.

Commentary

USP–NF 2025 Issue 2

February 3, 2025

In accordance with USP's *Rules and Procedures of the Council of Experts ("Rules*"), and except as provided in Section 9.02 *Accelerated Revision Processes*, USP publishes proposed revisions to the *United States Pharmacopeia and the National Formulary* (*USP–NF*) for public review and comment in the *Pharmacopeial Forum (PF),* USP's free bimonthly journal for public notice and comment. After comments are considered and incorporated as the Expert Committee (EC) deems appropriate, the proposal may advance to official status or be re-published in *PF* for further notice and comment, in accordance with the Rules. In cases when proposals advance to official status*,* a summary of comments received (including those requesting changes to the standard, as well as those supportive of the proposed standard) 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 (PF):

General Notices and Requirements
Section 5.15 Definition
Section 5.60 Impurities and Foreign Substances
Section 5.60.10 Impurities that are Unusually Toxic and/or Mutagenic
Section 5.60.40 Organic Impurities in Drug Substances and Drug Products

General Chapters
<72> Respiration-Based Microbiological Methods for the Detection of Contamination in Short-Life Products
<73> ATP Bioluminescence-Based Microbiological Methods for the Detection of Contamination in Short-Life Products
<382> Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery System
<467> Residual Solvents
<1060> Mass Spectrometry-based Multi-attribute Method for Therapeutic Proteins
<1071> Rapid Microbiological Methods for the Detection of Contamination in Short-Life Products—A Risk-Based Approach
<1079.2> Mean Kinetic Temperature in the Evaluation of Temperature Excursions During Storage and Transportation of Drug Products
<1467> Residual Solvents—Verification of Compendial Procedures and Validation of Alternative Procedures

Monographs
Acetyltributyl Citrate
Allopurinol Compounded Oral Suspension
Amitriptyline Hydrochloride Compounded Oral Suspension
Apigenin
Benzocaine, Lidocaine, & Tetracaine Compounded Cream
Bupivacaine Hydrochloride Compounded Injection
Buspirone Hydrochloride Compounded Oral Suspension
Crospovidone
Dabigatran Etexilate Mesylate
Diazepam Compounded Injection
1,2-Distearoyl-Sn-Glycero-3-Phosphocholine
Dronabinol Capsules
Dutasteride Capsules
Eslicarbazepine Acetate
Famotidine Compounded Injection
Fentanyl Citrate Compounded Injection
Flurbiprofen Sodium
Hydrochlorothiazide
Hydrocortisone Compounded Oral Suspension
Hydroxypropyl Betadex
Isoproterenol Hydrochloride
Ketamine Hydrochloride Compounded Injection
Lansoprazole Compounded Oral Suspension
Leucovorin Calcium Compounded Injection
Lidocaine Hydrochloride Compounded Injection

Lidocaine and Tetracaine Compounded Cream
Locust Bean Gum
Magnesium Sulfate Compounded Injection
Maltitol Solution
Metronidazole Compounded Oral Suspension
Morphine Sulfate Compounded Suppositories
Nadolol Tablets
Naltrexone Hydrochloride Compounded Oral Suspension
Phenol Compounded Injection
Polyethylene Glycol 60 Hydrogenated Castor Oil
Sodium Phosphates Compounded Injection
Sorafenib Tosylate
Terbinafine Compounded Oral Suspension
Teriflunomide
Teriflunomide Tablets
Tobramycin
Tolnaftate

No comments were received for the following proposals:

Monographs

Bifidobacterium Bifidum
Carprofen Compounded Oral Suspension, Veterinary
Doxycycline Compounded Oral Suspension, Veterinary
Dydrogesterone Tablets
Edrophonium Chloride
Edrophonium Chloride Injection
Etidronate Disodium
Etidronate Disodium Tablets
Gastrodia Rhizome
Gastrodia Rhizome Dry Extract
Gastrodia Rhizome Powder
Gramicidin
Lactobacillus Rhamnosus
Magaldrate
Magaldrate and Simethicone Chewable Tablets
Magaldrate and Simethicone Oral Suspension
Maltitol
Maltose
Noncrystallizing Sorbitol Solution
Polymyxin B for Injection
Sorbitol
Sorbitol Solution
Sorbitol Sorbitan Solution
Spearmint Oil
Stearyl Alcohol
Teniposide
Teniposide Injection
Torsemide Compounded Oral Suspension
Tributyl Citrate

General Notices and Requirements

Monograph/Section(s): General Notices and Requirements/Section 5.15 Definition
Expert Committee: Council of Experts
No. of Commenters: 2

Comment Summary #1: The commenter recommended clearly describing which aspects would be considered part of identity and which ones are not.
Response: Comment not incorporated. The comment is outside the scope of the current revision. The purpose of the current revision is restricted to distinguishing what statements in the definitions are requirements vs informational text.
Once this is clarified, USP may consider addressing and defining what requirements in a monograph definition are considered part of the identity in a future revision. USP welcomes commenter's opinions and recommendations on what requirements in definitions should be considered part of the identity in a future revision.
Comment Summary #2: The commenter indicated that the statement "when included in a definition" appears to be discretionary. The commenter recommends outlining the requirements on which aspects should be included in the definition. The commenter also recommended providing guidelines for monograph expert committees' consideration as they develop monographs.
Response: Comment not incorporated. No changes were made to the phrase, "when included in the definition". The phrase is intended to describe the status of official monographs currently in the compendium rather than providing discretion on what should be included as a requirement. USP notes, therefore, that the placement and location of specific statements both within, and outside, a definition, reflects the statement's status as a potential requirement. For example, some text would constitute a requirement "when included in definitions" but may be currently located outside of the definition, resulting in their informational status in other sections (e.g.: after the monograph title and before the section Definition). Guidelines for the Expert Committees on what requirements should be included in monograph definitions are specified and relayed to Expert Committees outside of the General Notices. Guidance to Expert Committees appears in the Submission Guidelines and is discussed with expert volunteers as part of the standard-setting process. USP would revise guidance on what requirements should be included in monographs once the current revision becomes official.
Comment Summary #3: The commenter recommended clarifying whether a statement in the definition that contains permissive language like "may contain" is a requirement or informational.
Response: Comment incorporated. The section has been reworded to make an exception when permissive language is used. The following statement has been added to the paragraph: "…*except when permissive language is used, such as statements preceded by the verb "may" (e.g., "may contain added substances")"*
Comment Summary #4: The commenter recommended clarifying which parts are informational. Include specific examples after this statement similar to those in the *Briefing*.
Response: Comment not incorporated. The proposed change was not identified as a necessary clarification, as items not specified in the list of requirements are not categorized as requirements. Using examples would produce an incomplete list that invites more uncertainty than the current language, which plainly excludes what is not in the specific list of requirements.

Monograph/Section (s): General Notices and Requirements/Section 5.60 Impurities and Foreign Substances
Expert Committee: Council of Experts
No. of Commenters: 2

Comment Summary #1: The commenter requested to retain the official text addressing the need to detect and control impurities, where the presence of such impurities/contaminants is inconsistent with cGMP. It is important to remind monograph users that this control is a matter of cGMP to ensure product safety.
Response: Comment incorporated. The relevant portion of official text has been retained as follows: "*(W)here the presence of the impurity is inconsistent with applicable good manufacturing practices*," and is connected to the need to manage and/or control impurities/contaminants to ensure product safety.
Comment Summary #2: The commenter recommended clarifying whether this section also covers extractables and leachables.
Response: Comment not incorporated. Any impurity, irrespective of its classification or source, is understood to fall within the broader scope and context of section 5.60. Leachables are impurities that have migrated into the product from a packaging/delivery system, packaging component, or packaging material. Extractables and leachables are within the scope of the ICH Q3 impurities guidelines and will be addressed in ICH Q3E, currently in development. Refer to Comment Summary #1 and its Response. The management and/or control of an impurity/contaminant (without regard to source) is a matter of cGMP.
Comment Summary #3: The commenter recommended relocating the sentence pertaining to excipients from the middle to the beginning of the second paragraph for clarity. Expand it to include the term contaminants and remove the adjective "minor" from "minor components," as definitions for excipient composition are not yet established.
Response: Comment partially incorporated. The section has been reworded for clarity: The sentence pertaining to excipients has been relocated at the end of the first paragraph, and the term "contaminants" has been added. The word "minor" is retained for consistency with the proposed definition of "minor component" in the Stimuli "Proposed Definitions of Excipient Components: Revisions to 2018 Definitions" published in *PF* 49(5) [Sep.-Oct. 2023]. If needed, a future revision may be considered when definitions for excipient composition are established.
Comment Summary #4: The commenter recommended to add language stating that impurities/contaminants may be limited through appropriate manufacturing controls.
Response: Comment incorporated. Refer to Comment Summary #1 and its Response. The management and/or control of an impurity/contaminant is established as a matter of cGMP.

Monograph/Section(s): General Notices and Requirements/Section 5.60.10 Impurities that are Unusually Toxic and/or Mutagenic
Expert Committee: Council of Experts
No. of Commenters: 2

Comment Summary #1: The commenter requested to revise the text "…as required by the regulatory authority or as described in ICH M7…" to read "…as required by the regulatory authority. See ICH M7…"
Response: Comment incorporated. The text has been revised accordingly.
Comment Summary #2: The commenter recommended to revise the text "…reporting thresholds (disregard limits) …" to remove "(disregards limits)," which is not a harmonized term.
Response: Comment incorporated. The text has been revised to remove "(disregard limits)" keeping only reporting thresholds term. The glossary of GC <1086> defines the compendial relationship between the terminology reporting threshold and disregard limit.
Comment Summary #3: The commenter recommended not to introduce the term "unusually toxic" as it is not defined.
Response: Comment not incorporated. The term and its usage are adopted from the ICH Q3A/Q3B guidelines.

Comment Summary #4: The commenter recommended to delay the introduction of the section 5.60.10 until broader policy pertaining to the control of ICH M7 on Potential Mutagenic Impurities in USP monographs is developed and implemented.
Response: Comment not incorporated. The applicability of ICH M7 is defined within the scope of the guideline. Additionally, Ph. Eur. has incorporated ICH M7 by reference in the General Monograph "Substances for Pharmaceutical Use."

Monograph/Section(s): General Notices and Requirements/Section 5.60.40 Organic Impurities in Drug Substances and Drug Products
Expert Committee: Council of Experts
No. of Commenters: 1

Comment Summary #1: The commenter requested to clarify whether the reference to GC <1086>, which in turn references GC <476>, creates a requirement making GC <476> mandatory.
Response: Comment not incorporated. General Notices and Requirements section 3.10. Applicability of Standards, states that general chapters numbered between 1000 and 1999 are for informational purposes and contain no mandatory tests, assays, or other requirements applicable to any official article, regardless of citation in a general chapter numbered below 1000, a monograph, or these *General Notices*. Therefore, citation of GC <1086> in these General Notices does not create additional requirements for GC <476>. Section 3.10 also states that "applicable general chapters" means general chapters numbered below 1000 or above 2000 that are made applicable to an article through reference in *General Notices*, a monograph, or another applicable general chapter numbered below 1000. At this time, GC <476> is not referenced in General Notices, a monograph, or another general chapter numbered below 1000. As such, the GC <476> is currently not applicable.

General Chapters

General Chapter/Section(s): <72> Respiration-Based Microbiological Methods for the Detection of Contamination in Short-Life Products / Multiple Sections
Expert Committee(s): General Chapters-Microbiology Expert Committee
No. of Commenters: 16

INTRODUCTION

Comment Summary #1: There were several comments related to the application of the general chapter. The comments are summarized as follows: 1. Consider extending the use to all types of pharmaceutical products compatible with Respiration-based technologies. 2. Provide a list of short-life products. 3. The chapter has not addressed the "negative-to date" release for immediate-release products. Suggest adding a statement that allows the release of products for infusion as "negative to date" when indicated (compassionate release, clinical trials). 4. Clarify the terms of short-life product, short shelf-life product and short manufacturing times.
Response: 1**.** Comment not incorporated. The Expert Committee will consider this suggestion for a future extension of the general chapter. 2. Comment not incorporated. Managing such a list can limit the scope and could challenge the utilization of the method with emerging products. Additional details can be found in reference <1071>. 3. Comment not incorporated. The topic is discussed in <1071>. 4. Comment incorporated. The definition of short life products is covered in <1071>.

Comment Summary #2: Several commenters requested clarification on if a full validation is required for rapid methods as well as if a conventional method still needs to be run for the products.
Response: Comment not incorporated. The Expert Committee added more details on method validation in <1071>.
Comment Summary #3: The commenter pointed out certain inconsistencies in the text. In 1. INTRODUCTION: The original statement discusses growth-based methods that utilize detection signals other than visible signs of microbial growth or precipitation within the media (e.g., turbidity, pellicle formulation, or floccular growth). This statement is counter to the later statement in CULTURE MEDIA AND INCUBATIONCONDITIONS section, where it is stated "Visual inspection of media containers may be required at the end of incubation for the detection of molds, especially if their presence was not automatically detected by the system during method suitability, even when mold balls were visible". The commenter suggested revising as the following for clarification: "Growth-based methods have been used to test a variety of products, but visual inspection may be routinely required for mold detection." 2. The Introduction section states that product-related turbidity does not interfere, because if a visual inspection is required, then product-related turbidity may remain a risk and present a patient safety risk. This is inconsistent with the same statement in CULTURE MEDIA AND INCUBATION CONDITIONS section regarding visual inspection of media containers. The commenter suggested revising it to "Further benefits include the automation of data analysis, acquisition, reporting and archiving and the isolation of the organism for identification and investigation."
Response: 1. Comment not incorporated. The statement concerning the visible signs in the INTRODUCTION section is generic for classical growth-based methods and not specifically for respiration-based methods. 2. Comment not incorporated. In rare cases molds are not automatically detected, they still form very visible mold balls at the end of incubation (even in turbid matrices such as by cell therapy products). In addition, bacteria and yeasts would remain automatically detectable by the system, so the respiration-based method still has an advantage over a classical method for turbid matrices.
Comment Summary #4: The commenter highlighted that only one manufacturer offers dual-temperature or flexible-temperature incubation. They requested revisions to the chapter for increased flexibility.
Response: Comment incorporated. The incubation conditions have been modified to allow for more than one incubation regime.
Comment Summary #5: The commenter suggests adding a risk assessment reference that addresses method equivalency to traditional compendial methods. Such a reference would be helpful in situations where non-CFU signals are used.
Response: Comment not incorporated. The topic is beyond the scope of this general chapter.
Comment Summary #6: The commenter indicated the lack of acknowledgment regarding the potential interference of a test article in direct inoculation methods with microbial proliferation. The proposed addition to the last paragraph of the introduction aims to address this concern: "Users should be aware that direct inoculation methods are more prone to product interference when compared to membrane filtration, the presence of the test article can interfere with microbial proliferation and the user should understand and/or mitigate this risk during method development." Additionally, the commenter suggested modifying the last sentence to emphasize the end-user's responsibility in selecting the most appropriate respiration method: "It is the end-user's responsibility to select the respiration method that is the most appropriate for the product, but in general, the technique of membrane filtration is used whenever the nature of the product permits."
Response: Comment not incorporated. GC <71> considers both methods to be appropriate.

CULTURE MEDIA AND INCUBATION CONDITIONS

Comment Summary #7: The commenter stated that some facultative anaerobes exhibit faster or better growth in anaerobic media. Specifically, they suggested adding the term “facultative” to the first sentence of this section: ...for the recovery of **“facultative”** anaerobic microorganisms…
Response: Comment not incorporated. The text in GC <72> maintains alignment with GC <71>.
Comment Summary #8: The commenter highlighted that European Pharmacopoeia 2.6.27 guidelines recognize the potential risk to patients from pathogenic organisms with an optimum growth temperature of approximately 36°C. Considering the final application risks of the product, the manufacturing process should be considered. Temperature acts as a significant barrier, determining whether an opportunistic organism entering an incubation system will proliferate. Consequently, a higher incubation temperature can be employed.
Response: Comment partially incorporated. The existing text allows for additional temperatures and incubation conditions, provided suitable justifications are given. The parameters are dependent on manufacturing processes and risk assessments. For clarity, the word “may” was revised to “can” in the sentence.
Comment Summary #9: The commenter requested to add “fast growth” in the following sentence: “…be applied where relevant to account for “fast growth” potential microorganisms associated with…”
Response: Comment partially incorporated. The text was revised as follows: “…be applied where relevant to ~~account for~~ **appropriately recover** potential microorganisms associated with…”
Comment Summary #10: The commenter requested allowing the use of manual testing in combination with automated culturing systems. Additionally, they suggested including a commercially available microbiological media that would enable the growth and detection of aerobic microorganisms at a temperature between 20º and 30º.
Response: Comment partially incorporated. The existing text already acknowledges that choice of media is risk-based with consideration of the manufacturing process. However, for better clarity, the text has been revised as follows: “…especially if their presence was not ~~automatically~~ detected by the system during method suitability, even when mold balls were visible**.”**
Comment Summary #11: A couple of commenters requested to provide more guidance on the “degree of exposure of oxygen” to inform the user on media selection criteria.
Response: Comment incorporated. The text has been revised as follows: “…consider the temperature and degree of exposure of oxygen used during the manufacturing process **(e.g., fully aerobic process and anaerobic microorganisms may not be required).**”
Comment Summary #12: The commenter requested a clarification why there is an option for visual inspection of the media containers for mold since the method suitability has a requirement for mold at 10 CFU or less. If the visual inspection is needed, the commenter requested to add the requirement in method suitability section.
Response: Comment not incorporated. It can occur that the metabolic activity of some molds in some specific media is too low to trigger a signal in the system even if growth occurs. Therefore, a visual inspection may be required at the end of incubation for the detection of molds in such media.
Comment Summary #13: The commenter suggested adding the following text at the end of second paragraph: “visual reading to take place after 14 days to limit the risk”.
Response: Comment not incorporated. If the system has been appropriately validated, with suitability tests performed and the right selection of microorganisms, there would be no need to extend the incubation period to 14 days.

Growth Promotion Test of Aerobes, Anaerobes, and Fungi

Comment Summary #14: The commenter noted that this section does not specify which media should be used for detecting which microorganisms. However, the combined set of media should be able to detect all the organisms listed. This approach provides flexibility in choosing the best conditions for microorganism detection.
Response: Comment acknowledged.
Comment Summary #15: The commenter recommended wording to be included that instructs the user to refer to the manufacturer's instruction for use of bottle types when testing the microorganisms listed in Table 1.
Response: Comment not incorporated. This is beyond the scope of this general chapter; Table 1 aligns with other general chapters for growth-based media.
Comment Summary #16: The commenter shared that they allowed 7 days for incubation based on the method suitability data and their experience.
Response: Comment acknowledged. To allow more flexibility for utilization of systems, the Expert Committee does not set fixed incubation times.
Comment Summary #17: The commenter recommends modifying the incubation time to reflect the results of method suitability studies.
Response: Comment not incorporated. These are the minimum requirements to demonstrate the fertility of the media.
Comment Summary #18: The commenter stated that determining the product's incubation time can be cumbersome. Some strains may not pass the 5-day requirement. The procedure would require careful monitoring to determine the time points for sampling, which may occur during off-hours. The commenter suggested an approach to incubate until positivity is detected and then add a percentage of time to the incubation length to allow growth detection for lower levels of contamination.
Response: Comment not incorporated. The stakeholder may decide whether to pursue further incubation or not. There is no requirement to prematurely end incubation. Using the calculated safety margin as stated in the general chapter is a reasonable approach and will remain as such.

METHOD SUITABILITY TEST

Comment Summary #19: The commenter pointed out that not all users may have the expertise to determine the appropriate organism to use and calculate the generation time. Additionally, the commenter noted there is a discrepancy between USP General Chapters <72> and <73> method suitability test inoculum sizes (i.e., 10 versus 100 CFU) compared to the requirements in USP General Chapters <60>, <61>, <62>, and <71>, as well as the recommendations in <1223>, and recommended including minimum method suitability qualification requirements.
Response: Comment partially incorporated. The assumption is that the stakeholders using microbiological rapid methods have a minimum expertise to determine a selection microorganism and the generation time or have the possibility to contact vendors, contract laboratories or consultants for advising. There is an example on how to determine the generation time in <72> and <73> and for additional flexibility it is now written that other formula may apply depending on the output signal.
Comment Summary #20: The commenter highlighted limitations in sterility test methods related to specificity, limit of detection, sample size, and time to detection. They emphasized that sterility tests should be fit for purpose, specifically targeting the detection of microorganisms most likely to contaminate the product and cause clinical infections in recipients. The commenter recommended that the USP Microbiology Expert Committee revisit the in-process revision and simplify the method suitability test requirements.

