based on product-specific factors.
Response: Comment not incorporated. A new USP general chapter, ⟨477⟩ *User-Determined Reporting Thresholds*, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.
Comment summary #3: The commenter indicated that in the test for *Organic Impurities,* Isotretinoin is liable to degrade under oxidative stress conditions and that "EP Impurity G", "EP Impurity H," and "EP impurity I" are potential oxidative degradation products of Isotretinoin. The commenter recommended including these impurities.
Response: Comment not incorporated. The degradation products indicated by the commenter can be separated by the procedure and are controlled at the "any unspecified degradation products" limit of 0.10%. If necessary, the Expert Committee will consider a future revision to this monograph upon receipt of supporting information.

Monograph/Section(s): Ketotifen Fumarate / Multiple sections

Expert Committee: Small Molecules 5
No. of Commenters: 1

Comment summary #1: The commenter recommended removing the "reporting threshold" in the test for *Organic Impurities* as it will vary based on product-specific factors.
Response: Comment not incorporated. A new USP general chapter, ⟨477⟩ *User-Determined Reporting Thresholds*, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.
Expert Committee-initiated Change #1: Update the chemical information for USP Ketotifen Related Compound A RS and USP Ketotifen Related Compound G RS to include fumarate salt.

Monograph/Section(s): Mannitol Compounded Injection / Multiple sections
Expert Committee: Compounding Expert Committee
No. of Commenters: 1

Comment Summary #1: The commenter suggests including information on what the final yield of each preparation should be. This would help ensure consistent reproducibility of the compounded preparations.
Response: Comment not incorporated. Monographs are written according to the *USP Style Guide*.
Comment Summary #2: The commenter recommends that appearance and visual inspection (i.e., to include looking for particles and if the solution is clear or other based on testing results) be included in the *Specific Tests* section.
Response: Comment incorporated.
Comment Summary #3: The commenter requests USP identify the type of glass vial that was used for storage, the size of the container, as well as the stopper utilized to mimic the storage conditions that were utilized to support the BUD dating.
Response: Comment not incorporated. The container material composition is incorporated according to <797> *Pharmaceutical Compounding – Sterile Preparations*.
Comment Summary #4: The commenter notes that this monograph may produce a drug product that is essentially a copy of an FDA approved product, as described in the final guidance document entitled "Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act." Commenter recommends using only FDA-approved drug products unless the patient has a specific medical need (e.g., an allergy) that cannot be met by the approved drug products. Because they do not go through the drug approval process, compounded drugs should only be used when an FDA-approved product is not available to meet the medical needs of an individual patient.
Response: Comment not incorporated. This monograph was created for when the FDA-approved product is not available to meet the medical needs of an individual patient.
Comment Summary #5: The commenter notes that the preparation includes instructions to autoclave the compounded preparation. We recommend that the autoclave cycle be defined (i.e., duration of the cycle, temperature, and pressure). This would ensure that the process is reproducible and robust.
Response: Comment partially incorporated. Changed "autoclave" to "autoclave to achieve terminal sterilization (See ⟨1229.2⟩ *Sterilization of Compendial Articles, Moist Heat Sterilization of Aqueous Liquids*.)."
Comment Summary #6: The commenter notes that in the *Bacterial Endotoxins Test* section, the endotoxin criteria currently state "NMT 2.5 USP Endotoxin Units/mg of mannitol". However, the mannitol injection monograph has the following criteria: "It contains not more than 0.04 USP

Endotoxin Unit per mg of mannitol where the labeled amount of mannitol in the Injection is 10% or less, and not more than 2.5 USP Endotoxin Units per g of mannitol where the labeled amount of mannitol in the Injection is greater than 10%." They recommend that USP review scientific studies to support this monograph to ensure that this is appropriate.
Response: Comment not incorporated. The mannitol concentration is 25% w/v, greater than 10%.
Comment Summary #7: The commenter notes the *Labeling* section reads as follows: "Label to indicate the Beyond-Use Date. If crystals are present, warm to dissolve. Administer with a filter." For clarity, they suggest stating that filtration should be performed each time the drug is administered. Additionally, the *Labeling* section should state that the product should not be used if visible particulates are present.
Response: Comment not incorporated. Monographs are written according to the *USP Style Guide*.
Comment Summary #8: The commenter recommends including the following statement: "In the absence of passing a sterility and endotoxin test, the beyond-use dates in *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩ apply." This makes it clear that testing has to be performed in order to use the extended BUDs in the monograph and would be consistent with the language used in the *Fentanyl Citrate* and *Bupivacaine Hydrochloride Compounded Injection* monograph.
Response: Comment incorporated.

