Commentary
USPNF 2026 ISSUE 2

September 25, 2025; updated November 21, 2025

In accordance with USP's *Rules and Procedures of the 2025-2030 Council of Experts* (*CoE Rules*), and except as provided in Section 10.02 *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.

For further information, contact:
USP Executive Secretariat
United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852-1790 USA

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

General Chapters
<315> NMR NUMBER-AVERAGE MOLECULAR WEIGHT DETERMINATION FOR LG POLYMERS
<316> GPC MOLECULAR WEIGHT AND POLYDISPERSITY DETERMINATION FOR LG POLYMERS USING UNIVERSAL CALIBRATION
<1154> LIPOSOME DRUG PRODUCTS
<2021> MICROBIAL ENUMERATION TESTS--NUTRITIONAL AND DIETARY SUPPLEMENTS
<2022> MICROBIOLOGICAL PROCEDURES FOR ABSENCE OF SPECIFIED MICROORGANISMS--NUTRITIONAL AND DIETARY SUPPLEMENTS

Monographs
ACETYLCYSTEINE
ACETYLCYSTEINE SOLUTION
ACYCLOVIR OINTMENT
AMBRISENTAN
CELECOXIB
CLOBETASOL PROPIONATE SHAMPOO
CLOBETASOL PROPIONATE TOPICAL SPRAY
DAPAGLIFLOZIN TABLETS
DEXAMETHASONE TABLETS
DL-LACTIDE HOMOPOLYMER 14000 ACID
DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE TABLETS
GONADORELIN ACETATE
MESNA INJECTION
METHAMPHETAMINE HYDROCHLORIDE
MOMETASONE FUROATE
N-ACETYL-DL-TRYPTOPHAN
PENTAZOCINE HYDROCHLORIDE
SILDENAFIL FOR ORAL SUSPENSION
SILODOSIN
SILODOSIN CAPSULES
SODIUM PERTECHNETATE TC 99M INJECTION
TECHNETIUM TC 99M ALBUIN AGGREGATED INJECTION
TECHNETIUM TC 99M EXAMETAZIME INJECTION
TECHNETIUM TC 99M MEDRONATE INJECTION
TECHNETIUM TC 99M OXIDRONATE INJECTION
TECHNETIUM TC 99M PYROPHOSPHATE INJECTION
TECHNETIUM TC 99M SUCCIMER INJECTION
TECHNETIUM TC 99M SULFUR COLLOID INJECTION
TESTOSTERONE
TETRABENAZINE

No comments were received for the following proposals:

Monographs
ACYCLOVIR CREAM

ACYCLOVIR FOR INJECTION
AMINOCAPROIC ACID TABLETS
BROMODIPHENHYDRAMINE HYDROCHLORIDE
BROMODIPHENHYDRAMINE HYDROCHLORIDE AND CODEINE PHOSPHATE
DEXTROMETHORPHAN
HYDROCORTISONE SODIUM SUCCINATE
KETOROLAC TROMETHAMINE OPHTHALMIC SOLUTION
LEVOCABASTINE HYDROCHLORIDE
METHYLPREDNISOLONE SODIUM SUCCINATE
MYRISTYL LACTATE 75
PHENDIMETRAZINE TARTRATE TABLETS
PIROXICAM CAPSULES
QUINIDINE GLUCONATE INJECTION
SACCHARIN SODIUM TABLETS
TETRABENAZINE TABLETS

General Chapter

General Chapter/Section(s):	<315> NMR NUMBER-AVERAGE MOLECULAR WEIGHT DETERMINATION FOR LG POLYMERS
Expert Committee:	Excipients Test Methods
No. of Commenters:	1

Comment Summary #1: The commenter suggested discussing the validation data of this method in detail with the FDA Government Liaisons to the Excipients Test Methods EC and LG Polymer Subcommittee to Complex Excipients EC before moving forward with this PF, because there is a lack of sufficient scientific knowledge regarding the use of the proposed method for number-average molecular weight for PLGA polymers with an acid end.
Response: Comment incorporated. After discussion, the title and the introduction have been revised to specify that this chapter is only for lactide-glycolide polymers with ester end groups, not PLGA polymers with an acid end. The phrase "LG polymer ester" in Analysis has been changed to "lactide-glycolide polymer with an ester end group" to correctly reflect the substances tested.
Comment Summary #2: The commenter recommended revising the chapter title to limit to the polymer with an ester-end-cap because the integration of the triplet from 0.8 to 1.3 ppm (r1) is applicable only for the methyl group of the ester.
Response: Comment incorporated. The title and the introduction have been revised to specify that this chapter is only for lactide-glycolide polymers with ester end groups. The phrase "LG polymer ester" in Analysis has been changed to "lactide-glycolide polymer with an ester end group" to correctly reflect the substances tested.

General Chapter/Section(s):	<316> GPC MOLECULAR WEIGHT AND POLYDISPERSITY DETERMINATION FOR LG POLYMERS USING UNIVERSAL CALIBRATION
Expert Committee:	Excipients Test Methods
No. of Commenters:	2

Comment Summary #1: The commenter suggested revising the text in the “Standard Solutions” section from “Allow the solutions to sit for 2 h to equilibrate before analysis” to “Allow

the solutions to sit for 2 h to equilibrate and shake thoroughly before analysis" to allow uniform distribution of molecules across the solvent.
Response: Comment partially incorporated. Polystyrene standards are readily soluble in tetrahydrofuran (THF), so shaking is not necessary even though shaking will not cause any foaming in THF. The sentence has been revised to "Mix well and allow the solutions to sit for 2 h to equilibrate before analysis" to provide clarity.
Comment Summary #2: The commenter suggested replacing gel permeation chromatography (GPC) with size exclusion chromatography (SEC) in the title of this GC to be consistent with other GCs, as gel permeation chromatography (GPC) and size-exclusion chromatography (SEC) are referenced together in several general chapters and <621>mentions only SEC.
Response: Comment incorporated. "Gel permeation chromatography (GPC)" has been changed to "Size-exclusion chromatography (SEC)" in the title and "GPC" has been changed to "SEC/GPC" in the texts for clarity and consistency.
Comment Summary #3: The commenter indicated MW, MP, and MV with a comma next to each of them appear as though they contain w', p' and v' (i.e., MW'; MP'; MV'). Similar issues were observed in General Chapters <312>, <313> and <314>. The commenter recommended revising these to appear correctly.
Response: Comment partially incorporated. The comment is valid for this general chapter. To avoid confusion, the changes have been incorporated in this general chapter. The EC can consider making changes to <312>, <313> and <314> in separate revisions in the future.
EC-Initiated Change #1: The wording reference to lactic acid or glycolic acid was removed in Title and Introduction as the chapter is only focused on lactide-glycolide polymers.

[The following commentary was updated on November 21, 2025 to correct an ISO reference and to indicate that the comments in Summary #7 were partially incorporated]

General Chapter/Section(s):	<1154> LIPOSOME DRUG PRODUCTS
Expert Committee:	General Chapters - Dosage Forms 2020
No. of Commenters:	4

General Requirements- Particle Size and Distribution
Comment Summary #1: The commenter provided the following comments regarding Table 2.

#1a. Dynamic light scattering (DLS):

- The commenter suggested replacing "liposome diameter" with "hydrodynamic diameter".
- The commenter suggested removing the brackets from "intensity distribution" and including "z-average" along with "intensity distribution" and "polydispersity index."

Response: Comment incorporated.
#**1b**. Scanning electron microscopy (SEM):

- The commenter recommended removing this method from the table because this method is unsuitable for liposomes, as drying affects their structure.

Response: Comment not incorporated. Indeed, SEM is not a commonly used method for liposome characterization. However, it could be argued that TEM (unless specifically referring to cryo-TEM) also typically operates in the dry state. Therefore, the justification provided in the comment presents an incomplete picture and could apply to other, more commonly used techniques as well. Another aspect to consider is whether the characterization techniques discussed here would be acceptable for certain product types. While liposomes are not typically analyzed by SEM, a liposomal delivery system immobilized on larger powder particles via spray

drying could certainly be characterized using SEM, as it is a widely used method for analyzing dry powders.

- The commenter stated that the protocol PCC-7 is “Measuring the Size of Nanoparticles Using Transmission Electron Microscopy (TEM).” So the protocol focuses on size measurement, not morphology investigation, and applies to TEM, not SEM.

Response: Comment not incorporated. Please refer to response in #1b and the protocol number mentioned for referenced purpose.

#1c. Cryogenic transmission electron microscopy (cryo-TEM):

- The commenter recommended including the size distribution parameter: “Morphology, shape and size distribution”.

Response: Comment incorporated.

- Typically, cryo-TEM is used to visualize a product/substance in liquid state. The commenter would like to understand the rationale behind using cryo-TEM in dry state.

Response: Comment not incorporated. Refer to #1b, SEM bullet point 1.

- As mentioned in the SEM sub-section (#1b), the commenter did not plan to include the dry cryo-TEM method in their chapter on liposomal preparations. The commenter stated that this method is not suitable for liposomes because drying impacts the liposome structure. The commenter recommended removing this method.

Response: Comment not incorporated. Refer to #1b, SEM bullet point 1.

- The commenter recommended adding the published standard ASTM E3143–18b “Standard Practice for Performing Cryo-Transmission Electron Microscopy of Liposomes” to the table.

Response: Comment incorporated.

#1d. Atomic force microscopy (AFM): The commenter requested checking the two references to ensure the relevancy.

- The full title of the protocol NIST-NCL Joint Assay Protocol, PCC-6 0 corresponds to “Size Measurement of Nanoparticles Using Atomic Force Microscopy”. The document does not describe how to perform morphology characterization.

Given that the title of ASTM 2859-11 (2017) is “Size Measurement of Nanoparticles Using Atomic Force Microscopy”, we wondered whether this document contained a procedure for morphology shape and surface characterization.

Response: Both comments are incorporated. The provided references in the AFM section were reconfirmed.

#1e. Nanoparticle tracking analysis (NTA):

- The commenter recommended updating the official name of the method to Particle Tracking Analysis (PTA).

Response: Comment not incorporated. NTA is a subset of PTA most suitable for liposomes.

- The commenter suggested replacing “Particle diameter” with “Liposome Hydrodynamic diameter” and to use the term “liposome” instead of “particle” throughout the text for consistency.

- Based on ISO19430, PTA is capable of measuring concentration; therefore, the commenter recommended adding it as reported parameter as well.

Response: Comments incorporated.
#1f. Centrifugal liquid sedimentation (CLS) (with a suitable detection method):

- In line with ISO standards, the commenter suggested replacing “Sedimentation behavior” with “Sedimentation coefficient distribution” or “Size distribution”.

Response: Comment incorporated. Changed to "sedimentation coefficient distribution".

- The commenter recommended adding ISO 18747-2:201 Determination of particle density by sedimentation methods.