Response: Comment not incorporated. The EC opted for a more flexible approach to system utilization. However, it remains essential to ensure adequate recovery of relevant microorganisms during the process or product testing. The EC expresses confidence in the procedure described in the chapter, which meets this requirement.

Comment Summary #21: Several commenters recommended maintaining consistency in the inoculum size, aligning it with references <71>, <60>, <61>, <62>, and the recommendation in <1223>. They expressed concerns that targeting less than 10 CFU could be challenging and might lead to true negatives being misinterpreted as failed Method Suitability Tests.

Response: Comment partially incorporated. Members of the EC have positive experiences with inoculum levels of 10 CFU or less, supported by experiments conducted by EC members and other stakeholders. The feasibility of an inoculum size of 10 CFU has been demonstrated. In cases where inoculum levels exceed 10 CFU, additional guidance was provided. The following text was added in third paragraph in Method Suitability Test section: *Considering the variability of the microbiological inoculum and assuming it follows a Poisson distribution it may happen that with a low sample size targeting not more than 10 CFU that the inoculum control measured might exceed 10 CFU. A scientific justification would be required if the inoculum control final mean value is exceeding 10 CFU and is maintained in the suitability test results*.

Comment Summary #22: The commenter suggested specifying the culture media and incubation conditions for the challenged microorganisms in Method Suitability Test section.

Response: Comment not incorporated. To allow a flexible application of respiration-based methods and to cover the large scope of short life products, the culture media and incubation conditions were not specified.

Comment Summary #23: Three comments received pertain to slow-growing microorganisms and environmental isolates. The commenters noted that the recommendation for including these in the test method remains open-ended in the text, and recommended that the conditions for the qualification and use of an official general test method should be clearly defined in the general chapter. Specifically, more clarity is required regarding strain testing expectations in terms of types and quantity. The commenters suggested the following revision: “Inclusion of environmental microorganisms including slow growing microorganisms, that represent risk to patient or product, or found in the manufacturing environment and product failures must be included.”

Response: Comment partially incorporated. While the inclusion of slow-growing microorganisms is not mandatory, the revised chapter text provides clarification: “*Inclusion of slow growing microorganisms may be considered* ***if relevant for the process or product risk.****”*

Comment Summary #24: A commenter emphasized that an important USP norm is to provide standard test methods that can be implemented across a wide range of manufacturers, promoting product quality and patient safety. They suggested that many companies would benefit from accepting a validated <72> general test method and utilizing <71> suitability tests with the listed cultures, preparing inoculum using commercially prepared cultures.

Response: Comment not incorporated. Considering the complexity of various products and processes to which <72> would apply, the EC opted for a more open procedure for the first version of <72 and <73>. This approach allows for the use of new products and processes, recognizing that a one-size-fits-all validation process is not feasible. These general chapters have been introduced now with the expectation that their use will generate additional data to support updates to the methodology and evaluation criteria. The Microbiology Expert Committee anticipates that the data will facilitate the establishment of a standardized method with fixed test parameters and an expansion of the relevant product types. This evolution of the methods can only occur with scientific evaluation of a significant amount of data covering a variety of product types.

Comment Summary #25: Some commenters requested clarification on the definition of the negative control. Additionally, a commenter suggested adding two controls—media-only and

product-only—when performing method suitability studies. The media-only control, which is lot-based, need not be performed with each inoculation study. However, the product-only control should be included in each inoculation study to verify that the product used is free of contamination and to assess the user's aseptic technique. The commenter also advised that the USP expert committee provide guidance on the total number of replicates for each inoculation study.
Response: Comment incorporated. The revised chapter text now reads as follows: "*The suitability test should also include negative controls ~~using~~* ***such as uninoculated nutrient media, uninoculated nutrient media with unspiked*** *product ~~a diluent, such as Fluid A~~, for each media type and incubation condition."* Regarding replicate for inoculum control, the requirements are aligned with <61> and <71>. If the commenter is referring to the replicates for suitability tests, those are described in <1071>.
Comment Summary #26: The commenter made two suggestions for the system suitability test. The first suggestion was to append the following statement after the third paragraph of this section to comply with USP <71>: "The product does not exhibit any antimicrobial activity under the test conditions if the results of the inoculated samples are similar to those of the positive controls." The second suggestion was to determine the microbial count in the micro-organism suspensions used for inoculation by streaking a suitable sample on agar plates. If a count of 1 to 100 CFU is detected for each strain during the assay duration, the method is deemed suitable.
Response: Comment partially incorporated. Since there is no specified incubation time, the requirement in USP <71> is not relevant in this context. An inoculum control has been included (See Comment #24). Additional explanatory text has been added at the end of the paragraph (See Comment #20).

Table 1 Strains of Test Microorganisms Suitable for Use in the Growth Promotion Test

Comment Summary #27: The commenter recommended including "Method Suitability Test" in the title of Table 1 for clarity.
Response: Comment incorporated. The title of Table 1 now reads: *Strains of Test Microorganisms Suitable for Use in the Growth Promotion Test and the Method Suitability Test.*
Comment Summary #28: The commenter recommended adding an asterisk to a reference stating "these microorganisms are appropriate for use in method suitability determination, but the list not comprehensive."
Response: Comment not incorporated. The general chapter reads clearly that Table 1 microorganisms and a selection of test strains relevant to the product/manufacturing process are used for method suitability.
Comment Summary #29: The commenter requested adding the NCTC/NCPF strains in Table 1: *Bacillus spizizenii* (ATCC 6633; NCTC 10400); *Pseudomonas paraaeruginosa* (ATCC 9027; NCTC 12924); *Clostridium sporogenes* (ATCC 11437; NCTC 12935); *Aspergillus brasiliensis* (ATCC 16404; NCPF 2275).
Response: Comment incorporated. The requested strains were added to the table.
Comment Summary #30: The commenter recommended shortening the reference to: *Aspergillus brasiliensis* because *A. niger* has not been in common usage.
Response: Comment incorporated. Change was made in Table 1.

DETERMINATION OF THE INCUBATION TIME IN THE PRODUCT TO BE EXAMINED

Comment Summary #31: Several commenters have proposed either simplifying or eliminating the determination of incubation time. They note that the current process is overly complex and challenging for users to implement, given that the results will vary between an automated

growth-based method and manual testing (such as microscopy, dilution, and plating). They also believe that this reduces the benefits of using automated growth-based methods, as the incubation time will be extended by slow-growing microorganisms, even with the safety margin.
Response: Comment partially incorporated. The text has been modified to state that the Rapid Microbial Method (RMM) system itself can be utilized to determine the incubation time. The inclusion of slow-growing microorganisms is based on risk, and the significant factor in time to detection is the time obtained in the suitability test, not the inclusion of the safety margin.
Comment Summary #32: The commenter stated that *C. acnes* is not a suitable organism for method suitability testing. As a skin-borne bacterium, *C. acnes* occupies a highly specialized niche and there is no evidence to suggest it is a human pathogen. People are constantly exposed to this bacterium, which likely enters the human body through injections and intravenous administration of medicinal products, without resulting in infection. In terms of risk, the commenter believes it is not an appropriate challenge organism.
Response: Comment not incorporated. The selection of test microorganisms is risk based and depends on the intended use of the method. *C. acnes* is not a mandatory method suitability test microorganism in <72>.
Comment Summary #33: The commenter suggested that reference sources should be added for the calculations and equations.
Response: Comment not incorporated. The EC intended to maintain the brevity of the chapter text. The technical information required is readily accessible through public sources.
Comment Summary #34: The commenter suggested adding parentheses as follows: "$T = t_{ttd} + (\log 2(10) \times G)$."
Response: Comment incorporated. Parentheses were added in the equation.
Comment Summary #35: The commenter recommended adding an explanation of the derivation of the values 3.32 and 3.3. It is not clear how the value of 3.3 in the generation time equation was obtained and whether it is the same as the value of 3.32 in the other equation.
Response: Comment incorporated. Changes made to keep the value consistent as 3.3.
Comment Summary #36: The commenter suggested to delete the phrase "In this example" in the following sentence "In this example, the generation time may be determined as follows…". The statement is a general statement not specific for this example.
Response: Comment incorporated. Change has been made as suggested.
Comment Summary #37: The commenter stated that the most practical method to calculate the generation time is using an automated kinetic system, where the detection time is inversely proportional to the initial inoculum. The method involves preparing a dilution series of the organism. This series is then graphed with the Time to Detection plotted against the inoculum CFU. The value for 't' can be determined as illustrated in Figure 1. The commenter stated that it is not practical to remove sealed media bottles from an automated incubation system to take aliquots for enumeration. This is particularly true for anaerobic bottles, where puncturing the septum would allow oxygen to enter and adversely affect the growth of the target organism. The commenter observed that such enumeration methods would disrupt the incubation process, thereby affecting the calculation of time to detection and rendering the process of calculating generation time both impractical and inaccurate.
The commenter requested an update to the example for the calculation of generation time, and suggested eliminating the recommendation to measure microbial cell numbers by microscopy, dilution/plating, or the use of optical density. Instead, the commenter proposed a more accurate and practical method using a dilution series of known inoculation counts, which is then plotted against the corresponding Time to Detection.
Response: Comment not incorporated. The existing text "…or other adequate means" covers the proposed method stated in the comment. An FAQ document will be drafted addressing the topic.

Comment Summary #38: The commenter suggested revising the second bullet point as follows: "*At time 0 and at determined intervals* ***that include the exponential phase*** *(e.g., 0.5–1 h), measure the microbial cell numbers (e.g., by microscopy, dilution/plating, the use of optical density measurements, or other adequate means).”*
Response: Comment incorporated. The change has been made according to the suggestions.
Comment Summary #39: The commenter highlighted that the current text does not have the requirement of the alternative method being validated but instead refers to traditional growth-based methods for determining microbial cell numbers. As it is recommended to perform this during method suitability, the ability of the alternative method to detect the organism based on signal detection should be assessed. The commenter proposed the following revision: "*At time 0 and at determined intervals (e.g., 0.5–1 h), measure the microbial cell numbers (e.g., by microscopy, dilution/plating, the use of optical density measurements, or other adequate means) or detectable signal (e.g., by the alternative method itself) including the exponential phase*."
Response: Comment incorporated. The bullet point states as follows: At time 0 and "...cell numbers (e.g., by microscopy, dilution/plating, the use of optical density measurements, ***the RMM system itself***, or other adequate means)."
Comment Summary #40: The commenter recommended adding generation times of the microorganisms included in Table 1.
Response: Comment not incorporated. The generation times are too specific to be generalized. The parameter depends on incubation temperature, test strain, growth media, etc.
Comment Summary #41: The commenter suggested adding an example calculation if the safety factor is retained.
Response: Comment not incorporated. The requested example calculation was already in the text of this general chapter.

Volume of Article to Be Tested

Comment Summary #42: There were a few comments regarding the requirement of the sample size. Some commenters requested to have similar guidance as ICH Q5D and Ph. Eur. 2.6.27.to allow a timely submission of sample for testing**.**
Response: Comment not incorporated. Considering the large scope of short life products, the risk-based approach provided in <72>, a unique sampling strategy can be applied. The general statement in the current text allows a more flexible application of <72>.
Comment Summary #43: The commenter requested to clarify the calculating detection probability instead of reference to <1071>.
Response: Comment not incorporated. The referenced formula for calculation in <1071> is a recommendation, other approaches may be used.
Comment Summary #44: The commenter cited the statement in USP <71>: "The technique of membrane filtration is used whenever the nature of the product permits". Membrane filtration allows for a greater sample volume to be tested from each sample unit for each resulting growth medium. The user must consider the volume of product tested to be reflective of the probability of detecting a contaminated unit. The commenter suggested adding a sentence in the text: "The transition alone to a direct inoculation rapid method for a filterable product does not preclude the user from testing the full recommended volume. This may require the use of multiple media for a single test."
Response: Comment not incorporated. Considering the large scope of short life products, the risk-based approach in <72> can be applied to a unique sampling strategy. So therefore, to allow a more flexible application of <72> the EC prefers to keep the statement general.
EC-initiated change: change the sentence "Use of appropriate culture collection **strains** that are identical to in-house isolates are acceptable." under the section "METHOD SUITABILITY TEST"

to " Use of appropriate culture collection **microorganisms** that are identical to in-house isolates are acceptable.".

General Chapter/Section(s):	<73> ATP Bioluminescence-Based Microbiological Methods for the Detection of Contamination in Short-Life Products / Multiple Sections
Expert Committee(s):	General Chapters-Microbiology Expert Committee
No. of Commenters:	10

TITLE

Comment Summary #1: The commenter stated that the advantages of the ATP Bioluminescence-Based Microbiological methods apply to not only the short shelf-life products but also all sterility tests. The commenter suggested to change the title to the following to reflect this: ATP Bioluminescence-Based Microbiological Methods for the Detection of Contamination or ATP Bioluminescence-Based Microbiological Methods for the Detection of Contamination (including sterility tests).
Response: Comment not incorporated. The scope of General Chapters <72> and <73> are within the framework of General Chapter <1071> for short shelf-life products only.

INTRODUCTION

Comment Summary #2: There are several comments related to the application of the general chapter. The comments are summarized as follows: 1. Consider extending the scope of the chapter to apply the ATP method to all types of pharmaceutical products. Suggests that this chapter is intended as a risk-based test for detecting microbial contamination in products, product intermediates, cell media or process solutions where appropriate. 2. Provide a list of short-life products. 3. Clarify the terms of short-life product, short shelf-life product, and short manufacturing times. 4. Requested information on cryopreserved products as well as in cases of drug shortage and medicine for emergency use.
Response: 1. Comments partially incorporated. A sentence ***"It may also be used as an in-process control for the testing of product intermediates, cell media, or process solutions.***" was added to the beginning of the "**Introduction"** section. 2. Including a list of short-life products may inadvertently omit new emerging products. 3. & 4. USP<1071> provides the framework for the application of <72> and <73> and the definition for short life products. More details and clarifications were included in GC <1071>.
Comment Summary #3: Several commenters requested clarification on if a full validation is required for rapid methods as well as if a conventional method still needs to be run for the products.
Response: Comment partially incorporated. The EC added more details on method validation in <1071>.
Comment Summary #4: A few commenters suggested including a statement that allows the release of products for infusion as 'negative to date' when indicated (compassionate release, clinical trials).
Response: Comment incorporated. More details and clarifications were included in GC<1071>.
Comment Summary #5: The commenter suggested replacing the word "luminometer" with "optical means" or "optical measurement" since "luminometer" is too restrictive technologically.
Response: Comment incorporated. The sentence now reads as the follow: "…is measured with *optical means (e.g., luminometer*)."

Comment Summary #6: The commenter suggested adding the following text “ATP bioluminescence detection can also be interpreted as colony forming units (CFU’s). CFU counts correlate with those of traditional methods.”
Response: Comment not incorporated. Not all ATP-based methods utilize CFU counts on plates but measure the amount ATP produced in a liquid nutrient media.
Comment Summary #7: The commenter recommended either cancelling this general chapter or revising it to state that only non-cell-based short-life products can be tested with ATP bioluminescence technology. There can be huge variations in background RLU values between samples, and the background impacts sensitivity when a method provider relies on background ATP as the cut-off multiplier. ATP bioluminescence is a common method for testing food hygiene, aseptic dairy, and plant-based beverages as well as non-sterile home and personal care products, but it has never been seen as a go-to technology for pharmaceutical products, especially cell-based products. There is very little if any history of using ATP bioluminescence for cell-based products.
Response: Comment not incorporated. ATP based methods are primarily designed to detect microorganisms growing in culture media. To differentiate background signal from positive growth, a cut-off is necessary.EC agrees that not all products may apply to ATP bioluminescence methods and as described in <1071> it is for the stakeholder to evaluate if this method is suitable. However, there are also sample preparation steps which may reduce the ATP background from cell-based preparations.
There is significant data available to support the ATP-based method accepted by regulatory authorities. There are numerous publications that show in the pharmaceutical field ATP bioluminescence systems have been used for a large variety of products (biologics, small molecule sterile products, blood culture, etc.).
Comment Summary #8: To align with GC <72>, the commenter suggested adding “The application of ATP-based methods for the detection of contamination in a variety of products has been published in peer reviewed literature.”
Response: Comment incorporated. The suggested text was added to align with GC<72>.
Comment Summary #9: To align with GC <72>, the commenter recommended to add “Further benefits include the detection of cultures without interference from product-related turbidity, the automation of data analysis, reporting and archiving.”
Response: Comment incorporated. The suggested text was added to align with GC<72>.
Comment Summary #10: There are ATP Bioluminescence methods available which are applicable for samples which cannot be filtered, and for small quantity samples. The commenter suggested revising the sentence regarding the method disadvantages. The commenter recommended to remove “Removed” and “limitations due to sample size and filterability.”
Response: Comment partially incorporated. The EC agreed to remove “limitations due to sample size and filterability” as direct inoculation methods exist for ATP-based methods. The EC revised the sentence now read as the following: “Disadvantages of these methods include the inability to detect microorganisms that do not grow under the culture conditions utilized and products with significant ATP background that cannot be *reduced* ~~removed~~, ~~and limitation due to sample size and filterability~~.” As it may not technically be possible to remove all non-microbial ATP but at least to reduce the level of background.
Comment Summary #11: The commenter requested the clarification that this is not a risk-based test, but rather a test that is implemented by weighing the risks of having a more basic validation approach compared to the need for faster release.
Response: Comment acknowledged. To align with <72>, sentence “This chapter is intended to be used as a risk-based test for the detection of microbial contamination in short-life products and encompasses short shelf-life products and/or short manufacturing times where the product must be administered as soon as possible.” was added in the beginning of the general chapter.

Comment Summary #12: The commenter suggested eliminating the sentence “It may also be used as an in-process control for the testing of product intermediates, cell media, or process solutions." ATP screening has been used to confirm cleaning effectiveness in food, beverage, and healthcare facilities, but the correlation between ATP levels and microbial counts is low especially with low numbers (Arkel et al, 2021).
Response: Comment not incorporated. The text does not refer specifically to bioburden testing but testing of product intermediates which may be sterile. In addition, some ATP bioluminescence methods count microbial colonies on plates so in this case bioburden testing could apply. The method may be applicable to bioburden but not in the scope of <73>.

CULTURE MEDIA AND INCUBATION CONDITIONS

Comment Summary #13: The commenter stated that the current text in the second paragraph of this section seems to limit the parameters to be considered during the risk-assessment. The commenter proposed the following revision: *“The choice of media and incubation conditions should be risk-based in consideration of manufacturing process parameters (e.g., temperature, oxygenation level).*”
Response: Comment incorporated. The revision was made according to the comment.
Comment Summary #14: The commenter requested to define the notion of “degree of exposure of oxygen.”
Response: Comment partially incorporated. An example was provided in the text for clarification.
Comment Summary #15: The commenter suggested aligning the text with GC<71>. The commenter stated that a gradient-layered facultative media such as fluid thioglycolate may capture aerobic and anaerobic growth in a single test condition at 30-35°, in alignment with traditional growth-based methods.
Response: Comment not incorporated. The actual text does not prevent the user from using FTM and incubating at 30-35°C. It is for the user to determine which culture media would be more appropriate for the type of microorganisms expected in the sample tested.
Comment Summary #16: The commenter emphasized the level of variability that ATP bioluminescence can have on testing. The sensitivity of the method can be impacted by lot-to-lot variability. The commenter recommended that a guideline for acceptable background ATP be included for each culture media.
Response: Comment partially incorporated. Testing is performed with a nutrient medium control without product. Therefore, the cut-off value is based on the same nutrient media lot than the one used for the DP testing thereby covering nutrient media variability in terms of ATP signal.
Comment Summary #17: The commenter suggested adding table of ATP Content of Representative Microorganisms (La Duc et al, 2007) to the general chapter. The ATP content of microorganisms varies widely. With larger microbial cells, e.g., yeast, as little as 10 cells retained on the membrane may be sufficient for ATP bioluminescence without incubation and colony formation. The data suggests that the incubation time for bacterial detection may be reduced compared to the formation of turbidity (>107 CFU) to achieve 5000 RLU (>103 CFU), which is usually 3 times the media baseline.
Response: Comment not incorporated. This is more explanatory information that is not part of a general chapter. The incubation time would also depend on your product matrix, and strains of microorganisms used. It is not necessary to provide fixed incubation times to allow a broader application of the method.
Comment Summary #18: The commenter proposed to add the sentence below: “*Visual inspection of media containers may be required at the end of incubation for the detection of*

molds, especially if their presence was not automatically detected by the system during method suitability, even when mold balls were visible."
Response: Comment not incorporated. The requested text addition was not included. No detection of molds that formed colonies was observed in respiration-based methods where the sample could not be treated before the measurement. For ATP based methods the sample may require an additional treatment after incubation and prior to measurement (e.g., stirring with glass beads) to shear the mold hyphae and increase the probability of capturing mold hyphae in the aliquot used for ATP bioluminescence treatment.