Monograph/Section(s): Mesalamine Delayed-Release Tablets / Organic Impurities
Expert Committee: Small Molecules 2
No. of Commenters: 3

Comment summary #1: The commentor indicated that they were able to execute the test for *Organic Impurities* without difficulty. However, the commentor noted that based on potential process impurities and degradation products there are potential critical pairs that are not well resolved and one that may coelute with mesalamine. To achieve resolution, the minor component of the mobile phase (methanol) was decreased by 24% relative, which resulted in an increase in run time.
Response: Comment not incorporated. The adjustment to the minor component (methanol) in the *Mobile phase* is within the permitted adjustments for mobile phase outlined in <621>.
Comment summary #2: The commenter indicated that, in the test for *Organic Impurities,* the proposed limits are lower than what was originally in the monograph want wanted to make sure other stakeholders are not put out of compliance, by tightening the impurities acceptance criteria.
Response: Comment not incorporated. The proposed *Acceptance criteria* are consistent with the sponsor's approved specifications The Expert Committee can consider a future revision upon the receipt approved specifications and supporting data.
Comment summary #3: The commenter recommended removing the "reporting threshold" in the test for *Organic impurities* as it will vary based on product-specific factors.
Response: Comment not incorporated. A new USP general chapter, ⟨477⟩ *User-Determined Reporting Thresholds*, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

Monograph/Section(s): Mesalamine Suppositories / Organic Impurities
Expert Committee: Small Molecules 2
No. of Commenters: 1

Comment summary #1: The commenter recommended deleting the relative retention times for Hydroxyanthranilic acid and Mesalamine dicarboxylic acid analog in *Table 1* in the test for *Organic Impurities.*
Response: Comment not incorporated. The relative retention times in *Table 1* are provided to aid in peak assignment.

Monograph/Section(s): Ofloxacin / Organic Impurities
Expert Committee: Small Molecules 1
No. of Commenters: 1

Comment summary #1: The commenter recommended removing the "reporting threshold" in the test for *Organic Impurities* as it will vary based on product-specific factors.
Response: Comment not incorporated. A new USP general chapter, ⟨477⟩ *User-Determined Reporting Thresholds*, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.
Comment summary #2: In the test for *Organic Impurities*, the commentor indicated that the currently official term "Individual impurities" is not the same as the proposed term "Any unspecified impurity". The commentor also indicated that an "Any unspecified impurity" limit of NMT 0.3% is not appropriate for a public standard and recommended revising the limit to be in line with the ICH Q3A Identification Threshold.
Response: Comment incorporated. The currently official term "Individual impurities" and the associated limit of NMT 0.3% are retained.

Monograph/Section(s): Ofloxacin Tablets / Assay
Expert Committee: Small Molecules 1
No. of Commenters: 0

Expert Committee-initiated Change #1: The *Sample solution* in the test for *Assay* is revised to incorporate a *Sample stock solution* for additional clarity to avoid potential preparation errors.

Monograph/Section(s): Polyethylene Glycol 40 Castor Oil / Impurities
Expert Committee(s): Complex Excipients
No. of Commenters: 1

Comment Summary #1: The commenter requested to include the Limit of Ethylene Glycol (EG) and Diethylene Glycol (DEG) tests in *Identification* because EG/DEG have long been recognized as highly toxic adulterants that can lead to renal failure and death.
Response: Comment not incorporated at the moment. USP is currently in the process of optimizing the EG/DEG GC method in the monograph which includes efforts to develop and validate a suitable EG/DEG Identification test for Polyethylene Glycol 40 Castor Oil. However, this will take time. Although the current proposed new monograph, Polyethylene Glycol 40 Castor Oil has the EG/DEG test in the *Impurities* section, the Complex Excipients Expert Committee has agreed that it is advantageous to include this DEG/EG test as soon as possible for stakeholder's use, and subsequently being revised to address FDA's immediate request (include the test in the ID section). A general announcement will be published to inform the stakeholders about the intent to revise in the near future as an accelerated revision after this monograph becomes official in *USP-NF 2024, Issue 3* (official date: Dec 1, 2024)

Monograph/Section(s): Soybean Phospholipids / Packaging and Storage
Expert Committee(s): Complex Excipients

No. of Commenters: 0

Expert Committee-initiated Change #1: The Expert Committee updated the *Packaging and Storage* to differentiate storage conditions for uses in non-injectable dosage forms and those in injectable dosage forms, to offer stakeholders more flexibility in storage.

Monograph/Section(s): Technetium Tc 99m Bicisate Injection / Multiple sections
Expert Committee: Small Molecules 4
No. of Commenters: 1

Comment summary #1: The commenter recommended including retention time from radio-chromatograms in the *Acceptance criteria* for the *Radiochemical Identity* test in the *Identification* section.
Response: Comment incorporated. The Expert Committee included retardation factor comparison from the test for *Radiochemical Impurities*.
Comment summary #2: The commenter recommends adding a test for pH with acceptance criteria that align with the approved standards.
Response: Comment not incorporated. Adding a test for pH is out of scope for this *PF* proposal. The Expert Committee will consider future revisions to the monograph upon the receipt of supporting data.