Response: Comment incorporated.
#1g. Laser diffraction (LD):

- The commenter recommended replacing “Liposome diameter” with “Equivalent spherical diameter”.

Response: Comment incorporated.

- The commenter recommended specifying which index the term “size distribution index” refers to and whether it refers to the calculated span.

Response: Comment incorporated. Clarification made in text by including the term size distribution index.
#1h. Asymmetrical flow field-flow fractionation (AF4) (with a suitable detection method):

- The commenter suggested adjusting the reported parameter to correspond to “size distribution” and not “In-flow separation behavior.”

Response: Comment not incorporated. The parameter depends on both size and flow.

- The commenter suggested adding ASTM E3409-24 Standard Test Method for Analysis of Liposomal Drug Formulations Using Multidetector Asymmetrical-Flow Field-Flow Fractionation.

Response: Comment incorporated.
#1i. Small-angle X-ray scattering (SAXS):
The commenter suggested adjusting the reported parameter to correspond to “radius of gyration” and not “lamellarity and structure.”
Response: Comment incorporated.

- Given that the title of ISO 17867:2020 is “Particle size analysis — Small angle X-ray scattering (SAXS)”, the commenter wondered if it contained a procedure on lamellarity and structure analysis.

Response: Comment not incorporated. The guidance is provided for reference purposes, so the procedure is not provided.
Comment Summary #2: The commenter recommended not to reference SO/TS21362:2018 in USP chapters.
Response: Comment not incorporated. While ISO standards broadly apply across industries, they are also relevant to pharmaceuticals, such as the NIH's doxorubicin encapsulation standard under ISO consideration.
Comment Summary #3: The commenter requested clarity on whether multiple methods were expected to be used as well as how specific the characterization should be.
Response: Comment not incorporated. Product-specific methodology and specification ranges must be determined individually; no general method or range should be provided in the USP chapter.
Comment Summary #4: The commenter suggests including the term “critical” before “quality attributes” in the first sentence: *“The particle size and size distribution are critical quality attributes of liposome drug products (2-3).”*
Response: Comment not incorporated. One of the guiding principles of this draft is providing guidance on the characterization of liposomes in various contexts and administration routes more broadly. Specific FDA guidance has more information on whether a quality attribute is considered critical.
Comment Summary #5: The commenter requested further clarification on the acceptable polydispersity index (PDI) and particle size for liposomal drug delivery.
Response: Comment not incorporated. Product-specific methodology and specification ranges must be determined individually; no general method or range should be provided in the USP chapter. The "particle size and size distribution" has been changed to "particle size distribution" in the chapter text.
Comment Summary #6: The commenter suggested revising the Table 2 content so that it lists only size/PDI measurement methods.
Response: Comment not incorporated. Table 2 listed methods to analyze quality attributes of liposomes. The EC would like to keep the content as is as the table defined all the quality attributes of liposomes.
Comment Summary #7: The commenter made the following suggestions for Table 2:
i. To clarify that the methods listed are specifically for size/size distribution, the commenter suggested revising the table’s title as follows: **“**Table 2. Non-USP Analytical Standards for the Characterization of Liposomes Particle Size and Size Distribution**.”**
ii. The commenter recommended replacing centrifugal liquid sedimentation (CLS) with sedimentation velocity analytical ultracentrifugation (SV-AUC). Measurement of sedimentation behavior by SV-AUC would be more sensitive to particle aggregation than CLS.
iii. The commenter requested to update the references to current documents (i.e., ISO 22412:2017, ISO 19430:2016, ISO 13318-1:2001, and ISO 13320:2009).

iv. The commenter suggested including the methods listed below:
1. Method: Reversed-phase high-performance liquid chromatography (RP-HPLC) and charged aerosol detection (CAD).
Rationale: to identify lipid content if multiple lipid types are mixed.
Reported Parameter: Lipid content of multiple lipid types
2. Method: Size Exclusion Chromatography (SEC).
Rationale: to ensure liposomes have not formed aggregates, as well as identify impurities other methods may not have identified.
Reported Parameter: Liposome size
3. Method: Electrophoretic Light Scattering (ELS).
Rationale: to determine colloidal stability of lipid nanoparticles.
Reported Parameter: Zeta potential and electrostatic repulsion/attraction within the lipid nanoparticle emulsion
Response: Comments partially incorporated.

General Considerations

Comment Summary #8: The commenters proposed to reevaluate Table 1.

Response: Comment not incorporated. As written, Table 1 is a necessary part of the chapter as it defines all the liposomal products by different routes of administration.

Comment Summary #9: The commenter suggested replacing the word “incorporated” with “encapsulated” in the following sentence: “Water-soluble drug substances, due to their hydrophilic nature, can be incorporated into the internal aqueous compartment(s) of liposomes”.

Response: Comment not incorporated. The term "encapsulated" is more descriptive and, as such, the EC would like to use a phrase that allows room for more products being described or included.

Comment Summary #10: The commenter suggested establishing a minimum size while keeping the maximum size flexible for spherical vesicles. The commenter suggested adding the following sentence: "Their size ranges from approximately 20 nm to several micrometers, depending on the route of administration."

Response: Comment partially incorporated. A physical definition might be preferable, as it is more inclusive. Many topical delivery systems are a size greater than 1000 nm. The text was revised as following: " ...in the nanometer size range (typically between 1-1000 nm) with at least one lipid bilayer. Some liposomal preparations can exceed the nanometer range beyond 1 micron."

Comment Summary #11: The commenter requested clarification on whether this chapter applies to gene therapy products and the use of liposomes according to USP <1047>. The commenter was interested in expanding the chapter to include the ex-vivo use of liposomes (transfection reagent liposome-based) for cell and gene-based products. The commenter also requested that further distinction be provided regarding what should be conducted in the development phase as well as release requirements to remove any reader interpretation from the standard.

Response: Comment not incorporated. The USP chapters specify quality standards, not drug development guidance. The change is out of scope of this revision. Possible revisions may be made in the next cycle.

Comment Summary #12: The commenter suggested adding the liposome definition with ISO/TS4958 to have a definition that is harmonized with the proposed chapter in European Pharmacopoeias.

Response: Comment not incorporated. The ISO guideline (https://www.iso.org/obp/ui/fr/#iso:std:iso:ts:4958:ed-1:v1:en) offers a broad definition, including a membrane thickness and common dimensions. The broader scope and most terminology of the ISO guideline are already included in the latest revision of this chapter (e.g., cholesterol was included as an example of a typical component).

Comment Summary #13: The commenters suggested modifying the following "They contain a significant amount of intentionally produced spherical vesicles..." to "They contain a significant amount of spontaneously produced vesicles...".

Response: Comment partially incorporated. Only processes that are meant to produce liposomes fall under the quality requirements. The sentence was revised to read as following: "They contain a significant amount of intentionally produced vesicles...".

Comment Summary #14: The commenter requested to clarify the application scope of this chapter. If the current chapter is intended to apply to lipid nanoparticles, the commenter suggested including the definition from ⟨1153⟩ in this section. However, if the chapter is not intended to apply to lipid nanoparticles, the commenter suggested clarifying this by including text to explicitly state so.

Response: Comment not incorporated. This chapter's scope includes liposomes without excluding other dosage forms such as lipid complexes, lipid nanoparticles, and other phospholipid-based carriers; the proposed change is unnecessary. Additional chapters on phospholipids-based dosage forms will be addressed in next cycle.

Specific Requirements–Sterility

Comment Summary #15: The commenter requested that references to the Sterility and Endotoxin USP chapters be added to this section.

Response: Comment incorporated.

General Requirements–Assay
Comment Summary #16: The commenter requested to add other examples in addition to antibiotics.
Response: Comment not incorporated. This section is not intended to be limited to specific categories. Antibiotics are included in the text as one example. For other products, similar considerations can be made.
Comment Summary #17: The commenter requested to revise the statement regarding assay acceptance criteria to the following: "Assay results are often reported as a percentage of the label claim. While acceptable assay results are specific to the drug product in question, acceptance criteria are typically in the range of 90.0%–110.0%."
Response: Comment partially incorporated. The section on antibiotic exceptions has been updated to clarify that certain drug product exceptions are acceptable.

Special Requirements–Sterility
Comment Summary #18: The commenter requested clarification of the last sentence on whether the lipids are extracted following the disruption of liposomes and what is meant by "unextracted material" in this context.
Response: Comment not incorporated. The chapter is intended for general guidance and not for specific procedures or methods.
Comment Summary #19: The commenter requested adding references to the methods to measure endotoxins if the unextracted material where the endotoxin may be masked by liposomes.
Response: Comment partially incorporated. The chapter is intended for general guidance not for specific procedures or methods. USP GC<85> was added as a reference chapter for this section.

General Requirements–Encapsulation
Comment Summary #20: The commenter suggested putting the sentence "Additionally, complementary separation techniques such as AF4, together with suitable detection methods, can be used for analysis of molecular weight and size distribution" following the sentence "Common methods to determine the percentage of drug encapsulated include the separation of the encapsulated from the unencapsulated fraction by centrifugation, dialysis, or solid-phase extraction techniques (8–9)."
Response: Comment not incorporated. The EC decided that the text flows better as it is.
Comment Summary #21: The commenter requested to state that the percentage of the drug encapsulated in liposomes impacts the efficacy and safety of the liposomes. In addition, the commenter suggested replacing the word "change" with "decrease" in the following sentence: "The percentage of the drug encapsulated into liposomes is a key quality attribute determining the function of liposomes in the dosage form and may change over the time of storage."
Response: Comment not incorporated. The encapsulation percentage of the drug determines the delivery of the liposome. The word "change" is not replaced as it is more accurate than "decrease".
Comment Summary #22: The commenter requested to use "critical" instead of "key" before quality attributes.
Response: Comment not incorporated. One of the guiding principles of this draft was to provide guidance on the characterization of liposomes in various contexts and administration routes more broadly. Specific FDA guidance has more information on whether a quality attribute considered as critical.

General Requirements–Impurities
Comment Summary #23: The commenter stated that that impurities may also be process-related, resulting from process aids such as organic solvents or buffers.
Response: Comment incorporated. A sentence was added in the text: "Other impurities may occur as a result of the manufacturing process".

Comment Summary #24: The commenter requested to add clarification on the analytic methods and specifications for these residual lipids.
Response: Comment not incorporated. The USP General Chapters specify quality standards, not drug development guidance.
Comment Summary #25: The commenter recommended to clarify the last sentence in this section by including the following text: “Quality of the lipid excipient may impact efficacy, safety, and quality of the drug product. Therefore, quantitation of impurities, degradants, and lipid composition are critical.” Further, the commenter suggested including references to ASTM publications: ASTM-E3323 Standard Test Method for Lipid Quantitation in Liposomal Formulations Using High Performance Liquid Chromatography (HPLC) with an Evaporative Light-Scattering Detector (ELSD) and ASTM-E3324 Standard Test Method for Lipid Quantitation in Liposomal Formulations Using Ultra-High-Performance Liquid Chromatography (UHPLC) with Triple Quadrupole Mass Spectrometry (TQMS) in this section.
Response: Comment incorporated. Table 1 now includes the methodologies and standards. The ASTM guidance addresses overall quality testing of lipid excipients, so the additional clarification in the sentence is not needed.