GROWTH PROMOTION TEST OF AEROBES, ANAEROBES, AND FUNGI

Comment Summary #19: The commenter recognized that this section does not specify which media should be detecting which microorganisms, but that the media used (in general) should detect all the organisms listed. This brings definitive flexibility to decide what condition is the best one for the microorganism's detection.
Response: Comment acknowledged.
Comment Summary #20: The commenter stated that the acceptance criteria for growth promotion tests are not strict enough. If the media is impaired, the acceptance criteria can still be achieved with a little bit of growth. Growth promotion test might be positive even if the doubling time of the microorganism is drastically slowed down. A traditional growth promotion test (GC<71>) is more suitable. The commenter requested to add clarification of "standard inoculum." The Commenter recommended the following changes for Growth Promotion Test :1. The liquid media are suitable if all organisms are detected (harmonized wording with USP<72> draft 2. The solid media are suitable if the CFUs detected do not differ by a factor greater than 2 compared to a standardized inoculum.
Response: Comment not incorporated. The scenario described would also be considered for the GC<71> growth promotion test with classical media. If the media lot is unsuitable, not all microorganisms tested would be detected within 3 days. The terminology of "Standard Inoculum" is defined in GC<61>. The current text is consistent with GC <61>, <71>, & <72>.
Comment Summary #21: Two commenters stated that a 3-time cut-off is not scientifically justified, and the 3-time cut-off is a recommendation from one instrument supplier. One of them suggested to change as following: *The liquid media are suitable if ATP bioluminescence is detected at a suitable level which is separated from the background of the media without microbial inoculation.*
Response: Comment partially incorporated. The text was revised to read as follows: "The liquid media are suitable if ATP bioluminescence is detected at ~~a~~ ***the pre-defined positive cut-off*** level ***compared to*** ~~of at least 3 times~~ the background of the media without microbial inoculation."

METHOD SUITABILITY TEST

Comment Summary #22: The commenter stated that the inoculation of growth promotion test and method suitability test may be the same to rule out medium issue when failure occurs.
Response: Comment acknowledged. Growth promotion test should be performed during suitability.
Comment Summary #23: Several commenters recommended maintaining consistency in the inoculum size, aligning it with references <71>, <60>, <61>, <62>, <1223> and European Pharmacopeia 2.6.27. They expressed concerns that targeting less than 10 CFU could be challenging and might lead to true negatives being misinterpreted as failed Method Suitability Tests.

Response: Comment partially incorporated. Members of the EC have positive experiences with inoculum levels of 10 CFU or less, supported by experiments conducted by EC members and other stakeholders. The feasibility of an inoculum size of 10 CFU has been demonstrated. In cases where inoculum levels exceed 10 CFU, additional guidance was provided. The following text was added in the last second paragraph in Method Suitability Test section: *Considering the variability of the microbiological inoculum and assuming it follows a Poisson distribution it may happen that with a low sample size targeting not more than 10 CFU that the inoculum control measured might exceed 10 CFU. A scientific justification would be required if the inoculum control final mean value is exceeding 10 CFU and is maintained in the suitability test results*.

Comment Summary #24: The commenter recommended that the microbial count in the microorganism suspensions used for inoculation is determined by streaking an appropriate sample on agar plates. If between 1 and 100 CFU are detected for each strain within the duration of the assay, the method is suitable for the intended test sample.

Response: Comment partially incorporated. Additional wording to the inoculum control has been included (see Comment #29).

Comment Summary #25: The commenter requested to provide specific instruction on test strains selection (which and how many) relevant to the product/manufacture process.

Response: Comment not incorporated. The current text clearly indicated the selection should be supported by a suitable justification.

Comment Summary #26: The commenter proposed the following revision: *Inclusion of environmental microorganisms including slow growing microorganisms, that represent risk to patient or product, or found in the manufacturing environment and product failures must be included*.

Response: Comment partially incorporated. While the inclusion of slow-growing microorganisms is not mandatory, the revised chapter text provides clarification: *Inclusion of slow growing microorganisms may be considered* ***if relevant for the process or product risk.***

Comment Summary #27: The commenter requested to delete the following text for clarity: "…if they diverge from the Table 1 microorganism with regard to growth capacity and/or their metabolic activity."

Response: Comment incorporated.

Comment Summary #28: The commenter stated that the source and concentration of the in-house isolates was not provided. The commenter recommended citing the challenge organisms in GC<71> as viable reference standards and establish a USP ATP reference standard for the test.

Response: Comment not incorporated. It is not mandatory to utilize in-house isolates. The local isolates may be considered if relevant to the product or process. ATP solution may be used to calibrate the detection system, but these are growth-based method test microorganisms that would still be required to verify the growth of the media.

Comment Summary #29: The commenter suggested revising the third paragraph as follows: *Include a non-inoculated nutrient medium control as a bioluminescence baseline control and an inoculated nutrient medium control as a positive control*.

Response: Comment not incorporated. The proposed text does not differentiate clearly between the direct inoculation method and the membrane filtration method. The EC made the changes to include clear separations for nutrient broth and membrane filtration method. The text now reads as follows: ***For the direct inoculation method****, include a non-inoculated nutrient medium control* ~~*for the direct inoculation method*~~ ***to determine the baseline of the media without product. For the membrane filtration method****,* ~~*and*~~ ***include*** *an inoculated nutrient medium control* ***to determine the count of test microorganisms without product*** ~~*for the membrane filtration method*~~*.*

Comment Summary #30: The commenter requested to clarify the purposes of a non-inoculated nutrient medium control for the direct inoculation method and an inoculated nutrient

medium control for the membrane filtration method and include negative controls for direct inoculation and membrane filtration methods.
Response: Comment incorporated. See revised text in response to comment #29.
Comment Summary #31: The commenter requested to include negative controls for both direct inoculation and membrane filtration methods.
Response: Comment not incorporated. The current text applies to both methods.
Comment Summary #32: The commenter requested to define negative controls.
Response: Comment incorporated. The current text is modified as following: "The suitability test should also include negative controls ***e.g.*** using a diluent, ~~such as Fluid A~~ for each media type and incubation condition."
Comment Summary #33: The commenter requested to include the sentence below in the text: Each *microorganism used for method suitability should have an associated positive control of the microorganism without product.*
Response: Comment not incorporated. The inoculum control is the enumeration of the microbial suspension used for the suitability test.
Comment Summary #34: The commenter suggested changing "for not more than a defined incubation time" to "for not more than the defined incubation time **used for the routine test.**" The incubation time for method suitability should be no more than the routine test.
Response: Comment not incorporated. The routine test also has an additional safety factor so the incubation time for routine test would systematically be longer than the suitability time. The example given in that section "**DETERMINATION OF THE INCUBATION TIME OF THE PRODUCT TO BE EXAMINED"** clearly specifies that the routine incubation time is the incubation time determined in method suitability test plus the safety factor.

Nutrient Broth Method

Comment Summary #35: A few commenters recommended to use the terminology in GC<71> "Direct Inoculation Method" as subheading instead of "Nutrient Broth Method" since nutrient broth method can be used for both membrane filtration and direct inoculation techniques.
Response: Comment incorporated.
Comment Summary #36: The commenters stated that the product may have antimicrobial activity in the case organism is detected at a much lower level than positive control. The commenter recommended to revise the first paragraph as follows: "*... The product possesses no antimicrobial activity if the results of the inoculated test samples are comparable to the results of the positive controls."*
Response: Comment partially incorporated. If the microorganism is not detected at the positive cut-off level, the incubation time can be increased, or the product should be neutralized as written in the section below in the text. For clarity, the text was revised to read: "…if the RLU level of the inoculated sample **exceeds the predefined positive cut-off level as compared to** ~~has a RLU value of at least 3 times~~ the value of the non-inoculated nutrient medium control."
Comment Summary #37: A few commenters noted that the nutrient broth method can be used as quantitative or qualitative method. The general chapter is currently written that membrane filtration is only for quantitative methods. A commenter also suggested including information from USP<71> on membrane filtration being the preferred technique, to enhance method suitability and performance. Another suggestion is to use different acceptance criteria for quantitative methods and qualitative methods.
Response: Comment not incorporated. The general chapter is not written so that the membrane filtration is used for quantitative methods but for detection of contamination. A factor of 2 recovery is considered sufficient for a method suitability with such a tight inoculum level.

Comment Summary #38: The commenter noted that the cut-off factor stated in the General Chapter is established for Celsis system only. The commenter recommended revising to include other multiplier values.
Response: Comment incorporated. The EC made changes to make the cut-off levels more generic. See Comment Summary #36.

Membrane Filtration Method

Comment Summary #39: The commenter highlighted that there is only one supplier on the market for the membrane filtration method which requires using ATP bioluminescent solutions to detect the growth of colonies on the surface of the membrane. The commenter requested to consider the membrane filtration method in which the broth is filtered as part of sample preparations.
Response: Comment acknowledged. The membrane filtration method may be developed by other suppliers. The membrane filtration method has been utilized as an appropriate sterility test for a very large scope of products and the EC is confident that it can be utilized in the context of GC <1071>. The membrane filtration method requires growth of (micro) colonies for detection. Therefore, filtering a broth on a membrane and then directly staining without pre-incubation would not trigger a detectable ATP Signal.
Comment Summary #40: The commenter requested to clarify if the membrane filtration method is considered a quantitative method. In the case of quantitative method, the acceptance criteria (the CFUs detected do not differ by a factor greater than 2) must be applied.
Response: Comment not incorporated. The membrane filtration method is used as a qualitative method but with an output utilizing enumeration of (micro) colonies. These (micro) colonies are detected after staining, and ATP-bioluminescence is captured by a CCD camera and then analyzed via the software. To verify if this method adequately recovers microorganisms in a sample, the relevant signal is the number of colonies and not the intensity of the ATP signal.
Comment Summary #41: The commenter suggested considering the pre analytical step for the cell therapy products since the cellular concentration can be high and may generate a lot of background because of the ATP released by the human cells. In some cases, it may clog the membrane making the analysis impossible. In addition, the membrane filtration from enrichment broth should be considered as part of the sample prep but not the ATP assay detection itself.
Response: Comment incorporated. A sentence was added to the end of the section as following: "*In addition, to allow filtration of cell-based products, a cell lysis protocol may be required prior to the method suitability test.*"
Comment Summary #42: The commenter requested to add text to allow adjust membrane material after neutralizing step.
Response: Comment not incorporated. The membrane used for ATP testing is specific since there is an ATP staining step. Changing the membrane needs to be investigated to make sure there is no impact on the primary validation results.
Comment Summary #43: The commenter requested to apply the same *Acceptance criteria* for both methods in Method Suitability Test.
Response: Comment not incorporated. The criterion applied is based on typical application of these methods. The systems of detection are different between the direct inoculation and membrane filtration method, so the results cannot be compared. The membrane filtration delivers colony counts as a result and not the ATP level.
Comment Summary #44: Several comments are related to sample interference study. 1. Add a subheading for sample interference; 2. Include acceptance criteria using multiple cut-offs and a set cut-off for flexibility; 3. More details are needed for the interference study.
Response: Comment incorporated. A new sub-heading "Sample Interference Study" was added. The acceptance criteria were removed from this section and the cut-off level was revised

in a more generic term in the previous section. (See **Comment Summary #36**). This section was revised and expanded for clarity.

Table 1 Strains of Test Microorganisms Suitable for Use in the Growth Promotion Test

Comment Summary #45: The commenter recommended further reconciliation and alignment expectations and methodologies between GC<72> and GC<73>, especially in terms of defining the growth promotion and method suitability challenge organisms as related to the certified reference strains found in GC <71>.
Response: Comment incorporated. GC<72> and <73> are aligned for growth promotion test and method suitability test.
Comment Summary #46: The commenter recommended to include "Method Suitability Test" in the title of Table 1 for clarity. In addition, the commenter requested to ensure that the heading information and bacteria strains in the table are correct.
Response: Comment incorporated. The title of Table 1 now reads: *Strains of Test Microorganisms Suitable for Use in the Growth Promotion Test and the Method Suitability Test.* The heading and bacteria strains are now aligned.
Comment Summary #47: The commenter requested adding the NCTC/NCPF strains in Table 1: *Bacillus spizizenii* (ATCC 6633; NCTC 10400); *Pseudomonas paraaeruginosa* (ATCC 9027; NCTC 12924); *Clostridium sporogenes* (ATCC 11437; NCTC 12935); *Aspergillus brasiliensis* (ATCC 16404; NCPF 2275).
Response: Comment incorporated. The requested strains were added to the table.
Comment Summary #48: The commenter recommended shortening the reference to: *Aspergillus brasiliensis* because *A. niger* has not been in common usage.
Response: Comment incorporated.
Comment Summary #49: The commenter noted that *Kocuria rhizophila* (formerly *Micrococcus luteus*), a Gram-positive coccus, is not a suitable alternative microorganism for *Pseudomonas paraeuginosa* (formerly *P. aeruginosa*).
Response: Comment not incorporated. We need to stay consistent with USP <71>.

DETERMINATION OF THE INCUBATION TIME IN THE PRODUCT TO BE EXAMINED

Comment Summary #50: A few commenters proposed either simplifying or eliminating the determination of incubation time. They argue that the current process is overly complex and challenging for users to implement. They also believe that this reduces the benefits of using automated growth-based methods, as the incubation time will be extended by slow-growing microorganisms, even with the safety margin. One commenter recommended using a percentage of the longest time to detection.
Response: Comment not incorporated. The inclusion of slow-growing microorganisms is based on risk assessment per user's specific application. This General Chapter is not intended to determine the generation time of all slow growing microorganisms, but the slowest test strain determined in method suitability test. Thus, the purpose is to define a safety margin that is data driven and specific for the product and method. Slow growing microorganisms may not need to be included in a fast-screening process, especially if they are not the most relevant microorganisms that would be detected. The general chapter allows this flexibility.
Comment Summary #51: The commenter requested clarity on how the growth rate is measured to determine the incubation time.
Response: Comment not incorporated. More detail on generation time determination is included in the current general chapter text.
Comment Summary #52: The commenter suggested that reference sources should be added for the calculations and equations.

Response: Comment not incorporated. The EC intended to maintain the brevity of the general chapter text. The technical information required is readily accessible either online or in a library.
Comment Summary #53: The commenter suggested adding parentheses as follows: "$T = t_{ttd} + (\log2(10) \times G)$."
Response: Comment incorporated. Parentheses were added in the equation.
Comment Summary #54: The commenter recommended adding an explanation of the derivation of the values 3.32 and 3.3. as it is not clear how the value of 3.3 in the generation time equation was obtained and whether it is the same as the value of 3.32 in the other equation.
Response: Comment incorporated. Changes made to keep the value consistent as 3.3.
Comment Summary #55: Commenter requested to include the other calculations or methods to determine the generation time if appropriately justified.
Response: Comment incorporated. A sentence was added to the end of the sections as following: "*Depending on the output signal measured, other formulas may apply*."
Comment Summary #56: The commenter requested clarification on if optical density (OD) measurements can be used for generation time determination; what is the difference between doubling time and generation time.
Response: Comment acknowledged. It is possible to use optical density for the generation time determination. As shown in the formula provided in GC<73> which is based on microbial cell numbers, the user can determine the generation time by transposing the OD to cell numbers. During the exponential phase, the generation is approximate the doubling time.
Comment Summary #57: The commenter suggested deleting "In this example" in the sentence: "In this example, the generation time may be determined as follows:".
Response: Comment incorporated. A change has been made according to the suggestions.
Comment Summary #58: The commenter suggested revising the second bullet point as follows: "*At time 0 and at determined intervals* ***that include the exponential phase*** *(e.g., 0.5–1 h), measure the microbial cell numbers (e.g., by microscopy, dilution/plating, the use of optical density measurements,* ***the RMM system itself*** *or other adequate means)."*
Response: Comment incorporated. A change has been made according to the suggestions.
Comment Summary #59: The commenter requested to add alternative method being validated for determination of generation time.
Response: Comment incorporated. See Comment Summary #58 for revised text.
Comment Summary #60: The commenter noted that it is difficult to implement the generation time determination. The readouts are different between an automated growth-based method and manual testing.
Response: Comment incorporated. See Comment Summary #58 and #59.

TEST FOR MICROBIAL DETECTION IN THE PRODUCT TO BE EXAMINED
Volume of Article to Be Tested

Comment Summary #61: The commenters requested to have a clear expectation of test volume and align with Ph. Eur. 2.6.27.
Response: Comment not incorporated. EP 2.6.27 is focused on cell-based preparations only. Considering the large scope of short life products (compounding pharmacy products, PET; cell-based preparations, etc.) and the risk-based approach in <73>, a specific sampling strategy cannot be applied. The general statement in the current text allows a more flexible application of <73>.
Comment Summary #62: The commenters recommended changing the range of between 1 and 1000 mL to 25-1000 mL to align with industry practices considering cell therapies.
Response: Comment not incorporated. Short-life products have a larger scope than only cell therapies.

Comment Summary #63: The commenters requested clarify the statement “the probability of detecting a contaminated unit should not be worse than <71>”.
Response: Comment acknowledged. The section on sampling was modified to allow a more flexible application of the test methods based upon justification and reference to <1071> to support the justification was included.
Comment Summary #64: The commenters requested clarification on the last paragraph in this section.
Response: Comment acknowledged. The section on sampling was modified to allow a more flexible application of the test methods based upon justification and reference to <1071> to support the justification was included.
Comment Summary #65: Commented suggest eliminating the statement of “stakeholders may contact their respective regulatory agencies to obtain an agreement on the proposed test sample sizes.”
Response: Comment not incorporated. As the methods in <73> apply to a very diverse set of short life products, USP<71> sample sizes might not meet the latest expectations from regulatory authorities and the recommendation was included only for release sterility tests.

Nutrient Broth Method

Comment Summary #66: The commenters requested to align the test environment with GC<71>.
Response: Comment incorporated. The revised text read as follows*: …into culture medium ~~using aseptic manipulation~~* ***under aseptic conditions*** *~~conducted in a biological safety cabinet or isolator system~~. Include a nutrient...*

Membrane Filtration Method

Comment Summary #67: The commenter requested to include aseptic practices for membrane filtration method.
Response: Comment incorporated. “Under aseptic conditions” was added in the text.
Comment Summary #68: The commenter noted that GC<73> is specifically about ATP bioluminescence-based detection methods using a luminometer, not fluorescence-based detection methods. Thus, the reference of nonfluorescence membrane filters is not correct.
Response: Comment incorporated. The term “nonfluorescence membrane filters” was replaced with “suitable membrane filters.”
Comment Summary #69: The commenter recommended eliminating the filter size requirement.
Response: Comment not incorporated. The current text is written in a flexible way so that either 0.22 or 0.45 µm filters can be used. Vendors that have performed primary validation also demonstrate the capacity of microbial retention or else they would not be detected.