Monograph/Section(s): Technetium Tc 99m Mertiatide Injection / Multiple sections
Expert Committee: Small Molecules 4
No. of Commenters: 1

Comment summary #1: The commenter recommended including retention time from radio-chromatograms in the *Acceptance criteria* for the *Radiochemical Identity* test in the *Identification* section.
Response: Comment incorporated.

Monograph/Section(s): Technetium Tc 99m Pentetate Injection / Multiple sections
Expert Committee: Small Molecules 4
No. of Commenters: 1

Comment summary #1: The commenter recommended including retention time from radio-chromatograms in the *Acceptance criteria* for the *Radiochemical Identity* test in the *Identification* section.
Response: Comment not incorporated. The retardation factor (RF) is included in the *Acceptance criteria*.
Comment summary #2: The commenter recommended tightening the acceptance criteria for "pH" to match what has been approved.
Response: Comment not incorporated. The *pH* test is out of scope for this *PF* proposal. The Expert Committee will consider future revisions to the monograph upon the receipt of supporting data.
Comment summary #3: The commenter recommended in the *Specific Tests* section, adding “colorless” in the acceptance criteria of *Appearance*.
Response: Comment not incorporated. The appearance criteria are consistent with the sponsor’s label. The Expert Committee will consider future revisions to the monograph upon the receipt of supporting data.

Monograph/Section(s): Technetium Tc 99m Tetrofosmin Injection / Multiple sections

Expert Committee: Small Molecules 4
No. of Commenters: 2

Comment summary #1: The commenter recommended including retention times from radio-chromatograms in the *Acceptance criteria* for the *Radiochemical Identity* test in the *Identification* section.
Response: Comment incorporated. The Expert Committee included retardation factor comparison from the test for *Radiochemical Purity*.
Comment summary #2: The commenter recommended in the *Assay* section, including acceptance criteria for the radioactivity of Tetrofosmin in the test for *Radiochemical Purity* to match the approved.
Response: Comment not incorporated. The *Radiochemical Purity* test is out of scope for this *PF* proposal. The Expert Committee will consider future revisions to the monograph upon the receipt of supporting data.
Comment summary #3: The commenter recommended not deleting the *Biological Distribution* test before revising the *Radiochemical Identity* test to include retention times from radio-chromatograms.
Response: Comment partially incorporated. The Expert Committee included retardation factor comparison from the test for *Radiochemical Purity*.
Comment summary #4: The commenter recommended revising the *pH* acceptance criteria from "8.3 to 9.1" to "7.5 to 9.0" indicating that the current *pH* acceptance criteria apply to the manufacture of the kits for the preparation of Tc-tetrofosmin.
Response: Comment not incorporated. The *pH* test is out of scope for this *PF* proposal. The Expert Committee will consider future revisions to the monograph upon the receipt of supporting data.

Monograph/Section(s): Tobramycin Inhalation Solution / Multiple sections
Expert Committee: Small Molecules 5
No. of Commenters: 2

Comment summary #1: The commenter recommended, in the test for *Organic Impurities,* retaining the acceptance criteria for unspecified impurities at the current limit of 0.1%. The commenter additionally recommended that deoxystreptamine kanosamide be retained as a specified impurity with its current limit of 0.3%.
Response: Comment not incorporated. The currently official procedure and limits are retained.
Comment summary #2: The commenter indicated that the proposed *Organic Impurities* method does not appear to be capable of controlling the specified unidentified impurity at RRT 0.36. This impurity needs to be controlled and the RRT should be established but not as a specified impurity.
Response: Comment not incorporated. The currently official procedure and limits are retained.
Comment summary #3: The commenter indicated changes to *Organic Impurities* method conditions may be required to achieve robust separation of several potential impurities and degradation products observed while evaluating the proposed procedure.
Response: Comment not incorporated. The currently official procedure is retained.
Comment summary #4: The commenter recommended changes to the logarithmic calibration for improved linearity for the *Organic Impurities* method.
Response: Comment not incorporated. The currently official procedure is retained.
Comment summary #5: The commenter recommended removing the "reporting threshold" in the test for *Organic Impurities* as it will vary based on product-specific factors.
Response: Comment not incorporated. The currently official procedure is retained.

Comment summary #6: The commenter recommended tightening the limits for any unspecified degradation products from “NMT 0.3%” to “NMT 0.1%” to be in line with FDA Guidance for Industry “Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation”, which states that all related impurities appearing at levels of 0.1% or greater should be specified.
Response: Comment not incorporated. The current procedure and limits are retained.
Comment summary #7: The commenter recommended revising the resolution requirement in the *System suitability* for the *Organic Impurities* test to be higher than the current requirement of NLT 1.0 between apramycin and tobramycin.
Response: Comment not incorporated. The current procedure and limits are retained.
Expert Committee-initiated Change #1: In the test for *Organic Impurities*, the sentence beginning with “For unknown peak determination…” under the *Analysis* section is revised to provide clarification for disregarding unknown peaks as follows: “For unspecified impurity determination, disregard any unidentified peak observed in the *Derivatized sample solution* also observed in the *Derivatized system suitability solution 1*.”