General Requirements–Morphology and Shape
Comment Summary #26: The commenter pointed out that AF4 separation and centrifugation methods alone do not provide morphological information unless they are coupled with detectors such as MALS and DLS. In addition, the commenter requested to remove the example provided in the text.
Response: Comment not incorporated. The comment rightly points out that although centrifugation methods may vary, none of these separation techniques can provide morphological information without an appropriate detection system. The section emphasizes the importance of considering and reporting both separation and characterization methods. However, in this context, specifying a particular centrifugation method would not enhance the section and might inadvertently suggest that only certain methods have this limitation.
Comment Summary #27: The commenter suggested modifying the second sentence to the following: “These imaging methodologies, in combination with light scattering, provide the foundational information needed to select appropriate particle characterization methods for determining particle size and size distribution”.
Response: Comment not incorporated. The European guidelines for medical devices do indeed mention favorable combinations (such as imaging techniques alongside light scattering data). While this analytical strategy is broadly applicable and sound, there are products characterized using automated particle imaging and/or other methods. The EC recommended against introducing further constraints (fixed combinations) to maintain an informative and broadly neutral stance regarding specific combinations of techniques.

Special Requirements–Surface Charge
Comment Summary #28: The commenter stated that there were two definitions of zeta potential (first sentence and third sentence). The commenter suggested deleting the first sentence and replacing it with the third sentence in the section.
Response: Comment not incorporated. The first sentence provided a clear idea of the meaning of zeta potential as a marker of surface charge.

General Requirements–Composition
Comment Summary #29: The commenter suggested providing more information on liposome components. For instance, the commenter noted that polymer-coated lipids and sterols (i.e., cholesterol) are not mentioned in the text.
Response: Comment not incorporated. Cholesterol is indeed a valuable component, as it is included in many liposome formulations (unless similar sterols are introduced to fulfill its role). The term “polymer coatings” is somewhat unusual and may refer to the incorporation of the aforementioned functionalized or functional excipients, or to examples like polydopamine coatings, which are primarily found in the literature but not in drug products. Therefore, the EC

recommended avoiding this specific terminology of polymer coated lipids and instead introducing coatings of actual relevance by describing pertinent lipids.
Comment Summary #30: The commenter requested to distinguish functional excipients and functionalized excipients.
Response: Comment not incorporated. Functionalization creates a different molecule while function, in line with the FDA guidance, indicates an important role of the excipient in therapeutic purpose. Functionalization related to excipients are outside the scope of this chapter.
Comment Summary #31: The commenter requested further detail on the liposome composition and how it reacts in the In Vitro drug release, i.e., information on the phospholipids and the importance of the composition and how it relates to the drug delivery. The commenter suggested adding information on how this is accomplished biologically. In addition, the commenter requested consideration of allowability of inter-assay variability.
Response: Comment not incorporated. Product-specific methodology and specification ranges must be determined individually; no general method or range should be provided in the USP chapter. Revisions to the liposomes chapter regarding dissolution, composition, mechanism of release will be considered in a future cycle.

General Requirements–In Vitro Drug Release Test* and *In Vitro Physical Stability
Comment Summary #32: The commenter requested clarifying the term "dispersion medium" and whether this refers to WFI or a biological media.
Response: Comment not incorporated. The chapter text is intended for all types of media. Clarifying the use of the term “dispersion medium” could restrict use to only certain types of media.
Comment Summary #33: The commenter requested to add further explanation to this section that the manufacturer should develop this evaluation based upon the product and its proposed shelf life. In addition, the commenter requested clarification as to why in vivo biological reactivity evaluation is not considered under this chapter (as in e.g., GC <1032>, GC <88>, GC <1088> and GC <1090>).
Response: Comment not incorporated. Generally, potency measurements should not replace stability-indicating release measures, except in duly justified, limited circumstances. Therefore the in vivo biological reactivity test was not included.
Comment Summary #34: The commenter suggested including the reference to ISO or other relevant standards.
Response: Comment not incorporated. The chapter did not specify the standards to use; however, the user can use relevant ISO/ASTM standards as mentioned in the chapter.
Comment Summary #35: The commenter suggested including information that requires in vitro physical stability in biological media pertinent to the route of administration.
Response: Comment not incorporated. The chapter is open to all types of media. It is not the intent of the chapter to list all types of biological media. FDA guidance on liposomes has more information regarding this topic.
Comment Summary #36: The commenter suggested making the revision as follows: The in vitro physical stability of liposome drug products should be evaluated over the (delete:) “time of storage” (add:) “proposed shelf-life.” In addition, the physical stability of liposome drug products should be evaluated under in-use conditions, such as after dispersion of the drug product. Stability studies should be monitored at different temperature ranges according to the stage and purpose of the drug product development – whether for short-term, long-term or forced degradation study (e.g., 5 to 25º, -20 to 0º, -80º to -60º, -200 to -180º). Physical stability can be measured…”
Response: Comment incorporated.

General Considerations–Table 1
Comment Summary #37: 1. Parenteral route section: The commenter suggested adding the following text for clarification purposes*:* “Liposomal preparations are composed of amphipathic molecules, primarily phospholipids, which could be naturally or synthetically derived. Other structural components such as sterols (e.g. cholesterol), which help maintain membrane

integrity, and PEGylated lipids, which are used to modify the surface properties of the liposomal preparations, may also be employed."
2. Oral route section: The commenter suggested adding the following statement: "These biocompatible carriers can be delivered using a solid, semisolid, or liquid vehicle and, most often, have been formulated to improve the bioavailability of drugs."
3. Topical route section: The commenter stated that administration of liposomes to an open wound would require them to be sterilized.
Response: Comment partially incorporated.
1. Comment not incorporated. The scope of the chapter is focused on the product quality tests not on the development requirements.
2. Comment incorporated.
3. Comment not incorporated. The chapter is to be used in conjunction with other chapters which already discuss requirements for parenterals. The scope is already clarified in the introduction of the chapter.

General Requirements–Particle Size and Size Distribution
Comment Summary #38: The commenter requested clarification whether compliance with the unofficial standard ASTM WK54615 is expected.
Response: Comment incorporated. This standard has been removed.

Specific Requirements–Lamellarity
Comment Summary #39: The commenter recommended using the word "technique" rather than "method" in the following sentence: Lamellarity can be determined using methods techniques described in Morphology and Shape.
Response: Comment incorporated.
Comment Summary #40: The commenter recommended including the updated versions of ISO 22412:2008, ASTM E2490-09(2015), ISO19430:2016,
ISO 13318-1:2001, ISO13320:2009.
Response: Comment incorporated. A table was compiled.

Measurement Technique	Measured Parameters	Standard
Dynamic Light Scattering (DLS)	Particle size (hydrodynamic diameter), size distribution	**ISO 22412:2008** – Particle size analysis – Dynamic light scattering (DLS)
Transmission Electron Microscopy (TEM)	Particle size, morphology, aggregation	**ASTM E2490-09(2015)** – Standard Guide for Measurement of Particle Size Distribution of Nanomaterials in Suspension by TEM
Small-Angle X-ray Scattering (SAXS)	Particle size, shape, internal structure	**ISO 19430:2016** – Nanotechnologies — SAXS
Sedimentation (Centrifugal)	Particle size (via sedimentation velocity)	**ISO 13318-1:2001** – Determination of particle size distribution by gravitational liquid sedimentation
Laser Diffraction	Particle size distribution (volume/mass-based)	**ISO 13320:2009** – Particle size analysis — Laser diffraction methods

General Requirements–In Vitro Drug Release Test
Comment Summary #41: The commenter requested further information and identification on the methods of how the drug releases in the human body. The commenter indicated that the

method used needs to justify how it relates to the biological use of the product (e.g., route of administration, target tissue/organ).
Response: Comment not incorporated. Product-specific methodology and specification ranges must be determined individually; no general method or range should be provided in the USP chapter.
Comment Summary #42: The commenter suggested including a refence to FDA Guidance for Industry Drug Products, Including Biological Products, that Contain Nanomaterials. In addition, the commenter suggested modifying the list in second paragraph to include HPLC, which is commonly used in release methods for lipid nanoparticles.
Response: Comment partially incorporated. FDA guidance was added as a reference. HPLC was not included because while HPLC separates chemicals, it does not detect their initial physical state, which is required for release testing.

Specific Requirements–Surface Functionalization and Reactivity
Comment Summary #43: The commenter requested to make the following changes in the chapter:

- Add more references to bioreactivity or biocompatibility within the chapter.
- Describe how biocompatibility is overall evaluated as it relates to Liposome Drug Products.
- Expand the relevancy on gene therapy products (a disclaimer for gene therapy).
- Provide further information on naturally occurring liposomes.

Response: Comment not incorporated. This chapter covers liposomal gene therapy products, whose testing must meet comparable quality standards; exceptions are acceptable with justification and do not require clarification. For naturally occurring liposomes, no further information is required as the same tests can be used as for liposomal gene therapy products.

Specific Requirements
Comment Summary #44: The commenter proposed the following addition to the end of the section: “Characterization studies that are not part of the stability specification should be, ideally, performed on samples at release and at the end of the proposed shelf life.”
Response: Comment not incorporated. The USP chapters specify quality standards, not drug development guidance.

Assay
Comment Summary #45: The commenter suggested to add "may be" in the following text: "The assay is specific and may be stability-indicating**.**"
Response: Comment not incorporated. Generally potency measurements should not replace stability-indicating release measures, except in duly justified, limited circumstances.

Surface Functionalization and Reactivity
Comment Summary #46: The commenter requested to change the last sentence by adding the text as following: "Surface functionalizations may require a specific in vitro test to determine the efficiency and binding characteristics, if not already covered by alternative tests (e.g., potency)."
Response: Comment not incorporated. Drug potency assays may actually serve as stability-indicating measures, with USP deviations permissible upon justification.

Sterility and Endotoxin Levels
Comment Summary #47: The commenter requested to delete the last sentence of this section and to add USP GC<85>BACTERIAL ENDOTOXINS TEST as a reference chapter. The suggested revised text is as following: “Therefore, the influence of liposomes on the test result should be evaluated (see also USP<85>) and the control strategy adapted adequately.”

Response: Comment partially incorporated. The current section enhances understanding of the issues faced with standard assays; therefore the commenter's suggestion is unnecessary. A reference to USP <85> has been added.

General Considerations
Comment Summary #48: The commenter requested to add a statement to cover products above 1000 nm: "This chapter may also apply to vesicles that fall outside the nanometer size range**.**"
Response: Comment incorporated. Liposomes larger than 1000 nm were included in the introduction section.