MONITORING AND INTERPRETATION OF RESULTS

Comment Summary #70: The commenter stated that monitoring growth in the microbiological media at the end of the determined incubation period is less useful than continuous monitoring for short-life products which may be administered prior to completion of the test (See <72>). The definition of contamination as a RLU value 3 times that of the uninoculated control is a common industry practice but needs further definition by applying the concept of the signal-to-noise ratio, as well as establishing statistical acceptance criteria. The commenter recommended including discussions of signal-to-noise ratio and establishing statistical acceptance criteria.

Response: Comment not incorporated. The explanation on the selection of the RMM is part of <1071> and will not be covered in <73>. The threshold was adapted to make the chapter applicable to a larger number of systems.
Comment Summary #71: The commenter noted that using 3 times of the broth blank is based on Celsis technology only. The commenter recommended including the importance of monitoring CV value.
Response: Comment partially incorporated. The text regarding the cut-off level was revised to make the general chapter applicable to a larger number of systems. Determining variability of nutrient media blanks is not required in routine use but may be part of primary validation (not covered in <73>).
Comment Summary #72: The commenter noted that detection of one colony-forming unit on the membrane filter is more likely to be a laboratory error than a measure of microbiological contamination hence may be unreliable.
Response: Comment acknowledged. More than one count of microorganisms could be a lab error as well. The statement in the chapter is related to a laboratory investigation.
Comment Summary #73: The commenter requested to clarify the last sentence apply to both methods.
Response: Comment incorporated. For clarity, “For both methods” was added at the beginning of the last sentence.
EC-initiated change: change the sentence "Use of appropriate culture collection **strains** that are identical to in-house isolates are acceptable." under the section "METHOD SUITABILITY TEST" to " Use of appropriate culture collection **microorganisms** that are identical to in-house isolates are acceptable.".

General Chapter/Sections:	<382> Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery System
Expert Committee(s):	General Chapters—Packaging and Distribution
No. of Commenters:	5

General

Comment Summary #1: The commenter suggested USP discusses when testing should be performed.
Response: Comment not incorporated. When to test and the frequency of testing is something that needs to be determined by each organization and USP does not give any guidance on this matter, see General Notices and Requirements - 3.10. Applicability of Standards.
Comment Summary #2: The commenter suggests revising the term “plastic systems” throughout the chapter to distinguish it more clearly from other plastic types (e.g., plastic bottles).
Response: Comment incorporated.

4. Packaging/Delivery Systems Integrity Tests

Comment Summary #3: The commenter suggests defining "inherent integrity" as the condition in which test samples have no defects.
Response: Comment incorporated. It was decided to remove the term from the general chapter.

Table 1

Comment Summary #4: The commenter suggests adding a footnote stating that “x” indicates the test should be performed and “-” indicates the test is not necessary.
Response: Comment incorporated.

5 Needle and Spike Access Functional Suitability Test

Comment Summary #5: The commenter suggests including examples of bracketing.
Response: Comment incorporated.

5.1 Fragmentation

Comment Summary #6: The commenter suggests that the acceptance criteria should be NMT 5 for the various fragmentation test as shown in <381>.
Response: Comment not incorporated. The acceptance criteria of NMT 5 in <381> specifically apply to elastomeric stoppers for vials. In <382>, the test has been expanded to include all elastomeric components for Blow-Fill-Seal, Plastic Infusion Systems, and Cartridge systems. Since USP did not have established acceptance criteria for these products, it was decided to adopt criteria from readily available international standards to ensure alignment where necessary.
Comment Summary #7: The commenter suggests revising all instances of the text to read: “…inject a volume of particle-free water into the vial or bottle through the inserted needle while removing an equal volume of air. The chosen volume should adequately purge the insertion needle of elastomeric fragments.” The revision should specify removing an equal amount of air through the inserted needle to avoid creating a high-pressure environment inside the container.
Response: Comment incorporated.
Comment Summary #8: The commenter suggests including a specific volume to give the reader an idea of an amount sufficient to adequately purge the insertion needle.
Response: Comment not incorporated. A single volume is difficult to determine if it needs to cover all practical possibilities.
Comment Summary #9: The commenter suggests harmonizing the bevel angle requirements between the United States Pharmacopeia (USP) and the Chinese Pharmacopoeia (ChP).
Response: Comment not incorporated. The bevel angle was aligned with the various ISO standards.

5.2 Penetration Force

Comment Summary #10: The commenter suggests harmonizing the bevel angle requirements between the United States Pharmacopeia (USP) and the Chinese Pharmacopoeia (ChP).
Response: Comment not incorporated. The bevel angle was aligned with the various ISO standards
Comment Summary #11: The commenter suggests deleting the current statement and defining acceptance limits for each test.
Response: Comment not incorporated. Penetration force limits are too individualized and dependent on the intended use.
Comment Summary #12: The commenter suggests adding a statement that for blow-fill-systems the acceptance criteria are based on the plastic material of construction not the elastomer.
Response: Comment incorporated.

5.3 Needle Self-Sealing Capacity-Blow-Fill-Seal

Comment Summary #14: The commenter suggests clarifying whether the closure is punctured a total of nine times or a total of three.
Response: Comment incorporated.

5.3 Needle Self-Sealing Capacity-Cartridge

Comment Summary #15: The commenter suggests clarifying how one may penetrate a closure half (0.5) of a time.
Response: Comment incorporated.

6.1 Plunger Break-Loose and Extrusion Forces

Comment Summary #16: The commenter suggested clarifying that the test speed should mimic actual use.
Response: Comment not incorporated. The statement is already present.
Comment Summary #17: The commenter suggests defining the plunger stick-slip behavior
Response: Comment not incorporated. Already mentioned in the general chapter.
Comment Summary #18: The commenter suggests clarifying if the intention is for manufacturer to characterize the lubrication consistency.
Response: Comment not incorporated. The intention is not for manufacturers to characterize the lubrication consistency

General Chapter/Section(s): <467> Residual Solvents
Expert Committee: General Chapters—Chemical Analysis
No. of Commenters: 1

Development of the Method

Comment Summary #1: The commenter, referring to the entry "*For example, potential sources of benzene may include its presence as an impurity in a solvent used in the manufacturing process; its use in the manufacture of starting material; or its production as a reaction by-product."* noted that some class II or III solvents contain class I solvent impurities (e.g., benzene in acetone, tetrachloromethane in dichloromethane, etc.), stated that it is currently unclear how the final content in the drug substance or drug product is determined. The commenter suggested including some text to clarify further.
Response: Comment was not incorporated. The expert committee rationalized that the referenced statement was put in the chapter for the reasons outlined in the comment. The expert committee believes that section 3. Control Strategy addresses the requirements for final content of residual solvents in the drug products via the following entries:
"Compliance with the chapter requires that all solvents LTBP comply with the control limits."
And "In all cases, the solvent levels in the final official product must not exceed the limits defined in the chapter."
Comment Summary #2: The commenter, referring to section 8.1 Chromatographic Systems, under Procedure B, noted that the Injection type is given as "*Split ratio, 1:5. [Note – Split ratio can be modified to optimize sensitivity.]*" The commenter stated that the Splits are dilutions, and the dilutions are typically given as larger: smaller. The commenter for readability suggested revising the text from 1:5 to 5:1.
Response: Comment not incorporated. The Expert Committee stated that the suggestion is a convention issue. The 1:5 and 5:1 have been used in GC literature. The chapter has always had the 1:5 since the time it was proposed in PF 29(4) in 2003. It is a general understanding among chromatographers that the smaller number indicates the portion of the flow that enters the

column and the larger the total gas flow. However, the expert committee, noting that the suggestion is outside this revision's scope, decided to further discuss in a future chapter revision.

General Chapter/section(s):	<1060> Mass Spectrometry-based Multi-attribute Method for Therapeutic Proteins
Expert Committee(s):	Biologics Monographs 2 – Proteins
No. of Commenters:	7

1. Introduction and Scope

Comment Summary #1: The commenter requested clarification on the scope of chapter, particularly regarding the use of NPD and the purity method for batch release/stability control.
Response: Comment not incorporated. NPD (New Peak Detection) is a part of MAM, and it is up to the end user to decide if NPD is needed.
Comment Summary #2: The commenter suggested revising the text/introduction section to clarify that while conventional assays provide powerful separation of CQA (critical quality attribute) of interest, UV-based analytics report low-resolution data that cannot capture the fine detail needed.
Response: Comment not incorporated. This introduction provides a high-level overview of conventional methods, and the low resolution and specificity limits of conventional methods will be detailed in later sections. For example, Section 2 includes: "While quantitative measurement of these PQAs can be good indicators of the overall quality and stability of therapeutic proteins, the root causes of any changes in charge or size distribution are often not specifically understood or directly monitored using conventional separation methods due to limited resolution and low specificity."
Comment Summary #3: The commenter suggested revising the text to clarify that MAM approaches, including intact MAM analysis, could be used as in-line monitoring tools during clinical and commercial manufacturing and serve as process analytical technology (PAT) tools.
Response: Comments partially incorporated. The text was revised to: "In addition, MAM approaches, including intact and subunit MAM analyses, could be utilized as in-line monitoring tools during clinical and commercial manufacturing. They can also serve as process analytical technology (PAT) tools."

2. Overview of the Multi-Attribute Method

Comment Summary #4: The commenter suggested removing high level from the description of protein heterogeneity, as it is overstated.
Response: Comment incorporated. Removed “high level” and the statement was revised to " Recombinant protein products are heterogeneous and contain product related substances and product related impurities."
Comment Summary #5: The commenter suggested deleting the statement about analytical separation technologies resolving species like recombinant protein products for clarification and to avoid confusion.
Response: Comment not incorporated. The original text is accurate.
Comment Summary #6: The commenter suggested revising the text to state that it is essential for industry to identify, quantify, and monitor CQAs of therapeutic proteins, noting that impurities are a subset of CQAs.
Response: Comment incorporated. The text has been changed to: "It is essential for industry to identify, quantify, and monitor CQAs of therapeutic proteins."
Comment Summary #7: The commenter suggested replacing "audit compliant" with the more generally applicable term "cGMP compliant”.

Response: Comment incorporated. The text has been changed to: "and sophisticated acquisition and analysis software that are cGMP compliant."
Comment Summary #8: The commenter noted that while MAM is a sensitive and high-resolution test method for site-specific PQAs (product quality attribute), it may be more challenging for non-Mab based biologics.
Response: Comment not incorporated. This sentence is applicable to both mAb and non-mAb proteins: "MAM is a sensitive and high-resolution test method that allows simultaneous detection, identification, and quantitation of site-specific PQAs."
Comment Summary #9: The commenter recommended revising the text to clarify that modifications and their locations in the peptide sequence are identified by in silico alignment and integration using software algorithms with MS/MS data.
Response: Comment not incorporated. In some but not all cases, modifications and their locations need to be analyzed manually at the initial characterization stage.
Comment Summary #10: The commenter suggested specifying that the categorization of PQAs is based on the assessment of their impact on bioactivity, PK, safety, and immunogenicity.
Response: Comment not incorporated. This general chapter mainly focuses on physico-chemical CQAs. "Bioactivity, PK, safety, and immunogenicity" are out of the scope of this chapter.
Comment Summary #11: The commenter suggested replacing "mass spectrometer in MS-only mode" with "mass spectrometry" to clarify the use of MS/MS.
Response: Comment not incorporated. The phrase "may be" is already mentioned in the sentence “Once a list of PQAs has been established, samples may be analyzed by the mass spectrometer operating in MS-only mode.”
Comment Summary #12: The commenter suggested acknowledging that while XIC (extracted ion chromatogram) peak areas are commonly used to calculate relative PQA abundance, alternative approaches such as using peak volumes from three-dimensional ion maps also exist, depending on the software used.
Response: Comment partially incorporated. Text changed to “In the targeted analysis, the relative abundance of each individual PQA is quantitated using the MS ion intensity of the peptides with or without modification. For example, the mass peak areas of the modified and the unmodified peptides can be obtained from extracted ion chromatogram (XIC) peak areas. The relative abundance of a PQA is calculated as the percentage of the modified peptide relative to the total mass peak area of the modified and unmodified peptides.”
Comment Summary #13: The commenter suggested clarifying that "peak area" is used for quantitation instead of MS ion intensity.
Response: The comment is partially incorporated. MS ion intensity can be peak area or peak height, both of which have been used in industry. If replaced by peak area, peak height is not covered. The sentence is revised to: "individual PQA is quantitated using the MS signal of the peptides with or without modification.”
Comment Summary #14: The commenter suggested replacing "MS data" with "LC-MS data" for new peak detection for clarification.
Response: Comment incorporated. The statement is revised to "In the non-targeted analysis, also known as new peak detection (NPD), the LC-MS data of a sample of interest are compared to a reference sample to detect any new ion peaks above a pre-defined threshold that may represent a new quality attribute."
Comment Summary #15: The commenter requested clarification on the term "monitoring," noting that the FDA"s definition excludes NPD, which seems inconsistent with its use in the chapter.

Response: Comment not incorporated. Multi-attribute monitoring does not include NPD. However, the monitoring here does not refer to multi-attribute monitoring; it refers to the MAM workflow.
Comment Summary #16: The commenter suggested clarifying the types of MS data suitable for "monitoring" and recommended including "LC-MS/MS" as an option for monitoring.
Response: Comment incorporated.
Comment Summary #17: The commenter suggested adding "for sequence confirmation" after "peptide mapping" to clarify its meaning within the right hexagon of Figure 1.
Response: Comment not incorporated. Peptide mapping can provide more information in addition to sequence confirmation.
Comment Summary #18: The commenter suggested adding "build peptide library" and mentioning "build processing method" to clarify the use of the peptide library within the bottom right hexagon of Figure 1.
Response: Comment incorporated.
Comment Summary #19: The commenter suggested explicitly stating that MS is useful because of its ability to detect and quantify anything that results in a mass change.
Response: Comment not incorporated. The suggested change to "mass change" does not add information and will narrow the application of MAM. MAM can detect mass changes and confirm those without mass changes. Therefore, the original text will be kept as is.
Comment Summary #20: The commenter suggested to clarify that chromatography and electrophoresis-based methods can also be peptide-based if performed after digestion, recommending the revised wording from "peptide-based MS analysis" to "peptide mapping-based MS analysis."
Response: Comment incorporated. The sentence was changed to, "In contrast to chromatography and electrophoresis-based methods, peptide mapping-based MS analysis allows site-specific identification and quantitation of PQAs."
Comment Summary #21: The commenter suggested replacing "-" with "+/-" to accurately describe the utility of conventional methods, noting that basic variants of the signal peptide can often be observed as a separate peak in charge separation methods.
Response: Comment incorporated.
Comment Summary #22: The commenter suggested providing a more specific description of MAM limitations, including examples, and mentioning the need for risk assessment.
Response: Comment not incorporated. Examples of MAM limitations are already listed as "protein purity-related and formulation-related PQAs." which was revised to ““MAM offers a higher specificity and efficiency for measuring molecular attributes, though it may not capture all PQAs. For example, protein higher-order structure may not be obtained by MAM; a cell-based assay may be used in conjunction with MAM to test for potency” as detailed in Comment Summary #23. Also, risk assessment of MAM has been discussed in section 12.6.
Comment Summary #23: The commenter suggested revising the statement to clarify that protein purity-related and formulation-related PQAs may not always be obtained by MAM, and to highlight Case Study 3 as an example of formulation effects.
Response: Comment partially incorporated. The phrase "formulation related" was considered vague and has been replaced with "protein higher-order structure" and "cell-based assay" as examples. The sentence "but protein purity-related and formulation-related PQAs may not be obtained by MAM" was revised to: “MAM offers a higher specificity and efficiency for measuring molecular attributes, though it may not capture all PQAs. For example, protein higher-order structure may not be obtained by MAM; a cell-based assay may be used in conjunction with MAM to test for potency.”
Comment Summary #24: The commenter suggested clarifying that MAM can detect product-related variants/impurities and be considered a purity assay if NPD is included.

Response: Comment partially incorporated. The text has been revised to: “MAM offers a higher specificity and efficiency for measuring molecular attributes, though it may not capture all PQAs. For example, protein higher-order structure may not be obtained by MAM; bioassays may be used in conjunction with MAM to test for potency.”

3. Considerations for MAM Sample Preparation

Comment Summary #25: The commenter mentioned that if the digestion pattern is consistent and reproducible from run to run, missed cleavage or non-specific cleavage is less of a concern, the commenter suggested changing "desired attributes" to "desired characteristics" to avoid confusion with product quality attributes.

Response: Comment not incorporated. Missed cleavage and non-specific cleavage add difficulty in quantitation, and a high number of missed cleavages leads to a higher probability of inconsistency over time. Therefore, the original text will be kept as is.

Comment Summary #26: The commenter suggested noting that, in addition to oxidation and deamidation, many other attributes are accessible by MAM (see Table 1) and recommended including "e.g." before listing examples.

Response: Comment partially incorporated. The term "e.g." is repetitive for "such as." The sentence has been revised to: "A typical MAM workflow uses a reduced peptide mapping workflow for the relative quantitation of PTMs such as oxidation and deamidation (see Table 1 for other examples)."

Comment Summary #27: The commenter suggested revising the text to include the consideration of automated sample digest to reduce RSD% across samples.

Response: Comment not incorporated. Automated sample preparation is already discussed in Section 3.

Comment Summary #28: The commenter suggested adding "that occur" before "during manufacturing and storage" to clarify what is being determined accurately.

Response: Comment not incorporated. The original text is clear and will be kept as is.

3.1 Sample Denaturation

Comment Summary #29: The commenter suggested clarifying which steps in sections 3.1 - 3.4 are optional and may be omitted and recommended considering alkylation as optional for the reducing workflow, as well as adapting Figure 2 accordingly.

Response: Comment not incorporated. The sentence "Some of the available choices and their technical considerations are listed below" already conveys this concept before section 3.1. Therefore, no changes are necessary.

Comment Summary #30: The commenter suggested removing the reference to Waters Rapigest to maintain vendor neutrality.

Response: Comment incorporated. The text has been changed to: "Some proprietary detergents can also be a convenient option."

Comment Summary #31: The commenter suggested italicizing "rapi" in "rapigest" to match Waters" formatting.

Response: Comment not incorporated. The reference to Waters Rapigest has been removed to maintain vendor neutrality. The text has been changed to: "Some proprietary detergents can also be a convenient option."

3.2 Sample Reduction

Comment Summary #32: The commenter noted that DTT is a thiol containing agent active at neutral and basic pH and provided a reference (Hao et al 2021) to support its use at neutral pH and recommended including this information.

Response: Comment partially incorporated. Both DTT and TCEP can be used at a wider pH range, so the following statement is deleted: "DTT is a thiol-containing agent that is active above-neutral pH"
Comment Summary #33: The commenter recommended not using a hyphen in “above - neutral.”
Response: Comment not incorporated.
The sentence is deleted as recommended by other commenter (Comment Summary #32).
Comment Summary #34: The commenter suggested adding an example of alternative workflows at the end of section 3.2, noting that sample denaturation and reduction can be combined in one step.
Response: Comment incorporated. The following text has been added to the end of section 3.2: "Sample denaturation and reduction can be combined in one step."

3.3 Sample Alkylation
Comment Summary #35: The commenter suggested adding an example of alternative workflows at the end of section 3.3, noting that alkylation may be optional if disulfide bond reformation is controlled by other means, such as acidification of the sample solution.
Response: Comment not incorporated. The sentence before section 3.1, "Some of the available choices and their technical considerations are listed below," already conveys this information.

3.4 Sample Desalting
Comment Summary #36: The commenter suggested adding an explanation at the end of section 3.4 to clarify why dilution is sometimes preferred over more complex desalting procedures, noting that complex desalting can introduce additional variability, making simple dilution during protease addition preferable.
Response: Comment not incorporated. The last sentence of this section contains this message, so no changes are necessary.

3.5 Choice of Digestion Protease
Comment Summary #37: The commenter noted that Lys-C is also active in high concentrations of chaotrope and can be used as a first enzyme before trypsin digestion in diluted samples. They suggested changing the statement to: "Addition of Lys-C protease to trypsin, or vice versa, reduces the possibility of missed cleavage."
Response: Comment incorporated. The text has been changed to: "Addition of Lys-C protease to trypsin or vice versa reduces the possibility of missed cleavage."