Morphology and Shape
Comment Summary #49: The commenter suggested adding the sentence in the following text: ...environmental scanning electron microscopy, atomic force microscopy, or asymmetrical-flow field-flow fractionation coupled with small angle X-ray scattering should be considered (5).
Response: Comment incorporated.

General Requirements
Comment Summary #50: The commenter recommended including additional quality tests (e.g., pH, osmolality, etc.) as well as some general guidance regarding the selection of the analytical methods (and standards) for common liposome components (e.g., cholesterol, etc.).
Response: Comment not incorporated. This chapter on liposome testing complements other chapters describing drug product characteristics (e.g., parenterals, oral products), and its methods are specifically for liposomes; all relevant monograph requirements for the chosen route of administration also apply.

Encapsulation/Drug Binding
Comment Summary #51: The commenter proposed to make the following changes: "Additionally, complementary separation techniques providing direct measures of encapsulation**,** such as AF4, or indirect measures of encapsulation, such as gel/capillary electrophoresis measurement of free active ingredient/DS, together with suitable detection methods, can be used for analysis of molecular weight and size distribution. The influences of the separation technique on the detect encapsulation should be systematically investigated (10–12)."
Response: Comment incorporated.

Particle Size and Size Distribution
Comment Summary #52: The commenter suggested deleting the sentence: "All analytical methods used for batch release must be validated."
Response: Comment incorporated.

General Chapter/Section(s):	<2021> MICROBIAL ENUMERATION TESTS--NUTRITIONAL AND DIETARY SUPPLEMENTS
Expert Committee:	General Chapters - Microbiology 2022
No. of Commenters:	5

Comment Summary #1: The commenter indicated that the term "doubtful result" is unclear and suggested clarifying the procedure.
Response: Comment incorporated. The term "doubtful" has been revised to "questionable or unexpected" to improve clarity.
Comment Summary #2: Commenter summarized wording changes, including addition of <1223> and a new sentence that defined the term "growth".
Response: Comment acknowledged. No comment or requested change was provided.
Comment Summary #3: The commenter requested clarification on how the reduced inoculum to less than 100 CFU could relate to previously performed suitability and whether suitability should be repeated for all products once the chapter is active. Additionally, the commenter

questioned the incubation time of less than 5 days for *Aspergillus brasiliensis*/*Candida albicans* and how it would impact the current turnaround time, as well as the applicable range for incubation.
Response: Comment not incorporated. Whether it is necessary to run method suitability again will depend on a company's risk assessment.
Comment Summary #4: The commenter suggested the incorporation of confirmatory biochemical tests in <2021> and <62> for specific pathogens. They noted that different ISO standards mention biochemical tests for the confirmation of specific pathogens.
Response: Comment partially incorporated. More information was added to the relevant chapter for specific pathogens, <2022>. Additions to <2022> include procedures for when selective media shows a positive test for a pathogen, it is recommended that alternative testing be performed on the isolates to confirm the organism identity. Chapter <62> is not in scope of this revision and no changes were made at this time.
Comment Summary #5: The commenter requested the method of TEST FOR ABSENCE as mentioned in <62> be considered for bile-tolerant gram-negative (BTGN) bacteria, noting that the USP currently shows the most probable number method.
Response: Comment not incorporated. The required criteria are only for limits, not absence.
Comment Summary #6: The commenter requested adding a note that colony-forming unit (CFU) and most probable number (MPN) are not interchangeable units or offering a solution for CFU specifications according to ISO standards for BTGN bacteria.
Response: Comment not incorporated. To report MPN when the specification is in CFU, conversion factors or statistical tables can be used to relate MPN values to CFU values. However, these units are not exactly equivalent and reporting MPN might require specific context or regulatory guidelines.
Comment Summary #7: The commenters suggested removing lactose from the selective media Violet Red Bile Glucose and Lactose Agar because all BTGN bacteria are able to utilize glucose.
Response: Comment incorporated. The media section was updated to remove lactose from BTGN.
Comment Summary #8: The commenter requested clarification on whether the inoculum can exceed the countable range for the total combined yeasts and molds count plate method and suggested including the countable range in the text.
Response: Comment incorporated. Statements from <61> have been added for both total aerobic microbial count (TAMC) and total combined yeasts and molds count, specifying the countable range to ensure consistency and clarity.
Comment Summary #9: The commenter suggested adding a note specifying that the terminology for BTGN bacteria can be adjusted to report coliforms if required.
Response: Comment not incorporated. This request is outside the purview of this chapter and will be considered in a future revision of <64> Probiotics for monographs that include absence of coliforms. These monographs reference Food Chemicals Codex, Appendix XV, not <2021>.
Comment Summary #10: The commenter suggested incorporating triplicate retesting for confirming questionable or unexpected results and provided proposed wording changes: “For the purpose of confirming a doubtful (removed doubtful, questionable/unexpected) result determined by a laboratory investigation by any of the procedures outlined in the foregoing tests following their application to a 10-g specimen, perform triplicate retesting of additional 10-g specimen from the original sample (if available) and if warranted triplicate additional retesting a 10-g specimen from the new sample of the dietary ingredient or supplement may be conducted. Proceed as directed under Procedure. Before disqualifying the original result, follow laboratory out-of-specification procedures based on regulatory guidance."
Response: Comment partially incorporated. The wording has been revised for clarity, including replacing "doubtful" with "questionable or unexpected." The recommendation for triplicate retesting was partially accepted, with modifications. A portion of the sentence was replaced with: “following the appropriate OOS procedure as prepared by the users’ organization.” This ensures alignment with standard laboratory out-of-specification (OOS) procedures.

Comment Summary #11: The commenter requested updating the method in USP <2021> to allow for both dibasic potassium phosphate and disodium hydrogen phosphate dihydrate for the preparation of Mossel EEB, to avoid conflicts when purchasing pre-made media.
Response: Comment incorporated. The ingredients list in the recommended media section was updated for EE Mossel Broth per Difco/BBL Manual.

Comment Summary #12: The commenter recommended changing the incubation time for the TAMC plate method from 48-72 hours to 3-5 days to align with the suitability test, which now includes yeast and mold. Additionally, the commenter suggested adding a note to count all growth present.
Response: Comment incorporated. The incubation time has been updated to 3-5 days.

Total Aerobic Microbial Count
Comment Summary #13: The commenter indicated that probiotics should not be tested for Total Aerobic Microbial Count (TAMC) and suggested referring to Chapter <64> for guidance.

Response: Comment incorporated. A note has been added stating that this testing procedure is not appropriate for most probiotics, as they require special conditions and are not typically aerobic.

Bile-Tolerant Gram-Negative Bacteria (BTGN)
Comment Summary #14: The commenter suggested adding an option to include additional dilutions based on the product's specification, up to 10,000 MPN or higher, in the section on BTGN Bacteria.
Response: Comment not incorporated. This is not a limit for any of the products in USP. Additional data would be needed to verify such limits.

[The following commentary was updated on November 21, 2025 to correct the response for the comment incorporation to Summary #1]

General Chapter/Section(s):	<2022> MICROBIOLOGICAL PROCEDURES FOR ABSENCE OF SPECIFIED MICROORGANISMS--NUTRITIONAL AND DIETARY SUPPLEMENTS
Expert Committee:	General Chapters - Microbiology 2022
No. of Commenters:	5

Comment Summary #1: The commenter suggested adding a note on typical or atypical test preparation to each section. The commenter indicated that without this addition, the text reads as being in conflict, especially if no growth matches the tables, implying that the test is absent.
Response: Comment partially incorporated. A sentence was added to the Test Preparation section to state that confirmation is needed for typical or suspect colonies on selective media.
Comment Summary #2: The commenter requested guidance on reporting results as either absent or not detected.
Response: Comment not incorporated. Reporting may vary depending on the regulatory agency or destination. Specifying terminology may inadvertently create a non-compliance issue.
Comment Summary #3: The commenter requested to combine <2021> and <2022> with <61> and <62>.
Response: Comment partially incorporated. General revisions for both <2021> and <2022> were made to ensure alignment with the methods in <61> and <62>, where possible.
Comment Summary #4: The commenter suggested incorporating ranges with tolerances of ±2 hours for incubation times, emphasizing the need for some range for the earliest pull to ensure suitability.
Response: Comment partially incorporated. Ranges are acceptable, and for incubation times not listed as a range, refer to in-house procedures on tolerance. The method suitability section was rewritten to mention that the method suitability should be performed at the shortest incubation time.

Comment Summary #5: The commenter suggested that the language in Table 1 should address the use of similar or equivalent strains.
Response: Comment not incorporated. No change was made as the current language already allows for the use of similar or equivalent strains by including the phrase “such as.”

Comment Summary #6: The commenter suggested reducing the incubation period to 18-24 hours for the primary dilution in the Test for Absence of E. coli. The commenter provided an attached method modification report to support this change.
Response: Comment incorporated. The requested change was made to the text.
Comment Summary #7: The commenter recommended rejecting the revision to USP <2022> that changed the growth promotion and suitability test requirements to a quantitative recovery of not more than 100 CFU. The commenter indicated that while this revision is suitable for microbial enumeration using general microbiological growth media, it is not appropriate for the qualitative presence/absence test where streaking an inoculum on selective/diagnostic solid media is used to demonstrate recovery.
Response: Comment partially incorporated. The final wording states: "For other media, streak agar plates to obtain isolated colonies of appropriate microorganisms and inoculate the fluid media with the appropriate microorganisms at a dilution of approximately not more than 100 CFU."
Comment Summary #8: A query was received during the comment period which requested corrections to typos contained in the suggested media section. Brilliant Green agar medium phenol red should be 80 mg (not 80 g) and there is a spelling error of xylose-lysine deoxycholate agar.
Response: Comment incorporated. The requested changes were made.
Comment Summary #9: The commenter suggested clarifying which medium should be incubated for the Salmonella Species test, specifically the incubation process and subsequent steps involving Rappaport–Vassiliadis Salmonella Enrichment Broth and streaking onto various media surfaces.
Response: Comment incorporated. The wording has been changed to clarify the incubation process: “After incubation, subculture onto individual surfaces of one or more of the following media.” Additionally, the wording around suspected colonies has been updated to specify the need for confirmatory identification tests if colonies with characteristics described in Table 3 are present. Suspect colonies may be confirmed by transferring to a slant of Triple Sugar Iron Agar (TSI) using an inoculating wire.
Comment Summary #10: The commenter suggested including an option for chromogenic media, such as Rapid Salmonella and ASAP, which are more effective in differentiating Salmonella from other species of Enterobacteriaceae.
Response: Comment partially incorporated. The introduction contains a statement regarding alternative methods, with added clarifying language. The addition of other tests to the chapter will be addressed in a future revision and requires additional validation information.
Comment Summary #11: The commenter suggested new text for the RETEST section. The proposed change clarifies that if a positive result is found in a test for absence, the product does not comply with the requirement unless it can be clearly demonstrated that the test was invalid due to causes unrelated to the product examined, such as laboratory error or fault in testing materials. If the test is declared invalid, it is repeated with the same sample size as in the original test, and the new result is reported.
Response: Comment incorporated. The proposed text has been added to the RETEST section.
Comment Summary #12: The commenter suggested including the addition of Lysine Iron Agar (LIA) in the confirmation process, following the FDA Bacteriological Analytical Manual (BAM) procedure for the Test for Absence of Salmonella Species.
Response: Comment not incorporated. Will consider adding in a future revision after further evaluation. It is possible that the current FDA method may be changed or unavailable in the future.
Comment Summary #13: The commenter suggested an option for seed lot cultures or frozen cultures in the Test Microorganisms section.

Response: Comment partially incorporated. Added language to broaden culture preparation: "Use standardized stable suspensions of test strains as stated below. Seed-lot culture maintenance techniques (seed-lot systems) are used so that the viable microorganisms used for inoculation are not more than five passages removed from the original master seed-lot."

Comment Summary #14: The commenter suggested adding a method for *Listeria* spp. and referenced the FDA BAM cultural method.
Response: Comment not incorporated. Will consider adding in a future revision after further evaluation of the method. USP plans to evaluate the addition of other specified microorganisms, such as *Listeria* spp. in a future revision of this chapter.

Monograph

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

Comment Summary #1: The commenter indicated that they had reviewed Acetylcysteine proposal for Organic impurities test and compared with Related substances test as per British Pharmacopoeia. The resolution was not achieved when performing the Related substances test as per British Pharmacopeia. The commenter requested column part number detail and chromatograms be added.
Response: Comment not incorporated. The Expert Committee determined that the proposed method is suitable and is based on the sponsor's validation. The PF Briefing lists the column used by the sponsor. Chromatograms are not included in USP monographs.
Comment Summary #2: The commenter indicated that the use of L-phenylalanine as internal standard for the quantitation is not necessary due to the non-complex nature of the sample matrix and the modern HPLC systems with autosamplers. The commenter requested revising the quantitation method by using acetylcysteine for external standard calibration and removal of L-Phenylalanine from all solutions. The commenter also suggested adding a system suitability solution containing, e.g., 0.5 mg/mL acetylcysteine and L-phenylalanine to monitor the resolution.
Response: Comment not incorporated. The comment is out of scope for this proposal. A future revision may be considered upon receipt of approved specifications and supporting data. Use of alternate procedures is discussed in General Notices "6.30. Alternative and Harmonized Methods and Procedures"
Comment Summary #3: The commenter indicated the limited stability of the standard solution in Assay. The commenter requested replacing the requirement for the relative standard deviation of NMT 0.73% by NMT 0.41% implicating only 3 reference injections with respect to USP <621> or removing the numerical requirement from the monograph and replacing it by a general reference to the Table 2 in USP <621> leaving the number of injections open to the respective laboratory, where the method is applied.
Response: Comment not incorporated. The Expert Committee determined that the proposed system suitability requirements are suitable.
Comment Summary #4: The commenter requested replacement of Assay by HPLC with potentiometric titration for harmonization with the current method for assay as per Ph.Eur, this would increase the efficiency and reduce the complexity of the analysis.
Response: Comment not incorporated. The comment is out of scope for this revision proposal. Use of alternate procedures is discussed in General Notices "6.30. Alternative and Harmonized Methods and Procedures".
Comment Summary #5: The commenter indicated difficulties applying the Organic Impurities method in their laboratory, including interference of a blank peak with the peaks of L-Cystine and L-Cysteine, poor accuracy and precision. The commenter recommended aligning the chromatographic conditions and parameters with the current method on related substances

published in the Ph.Eur. monograph for Acetylcysteine, as included in their DMF for acetylcysteine, which they validated and show suitability for the intended use.
Response: Comment not incorporated. The Expert Committee determined that the proposed method is suitable and is based on the sponsor's validation. The sponsor indicated that they have not experienced any issues when the column is conditioned prior to running the analysis. A note is included indicating that the column should be conditioned prior to use to improve chromatography. Use of alternate procedures is discussed in General Notices "6.30. Alternative and Harmonized Methods and Procedures".
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. A new USP General Chapter, ⟨477⟩ User-Determined Reporting Thresholds supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee may consider incorporating this new approach in future revisions, as applicable.
Comment Summary #6: The commenter recommended under Additional Requirements including a labeling statement that it is sterile or must be subjected to further processing when intended for use in preparing injectable dosage forms. The commenter also requested including applicable tests to confirm sterility to support the labeling statement.
Response: Comment not incorporated. The comment is out of scope for this revision proposal. This is a new requirement and cannot be added through the commenting process. The Expert Committee may consider a future revision upon receipt of approved specifications and supporting data.
Comment Summary #7: The commenter indicated that the proposed PF 49(2) method for organic impurities can be performed as written using HPLC conditions (Waters Alliancee2695)i. However, the insufficient separation between the L-Cystine and the diluent peak and the L-Cysteine and unspecified impurity caused shouldering of these specified impurities peaks. The commenter indicated the separation of Cystine/Cysteine can be improved using UPLC system (Waters H-Class), which requires reduction of the flow rate from 1.5 mL/min to 1.1 mL/min to lower the column backpressure.
Response: Comment not incorporated. The Expert Committee determined that the proposed method is suitable and is based on the sponsor's validation. The sponsor indicated that they have not experienced any issues when the column is conditioned prior to running the analysis. A note is included indicating that the column should be conditioned prior to use to improve chromatography. Use of alternate procedures is discussed in General Notices "6.30. Alternative and Harmonized Methods and Procedures".

Monograph/Section(s): ACETYLCYSTEINE SOLUTION/Organic Impurities
Expert Committee: Small Molecules 2
No. of Commenters: 2

Comment Summary #1: The commenter recommended removing "Methylthiazoline Carboxylic Acid" from the impurity table (Table 4).
Response: Comment not incorporated. The tests for Limit of -Cysteine, Acetylcysteine Related Compound C, and Acetylcysteine Related Compound D and Organic Impurities are cancelled and may be re-published in the future to address comments. The removal of Methylthiazoline Carboxylic Acid will be considered in the future revision.
Comment Summary #2: The commenter requested revising the acceptance criteria for "Acetylcysteine related compound C", "Acetylcysteine related compound D" and "Total impurities" to be consistent with what has been approved.
Response: Comment not incorporated. The tests for Limit of -Cysteine, Acetylcysteine Related Compound C, and Acetylcysteine Related Compound D and Organic Impurities are cancelled and may be re-published in the future to address comments.
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. The tests for Limit of -Cysteine, Acetylcysteine Related Compound C, and Acetylcysteine Related Compound D and Organic Impurities are cancelled and may be re-published in the future to address comments.
Comment Summary #4: The commenter requested changing the specification and provided their approved specifications.
Response: Comment not incorporated. The tests for Limit of -Cysteine, Acetylcysteine Related Compound C, and Acetylcysteine Related Compound D and Organic Impurities are cancelled and may be re-published in the future to address comments.
Comment Summary #5: The commenter indicated there is insufficient separation between the L-Cystine and L-Cysteine (resolution was 1.3). The commenter requested to change the chromatographic condition (from HPLC to UPLC, reduce flow rate) to improve the resolution and backpressure in Organic Impurities.
Response: Comment not incorporated. The tests for Limit of -Cysteine, Acetylcysteine Related Compound C, and Acetylcysteine Related Compound D and Organic Impurities are cancelled and may be re-published in the future to address comments.
Comment Summary #6: The commenter indicated in the test for Organic impurities the USP Cystine RS did not dissolve in diluent or purified water even after sonication, and the addition of HCl was required to dissolve the reference standard. The commenter requested to adjust the system suitability solution preparation to indicate that stock solution can be prepared with the aid of HCl added to improve the solubility of USP Cystine RS.
Response: Comment not incorporated. The tests for Limit of -Cysteine, Acetylcysteine Related Compound C, and Acetylcysteine Related Compound D and Organic Impurities are cancelled and may be re-published in the future to address comments.

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

Comment Summary #1: The commenter indicated in the test for Organic Impurities, that the acceptance criteria for “Any unspecified degradation products” is different than what has been approved and recommended revising the acceptance criteria to be consistent with what has been approved.
Response: Comment incorporated. The acceptance criteria for "Any unspecified degradation products" is widened from NMT 0.20% to NMT 0.2%.

Monograph/Section(s):	AMBRISENTAN/Multiple sections
Expert Committee:	Small Molecules 5
No. of Commenters:	4

Comment Summary #1: The commenter indicated that the acceptance criterion for the Enantiomeric Purity test is different from what has been approved and recommended revising the acceptance criterion to be consistent what has been approved.
Response: Comment incorporated. The acceptance criterion in the Enantiomeric purity test is widened from NMT 0.15% to NMT 0.5%.
Comment Summary #2: The commenter stated that, in the test for Organic Impurities, the relative retention time observed for Ambrisentan related compound C was 1.04 instead of 1.17.
Response: Comment incorporated. Based on supporting data, the relative retention time for Ambrisentan related compound C is changed from 1.17 to 1.04.
Comment Summary #3: The commenter indicated, in the test for Organic Impurities, that there are additional specified impurities approved for their product and recommended including them.
Response: Comment not incorporated. The Expert Committee may consider a future revision to the monograph upon receipt of supporting data.
Comment Summary #4: The commenter indicated, in the test for Organic Impurities, that total impurities limit is different from what has been approved by the agency.