3.6 Digestion pH and Temperature
Comment Summary #38: The commenter suggested adding "C" after the degree sign to avoid confusion with Fahrenheit.
Response: Comment not incorporated. Per the USP General Notice, Section 8.240, Weights and Measures, “The symbol for degrees (°) without a qualifying unit of measure represents degrees celsius.”
Comment Summary #39: The commenter suggested specifying "degrees C" instead of just "degrees" at the end of the section, as well as in case study 1 (first paragraph) and figure 4.
Response: Comment not incorporated. Per the USP General Notice, Section 8.240, Weights and Measure, “The symbol for degrees (°) without a qualifying unit of measure represents degrees celsius.”

3.8 Digestion Time

Comment Summary #40: The commenter noted the absence of guidance on stopping digestion and suggested adding approaches to quench or stop the digestion, while ensuring that the quench condition does not induce artifacts before sample analysis.
Response: Comment incorporated. The following text has been added to Section 3.1.8 (Digestion Time) as a second sentence: "After the intended digestion time, the digestion should be terminated by either removing the protease from the digest or quenching the protease activity, e.g., reducing digestion solution pH for trypsin."
Comment Summary #41: The commenter recommended specifying an actual time frame for digestion instead of the non-specific term 'overnight'.
Response: Comment not incorporated. The typical digestion time can range from 30 minutes to overnight, so no changes are necessary.
Comment Summary #42: The commenter suggested adding text to discuss the quenching of enzymatic digestion and the removal of trypsin after digestion, either immediately after the statement about buffer-exchanging out the denaturing or alkylating reagent, or in an appropriate location later in the section.
Response: Comment incorporated. The following text has been added to Section 3.1.8 (Digestion Time) as a second sentence: "After the intended digestion time, the digestion should be terminated by either removing the protease from the digest or quenching the protease activity, e.g., reducing digestion solution pH for trypsin."
Comment Summary #43: The commenter suggested that only the first two lines (one paragraph) belong in this section, and that the text starting from "typically, during method development..." should be moved to section 3.9.
Response: Comment partially incorporated. Reorganized the sub-section numbers for Section 3. We understand that Sections 3.1-3.8 discuss digestion choices and only cover a portion of Section 3. Therefore, we will reorganize Section 3 as follows: Sections 3.1-3.8 will be renumbered to 3.1.1-3.1.8. Text starting from "typically, during method development..." is now section 3.2.
Comment Summary #44: The commenter suggested replacing "mass spectrometric and separation performance" with "chromatographic separation and mass spectrometric performance" for clarity.
Response: Comment incorporated. The text has been changed to: "3) resulting peptides' chromatographic separation and mass spectrometric performance, especially the peptides containing PQAs;" for clarification.
Comment Summary #45: The commenter suggested correcting a possible typo by replacing "PQAs" with "PTMs" in the phrase "peptides containing PQAs".
Response: Comment partially incorporated. The term "PQA" is more precise in this context. Changed "containing" to "associated" for clarity. The text has been revised to: "3) resulting peptides' mass spectrometric and separation performance - especially the peptides associated with PQAs."
Comment Summary #46: The commenter suggested adding "adequate sequence coverage" to the list of metrics.
Response: Comment incorporated.
Comment Summary #47: The commenter suggested changing "minimum missed cleavages" to "consistency of digestion" within the list.
Response: Comment not incorporated. "Minimum missed cleavages" is a desired feature during the optimization step.
Comment Summary #48: The commenter suggests that the sample preparation procedure might introduce additional modifications beyond deamidation. They recommend changing the phrase from "List: Low level of artifactual modifications like deamidations" to "Low level of artifactual modifications like, e.g., deamidations, oxidations, or clips."
Response: Comment incorporated.

Comment Summary #49: The commenter suggested including additional details on what is involved in a "feasibility check" during sample preparation to aid the reader.
Response: Comment incorporated. The following sentence has been added after "feasibility check": "The MAM sample preparation method should be evaluated against all sample types (e.g., concentrations, matrices, etc.) intended for the MAM assay, to ensure the digest is robust enough to function across all types intended for the MAM assay."
Comment Summary #50: The commenter noted that the sentence starting with "to extend the scope of a common..." in this section is unclear.
Response: Comment incorporated. Deleted "to extend the scope of a common sample preparation" and changed it to "To apply sample protocol to."
Comment Summary #51: The commenter suggested revising the text to clarify that a typical reduced peptide mapping-based MAM workflow involves two alkylations: one before reduction and one after reduction.
Response: Comment partially incorporated. The term "differential alkylation" is not widely used and is not pre-defined in this chapter. For clarity, the sentence has been changed to: “To evaluate unpaired cysteines, a combination of two different alkylation agents can be used (see 3.1.3)."
Comment Summary #52: The commenter suggested adding "without buffer exchange" to clarify the sentence "Lys C is the most used enzyme for digestion following denaturant dilution.
Response: Comment incorporated.
Comment Summary #53: The commenter noted that the sentence "If the enzyme or combination of enzymes used in dilution protocol provides reproducible digestion and peptides suitable in identifying attributes of interest, it is a viable automation strategy." is missing a "the" between "in" and "dilution."
Response: Comment partially incorporated. Changed to: “If the protocol provides reproducible digestion and peptides suitable for identifying attributes of interest, it is a viable automation strategy.”

4. Considerations for MAM Instrumentation
Comment Summary #54: The commenter suggested using bullet points to highlight key considerations, as the current format is visually challenging to read.
Response: Comment not incorporated. There are four paragraphs in Section 4. Converting them into bullet points will not change the content.
Comment Summary #55: The commenter suggested changing the term "low-resolution" to "unit resolution" on page 7, as "low-resolution" is ambiguous and sometimes used to refer to high resolution operated at a lower setting like 15k.
Response: Comment not incorporated. "Unit-resolution" is not a widely used term and is also too specific.
Comment Summary #56: The commenter suggested revising the text for clarity to: "However, they may not resolve isotopic peaks to obtain charge state identity, isotopic abundance information, or provide measurement of monoisotopic mass." They also recommended changing other instances of "isotopes" and "isotope ions" to "isotopic peaks" throughout the chapter, including in Table 2, Table 4, and Table 5.
Response: Comment partially incorporated. The statement was changed to "However, they may not resolve peptide isotopic peaks to obtain charge state identity, isotopic abundance information, or provide measurement of monoisotopic mass." Furthermore, there are eight more instances of the term "isotopes" in this chapter that were replaced on a case-by-case basis.
Comment Summary #57: The commenter suggested revising the text from “Modern high-resolution mass spectrometers (e.g., TOFs, Orbitraps) are sensitive, fast, capable of measuring a wide mass range, resolving and measuring monoisotopic masses with high mass accuracy.” to "Modern high-resolution mass spectrometers (e.g., TOFs, Orbitraps) are sensitive, fast,

capable of measuring a wide mass range, and resolving and measuring monoisotopic masses and isotopic patterns with high mass accuracy" for clarification.
Response: Comment incorporated.
Comment Summary #58: The commenter suggested including a requirement for MS/MS analysis to identify mutable PTM sites within the target peptide for non-mAb products.
Response: Comments partially incorporated. This sentence refers to the initial characterization stage, and LC-MS/MS is required.
The text was revised to "Peptide sequencing by LC-MS/MS is required to identify peptides and unambiguously site-localize their modifications during initial characterization stage."
Comment Summary #59: The commenter suggested adding "monitoring" for clarification and changing the statement into "MAM monitoring analyses do not require MS/MS-enabled instrumentation."
Response: Comment not incorporated. MAM in this context refers to MAM analyses, including new peak detection.
Comment Summary #60: The commenter recommended capturing the detail that a high-resolution system should be favored in the above case.
Response: Comments incorporated. The text was revised to: "In general, users should consider higher resolution mass spectrometers, possibly MS/MS-enabled, as the risks from data complexity increase."

5. Considerations for MAM Software
Comment Summary #61: The commenter suggested stating "LC-MS or LC-MS/MS" instead of just "LC-MS" for heightened characterization for clarification.
Response: Comment incorporated. The statement was revised to "Conventional heightened characterization of peptide maps by LC-MS or LC-MS/MS and the necessary software to perform it will be considered largely out of scope for this section."
Comment Summary #62: The commenter recommended capturing the detail that only monoisotopic masses should be considered for peptide MS analysis in MAM software in Table 2.
Response: Comment not incorporated. The scope of Table 2 already includes both high- and low-resolution MS, so "average mass" should be included as well.
Comment Summary #63: The commenter requested clarification that Table 2 recommendations for all minor- and major-level charge states will be used for PQA quantitation.
Response: Comment incorporated. The text has been revised to: "Recommended for all minor- and major-level charge states, which will be used for the PQA quantitation."
Comment Summary #64: The commenter noted that "peptide" may not be the appropriate term since detected peaks may not always be identified as peptides. They suggested revising the statement to: "The nontargeted component of MAM requires software to agnostically detect and integrate every peak within defined sensitivity and magnitude of change thresholds.
Response: Comment incorporated.
Comment Summary #65: The commenter suggested replacing "automatic identification of new peaks" with "automatic detection of potential new peaks" and questioned if "software recommendation" is better than "software requirement" in the header of Table 4.
Response: Comment incorporated. The text has been revised to: "Automatic detection of potential new peaks," and the heading has been changed to "Desired Software Feature" to align all three tables (Table 3, Table 4, and Table 5).
Comment Summary #66: The commenter suggested including additional discussion on the feasibility of software performing automatic filtration and identification of new peaks, considering potential challenges with artifactual peaks and noise.
Response: Comment partially incorporated. The last two bullet points for "Software Requirements" in Table 5 are desirable features but not required. Change the column title from

"Software Requirements" to "Desired Software Features." Table 3 and Table 4 will also have their column titles changed to "Desired Software Features."
Comment Summary #67: The commenter suggested adding peptide library capability to the software requirements.
Response: Comment incorporated. The text has been revised to "It contains two main components: 1) targeted monitoring of a peptide library in which known attributes are quantitated based on previous characterization."

6. System Readiness
Comment Summary #68: The commenter suggested either removing "high throughput" from the third sentence from the end or rephrasing it to provide better context.
Response: Comment not incorporated. Removing "High throughput" does not sufficiently emphasize that MAM can be a more efficient monitoring method.

6.1 System Readiness Metrics
Comment Summary #69: The commenter suggested correcting a typo by adding the missing verb in the sentence "Recommendations for common system attributes to monitor system readiness included in Table 6."
Response: Comment incorporated. The statement was revised to "Recommendations for common system attributes to monitor system readiness are included in Table 6."
Comment Summary #70: The commenter suggested changing "peptide area" to "peak area" in Table 6 for accuracy in Table 6.
Response: Comment incorporated.
Comment Summary #71: The commenter suggested adding another attribute to link the SST to the intended reportable result in Table 6, ideally selecting a PQA with difficult LC separation or prone to artificial degradation, so the commenter suggested adding a new row called “Relative PQA abundance” to Table 6
Response: Comment not incorporated. Table 6 lists the attributes for the system metrics, but "relative PQA abundance" is not considered a system metric.

6.2 System Readiness Standards and Methodology
Comment Summary #72: The commenter suggested using either "standard" or "reference material" consistently or indicating if the terms are used interchangeably.
Response: Comment incorporated. The term "reference material" has been changed to "reference standard," while keeping "standard" unchanged throughout the chapter.
Comment Summary #73: The commenter suggested correcting the typo from "access" to "assess" in Table 7.
Response: Comment incorporated.
Comment Summary #74: The commenter suggested including the disadvantage "May require a different LC-MS method than that used for the project-specific MAM assay" for both "Commercial peptide mix" and "Commercial protein standard" MAM standards in Table 7.
Response: Comment incorporated.
Comment Summary #75: The commenter proposed adding "predigested protein standards," such as the NIST mab predigested standard, as an option in Table 7."
Response: Comments partially incorporated. Changed "Commercial Peptide Mix" to "Commercial predigested protein standard / peptide standard."
Comment Summary #76: The commenter noted that some disadvantages of an in-house manufactured protein standard also apply to a commercial protein standard (row#2 Commercial peptide mix and row#3 Commercial protein standard) in Table 7.
Response: Comments incorporated. The following two bullet points have been added to Table 7: “Does not allow for evaluation of the exact data processing method used for the project-

specific samples." and "May require a different LC-MS method than that used for the project-specific MAM assay."
Comment Summary #77: The commenter suggested adding or clarifying the advantage of "commercial protein standards" in assessing sample preparation quality (reduction, alkylation, and digestion) in Table 7.
Response: Comments partially incorporated. The text has been revised to: "Opportunity to assess quality of sample preparation."
Comment Summary #78: The commenter suggested adding "more representative of test articles" as an advantage for "in-house manufactured protein standards" and removing "additional sample handling" from the disadvantage column in Table 7.
Response: Comments partially incorporated. The disadvantage "Requires additional sample handling, which can increase variability" has been removed. The phrase "more representative of test articles" will not be added, as the standard may not be project specific.

6.3 Establishing System Readiness Criteria
Comment Summary #79: The commenter suggested correcting "revaluated" to "re-evaluated" and changing "anytime" to "any time."
Response: Comment partially incorporated. The text has been revised to change "revaluated" to "re-valuated." The term "anytime" remains unchanged per USP style guide.
Comment Summary #80: The commenter suggested strengthening the benefits of data trending via control charts. Commenter recommend changing "Some system readiness criteria will need to be revaluated for new methods or anytime the system setup significantly changes" to "The use of these control charts and data trending allows to confirm the suitability of the system readiness metrics and criteria and to anticipate that some will need to be revaluated for new methods or anytime the system setup significantly changes."
Response: Comments not incorporated. The terms "control charts" and "data trending" were never defined in this chapter. Adding these concepts will not add value to the sentence.

6.4 Employing System Readiness Criteria
Comment Summary #81: The commenter suggested clarifying that system readiness standards may be implemented after several injections or a specified time to control instrumentation drift during the run, such as due to fouling of the ionization source.
Response: Comment not incorporated. There are many situations for drifting or not passing system suitability. Adding "instrumentation drift during the run due, e.g., to the fouling of the ionization source" is not helpful as it narrows the possibilities without providing a clear solution.
Comment Summary #82: The commenter suggested correcting "clearly capture" to "clearly captures in this sentence "It is recommended that a written record (e.g., electronic notebook entry, MAM report) clearly capture the association of each set of system readiness data with the corresponding MAM data."
Response: Comment incorporated. The text has been revised to: "clearly captures."

7.1 Characterization Method
Comment Summary #83: The commenter suggested modifying the statement to clarify that while the characterization MS/MS method may not align with the MS method in monitoring, it may share some parameters (e.g., ion source parameters) for a smooth transition.
Response: Comment incorporated. The statement has been revised to: "To ensure a smooth transition between characterization and monitoring, the characterization method should ideally be closely aligned with MAM to be used in monitoring or QC in terms of sample preparation, instrumentation, LC method, and MS method (e.g., ion source parameters)."

7.2 Characterization Data Analysis
Comment Summary #84: The commenter recommended including a note to indicate that characterization will require an HRMS system.
Response: Comments incorporated. The text was revised to: "For characterization, a high-resolution mass instrument is normally used, and data analysis should begin with a broad MS/MS search with the goal of identifying the observed peaks."

7.3 MAM Attribute Selection
Comment Summary #85: The commenter suggested clarifying that accuracy and precision of attribute quantification need to be achieved and providing an example of attributes not accessible by peptide mapping MAM. They also recommended monitoring quality attributes that rely on higher order structure or are reliably quantifiable by MAM with an appropriate orthogonal method.
Response: Comment incorporated. The text has been revised to: "Quality attributes that are not reliably detectable or quantifiable by MAM, such as higher order structure, should be monitored by an appropriate orthogonal method."
Comment Summary #86: The commenter suggested adding bioactivity/potency and PK assessment as additional input factors in attribute selection.
Response: Comments partially incorporated. The first paragraph of Section 7.3 has been replaced with the following paragraph: "MAM attribute selection follows QbD principles described in ICH guideline Q8(R2). A PQA assessment is used to assess the impact of PQAs on safety and efficacy and determine the CQAs. The CQAs or PQAs identified by heightened characterization can be monitored by MAM. Quality attributes that are not reliably detectable or quantifiable by MAM should be monitored by an appropriate orthogonal method."

8 Considerations for MAM Targeted Analysis
Comment Summary #87: The commenter suggested correcting the typo "C-terminal" to "C-terminus."
Response: Comments incorporated.
Comment Summary #88: The commenter suggested revising the sentence to clarify that peptides with lysine glycation and clips cannot be simply compared to the same peptides without the modification, as the "same" peptide does not exist for clips.
Response: Comment incorporated. The text has been revised to: "Relative quantities of lysine glycation and clips also require special considerations as the peptides with the attribute cannot be simply compared to the same peptides without the modification."
Comment Summary #89: The commenter suggested adding the possible use of reporter ions or surrogate peptides instead of a complete list of peptide attributes or species of interest with poor method performance.
Response: Comment incorporated. The following text has been added after the Introduction paragraph of Section 8: “Monitoring product quality by MAM does not typically require comprehensive monitoring of every amino acid site on the molecule. In fact, monitoring a large library of attributes may challenge method robustness, particularly for attributes typically present at trace levels. To keep the method as simple and robust as possible, it is typically appropriate to monitor a small set of critical 'reporter' attributes by MAM which serve to indicate whether the larger molecular structure is appropriately maintained. The reporter attributes can be used for routine product quality monitoring, either in lieu of a more complete list of peptide attributes, or instead of actual species of interest (which may have poor method performance regarding signal intensity or separation resolution). They should be selected to appropriately represent the relative abundance of the CQA of interest, or to adequately indicate changes in relative abundance that may occur during manufacturing and storage.”

8.1 Characterization versus Monitoring Phase
Comment Summary #90: The commenter suggested adding "DIA, e.g. MSe."
Response: Comment partially incorporated. The sentence has been revised to: "Characterization is performed using LC-MS/MS to generate a library of m/z, charge states, isotopic patterns, fragmentations, and retention times of the native and modified peptides."

8.2 MAM for Monitoring
Comment Summary #91: The commenter noted that at least one published (middle-up) MAM method uses Waters' QDa, which is a low-resolution instrument.
Response: Comment incorporated. The sentence "The drawbacks of using MAM on low resolution instruments are: "has been revised to: "Potential drawbacks to consider for MAM on low resolution instruments include: 1)..."
Comment Summary #92: The commenter recommended revising the text to clarify that the mass-to-charge ratio scan range of the instrument may be too narrow to cover large modifications like glycosylation or very small changes like deamidation.
Response: Comment not incorporated. The text already mentions that low-resolution MS is not suitable for small mass differences in point 4. It states that low-resolution MS may be less robust for quality attributes that coelute with other interfering species with a small mass difference that are not well resolved by the low-resolution mass spectrometer.

9. Considerations for MAM Nontargeted Analysis (New Peak Detection)
Comment Summary #93: The commenter suggested modifying the statement to clarify that a detected peak not on the targeted list or with increased abundance compared to reference material is considered a new peak, and changes in abundance beyond thresholds identify changing peaks.
Response: Comment not incorporated. "New peak" means the ion was not observed in the reference sample, while "changing peak" means the peak was observed in the reference sample, but its intensity has changed.

9.2 NPD Parameters and Optimization
Comment Summary #94: The commenter requested to replace "Isotope distribution" with "Isotopic distribution pattern" for clarification.
Response: Comment incorporated.
Comment Summary #95: The commenter requested clarification on whether "mass to charge ratio value" and "molecular weight" refer to instrument mass accuracy or selecting a part of the m/z region with minimal signal interference.
Response: Comment partially incorporated. The m/z value is understood to mean the window of setting criteria for NPD. However, "Molecular weight" is deleted from Section 9.2 (list) as it is not a Mass Spec attribute.
Comment Summary #96: The commenter suggested revising "Number of isotopes" to "Number of isotropic peaks" or deleting it, as it is covered by the previous bullet point, "isotropic distribution pattern."
Response: Comment incorporated. The bullet point has been revised to "Isotopic distribution pattern," and the bullet point "Number of isotopes" has been removed.
Comment Summary #97: The commenter suggested revising "Molecular weight" to "m/z values of the monoisotopic and isotopic peaks," as molecular weight is not directly measured by MS.
Response: Comment partially incorporated. The "m/z values of the monoisotopic and isotopic peaks" are already covered under "Isotopic distribution pattern." "Molecular weight" is deleted from Section 9.2 (list) as it is not a Mass Spec attribute.