Response: Comment incorporated. The limit for total impurities was widened from NMT 0.5% to NMT 1.0%.
Comment Summary #5: The commenter indicated that in the Limit of Ambrisentan Related Compound E test, the test procedure is not specific. The commenter indicated that their in-house specified impurities eluted at the retention time of ambrisentan related compound E.
Response: Comment not incorporated. The Expert Committee determined that the proposed method is suitable and consistent with the validation data.
Comment Summary #6: The commenter commented that one of the in-house specified impurities is eluting closely with the ambrisentan peak and the R-enantiomer is merging with the ambrisentan peak in the Assay.
Response: Comment not incorporated. The Expert Committee determined that the proposed method is suitable and consistent with the validation data.
Comment Summary #7: The commenter stated that their in-house Enantiomeric Purity test is better than the proposed procedure. The commenter provided chromatogram indicating one of the in-house specified impurity elutes closely with the R-enantiomer.
Response: Comment not incorporated. The Expert Committee determined that the proposed method is suitable and consistent with the validation data.
Comment Summary #8: The commenter commented that the relative standard deviation (RSD) requirement in the Assay is challenging to meet and recommended widening the limit from NMT 0.73% to NMT 2.0% in the system suitability section.
Response: Comment not incorporated. The Expert Committee determined that the proposed requirement is suitable and consistent with the validation data.
Comment Summary #9: The commenter requested widening the acceptance criterion for Residue on Ignition test from NMT 0.1% to NMT 0.2% to be consistent with their approved specifications.
Response: Comment incorporated. The acceptance criterion in the Residue on Ignition test was widened from NMT 0.1% to NMT 0.2%.
Comment Summary #10: The commenter requested to widen the acceptance criterion for Water Determination test from NMT 0.5% to NMT 1.0% to be consistent their approved specifications.
Response: Comment incorporated. The acceptance criterion in the Water Content test was widened from NMT 0.5% to NMT 1.0%.
Comment Summary #11: The commenter requested to use the system suitability solution instead of standard solution in the identification B test, as the standard solution in Enantiomeric Purity test has USP Ambrisentan R-enantiomer RS.
Response: Comment incorporated. Identification B is revised to read “The retention time of the ambrisentan peak of the Sample solution corresponds to that of the ambrisentan peak in the System suitability solution, as obtained in the Enantiomeric Purity test”.
Comment Summary #12: The commenter requested revising the reporting threshold from 0.1% to 0.05% in the test for Organic Impurities.
Response: Comment incorporated. In the Organic Impurities test, the reporting threshold is updated to “[Note-A reporting threshold of 0.05% may be suitable when the maximum daily dose is ≤1 g].”

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

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: The commentor observed that resolution requirements between celecoxib related compound A and celecoxib could not be met using two different manufacturers' instruments.
Response: Comment not incorporated. The Expert Committee determined that the proposed method is suitable and addresses significant comments previously received, and also aligns the resolution with the EP monograph, which are wider. Use of alternate procedures is discussed in General Notices "6.30. Alternative and Harmonized Methods and Procedures".

Monograph/Section(s): CLOBETASOL PROPIONATE SHAMPOO/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 may consider incorporating this new approach in future revisions, as applicable.
Comment Summary #2: The commenter requested to revise the acceptance criteria for "pH", under Specific Tests, to be consistent with what has been approved.
Response: Comment incorporated. The acceptance criterion for the pH test was widened from "5.4-6.2" to "5.3-6.7".

Monograph/Section(s): CLOBETASOL PROPIONATE TOPICAL SPRAY/Multiple Sections
Expert Committee: Small Molecules 5
No. of Commenters: 4

Comment Summary #1: The commenter indicated in the test for Organic Impurities, that the acceptance criteria for "Clobetasol" and "Clobetasol propionate related compound A" are different from what has been approved and recommended revising to be consistent with what has been approved.
Response: Comment incorporated. The acceptance criteria for Clobetasol was widened from NMT 0.5% to NMT 1.0% and Clobetasol propionate related compound A was widened from NMT 0.5% to NMT 1.0%.
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 commented, in the test for Organic Impurities, that Betamethasone, Clobetasol 16-ene and Clobetasone 17-Propionate impurities are synthetic impurities and indicated not to quantitate these impurities.
Response: Comment not incorporated. The Expert Committee determined that the three specified impurities can be potential degradants based on the structure and consistent with sponsor's approval.
Comment Summary #4: The commenter requested omission of the Uniformity of Delivered Units test from the monograph as USP general chapter <905> for the said dosage form is not required.
Response: Comment incorporated. The Uniformity of Delivered Units test is removed

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

Comment Summary #1: Commenters recommended adding a dissolution test to the monograph because the molecule is BCS class III (high solubility–low permeability). In addition, Dissolution is a required test in EDA regulations in Egypt.
Response: Comment not incorporated.
An additional dissolution test can be considered for inclusion as a future revision upon receipt of approved specifications and supporting data.

Comment Summary #2: The commenter indicated that their FDA-approved specifications for dissolution are not present in the proposal. The commenter requests USP to consider their dissolution specifications in the monograph.
Response: Comment not incorporated. An additional dissolution test can be considered for inclusion as a future revision upon receipt of approved specifications and supporting data.
Comment Summary #3: The commenter indicated that their FDA-approved specifications for organic impurities does not include Hydroxydapagliflozin and they request USP revisit the proposal for incorporation of this impurity in the monograph specification.
Response: Comment not incorporated. The proposed acceptance criteria for organic impurities are consistent with the sponsor's approved specifications**.** The Expert Committee can consider future revisions to the monograph upon the receipt of approved specifications and supporting data.
Comment Summary #4: The commenter requested that USP consider widening the limits for organic impurities as per their FDA-approved stability specification.
Response: Comment not incorporated. The proposed acceptance criteria for organic impurities are consistent with the sponsor's approved specifications. The Expert Committee can consider future revisions upon the receipt of approved specifications and supporting data.
Comment Summary #5: The commenter indicated that their FDA-approved specification for the 2nd identification tests by HPLC PDA which is widely accepted and present in many of USP's official monographs. They request USP to consider their approved specification for Identification by PDA.
Response: Comment not incorporated. The proposed specifications for Identification are consistent with the sponsor's approved specifications. The Expert Committee can consider future revisions upon the receipt of approved specifications and supporting data.

Monograph/Section(s): DEXAMETHASONE TABLETS/ Organic Impurities
Expert Committee: Small Molecules 5
No. of Commenters: 2

Comment Summary #1: The commenter indicated in the test for Organic Impurities that key degradation products are missing in the acceptance criteria table and recommend adding key degradation products with acceptance criteria consistent with what has been approved.
Response: Comment not incorporated. The Expert Committee determined to cancel the proposed organic impurities procedure and re-publish in the future to address comments.
Comment Summary #2: The commenter requested in the test for Organic Impurities tightening the acceptance criteria for unspecified impurities to be consistent with the identification threshold per ICH Q3B.
Response: Comment not incorporated. The Expert Committee determined to cancel the proposed organic impurities procedure and re-publish in the future to address comments.
Comment Summary #3: The commenter indicated in the test for Organic Impurities that the acceptance criteria for "Total degradation products" are different from what has been approved and recommended revising the acceptance criteria to be consistent with what has been approved by the agency.
Response: Comment not incorporated. The Expert Committee determined to cancel the proposed organic impurities procedure and re-publish in the future to address comments.
EC-initiated change #1: The Assay system suitability section is revised to include the relative retention times for betamethsone and dexamethasone as "[Note—The relative retention times for betamethasone and dexamethasone are 0.93 and 1.0, respectively.]"

Monograph/Section(s): DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE TABLETS/Multiple Sections
Expert Committee: Small Molecules 2
No. of Commenters: 1

Comment Summary #1: The commenter indicated that in the Definition and Assay sections, the acceptance criterion is different from what has been approved and recommended revising the acceptance criteria to be consistent with what has been approved.
Response: Comment incorporated. The Definition and Assay are widened from 93.0–107.0% to 90.0-110.0%.
Comment Summary #2: The commenter noted that the acceptance criteria for desacetyl diltiazem and Total degradation products in the organic impurities test are different from what has been approved and recommended revising the acceptance criteria to be consistent with what has been approved.
Response: Comment incorporated. The acceptance criteria for desacetyl diltizem is widened from NMT 0.3% to NMT 1.0% and total degradation products is widened can be revised from NMT 0.5% to NMT 1.5%.
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): DL-LACTIDE HOMOPOLYMER 14000 ACID
EXPERT COMMITTEE: COMPLEX EXCIPIENTS
No. of Commenters: 1

Limit of Tin
EC-initiated change #1: In Analysis under Limit of Tin, the word was corrected from "copolymer" to "polymer".
EC-initiated change #2: In Blank and Standard solutions 1-6 under Limit of Tin, "with diluent" was added after "Prepare all of the solutions in volumetric flasks" to clarify the use of diluent.

Monograph: GONADORELIN ACETATE
Expert Committee(s): Biologics Monographs 1 – Peptides and Oligonucleotides
No. of Commenters: 3

Identification, Assay, Product-Related Substances and Impurities

Comment Summary #1: The commenter proposed implementing the HPLC method for assay and related substances as described in the current Ph. Eur. monograph for gonadorelin acetate.
Response: Comment not incorporated. The proposed changes align with the submission received.

Product-Related Substances and Impurities
Comment Summary #2: The commenter indicated that the impurity profile is different from what has been approved by the agency.
Response: Comment not incorporated. The impurity profile was confirmed to align with what has been approved.

Gonadorelin-Related Impurities, Procedure 1

Comment Summary #3: The commenter recommended providing more details about Impurity J in the monograph.

Response: Comment not incorporated. Impurity J is an unidentified impurity. EC decided to keep Impurity J because having Impurity J listed still adds value.

Gonadorelin-Related Impurities, Procedure 2
Comment Summary #4: The commenter stated that there is no need to use Procedure 2 to determine [D-His2]-Gonadorelin because [D-His2]-Gonadorelin can be detected by Procedure 1.
Response: Comment not incorporated. Procedure 1 was not validated for [D-His2]-Gonadorelin specifically and this impurity is treated as an unspecified impurity in Procedure 1.

Gonadorelin-Related Impurities, Procedure 2
Comment Summary #5: The commenter proposed to reconsider the method to be used for the determination of [D-Tyr5]-Gonadorelin because [D-Tyr5]-Gonadorelin is not properly detected with Procedure 2.
Response: Comment not incorporated. The commenter had high backpressure and therefore changed the chromatographic conditions.

Monograph/Section(s): MESNA INJECTION/Organic Impurities
Expert Committee: Small Molecules 2
No. of Commenters: 2

Comment Summary #1: The commenter inquired why, in the test for organic impurities, Mesna related compound B is not included in the total Impurities.
Response: Comment not incorporated. The limits in the test for organic impurities are based on FDA-approved specifications.
Comment Summary #2: The commenter proposed in the *Bacterial Endotoxins Test,* revising the endotoxin limit to 0.17 UE/mg of MESNA based on dose and equation for its calculation.
Response: Comment not incorporated. USP no longer includes the endotoxin limit in the individual monographs. The current language of *meets the requirements* takes into account the different dosages that are approved since the limit incorporates the dose into the calculation. The manufacturer is required to do this calculation E=K/M where M = max bolus dose per kg of body weight.

The FDA guidance states: “The endotoxins limit table is out of date due to the increase in numbers of dosage (regimes) and drug strengths since the publication of the 1987 Guidance. The appropriate way to establish the endotoxins limit is to use the calculation methods provided in the USP or AAMI standards. Monograph limits may also not account for current product strengths or dosage regimes; these should also be checked using the calculations recommended in the standards.”

Monograph/Section(s): METHAMPHETAMINE HYDROCHLORIDE/Assay
Expert Committee: Small Molecules 2
No. of Commenters: 1

Comment Summary #1: The commenter requested not specifying a column particle size in the test for Assay to retain flexibility.
Response: Comment incorporated.

Monograph/Section(s): MOMETASONE FUROATE/Multiple sections
Expert Committee: Small Molecules 2
No. of Commenters: 4

Comment Summary #1: The commenter asked if the same IR procedures as described in the EP monographs (two EP monographs, one for the anhydrous form and the other for the monohydrate form) by using two reference standards in the anhydrous form and monohydrate form can be adopted.
Response: Comment not incorporated. The Expert Committee determined that the proposed infrared procedure can confirm the differences between the IR spectra of the anhydrous and monohydrate forms. The drying/recrystallizing process in the proposal converts the monohydrate form to the anhydrous form as the USP reference standard. A monohydrate form of USP Mometasone Furorate RS can be considered in a future revision, upon receipt of appropriate materials and supporting data.
Comment Summary #2: The commenter requested that USP establish a monohydrate reference standard for FTIR identification
Response: Comment not incorporated. The Expert Committee determined that the proposed infrared procedure can confirm the differences between the IR spectra of the anhydrous and monohydrate forms. A monohydrate form of USP Mometasone Furorate RS can be considered in a future revision, upon receipt of appropriate materials and supporting data.
Comment Summary #3: The commenter indicated the specification for water determination is not aligned with their approved specification, EP monograph for Mometasone Furoate Monohydrate, nor is it centered on the stoichiometric water content for the monohydrate form, which is 3.3%. The commenter requested that USP align with the EP for water determination acceptance criterion (2.5-4.0%).
Response: Comment incorporated. The water determination acceptance criterion is widened from 2.5-3.5% to 2.5-4.0% based on FDA-approved specifications.
Comment Summary #4: The commenter requested USP use ethanol as a solvent instead of dioxane to align with the EP monograph method and acceptance criterion for specific optical rotation of Mometasone Furoate Monohydrate.
Response: Comment not incorporated. The comment is out of scope for this proposal. The Expert Committee can consider a future revision upon receipt of approved specifications and supporting data.
Comment Summary #5: The commenter stated the impurity profile is dependent on the material source indicating there are 11 known impurities, including the USP specified 6-Methylmometasone Furoate impurity which are controlled at NMT 0.15% on their approved specification. The commenter requested USP to change specifications to NMT 0.15% for any unspecified impurity and NMT 0.6% for total impurities.
Response: Comment not incorporated. The Expert Committee can consider a future revision upon receipt of approved specifications and supporting data.
Comment Summary #6: The commenter requested revising Assay acceptance criteria to a range that is typical for HPLC tests as in many USP drug substance monographs and referred to the EP monograph for Mometasone Furoate to obtain the relevant information (98.0-102.0%, dried substance for Mometasone Furoate; anhydrous substance for monohydrate). The commenter also requested revising the Definition accordingly.
Response: Comment not incorporated. The Assay Acceptance criteria has a range of 97.0-102.0% is not part of the proposed revision. The Expert Committee can consider a future revision upon receipt of approved specifications and supporting data.
Comment Summary #7: The commenter requested, in the Water Determination, widening the upper limit of the monohydrate because the proposed 3.5% limit is too close to the theoretical water content of 3.34%. The commenter referred to EP monograph for Mometasone Furoate to obtain the relevant information.
Response: Comment incorporated. The water determination acceptance criterion is widened from 2.5-3.5% to 2.5-4.0% based on FDA-approved specifications.
Comment Summary #8: The commenter recommended removing the “reporting thresholds” 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):	N-ACETYL-DL-TRYPTOPHAN
Expert Committee:	Simple Excipients
No. of Commenters:	0

Assay
EC-Initiated Change #1: In the Analysis under Assay, the equivalent factor was corrected from 24.63 mg/mEq to 246.3 mg/mEq.

Organic Impurities
EC-Initiated Change #2: In the Buffer preparation under Organic Impurities, the text was changed from "3.9 g/L of sodium dihydrogen phosphate in water and 700 mL of 2.9 g/L of phosphoric acid in water. Adjust to a pH of 2.3." to "Add 1000 mL of 3.9 g/L of sodium dihydrogen phosphate in water and 700 mL of 2.9 g/L of phosphoric acid in water. Adjust to a pH of 2.3 with the same acid," to add clarity on the preparation.

Specific Tests
EC-initiated Change #3: In Analysis under Loss on Drying, the text "to constant weight" was added after "Dry the Sample at 105°" to increase clarity of the end point.

Monograph/Section(s):	PENTAZOCINE HYDROCHLORIDE/ Multiple sections
Expert Committee:	Small Molecules 2
No. of Commenters:	1

Comment Summary #1: The commenter indicated in the Assay, that the limit for the tailing factor in the System Suitability seems to be too wide. They recommend tightening the limit.
Response: Comment not incorporated. The Expert Committee determined that the proposed method is suitable and is based on the sponsor's validation.
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 in the test for organic impurities, Pentazocine chloro analog is listed in Table 2 whereas Chloropentazocine hydrochloride is listed in Table 3 and requested confirmation if both names refer to the same impurity. If so, they recommended using the same name in both places to avoid confusion to users.
Response: Comment incorporated. The impurity name in Table 2 is changed from "Pentazocine chloro analog" to "Chloropentazocine".
Comment Summary #4: The commenter observed under the Reference Standards section, the chemical name of USP Pentazocine Related Compound B RS (RC B) is the same as the 2R,6R,11R enantiomer of the free base (Pentazocine) of the drug substance. They requested confirmation if RC B is the enantiomer of the drug substance and if this is the case if it is treated as an impurity under the organic impurities test.
Response: Comment incorporated. The chemical name in section <11> is incorrect. The chemical name is changed to (2*R*,6*R*,11*R*)-3-(3-hydroxy-3-methylbutyl)-6,11-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-8-ol.

Monograph/Section(s):	SILDENAFIL FOR ORAL SUSPENSION/Multiple Sections
Expert Committee:	Small Molecules 5
No. of Commenters:	2

Comment Summary #1: The commenter stated that the acceptance criteria for the “pH” are different from what has been approved, and recommended removing this test or including acceptance criteria to accommodate different formulations.
Response: Comment incorporated. The acceptance criterion for the pH test was widened from 3.9-4.9 to 3.0-4.9.
Comment Summary #2: The commenter indicated that the time in the Dissolution test is different from what has been proposed and recommended updating the proposal to be consistent with their approval.
Response: Comment incorporated. The Dissolution test was updated to widen the time from 15 min to 20 min.
Comment Summary #3: The commenter indicated that in the test for Organic Impurities the specified impurity limit is different for their product.
Response: Comment incorporated. The limit for Sildenafil N-oxide is widened from NMT 0.20% to NMT 0.2%.

Monograph/Section(s): SILODOSIN/ Organic Impurities
Expert Committee: Small Molecules 3
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: The commenter observed baseline disturbance in the test for Limit of Silodosin S-Enantiomer indicating that the enantiomer and Silodosin peaks do not have symmetry.
Response: Comment not incorporated. The Expert Committee determined that the proposed method was suitable and consistent with the validation data.
Comment Summary #3: The commenter noted that in the test for Organic impurities the limit for the Silodosin indole analog impurity is specified NMT 0.15% and requested increasing the limit to NMT 0.50%. They indicated that Silodosin indole analog impurity is a metabolite as well as a degradant impurity and indicated that for metabolites, the impurity limits can be increased as per ICH guidelines ICHQ3A(R2).
Response: Comment not incorporated. The proposed limits are consistent with the sponsor’s approved specifications. A revision to the limit of Silodosin indole analog impurity may be considered upon the receipt of FDA-approved specifications and supporting data.
Comment Summary #4: The commenter requested confirmation of the chemical name for the Silodosin Dimer analogue impurity. They indicate that while the PF proposal lists (R)-5-[2-(Bis{2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl}amino)propyl]-1-(3-hydroxypropyl)-1H-indole-7-carboxamide, suppliers for Silodosin Dimer impurity list (R)-5-(2-(bis(2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)-1-(3-hydroxypropyl)indoline-7-carboxamide
Response: Comment incorporated. The chemical name for Silodosin Dimer analogue impurity is updated to (R)-5-[2-(Bis{2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl}amino)propyl]-1-(3-hydroxypropyl)indoline-7-carboxamide.
Comment Summary #5: The commenter indicated that the chemical name for Silodosin dimer analog is listed as “-1H-indole”. They state that the name should be “2,3-dihydro-1H-indoline ".
Response: Comment partially incorporated. The commenter’s suggested chemical name is correct, however the chemical name for Silodosin Dimer analogue impurity is changed to (*R*)-5-[2-(Bis{2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl}amino)propyl]-1-(3-hydroxypropyl)indoline-7-carboxamide, based on IUPAC format.
Comment Summary #6: The commenter indicated that in the Assay, the reagent link provided for Phosphoric Acid for Solution A preparation is incorrect. When clicked, the link goes to Phosphorous Acid (H3PO3) instead of Phosphoric Acid (H3PO4).
Response: Comment incorporated. The link for Phosphoric Acid is corrected.

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

Comment Summary #1: The commenter noted that in the Definition and Assay sections, the acceptance criterion is different from what has been approved and recommends revising the acceptance criteria to be consistent with what has been approved.
Response: Comment incorporated. The Definition and Assay are widened from 95.0-105.0% to 90.0-110.0%.
Comment Summary #2: The commenter that in the Impurities section, the acceptance criteria for “Silodosin indole analog” and “Total degradation products” are different from what has been approved and recommends revising the acceptance criteria to be consistent with what has been approved.
Response: Comment incorporated. The limit for Silodosin indole analog is widened from NMT 0.60% to NMT 0.63% and the limit for total degradation products is widened from NMT 1.5% to NMT 3.0%.
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): SODIUM PERTECHNETATE Tc 99M INJECTION/Specific Tests
Expert Committee: Small Molecules 4
No. of Commenters: 1

Comment Summary #1: The commenter requested adding “colorless” to the acceptance criteria in the test for *Appearance*.
Response: Comment not incorporated. The Expert Committee will consider incorporating this text in future revisions, as applicable.
Expert Committee-initiated change #1: Section numbers were added to the section titles of referenced general chapters as applicable.
Expert Committee-initiated change #2: The forms of units in the *Analysis* sections of the *Assay* and of *Radionuclidic Purity* and in the *Labeling* section were updated from singular to plural, as appropriate.

Monograph/Section(s): TECHNETIUM Tc 99M ALBUMIN AGGREGATED INJECTION/Specific Tests
Expert Committee: Small Molecules 4
No. of Commenters: 1

Comment Summary #1: The commenter requested adding “colorless and free from foreign particles” to the acceptance criteria in the test for Appearance.
Response: Comment not incorporated. The Expert Committee will consider incorporating this text in future revisions, as applicable.
Comment Summary #2: The commenter requested retaining the test for Biological Distribution until tests for the number of particles per volume and particle size distribution are added, as these tests are crucial in predicting the biological distribution of the drug.
Response: Comment incorporated. The Expert Committee is interested in validated analytical procedures such as a more specific Identification test, a test for the number of particles per volume, and a test for particle size distribution.
Expert Committee-initiated change #1: The forms of units in the Definition, in the Analysis sections of the Assay and of Radionuclidic Purity, and in the Labeling section were updated from singular to plural, as appropriate.