Comment Summary #98: The commenter suggested changing "protein" to "spiked-in protein" in the sentence: "New peak model systems, such as protein or peptide co-mixes, can be used to mimic scenarios where new peaks may be detected." for clarification.
Response: Comment incorporated.

9.4 Interpretation of New Peak Detection Data
Comment Summary #99: The commenter suggested revising the statement to: "Ideally, potential new peaks will either have been previously identified as false positives or assessed as non-critical during initial characterization and method development" by adding "either" for clarification purposes.
Response: Comment incorporated.
Comment Summary #100: The commenter noted that later text in the section refers to new peaks being characterized as “false positives,” “non-critical,” “product degradation,” etc. These descriptors are not single identifiers. For example, a new peak may be a false positive product degradant. As such, the term “categorizing” is not clear. The commenter suggested revising the term "categorizing" to "establishing a list or database of known peaks" for clarification.
Response: Comment incorporated.

10 Use of MAM in Product Development
Comment Summary #101: The commenter suggested revising the statement to acknowledge that degradation during screening and stability studies may not necessarily be chemical but could also be enzymatic or photo-catalyzed. The revised statement should end with: "... and to site-localize and quantify degradation during formulation screening and stability studies" by deleting the word "chemical."
Response: Comment incorporated.
Comment Summary #102: The commenter suggested using "comparability exercise" or "comparability study" to describe how consistent quality attribute profile data provided by the MAM would support comparability following process changes.
Response: Comment incorporated. Revised the statement to "Consistent quality attribute profile data provided by the MAM would support the comparability exercise following the process changes."
Comment Summary #103: The commenter suggested adding "using conventional methods" to the end of the sentence"...or in cases where differences following process changes are detected" for clarity.
Response: Comment partially incorporated. This sentence is in reference to MAM, not conventional methods. For clarity text revised from "following process changes are detected" to "due to process changes are detected."
Comment Summary #104: The commenter suggested simplifying the sentence from “1) assess the PQA severity risk of the affected specific quality attribute by leveraging literature or platform knowledge” to: "1) assess the criticality of the affected quality attribute by leveraging literature or platform knowledge."
Response: Comment incorporated.

10.1 Product Development Case Studies
Comment Summary #105: The commenter suggested including other potential causes for discrepancies in absolute quantitation between methods. For example, MAM solely quantifies deamidation, while icIEF includes acidic variants from other modifications, contributing to nonmatching absolute quantitation.
Response: Comment partially incorporated. The following text was added to emphasize that the aim of MAM is not to comprehensively quantify all changes in a molecule: “In this case

study, MAM solely quantitates deamidations while icIEF includes other acidic variants in addition to deamidations. This contributes to the nonmatching quantitation."
Comment Summary #106: The commenter suggested using "a mAb" instead of "an mAb" and adding a section break before the final paragraph of the case studies.
Response: Comment incorporated. Changed "an mAb" to "a mAb" in Figure 3. and Figure 4.
Comment Summary #107: The commenter suggested elaborating on how the % abundance was calculated to provide an example of less straightforward PQA quantitation, as no easy comparison between modified and unmodified forms is possible in the case of a tryptic digest.
Response: Comment incorporated. The following sentence was added to the end of Case Study 3: " It is worth noting that two of the most common enzymes used for protein digestion (trypsin and Lys-C) typically do not cleave glycated lysines well. Consequently, the majority of glycated peptides will be miscleaved, necessitating consideration of three peptide populations when performing relative quantitation: 1) The miscleaved and glycated peptide, 2) the properly cleaved peptide containing the unmodified lysine, and 3) the properly cleaved peptide directly C-terminally downstream of the lysine. It may be appropriate for a MAM to simply use the first two populations, or one may find it more appropriate to average the signal of the two unmodified peptides to balance the influence of their combined sequence on the miscleaved and glycated peptide. Most importantly, the MAM must use a consistent means of quantitation per attribute."
Comment Summary #108: The commenter suggested correcting the typo by replacing "glycation" with "glycosylation" in the phrase "all three glycation elements.
Response: Comment incorporated.
Comment Summary #109: The commenter suggested elucidating the advantages of MAM over conventional assays in Figure 6, using the structure on the left panel to clearly indicate these benefits.
Response: Comment not incorporated. The advantage of MAM has already been mentioned in the text: "The conventional assay is agnostic to non-glycosylation, the presence of O-glycosylation, and the original location of N-glycosylation."
Comment Summary #110: The commenter suggested revising the term "glycation" to "glycosylation" in the text to accurately reflect the nature of the modifications being discussed, "glycation" refers to a chemical/non-enzymatic reaction between a protein and a carbohydrate, whereas "O-glycosylation" is an enzymatic post-translational modification.
Response: Comment incorporated. Revised the statement to "MAM provided information on all three glycosylation elements, while monitoring other PQAs in the same assay".
Comment Summary #111: The commenter noted that Figure 6 does not mention non-glycosylated species or O-glycosylation. However, the test stated MAM providing information on all three glycation elements while monitoring N-glycosylation and other PQAs in the same assay.
Response: Comment not incorporated. This sentence is intended to highlight the ability of MAM. While it is true that Figure 6 does not provide those examples, it is still appropriate to make the point in this section that MAM can provide glycosylation-related information in tandem with N-glycosylation quantitation.
Comment Summary #112: The commenter suggested adding a sentence before the last sentence to clarify that the list of changes or modifications can occur on a mixture of CQAs and non-CQAs (critical or non-critical PQAs).
Response: Comment not incorporated. The last paragraph of section 10 is clear and does not require any clarification.

11.1 Considerations for Aligning MAM with Control Strategy

Comment Summary #113: The commenter suggested including "stability" in the paragraph before Table 8, as it is mentioned in the table but not in the statement: "...it can be incorporated in all four analytical control elements in the control strategy including…"

Response: Comment incorporated. The text was revised to: "it can be incorporated in all analytical control elements in the control strategy, including in-process control testing, release and specification testing, product characterization and process monitoring."
Comment Summary #114: The commenter suggested further differentiating and clarifying the difference between "Characterization" and "Process monitoring" in Table 8.
Response: Comment partially incorporated. First, deleted the "Process monitoring" row from Table 8. Changed the row title from "Characterization" to "Characterization and Process monitoring". Second, changed the text from "Characterization outside of release and stability testing to demonstrate that the manufacturing process is well controlled" to "Characterization and process monitoring to demonstrate that the manufacturing process is well controlled". Third, changed the text from "For analytical characterization MAM development and validation should minimally demonstrate method specificity and precision (repeatability and intermediate) on measured attributes for monitoring purposes." to "For analytical characterization and process monitoring MAM development and validation should minimally demonstrate method specificity and precision (repeatability and intermediate precision) on measured attributes for monitoring purposes."
Comment Summary #115: The commenter suggested spelling out "intermediate precision" instead of intermediate.
Response: Comment incorporated. The "Process monitoring" row was merged with “characterization.” In this row, the text was changed from "method specificity and precision (repeatability and intermediate) on measured attributes for monitoring purposes" to "method specificity and precision (repeatability and intermediate precision) on measured attributes for monitoring purposes."
Comment Summary #116: The commenter suggested using the term "assessment criteria" to clarify that comparison against these criteria does not govern lot disposition. The statement should be revised to: "May require comparability assessment criteria for additional characterization tests.”
Response: Comment incorporated. The text was revised to: "May require comparability assessment criteria for additional characterization tests." and deleted: "The acceptance criteria of analytical characterization do not govern lot disposition."

11.2 Specifications When Transitioning from Conventional Methods to MAM

Comment Summary #117: The commenter suggested revising the statement to clarify that MAM can report each individual attribute with a specific acceptance limit as well as the sum of all to enable a direct comparison with a conventional method.
Response: Comment incorporated. Removed "either" and "or" and added the third condition as "both," and changed the text to: “In these cases, a feasible option for bridging MAM to conventional methods may be to: 1) report the sum of selected MAM attributes in a way to reflect the summation inherent to the conventional method and set acceptance criteria on this sum result; 2) report MAM attributes individually and set appropriate attribute-specific acceptance criteria; 3) Implement both 1) and 2).”

12. Guidance on Method Qualification and Validation

Comment Summary #118: The commenter suggested that both cGMP and non-cGMP qualification should be conducted in a phase-appropriate manner.
Response: Comment not incorporated. This sentence is discussing the early stage, and the characterization is fit for intended use. It is not in conflict with "cGMP is also phase-appropriate." However, to avoid confusion, the sentence was revised to: "On the other hand, MAM used for characterization is non-cGMP and fit-for-purpose, where the qualification is phase-appropriate and focuses on the assessment of analytical method performance and variability to fit for intended use."

Comment Summary #119: The commenter suggested using the abbreviation "FFP" for "fit-for-purpose," as it was introduced earlier.
Response: Comment incorporated.

12.1 Considerations for Qualification of MAM
Comment Summary #120: The commenter suggested deleting the sentence as it is redundant: "All MAM assays need to be scientifically sound and used to ensure the desired product quality, safety, and efficacy."
Response: Comment incorporated.

12.2 Considerations for Validation of MAM
Comment Summary #121: The commenter suggested advocating for the use of certain peptides or CQA as surrogates to validate multiple CQAs, and proposed adding the statement "It is acceptable to use certain CQA as surrogates for the validation of others".
Response: Comment not incorporated. It is up to the end user to decide if surrogates are needed.
Comment Summary #122: The commenter recommended emphasizing that MAM is ideal for using prior knowledge, even for validation, and suggested adding a statement "Use of prior knowledge from similar classes of molecules can be used for validating certain CQAs, e.g., CQAs in constant domains of mAbs or conjugation sites for ADCs."
Response: Comment not incorporated. It is up to the end user to decide if surrogates are needed.

12.2.1 Specificity
Comment Summary #123: The commenter recommended mentioning MS/MS (tandem mass spectrometry) in relation to MAM, as it may allow for greater demonstration of specificity.
Response: Comment not incorporated. At the validation stage of MAM, only MS data is used.
Comment Summary #124: The commenter suggested that the control of isobaric or near-isobaric interferences should be part of method development, not validation, and proposed moving this content to the development section.
Response: Comment incorporated. The sentence "Isobaric or near-isobaric interferences can be eliminated or controlled by combining the mass-to-charge ratio with a specific RT window or adjusting the gradient during method development" has been removed.

12.2.2 Linearity
Comment Summary #125: The commenter noted that while the results are linear, the MS response can be quadratic and emphasized that linearity of the results is expected across the desired range for each attribute.
Response: Comment incorporated. Text was changed from: "As a quantitative method, a linear response is expected across the desired range for each attribute." to: "As a quantitative method, linearity of the results is expected across the desired range for each attribute."
Comment Summary #126: The commenter suggested considering a spike-in approach for linearity and accuracy, as enrichment or forced degradation may be challenging for creating samples with known amounts.
Response: Comment incorporated. Revised the statement from “Materials with a different amount of product variants or impurities can be prepared (through enrichment or forced degradation) and used to create a set of samples for demonstration of linearity.” to: “Materials with a different amount of product variants or impurities can be prepared (through a spike-in approach, or using materials from enrichment or forced degradation) and used to create a set of samples for demonstration of linearity.”

12.2.4 Precision

Comment Summary #127: The commenter suggested extending the section on precision to specifically include repeatability and intermediate precision, noting that parameters like protease lots/vendors or column lots in Table 9 would be tested as part of an intermediate precision experiment.

Response: Comment incorporated. The text was changed from: "12.2.4 Precision – In general, precision performance for MAM is expected to be comparable with conventional purity methods." to: "12.2.4 Precision – In general, precision performance (repeatability and intermediate precision) for MAM is expected to be comparable with conventional purity methods.", and the text was changed from: "(repeatability and intermediate)" to: "(repeatability and intermediate precision)" in Table 8, Row "Characterization and process monitoring."

12.2.6 Range

Comment Summary #128: The commenter suggested adding a section on the particularities of NPD validation, including QL and specificity, and proposed text "NPD allows for an unbiased comparison of the samples against a reference to identify new, absent species or species with a significant change in abundance. Therefore, NPD can be considered as a limit test necessitating validation of specificity and detection limits following ICH Q2 guidelines“ as section 12.2.7 to describe NPD as a limit test requiring validation of specificity and detection limits per ICH Q2 guidelines.

Response: Comment not incorporated. This section focuses on ICH Q2 guidelines, and "Particularities linked to validation of NPD parameters" is not one of them. NPD is discussed in section 9.

Comment Summary #129: The commenter suggested aligning with the upcoming ICH Q2(R2) language by using the term "Reportable range."

Response: Comment not incorporated. The 2023 version of ICH Q2(R2) uses the term "range".

12.3 MAM Robustness Evaluation

Comment Summary #130: The commenter suggested mentioning design of experiments (DoE) as the preferred option for handling the complexity of multiple critical method parameters and proposed revising the text to include DoE approaches for representing the worst case of deviations.

Response: Comments incorporated. The text was revised from "It can be evaluated as per method condition change, or in some cases, combining changes in several method conditions to represent the worst case of deviations." to "It can be evaluated as per method condition change, or in some cases, combining changes in several method conditions to represent the worst case of deviations (e.g., by Design of Experiments approaches)."

Comment Summary #131: The commenter suggested replacing "MAM" in the phrase "Due to the complexity of a MAM" with "MAM assay" or "MAM method".

Response: Comment not incorporated. The "M" in MAM stands for "method." However, it is recommended to remove "a" in front of MAM. The test is revised to read: "Due to the complexity of MAM and the many method conditions involved, the method robustness study should be designed to select the conditions that impact the expected MAM outcome."

Comment Summary #132: The commenter suggested adding MS instrument parameters, such as ion source parameters and MS method parameters, to the condition column in Table 9 of subsection 12.3 MAM Robustness Evaluation.

Response: Comment incorporated. The text was revised from "Mass spectrometer – model, maintenance status (cleaning, calibration)" to "Mass spectrometer – model, maintenance status (cleaning, calibration), instrument parameters (e.g., ion source parameters, MS method parameters, etc.)".

Comment Summary #133: The commenter suggested including pH in the Sample Preparation row and adding "mass spectrometer settings (e.g., voltages, gas flows, etc.)" to the Conditions column in the Mass Analysis row of Table 9.
Response: Comment partially incorporated. First, pH will not be added as it is too specific. Second, the text was revised from "Mass spectrometer – model, maintenance status (cleaning, calibration)" to "Mass spectrometer – model, maintenance status (cleaning, calibration), instrument parameters (e.g., ion source parameters, MS method parameters, etc.)".
Comment Summary #134: The commenter suggested adding "less than" or "less than or equal" symbols to most of the example range variations listed, as the current ranges may be too wide.
Response: Comment not incorporated. The text was written according to the USP style guide.

12.4 Considerations for MAM System Suitability Testing
Comment Summary #135: The commenter suggested adding additional text to clarify the meaning of "when the requirement is less than 2%" in the statement "USP ⟨621⟩ requires 5 replicate injections to calculate the relative standard deviation when the requirement is less than 2%."
Response: Comment incorporated. The text was revised from "USP <621> requires five replicate injections to calculate the relative standard deviation when the requirement is less than 2%." to "USP <621> requires five replicate injections when the requirement of relative standard deviation of peak response is less than 2%."
Comment Summary #136: The commenter suggested adding a cross-reference to Section 6 for the term "system readiness," which is used in the industry, often in non-cGMP environments, and described in detail throughout the chapter.
Response: Comment incorporated. The text was revised to: "Another term, 'system readiness,' has also been used in the industry, often in non-cGMP environments, and is described in detail throughout this chapter (see Section 6)."

Comment Summary #137: The commenter noted that most components for HPLC system suitability testing are covered in Chromatography ⟨621⟩ and suggested discussing the most relevant ones in Section 6.1 of the chapter. They also mentioned that peak symmetry is not meaningful for MAM if "integrated peak area" or "relative PQA abundance" criteria are met".
Response: Comment incorporated. The text was revised to: "For HPLC system suitability testing, most of the components are covered in Chromatography ⟨621⟩ and the relevant attributes are discussed in Section 6.1 of this chapter."

Comment Summary #138: The commenter requested specifying what the SD is calculated for (e.g., retention times of extracted ion chromatograms or peak areas) and suggested that the 2% requirement might be too tight or too wide depending on the signal. They proposed defining the SD requirement in line with the performance requirements of the MAM.
Response: Comment incorporated. The text was revised from "USP <621> requires five replicate injections to calculate the relative standard deviation when the requirement is less than 2%." to "USP <621> requires five replicate injections when the requirement of relative standard deviation of peak response is less than 2%."

12.5 Considerations for Analytical Transfer of MAM
Comment Summary #139: The commenter suggested aligning terminology with USP ⟨1224⟩ by changing "donor laboratory" to "transferring unit" and "receiving laboratory" to "receiving unit".
Response: Comment incorporated. To align with <1224>, all instances of "donor laboratory" were changed to "transferring unit" and all instances of "receiving laboratory" were changed to

"receiving unit." Changed "donor laboratory" to "transferring unit" (two changes in Section 12.5). Changed "receiving laboratory" to "receiving unit" (two changes in Section 12.5). Changed "receiving laboratories" to "receiving units" (one change in Section 12.5). Changed "receiving labs" to "receiving units" (one change in Section 13.1).

13.1 PAT and MAM

Comment Summary #140: The commenter suggested adding a discussion on the need to address the LC-MS method for robust and high-throughput analysis to enable real-time monitoring and process control in subsection 13.1 PAT and MAM.
Response: Comment not incorporated. Examples are provided in this section.

13.2 Intact and Subunit Workflow Using MAM

Comment Summary #141: The commenter (Biologics Monographs 2, Expert Committee) initiated the inclusion of intact and subunit MAM as potential applications for PAT.
Response: Comment incorporated. The text was revised from "The method is suitable for quantitation of PTM attributes with larger mass shifts, for example, glycan components, protein terminal variants, clipping forms, glycation, certain amino acid substitutions, cysteinylation." to "The method is suitable for quantitation of PTM attributes with larger mass shifts, for example, glycan components, protein terminal variants, clipping forms, glycation, certain amino acid substitutions, cysteinylation. Intact and subunit MAM has the potential of being used in PAT application."
Comment Summary #142: The commenter suggested noting that it can localize to a subunit and mentioned that the level of LMW species could also be included when quantitating the total glycation level.
Response: Comment not incorporated. The phrases "in some cases" and "for example" have already been mentioned. These advantages are not intended to provide comprehensive coverage.
Comment Summary #143: The commenter suggested revising the text to clarify that employing native MS with MS-compatible buffers allows the use of LC separation methods such as SEC, IEX, HIC, and Affinity. This approach can separate the relative CQAs of interest with MS identification and aligns directly with process analytics, providing a more direct analysis than using a peptide map approach.
Response: Comment not incorporated. Performing MS for fractions separated from SEC/IEX/HIC and Affinity methods is a good strategy for analyzing certain CQAs, but it is not within the scope of intact/subunit MAM.
Comment Summary #144: The commenter suggested clarifying how intact and subunit MAM methods employing MS can be used for sequence confirmation.
Response: Comment partially incorporated. The text was revised from "These methods can also be used for sequence confirmation." to "These methods can also be used for molecular weight confirmation."
Comment Summary #145: The commenter noted that it is difficult to detect mass shifts smaller than 20 Da in the comparison of MAM workflows between intact and subunit and peptide mapping in Table 10.
Response: Comment not incorporated. "Difficult for mass shift < 20 Da" does not mean impossible, and it is challenging to separate deamidation using IEX at the intact/subunit level.
Comment Summary #146: The commenter noted that enzymatic digestion and reduction can be combined, as shown in Figure 7.
Response: Comment not incorporated. The purposes of these two middle-down approaches are different.

The Entire Chapter

Comment Summary #147: The commenter believed it was a well-written document that comprehensively covered the topic and fully supported its issuance.
Response: Comment acknowledged. Thank you for your positive feedback.
Comment Summary #148: The commenter suggested breaking up long text sections with bullets or additional figures, such as using unmodified and modified peptide isotope patterns to make the content more accessible for audiences with little to no MS background.
Response: Comment not incorporated. The chapter includes subsections for complex sections and utilizes multiple figures and tables for illustration.