Expert Committee-initiated change #2: Section numbers were added to the section titles of referenced general chapters as applicable.
Expert Committee-initiated change #3: The abbreviations “d” and “y” were expanded in Table 2 to days and years, respectively, for clarity and to align with current USP style.

Monograph/Section(s): TECHNETIUM Tc 99M EXAMETAZIME INJECTION/Multiple sections
Expert Committee: Small Molecules 4
No. of Commenters: 2

Comment Summary #1: The commenters requested revising the text about the stabilizing solution within *Definition* section to be more flexible.
Response: Comment incorporated.
Comment Summary #2: The commenter requested adding a retention time from radiochromatograms in the acceptance criteria for Identification B, Radiochemical Identity.
Response: Comment not incorporated. The Expert Committee may consider future revisions upon receipt of a validated analytical procedure that is more specific.
Comment Summary #3: The commenter requested retaining the Biological Distribution test until Identification B, Radiochemical Identity includes a retention time from radiochromatograms in the acceptance criteria.
Response: Comment not incorporated. The Expert Committee determined that the removal of the Biological Distribution test was appropriate.
Comment Summary #4: The commenter requested using more generic terminology like “up to the end of the reconstituted shelf life” to indicate the stabilization time, considering that it depends on the specific stabilizer used within the Radiochemical Purity section.
Response: Comment not incorporated. The Expert Committee will consider incorporating a different approach in future revisions, as applicable.
Comment Summary #5: The commenter requested adding “colorless” to the acceptance criteria in the test for Appearance.
Response: Comment not incorporated. The Expert Committee will consider incorporating this text in future revisions, as applicable.
Comment Summary #6: The commenter requested including the pH values for all approved stabilized versions, including methylene blue and cobalt chloride, as the pH is dependent on the stabilizer used.
Response: Comment incorporated. The acceptance criteria for the pH of stabilized injection were widened from 6.5-7.5 to 5.0-8.0.
Expert Committee-initiated change #1: Section numbers were added to the section titles of referenced general chapters as applicable.
Expert Committee-initiated change #2: The forms of units in the Analysis section of the Assay and of the test for Radionuclidic Purity as well as the Labeling section were updated from singular to plural, as appropriate.
Expert Committee-initiated change #3: The abbreviations “d” and “y” were expanded in Table 2 to days and years, respectively, for clarity and to align with current USP style.

Monograph/Section(s): TECHNETIUM Tc 99M MEDRONATE INJECTION/Multiple sections
Expert Committee: Small Molecules 4
No. of Commenters: 1

Comment Summary #1: The commenter requested adding a retention time from radiochromatograms in the acceptance criteria for Identification B, Radiochemical Identity.
Response: Comment not incorporated. The Expert Committee may consider future revision upon receipt of a validated analytical procedure that is more specific.
Comment Summary #2: The commenter requested adding “colorless” to the acceptance criteria in the test for Appearance.

Response: Comment not incorporated. The Expert Committee will consider incorporating this text in future revisions, as applicable.
Comment Summary #3: The commenter requested retaining the Biological Distribution test until Identification B, Radiochemical Identity includes a retention time from radiochromatograms in the acceptance criteria.
Response: Comment not incorporated. The Expert Committee determined that the removal of the Biological Distribution test was appropriate.

Comment summary #4: The commenter requested tightening acceptance criteria for pH values to align with what has been approved.
Response: Comment not incorporated. The acceptance criteria for pH can be considered for revision upon receipt of FDA-approved specifications.
Expert Committee-initiated change #1: Section numbers were added to the section titles of referenced general chapters as applicable.

Monograph/Section(s): TECHNETIUM Tc 99M OXIDRONATE INJECTION/Multiple sections
Expert Committee: Small Molecules 4
No. of Commenters: 1

Comment Summary #1: The commenter requested adding a retention time from radiochromatograms in the acceptance criteria for Identification B, Radiochemical Identity.
Response: Comment not incorporated. The Expert Committee may consider future revision upon receipt of a validated analytical procedure that is more specific.
Comment Summary #2: The commenter requested retaining the Biological Distribution test until Identification B, Radiochemical Identity includes a retention time from radiochromatograms in the acceptance criteria.
Response: Comment not incorporated. The Expert Committee determined that the removal of the Biological Distribution test was appropriate.
Comment Summary #3: The commenter requested revising the acceptance criteria for pH values to align with what has been approved.
Response: Comment not incorporated. The acceptance criteria for pH can be considered for revision upon receipt of FDA-approved specifications.
Expert Committee-initiated change #1: Section numbers were added to the section titles of referenced general chapters as applicable.

Monograph/Section(s): TECHNETIUM Tc 99M PYROPHOSPHATE INJECTION/Multiple sections
Expert Committee: Small Molecules 4
No. of Commenters: 1

Comment Summary #1: The commenter requested adding a retention time from radiochromatograms in the acceptance criteria for Identification B, Radiochemical Identity.
Response: Comment not incorporated. The Expert Committee may consider future revision upon receipt of a validated analytical procedure that is more specific.
Comment summary #2: The commenter requested retaining the Biological Distribution test until Identification B, Radiochemical Identity includes a retention time from radiochromatograms in the acceptance criteria.
Response: Comment not incorporated. The Expert Committee determined that the removal of the Biological Distribution test was appropriate.
Comment summary #3: The commenter requested adding “colorless” to the acceptance criteria in the test for Appearance.
Response: Comment not incorporated. The Expert Committee will consider incorporating this text in future revisions, as applicable.

Expert Committee-initiated change #1: The forms of units in the Definition, in the Analysis section of the Assay and of the test for Radionuclidic Purity as well as the Labeling section were updated from singular to plural, as appropriate.
Expert Committee-initiated change #2: Section numbers were added to the section titles of referenced general chapters as applicable.

Monograph/Section(s): TECHNETIUM Tc 99M SUCCIMER INJECTION/Multiple sections
Expert Committee: Small Molecules 4
No. of Commenters: 1

Comment summary #1: The commenter indicated that the thin-layer chromatography procedure within proposed Identification B, Radiochemical Identity cannot distinguish the radioactive drug substance Tc(III) DMSA complex from the Tc(V) DMSA complex that can be formed in poorly controlled formulations.
Response: Comment not incorporated. The Expert Committee may consider future revision upon receipt of a validated analytical procedure that is more specific.
Comment summary #2: The commenter requested replacing "^{99m}Tc succimer complex" with "Technetium Tc 99m succimer" within the Acceptance criteria section of the test for Radiochemical Purity to align with the approved product.
Response: Comment incorporated.
Comment summary #3: The commenter requested using the text "clear without visible particles" in the acceptance criteria within the test for Appearance.
Response: Comment not incorporated. The Expert Committee determined that the text as published was appropriate.
Comment summary #4: The commenter requested retaining the Biological Distribution test until Identification B, Radiochemical Identity is more specific.
Response: Comment incorporated.
Comment summary #5: The commenter requested revising the acceptance criteria for pH values to align with what has been approved.
Response: Comment incorporated. The acceptance criteria for the pH was widened from 3.0-3.5 to 2.0-3.5.
Expert Committee-initiated change #1: Section numbers were added to the section titles of referenced general chapters as applicable.
Expert Committee-initiated change #2: The abbreviations "d" and "y" were expanded in Table 2 to days and years, respectively, for clarity and to align with current USP style

Monograph/Section(s): TECHNETIUM Tc 99M SULFUR COLLOID INJECTION/Multiple sections
Expert Committee: Small Molecules 4
No. of Commenters: 1

Comment summary #1: The commenter requested adding a retention time from radiochromatograms in the acceptance criteria for Identification B, Radiochemical Identity.
Response: Comment incorporated. The acceptance criteria was updated to "In Radiochemical Purity, the chromatogram shows the principal peak is at the point of application."
Comment summary #2: The commenter requested revising the text to remove "clear" and to add the color of the colloid in the acceptance criteria within the test for *Appearance*.
Response: Comment not incorporated. The Expert Committee will consider incorporating this text in future revisions, as applicable.
Comment summary #3: The commenter requested retaining the Biological Distribution test until adding a test for particle size distribution to ensure consistent uniformity and physical stability of the Tc 99m Sulfur Colloid Injection.
Response: Comment incorporated.
Expert Committee-initiated change #1: The forms of units in the Definition, in the Analysis section of the Assay and of the test for Radionuclidic Purity as well as the Labeling section were updated from singular to plural, as appropriate.

Expert Committee-initiated change #2: Section numbers were added to the section titles of referenced general chapters as applicable.
Expert Committee-initiated change #3: The abbreviations “d” and “y” were expanded in Table 2 to days and years, respectively, for clarity and to align with current USP style.

Monograph/Section(s):	TESTOSTERONE
Expert Committee:	Small Molecules 5
No. of Commenters:	5

Comment Summary #1: Commenter indicated that the mobile phase composition is missing in the Assay and Organic impurities method.
Response: Comment incorporated. The tests for *Assay* and *Organic Impurities* are revised for clarity to add Solution A: Water and Solution B: Acetonitrile. In addition, Table 1 is updated accordingly.
Comment Summary #2: Commenter noted that the test for “Melting Range or Temperature” is removed from the monograph, and recommended including a test for “Residue on Ignition” with a suitable acceptance criterion to limit the presence of inorganic impurities.
Response: Comment not incorporated. The Expert Committee may consider a future revision to include a test for Residue on Ignition upon receipt of approved specifications and supporting data.
Comment Summary #3: Commenter recommended that the analysis in the Loss on Drying (LOD) test should be revised from “Analysis: Dry in an oven at 105° for 2 h” to “Analysis: Dry in an oven at 105° for constant weight”.
Response: Comment not incorporated. The proposed Loss on Drying test and acceptance criteria are consistent with the sponsor’s approved specifications. If needed a future revision can be considered upon receipt of approved specifications and supporting data.

Monograph/Section(s):	TETRABENAZINE/Multiple Sections
Expert Committee:	Small Molecules 4
No. of Commenters:	2

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: The commenter requested to include a test for water content in the monograph with an acceptance criterion of NMT 1.0% w/w using <921> Water Determination, Method Ia (corresponding to European Pharmacopeia 2.5.12) which would necessitate removing the proposed test for <731> Loss on Drying with an acceptance criterion of NMT 0.50%.
Response: Comment not incorporated. The replacement of the test for <731> Loss on Drying with a test for <921> Water Determination can be considered for revision upon receipt of FDA approved specifications.
Comment summary #3: The commenter provided information which supported the proposed test for *Organic Impurities*.
Response: Comment acknowledged.