References
Comment Summary #149: The commenter recommended additional technical references for the text, including articles on method validation, new peak detection, and multi-attribute methods for quality control of therapeutic proteins.
Response: Comment not incorporated. USP typically does not reference journal articles unless figures, tables, or text are directly used from the article.

General Chapter/Section(s):	<1071> Rapid Microbiological Methods for the Detection of Contamination in Short-Life Products—A Risk-Based Approach / Multiple Sections
Expert Committee(s):	General Chapters-Microbiology Expert Committee
No. of Commenters:	13

General Comments

Comment Summary #1: The commenter requested to explicitly state the following expectations: Any test methods including those described in GC<72> and <73>, when used for the purpose of product release, must be validated to demonstrate that the method is equivalent or better than GC<71>. When a rapid method has not been demonstrated the above, it may still be used proactively as a screening test and/or extra check. In addition, a statement that manufacturers should seek regulatory input should be included in the text. Finally, the commenter recommended clarifying the requirements for use of the RMM chapters in the introduction section.
Response: Comment partially incorporated. The purpose of GC<1071> is to provide guidance on selecting RMMs in case the GC <71> test is not the most appropriate. Clarifications with regards to method validation have been written in the section “METHOD VALIDATION AND SUITABILITY TESTING” where not only an enhanced method suitability test as per <72> or <73> is required but also that a primary validation must be conducted for the system. The chapter title was changed to remove focus on the release test and allow utilization of these methods also as in process controls (IPCs) or as parallel testing to GC<71>. At the end of the “Introduction” section, a recommendation statement of contacting the regulatory authority for further guidance is included.

INTRODUCTION

Comment Summary #2: The commenter recommended providing clear definition of short-life products.
Response: Comment not incorporated. The definition is included in the Glossary section of the chapter.
Comment Summary #3: The commenter suggested changing “autologous cells” to “individualized cellular products used without cryopreservation.” Allogeneic products can have the same issues, and some autologous products are cryopreserved.

Response: Comment partially incorporated. The term “autologous cells” was replaced by “Advanced Therapy Medicinal Products (ATMP).”
Comment Summary #4: The commenter requested to add some text on contamination control strategies.
Response: Comment not incorporated. Contamination control strategy is not in the scope of <1071>. A new GC<1110> is proposed for microbial contamination control strategy.
Comment Summary #5: The commenter suggests deleting the last sentence of the 1st paragraph in the “Introduction” section to avoid having a contradictory statement in another section.
Response: Comment incorporated.
Comment Summary #6: The commenter requested to emphasis that each manufacturer should perform risk-assessments based on the specific manufacturing conditions and products.
Response: Comment incorporated. The clarification text was added under the section of “The Concept of Risk-based Detection of Contamination in Short-life Products”
Comment Summary #7: The commenter requested to change “assay sensitivity” to “assay sensitivity and reliability”. In addition, the commenter recommended adding text to cover sampling strategy.
Response: Comment incorporated. The text on sampling strategy was added under the section of “The Concept of Risk-based Detection of Contamination in Short-life Products.”

USER REQUIREMENT SPECIFICATION FOR A RAPID MICROBIOLOGICAL METHOD FOR THE DETECTION OF CONTAMINATION IN SHORT-LIFE PRODUCTS

Comment Summary #8: The commenter requested to add automation and automated continuous/periodic monitoring as part of the list of user requirement specifications.
Response: Comment incorporated. A bullet point was added for the requested text.
Comment Summary #9: The commenter suggested adding the following consideration to the user requirement specifications: the ability of the method (typically automated) to test multiple samples at once from the same or different batches.
Response: Comment incorporated. A bullet point was added for the requested text.
Comment Summary #10: The commenter suggested changing the first bullet point of URS to "*A rapid result time, preferably before the product is administered, which is based on a risk assessment should that consider the shelf life of the therapeutic product and relative risk to the patient based on the route, site of administration and the volume of product injected or infused*. "
Response: Comment not incorporated. The consideration for the risk assessment is described in “The Concept of Risk-based Detection of Contamination in Short-life Products” section.
Comment Summary #11: The commenter requested to set the same expectation of ability to detect as in GC<72> and <73>.
Response: Comment not incorporated. GC<1071> has a larger scope than <72> and <73> which are focused on specific RMM methods. Other methods may be used that do not have an LOD of 10 CFU. The requirements in <72> and <73> are for enhanced suitability, not an LOD study.
Comment Summary #12: The commenter requested a clarification on what a low quantity of microorganisms could be.
Response: Comment acknowledged. It would depend on the application, and it is for the user to determine since there are different methods that can be used. Refer to Comment Summary #11.
Comment Summary #13: The commenter suggested mentioning that RMM should be able to detect facility isolates.
Response: Comment incorporated. Facility isolates were added.

Comment Summary #14: The commenter recommended adding “available sampling points that would provide the most meaning results” in the fourth bullet points.
Response: Comment incorporated. The text now reads: … the manufacturer should consider ***available sampling points that would provide the most meaning results***, ***along with*** assay requirements during process design.
Comment Summary #15: The commenter suggested adding text regarding evaluation of test materials handling as part of the aseptic process simulations.
Response: Comment not incorporated. Aseptic process simulation is out of scope of <1071>.
Comment Summary #16: The commenter stated that ISO5 environment would be a good recommendation to avoid contamination during testing without requiring a closed system. The commenter suggested changing “i.e. closed systems” to “*Aseptic test material handling, to reduce inadvertent contamination during testing. i.e., ISO 5 environment to reduce inadvertent contamination during testing”.*
Response: Comment partially incorporated. The “i.e.” in the sentence was changed to “e.g.,” for flexibility.
Comment Summary #17: The commenter stated that multiple vendors could potentially limit novel technology implementation due to the availability in the market. The commenter requested to remove the bullet point or replace it with “consider supply chain management.”
Response: Comment incorporated. The text “from multiple vendors” was removed from the bullet point.
Comment Summary #18: The requested to change the seventh bullet point as the following for clarity purposes: *Availability of reference standards as well as negative and positive controls appropriate for technologies...” or “Availability of reference standards and controls appropriate for technologies*...
Response: Comment partially incorporated. The text now read as follows: *Availability of reference* ~~*standards*~~ ***material and controls***, ~~*negative and positive controls,*~~ *appropriate for* ***the technology*** ~~*technologies that use signals other than the colony-forming unit (CFU).*~~
Comment Summary #19: The commenter suggested using primary vendor validation data to assess the false positive and false negative rates when compared to <71>.
Response: Comment not incorporated. By leaving the text unchanged the stakeholder may apply different ways of determining these results. That could also include primary validation. Prefer leaving the text unchanged to allow flexibility for additional studies to the primary validation.
Comment Summary #20: The commenter requested clarification on an acceptable low rate of false positive results.
Response: Comment not incorporated. The false positive and false negative rates may vary depending on the utilization of the method. For instance, for a rapid screening a higher rate may be more acceptable than for a release sterility test. Therefore, to allow flexibility of use no detailed rate was written.
Comment Summary #21: The commenter stated there was no false positive and false negative since the rapid method should be comparable or non-inferior to the existing method.
Response: Comment not incorporated. Refer to the response for Comment Summary #20.
Comment Summary #22: The comments suggested changing “a method suitability testing strategy for each specific product” to “a method suitability testing strategy for each specific product, such as evaluating for inhibitory properties of the product.”
Response: Comment partially incorporated. The bullet point was deleted.
Comment Summary #23: A commenter requested to clarify whether “ability to identify the detected microorganisms” refers to the assay itself having such capability, or that the samples can be resampled by another method. It is also not clear whether this refers to species level identification or a much higher level such as a general class of microorganism (e.g., mold versus bacteria).

Response: Comment not incorporated. It could be understood as both ways, either through the system directly or after having recovered the microorganism.
Comment Summary #24: The commenter requested to clarify the last bullet point because the sample volume is often limited.
Response: Comment acknowledged. The statement refers to the sample preparation not the sample volume.
Comment Summary #25: The commenter recommended adding considerations for products which are for immunocompromised or immunodeficient patients and immunosuppressive agents.
Response: Comment partially incorporated. Text was added in the "Introduction" section to allow consideration of additional URS.

THE CONCEPT OF RISK-BASED MICROBIOLOGICAL MONITORING AND RELEASE TESTING

Comment Summary #26: The commenter suggested specifying that the current compendial test is USP<71>.
Response: Comment incorporated. USP<71> was added in the text for clarification.
Comment Summary #27: The commenter stated that the user can choose to use a RMM even if a USP <71> method could be used. Therefore, the commenter suggested revising the second sentence as follows: "*A risk assessment for RMM selection should be performed in all cases where use of a RMM in place of USP <71> is being considered*."
Response: Comment partially incorporated. Additional text on risk assessment was added at the end of the first paragraph.
Comment Summary #28: The commenter suggested changing the second bullet point to "Use *of a growth-based RMM that can provide earlier detection of microorganisms with tests that have a single reading at the end of the incubation period or continuous readings, i.e., "negative to date" results. Earlier detection of a contaminant would allow for timely clinical intervention*."
Response: Comment partially incorporated. The text was revised as follows: *Use of a growth-based RMM that can provide earlier detection of microorganisms. This would allow for timely clinical intervention.*
Comment Summary #29: The commenter request clarification on what is acceptable above 1 CFU.
Response: Comment acknowledged. It all depends on how the users utilize these RMMs. These RMMs might not necessarily be used as a replacement for a release sterility test but as a rapid screening process prior to release. In this case if the result is almost on time, it might be more interesting in short life cycle products to have a result earlier.
Comment Summary #30: The commenter stated that in the case of autologous cell therapies, sterility testing is not appropriate because these products cannot be filtered, or sterilized.
Response: Comment not incorporated. Sterility tests using direct inoculation techniques are widely used for all products that cannot be filtered.

CRITICAL OPERATING PARAMETERS TO BE USED IN DETERMINING A RISK-BASED RAPID MICROBIOLOGICAL METHOD FOR THE DETECTION OF CONTAMINATION IN SHORT-LIFE PRODUCTS

Comment Summary #31: A few commenters suggested including isothermal microcalorimetry as in the original chapter and updating sensitivity based on some suppliers' information.
Response: Comment not incorporated. The EC decided not to include the technology because there was no sufficient data provided for the EC review to include this technology at this stage.

However, a sentence was added at the end of the first paragraph to clarify that Table 1 is not an exhaustive list of examples, other technologies may be used.
Comment Summary #32: The commenter suggested removing the Sample Size Range column in Table.
Response: Comment not incorporated. Table 1 provides typical operating parameters based on literature and USP Subcommittee experience. The table's goal is to give a general overview of the different methods described but not to set allowable minimum and maximum values. Other volumes may apply.
Comment Summary #33: The commenter proposed to include sample test volumes for cell-based therapeutics in Table 1.
Response: Comment not incorporated. <1071> is not merely for cell therapy products. The typical sample volume in the table is based on the principles of the technology not on the product type.
Comment Summary #34: The commenter recommended updating the 10-100 CFU limit of detection (LOD) for nucleic acid methods in Table 1 with the next-generation sequencing (NGS) LOD or adding a separate row for NGS technology.
Response: Comment not incorporated. The EC decided to retain a conservative approach which may evolve as more data becomes available for NGS.
Comment Summary #35: The commenter stated that respiration-based methods are not able to confirm negative results at 110 CFU of certain organisms overnight. The commenter suggested deleting “overnight” for this method.
Response: Comment not incorporated. There are cases of respiration-based methods used with very short timelines. It all depends on the level of contamination. The time to result listed “overnight to 7 days” serves a range for user to choose based on their specific applications.
Comment Summary #36: The commenter suggested revising the sample size for respiration-based method because sensitivity is limited by volume. The table should reflect what publicly available validation exists.
Response: Comment not incorporated. The sample size is based on the common practice of nowadays. This size provides an estimate as a starting point.
Comment Summary #37: The commenter request to elaborate within Table 1 on the CFU expectations for cell therapy products. The commenter also suggested having an additional column of expected LOD with cell material or add reference with this LOD and TTD with cell material using solid phase cytometry.
Response: Comment not incorporated. <1071> is not merely for cell therapy products. Table 1 provides typical operating ranges to give a general idea of what technology may be used.
Comment Summary #38: The commenter suggested revising the sample size for solid phase cytometry to µl-mL
Response: Comment not incorporated. Reference to Comment Summary #32.
Comment Summary #39: The commenter stated that an appropriate enrichment protocol would be required to support method validation and justify risk assessment. The commenter suggested adding such text in the “Method Validation and Suitability Testing” section.
Response: Comment acknowledged. Some discussion on enrichment is included in the following “Technology Description” section.

SAMPLE SIZE CONSIDERATION

Comment Summary #40: A few commenters requested to have similar guidance with specified sample size as Ph. Eur. 2.6.27.
Response: Comment not incorporated. Ph.Eur. 2.6.27 is specific for cell-based preparations. USP <1071> has a much larger scope. Therefore, USP prefers to keep the general statement.

Comment Summary #41: The commenter recommended removing the reference to 21 CFR 610.12 in the text.
Response: Comment incorporated. The reference was removed from the text to avoid confusion.
Comment Summary #42: The commenter suggested defining "N" in the sentence after the equation.
Response: Comment incorporated. The sentence was deleted as the content is discussed elsewhere in the text.
Comment Summary #43: The commenter proposed to include sample test volumes for cell-based therapeutics product in Table 2. The commenter requested more clarity if the volume to be tested will be determined by the manufacturer.
Response: Comment not incorporated. USP <1071> has a much larger scope than cell-based therapy products. The text in the chapter allows alternative appropriate statistical approaches if scientifically justified. This would allow in some cases manufacturer-based sample size considerations.

EXAMPLE TECHNOLOGIES FOR THE DETECTION OF CONTAMINATION IN SHORT-LIFE PRODUCTS

Comment Summary #44: The commenter stated that the chapter should address emerging and future technologies if they meet the URS and ensure patient safety.
Response: Comment not incorporated. There is a sentence at the end of the section which states other technologies may apply based in the user's URS evaluation.
Comment Summary #45: The commenter requested to address flow cytometry as a current technology.
Response: Comment not incorporated. A sentence at the end of the section states that these are example technologies and other technologies may apply based in the user's URS evaluation.
Comment Summary #46: The commenter suggested adding the following in sentence after the bullet points: …*such as developing technologies based on Raman Spectroscopy and cytology*.
Response: Comment not incorporated. There may be developing technologies based on other fields. There is no need to call out specific technologies.
Comment Summary #47: The commenter requested clarification on the first sentence of ATP technology description.
Response: Comment incorporated. The sentence was revised to "*Generation of ATP is a marker of cell viability."*
Comment Summary #48: The commenter suggested changing the last sentence in ATP bioluminescence section to "*Products with a high ATP background may require additional test modifications to reduce non-microbial ATP. As detection is not visual interference, there is no interference from product-related turbidity (subject to non-microbial ATP being managed)*"
Response: Comment partially incorporated. The sentence was revised to "***Product with high ATP backgrounds may require additional test modifications to reduce non-microbial ATP,*** *and since it is…"*
Comment Summary #49: The commenter requested to include the following text (currently official as of Dec-01-2019) in this proposed revised version. "Alternatively, for DNA-based PCRs, a sample pretreatment with ethidium monoazide or propidium monoazide may also provide the capability to differentiate live from dead microbial cells (10,11), or free microbial DNA may be removed from a test sample by a centrifugation/washing step and the bacterial pellet used for analysis." "As noted by the authors of a recent study of the use of 16S rRNA PCR sterility test for stem cells, with the demonstrated bacterial sensitivity of 10–100 cfu/mL, a

test method with a sensitivity of 100 cfu/mL would be suitable to detect clinically significant bacterial contamination of blood and cell products (13)."
Response: Comment partially incorporated. The EC agreed to partially update the current official text. Reference 10 and 11 in the current official text was added.

METHOD VALIDATION AND SUITABILITY

Comment Summary #50: The commenter recommended considering the method suitability strategy as a product family approach with appropriate justification rather than for each specific product.
Response: Comment not incorporated. Method suitability for each product is a CFR requirement. In very rare cases FDA have accepted "product family approach" but it is not widely accepted.
Comment Summary #51: The commenter requested to add guidance on the selection of microorganisms.
Response: Comment not incorporated. There is some guidance on selection of microorganisms in USP<1223> as well as the respective RMM chapters <72> and <73>
Comment Summary #52: The commenter requested to clarify whether it is "lot" of products that is expected. Suggest changing "three different lots" to "three different lots of products."
Response: Comment incorporated. Change "three different lots" to "*three different product lots*"
Comment Summary #53: The commenter requested to provide an alternative strategy in the event the material is not available for test, e.g., in early pharmaceutical development the firms typically use donor material for method qualification.
Response: Comment not incorporated. The situation should be handled on a case-by-case basis. However, the specific strategy cannot be defined in a USP general chapter.
Comment Summary #54: The commenter stated that the three lots for suitability testing are arbitrary. The commenter recommended changing the text to read as follows: *It is recommended that an appropriate number of lots of product to be determined prospectively for suitable testing to enable an assessment for the potential of lot-to-lot variability. This is especially important for products where significant lot-to-lot variability is indicated. Products with greater variability in their starting material, API and manufacturing process will require additional lots, whereas for products with little or no process or product variability less may suffice. The number of lots tested for suitability should be supported by a risk assessment, information on the life cycle stage of the product (clinical/commercial), known sources of variability and material testing history that could support an increased or decreased number of lots chosen for suitability testing.*"
Response: Comment partially incorporated. The text was revised as follows: "*It is recommended that an appropriate number of lots of product be determined prospectively for suitable testing to enable an assessment for the potential of lot-to-lot variability and justified in a risk assessment. The method suitability test is performed on three different product lots, or three independent runs if three lots are not available. Products with greater variability in their starting material, API and manufacturing process will require additional lots."*
Comment Summary #55: The commenter requested clarification on statement regarding equivalency.
Response: Comment incorporated. The sentence was revised for clarity as follows: …*method suitability testing should also verify if the sample interferences with the assay (e.g., by impeding the detection, or by generating a high background).*

General Chapter/Section(s): <1079.2> Mean Kinetic Temperature in the Evaluation of Temperature Excursions During Storage and Transportation of Drug Products

Expert Committee(s): General Chapters—Packaging and Distribution
No. of Commenters: 7

General

Comment Summary #1: The commenter suggested there can be a lot of data that is generated during the storage of a product and requested clarity on whether it is necessary to use all data when calculating Mean Kinetic Temperature.
Response: Comment not incorporated. Yes, all data must be used
Comment Summary #2: The commenter suggests defining what is meant by “transient spike”.
Response: Comment not incorporated. USP is looking to define the term and add to <659>, so will be addressed in the future.
Comment Summary #3: The comment suggests advising on handling CRT excursions between 30–40°C lasting less than 24 hours. It recommends guidance like: “For excursions under 24 hours between 30–40°C, calculate MKT to confirm the drug stayed within the 20–25°C storage range.”
Response: Comment not incorporated. For excursions less than 24 hours between 30-40 Celsius, a MKT will need to be calculated to verify that the drug has a MKT of less than 25 Celsius.
Comment Summary #4: The comment suggests replacing "recommended" with "necessary" for MKT calculation to ensure a 30-day basis is required, avoiding potential ambiguity.
Response: Comment incorporated. Replacing "recommended" with "should"
Comment Summary #5: The comment suggests clarifying whether the guidance applies only to drug products manufactured, stored, and distributed within the USA, North America, or globally.
Response: Comment not incorporated. Written as a global document
Comment Summary #6: The commenter recommends addressing the topic of whether Mean Kinetic Temperature can be used for Biologic and Vaccines.
Response: Comment not incorporated. The statement already appears in this general chapter.
Comment Summary #7: The comment suggests that USP’s future revision of the chapter should clearly define climatic zone IVb.
Response: Comment not incorporated. Chapter already have the temperature ranges outlined in Table 1

Scope

Comment Summary #8: The commenter suggests clarifying that veterinary offices for both inpatient and outpatient care should also be included within the scope.
Response: Comment incorporated.
Comment Summary #9: The commenter recommended making a difference between drug drug-device and biologic-device combination devices products in the chapter.
Response: Comment not incorporated. Within the USP there are no distinction between these two products.

3.0 Mean Kinetic Temperature

Comment Summary #10: The commenter suggests clarifying whether you are measuring “air” temperature or “product” temperature.
Response: Comment not incorporated. What is being proposed may add more confusion.

4.0 Application of Mean Kinetic Temperature

Comment Summary #11: The commenter suggests considering phase change as a factor when evaluating the impact of an excursion.
Response: Comment not incorporated. The statement already appears in this general chapter.
Comment Summary #12: The commenter suggested some products' absolute temperature limits may be lower than 40 °C and this point should be reflected in the chapter
Response: Comment not incorporated. There is a footnote for Table 1 that addresses this.
Comment Summary #13: The commenter suggests a more restrictive temperature excursion allowance to align with ICH Q1.
Response: Comment not incorporated. USP finds no added value in being more restrictive at this time, as the current excursion range is supported by data.

Table 1 Controlled Cold Temperature

Comment Summary #14: The commenter suggests defining the application of the 24-hour window.
Response: Comment not incorporated. Text was drafted to address, but once text was reviewed within the context of the general chapter it created more confusion than clarity.

4.0 Application of MKT--Use of MKT for Controlled Cold Temperature Excursions

Comment Summary #15: The commenter suggested adding an acceptable limit for repeated deviations.
Response: Comment not incorporated. There is no acceptable limit for repeated deviations; recurring deviations indicate a lack of control in the system. For multiple excursions along the supply chain, limits can only be established by the manufacturer.

General Chapter/Section(s): <1467> Residual Solvents—Verification of Compendial Procedures and Validation of Alternative Procedures
Expert Committee: General Chapters—Chemical Analysis
No. of Commenters: 1

1. General

Comment Summary #1: The commenter referring to an entry from the third paragraph of the introductory part of the chapter: "*A risk-based approach may be appropriate to determine the degree and extent of the verification or validation process to assure the fitness for purpose of the procedure.*" suggest adding references to General Chapters <1224> Transfer of Analytical Procedures and <1226> Verification of Compendial Procedures.
Response: Comment not incorporated. The Expert Committee determined that the comment is outside the scope of this revision proposal.

1. Table 1. Summary of Verification and Validation Requirements

Comment Summary #2: The commenter noting that for "*Linearity*" the "*Quantitative Methods*" requirement is given as "*No*", stated it should be a "Yes" reasoning that
Relative Response Factor (RRF) values are critical in the calculation of control quantity. RRF values can be derived from Slope of Linearity so if RRF is being used in quantitative calculation, Linearity must be determined.
Response: Comment not incorporated. The Expert Committee determined that the comment is outside the scope of this revision proposal.

Comment Summary #3: The commenter noting that for “Robustness” the “Quantitative Methods” requirement is given as “No”, stated it should be a “Yes” reasoning that robustness is specific to the system in use; instrument limitations must be verified to account for this variation in value. The commenter recommended revising the current text, including the footnote “d,” and suggested a text revision.
Response: Comment not incorporated. The Expert Committee determined that the comment is outside the scope of this revision proposal. The Expert Committee will consider the recommendations in a future revision.

3. VERIFICATION OF COMPENDIAL PROCEDURES-Limit Procedures: Procedure A and Procedure B-VERIFICATION WHEN SOLVENTS LIKELY TO BE PRESENT (LTBP) ARE KNOWN

Comment Summary #4: The commenter noting under the Specificity subheading the following statement: “The procedure must be able to separate each of the solvents in the Standard solution(s) from each other and from other peaks in the spiked sample solution with a resolution of NLT 1.0.,” stated that current regulatory thinking indicates that integration accuracy is achieved by resolution of NLT 1.5 and recommended revising it to NLT 1.5.
Response: Comment not incorporated. The Expert Committee determined that the comment is outside the scope of this revision proposal. The Expert Committee will consider the recommendations in a future revision.

5. VALIDATION OF ALTERNATIVE PROCEDURES

Comment Summary #5: The commenter referring to the recommended acceptance criteria Quantitative Procedures section, under Linearity and Range: “*The coefficient of determination, r^2, is NLT 0.90*.”, stated that this is too permissive and inconsistent with regulatory thinking. The commenter recommended changing the r^2 to NLT 0.990.
Response: Comment not incorporated. The Expert Committee determined that the comment is outside the scope of this revision proposal. The Expert Committee will consider the recommendations in a future revision.

Monographs

Monograph/Section(s): Acetyltributyl Citrate/Organic Impurities
Expert Committee(s): Simple Excipients
No. of Commenters: 2

Comment Summary #1: The commenter requested clarification on the difference between tributyl 2-hydroxypropane-1,2,3-tricarboxylate and tributyl citrate.
Response: Comment incorporated. The name tributyl 2-hydroxypropane-1,2,3-tricarboxylate was changed to 1,2-dibutyl 3-(2-methylpropyl) 2-(acetyloxy)propane 1,2,3-tricarboxylate.
Comment Summary #2: The commenter suggested adding the Relative Retention Time information of Acetyltributyl Citrate in Table 2.
Response: Comment incorporated. It was added to the table as Acetyltributy Citrate, RRT = 1.00.

Monograph/Section(s): Allopurinol Compounded Oral Suspension
Expert Committee: Compounding Expert Committee
No. of Commenters: 1

Comment Summary #1: Commenter recommends including the manufacturer of the Allopurinol tablets used in the currently official preparation.
Response: Comment not incorporated. USP is unable to provide identifying manufacturer information.
Comment Summary #2: Commentor notes, the first formula for both suspension and solution is confusing. The information lacks clarity to ensure that the dose of 20 mg/mL is clearly understood by the compounder. The suspension formula states to add only 45mL of Vehicle for Oral Suspension which will not lead to a dose of 20mg/mL without addition of the Vehicle for Oral Solution. The current formulation can lead to mistakes and in turn patient harm. For clarity, in the first table, they suggest revising the Vehicle for Oral Solution amount from "100 mL" to "qs to 100 mL."
Response: Comment not incorporated. Both formulae already have vehicles that specify to use, "a sufficient quantity to make."
Comment Summary #3: Commenter recommends including some text to indicate that the glycerin used in the original method should be tested for diethylene glycol and ethylene glycol before use in the compounded preparation**.**
Response: Comment not incorporated. Consistent with <795>, compounders must verify their glycerin meets the criteria of the Glycerin USP monograph that requires performance of these tests already.
Comment Summary #4: Commenter notes that the newly proposed text directs the user to "Place the Allopurinol in a suitable container and triturate to a fine powder." For clarity, they recommend revising the text to state the type of API for these new preparations, as done in the original preparation (i.e., "Allopurinol powder"). For example, the aforementioned statement could be revised as follows: "Place the Allopurinol 'powder/tablets/etc.' in a suitable container and triturate to a fine powder
Response: Comment incorporated.
Comment Summary #5: Commenter notes that the new text provides the quantity of allopurinol using trailing zeros (e.g., "1.0 g" and "2.0 g"), however, it seems that the use of trailing zeros in formulation instructions is inconsistent across compounded monographs. For example, the Flucytosine Compounded Oral Suspension monograph does not include trailing zeros in its preparation directions. For consistency, they recommend clarifying the use of trailing zeros in compounding monographs, specifically when included in preparation directions.
Response: Comment incorporated.
Comment Summary #6: Commenter notes that the two new preparations state to use SuspendIt (a proprietary suspending agent manufactured by PCCA, Houston, Texas) as the vehicle, while the current preparation states to use SyrSpend SF pH 4 (a proprietary suspending agent manufactured by Fagron, St. Paul, Minnesota) as the vehicle. To help the public evaluate the clinical risks/benefits associated with the use of the compounded product using these proprietary formulations, they recommend that the ingredients of these excipients be included in the monograph.
Response: Comment not incorporated. This information can be readily obtained by compounders from the manufacturers or distributors of these bases.
Comment Summary #7: Commenter notes the A*ssay Acceptance criteria* range is given as 90.0%-110.0%. This is inconsistent with our observations of the raw data. They recommend tightening this range to be consistent with the raw data.
Response: Comment not incorporated. The Expert Committee also bases its acceptance criteria on existing USP monographs and expert opinion, not solely on laboratory testing criteria.
Comment Summary #8: Commenter notes the pH *Acceptance criteria* are inconsistent with our observations of the raw data. Additionally, they note that the original instructs the compounder

to “Adjust the pH, if necessary.” They suggest also including this instruction in the directions for the new formulations.
Response: Comment not incorporated. The pH *Acceptance criteria* are based on an average of the data and a suitable window for preparation. There were no pH adjustments in the new formulations.
Comment Summary #9: Commenter recommends including Appearance recommendations/criteria for the final compounded product developed using the monograph’s currently official preparation, similar to the newly proposed Appearance criteria for preparations using Vehicle A and Vehicle B.
Response: Comment not incorporated. Information is either included in the monograph or not available after reviewing previous studies.
Comment #10: Commenter recommends specifying the containers used (e.g., glass type). This should be consistent with the containers used to support Beyond-Use Date criteria.
Response: Comment incorporated.
Comment #11: Commenter notes it is unclear whether the Beyond-use Date criteria included accurately reflects data from the scientific studies utilized to support the monograph. Unsubstantiated Beyond-Use Date criteria could potentially lead to instability if the product is not appropriately stored and maintained.
Response: Comment not incorporated. This revision proposed to add two formulations based on a validated stability-indicating method for Allopurinol Compounded Oral Suspension, 10 mg/mL, and 20 mg/mL, in SuspendIt. The study data for the monograph official as of November 1, 2020, was previously evaluated.

Monograph/Section(s): Amitriptyline Hydrochloride Compounded Oral Suspension
Expert Committee: Compounding Expert Committee
No. of Commenters: 1

Comment Summary #1: Commenter has concerns about developing monographs for preparations that may present particular safety risks (e.g., Amitriptyline Compounded Oral Suspension) given the limited labeling that generally accompanies compounded drug products. FDA-approved amitriptyline HCl oral tablets are labeled with a boxed warning regarding an increased risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults. Because of the serious side effects that can occur with the use of this drug, an approved package insert should be available to inform both practitioner and patient of the serious side effects and provide recommendations for appropriate follow up. Such package inserts are not required and will not be available for this compounded drug.
Response: Comment not incorporated. The Expert Committee considered the risks identified, but the cited product labeling suggestions are not directly applicable to compounded preparations.
Comment Summary #2: Commenter suggests revising the text throughout the monograph to plainly state the type of API used. For example, “Place Amitriptyline hydrochloride and Steviol glycosides 95% in…” could be revised to “Place Amitriptyline hydrochloride powder and Steviol glycosides 95% in…”
Response: Comment partially incorporated. Amitriptyline hydrochloride changed to Amitriptyline hydrochloride powder.
Comment Summary #3: Commenter notes that SuspendIt, a proprietary suspending agent manufactured by PCCA, Houston, Texas, is used as the vehicle. They have concerns with using proprietary excipients when there is no information about the identity of the excipient provided in the monograph. They recommend that the ingredients in the proprietary excipients be provided so that the public understands their identity. It is important that the public has the information

that will help them understand the risks and benefits associated with the use of the drug product, including any excipients in the drug product.
Response: Comment not incorporated. USP is unable to disclose the requested information but notes that the information can be obtained directly from the manufacturer.

Monograph/Section(s): Apigenin/Multiple *sections*
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 0

EC Committee initiated change #1: Under the chemical information section of the monograph, the molecular formula and molecular weight were corrected from $C_{15}H_{12}O_5$ and 272.26, respectively to $C_{15}H_{10}O_5$ and 270.24, respectively.
EC Committee initiated change #2: Under *Related Compounds*, Table 3, an additional significant figure was included in the acceptance criteria of related compounds.

Monograph/Section(s): Benzocaine, Lidocaine, & Tetracaine Compounded Cream
Expert Committee: Compounding Expert Committee
No. of Commenters: 1

Comment Summary #1: Commenter notes concern regarding the safety of the compounded product and the communication of the risks to patients due to compounded products being exempt from section 502(f)(1) concerning the labeling of drugs with adequate directions for use. They have published safety information about the risk of methemoglobinemia associated with local anesthetics and public health advisories regarding the potential hazards of using topical anesthetics.
Response: Comment not incorporated. Safety information is generally not included in USP CPMs and adding information on this may cause confusion.
Comment Summary #2: Commenter notes that the proposed monograph title is inconsistent with what was balloted and approved in June 2022 by the USP Nomenclature and Labeling Expert Committee. They recommend revising the title to be consistent with what was approved, as follows: “Benzocaine, Lidocaine, and Tetracaine Compounded Cream.”
Response: Comment incorporated.
Comment Summary #3: Commenter suggests revising the text throughout the Definition section to plainly state the type of API used. For example, “Add the Benzocaine, Lidocaine, and Tetracaine into a glass mortar and pestle” should be revised to “Add the Benzocaine powder, Lidocaine powder, and Tetracaine powder into a glass mortar and pestle.”
Response: Comment incorporated.
Comment Summary #4: Commenter notes that the directions state to use Emollient cream, a proprietary agent manufactured by PCCA, Houston, Texas. To help the public evaluate the clinical risks/benefits associated with the use of the final compounded product prepared with this proprietary formulation, they recommend that the ingredients of these excipients be included in the monograph.
Response: Comment not incorporated. USP is unable to disclose the requested information but notes that the information can be obtained directly from the manufacturer.
Comment Summary #5: Commenter notes the *Assay* acceptance criteria range is given as 90.0%-110.0%. This is inconsistent with our understanding of the data. They recommend tightening this range to be consistent with the raw data.
Response: Comment not incorporated. The Expert committee bases its acceptance criteria on existing USP monographs and expert opinion, not solely on laboratory testing criteria.

Comment Summary #6: Commenter notes the pH *Acceptance criteria* range is given as 8.6-9.6. This is inconsistent with our observations of the raw data. They recommend tightening this range to be consistent with the raw data.
Response: Comment incorporated. The pH *Acceptance criteria* are based on an average of the data and a suitable window for preparation. The pH acceptable criteria range was revised to 8.8-9.8.
Comment Summary #7: Commenter notes that the Packaging and Storage section states to "Store at controlled room temperature" while the Beyond-Use Date section seems to indicate that the compounded preparation can also be stored in the refrigerator. This is unclear. If the compounded product can also be stored in the refrigerator, the storage conditions should be updated to reflect such.
Response: Comment incorporated.

Monograph/Section(s): Bupivacaine Hydrochloride Compounded Injection
Expert Committee: Compounding Expert Committee
No. of Commenters: 1

Comment Summary #1: Commenter notes that the monograph for Bupivacaine Hydrochloride Compounded Injection, 5 mg/mL may produce a drug product that is essentially a copy of an FDA-approved product. Please see the final guidance for industry Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act (January 2018). FDA recommends using only FDA-approved drug products unless the patient has a specific medical need that cannot be met by the approved drug products. Because compounded drug products do not go through the drug approval process, they should only be used when an FDA-approved product is not available to meet the medical needs of an individual patient. However, they recognize that bupivacaine HCl injection is currently on the FDA Drug Shortage list and, as stated in the final guidance for industry Compounded Drug Products That are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act (January 2018), under section 503A they do not consider a drug product to be commercially available if the drug product appears on the FDA Drug Shortage list.
Response: Comment not incorporated. The Expert Committee notes that the uses of compounded drug products extend beyond the circumstances listed by the commenter, including circumstances when the drug product is unavailable, such as when it is on shortage, or uses outside of the United States.
Comment Summary #2: Commenter has concerns about developing monographs for preparations that may present safety risks (e.g., Bupivacaine Hydrochloride Compounded Injection) given the limited labeling that generally accompanies compounded drug products. FDA-approved bupivacaine HCl injection products are labeled with a boxed warning regarding the risk of cardiac arrest with difficult resuscitation or death during use for epidural anesthesia in obstetrical patients.4 While the reports have typically followed use of the 0.75% (7.5 mg/mL) concentration, because of the serious side effects that can occur with the use of this drug, an approved package insert should be available to inform both practitioner and patient of the serious side effects and provide recommendations for appropriate follow up. Such package inserts are not required and will not be available for this compounded drug.
Response: Comment not incorporated. The Expert Committee considered the risks identified, but the cited product labeling suggestions are not directly applicable to compounded preparations.
Comment Summary #3: Commenter notes that the batch record used to support the study (upon which this monograph is based) states that "The amount of Bupivacaine Hydrochloride required needs to be calculated based on the potency and water content stated on certificate of

analysis." They recommend including this directive in the monograph alongside an example of the calculation. Further, to aid the compounder, they recommend including the calculations used to determine the API (bupivacaine hydrochloride powder).
Response: Comment not incorporated. The Compounding Expert Committee considers incorporating example calculations on a case-by-case basis.
Comment Summary #4: Commenter notes that there is insufficient detail to appropriately create the 0.1% hydrochloric acid and 0.1% sodium hydroxide solutions. They recommend including the concentration of the hydrochloric acid and sodium hydroxide.
Response: Comment not incorporated. Concentration and material type information provided in respective USP-NF monographs.
Comment Summary #5: For clarity, commenter recommends revising the final sentence of the Definition section as follows: "Pass the final solution through a sterile filter of about 0.2-µm-pore size into sterile containers *and place in a glass vial with septum and aluminum cap."*
Response: Comment not incorporated. Final container specified in Packaging and Storage.
Comment Summary #6: Commenter recommends including <788> Particulate Matter in Injections in the Specific Tests section.
Response: Comment not incorporated. <788> was performed in the stability study but is not required for Specific Testing.
Comment Summary #7: For consistency with the marketed approved product, commenter recommends revising the Labeling section as follows: "**Label to indicate it is not for caudal, epidural, or intrathecal anesthesia**. Label it to indicate the Beyond-Use Date."
Response: Comment incorporated.

Monograph/Section(s): Buspirone Hydrochloride Compounded Oral Suspension
Expert Committee: Compounding Expert Committee
No. of Commenters: 1

Comment Summary #1: Commenter recommends including the calculations used to determine the API (buspirone hydrochloride powder).
Response: Comment partially incorporated. The text was revised to indicate a calculation is required for the Buspirone Hydrochloride Compounded Oral Suspension, 2.5 mg/mL, formula made with powder. A note was added stating to, "Calculate the amount of *Buspirone hydrochloride* powder required by dividing the weight of buspirone hydrochloride required by the potency of the *Buspirone hydrochloride* powder obtained from the Certificate of Analysis. [NOTE – Unit conversion is needed in the calculation.]"
Comment Summary #2: Commenter notes that the preparation states to use Ora-Blend, a proprietary agent manufactured by Perrigo Pharmaceuticals, Allegan, Michigan. To help the public evaluate the clinical risks/benefits associated with the use of the final compounded product prepared using this proprietary agent, they recommend that the ingredients of these excipients be included in the monograph.
Response: Comment not incorporated. USP is unable to disclose the requested information but notes that the information can be obtained directly from the manufacturer.
Comment Summary #3: Commenter notes the *Assay Acceptance criteria* range is given as 90.0%-110.0%. This is inconsistent with our understanding of the raw data. They recommend tightening this range to be consistent with the raw data.
Response: Comment not incorporated. The Expert committee bases its acceptance criteria on existing USP monographs and expert opinion, not solely on laboratory testing criteria.
Comment Summary #4: Commenter notes the pH *Acceptance criteria* are inconsistent with our observations of the raw data. They recommend revising the acceptance criteria to be consistent with the raw data.

Response: Comment not incorporated. The pH *Acceptance criteria* are based on an average of the data and a suitable window for preparation.
Comment Summary #5: Commenter recommends revising the *Labeling* as follows: "Label to shake well before use, and to state the *Beyond-Use Date*."
Response: Comment not incorporated. The *Labeling* section is consistent with existing *USP* stylistic practices .
Comment Summary #6: Commenter notes that the lab report states that the products used were produced on April 3, 2018, but that the studies did not commence until August 14, 2018. The reason for this delay is unclear. If a different compounded product was used for these studies, the raw data and compounding records should be reviewed before developing monograph criteria.
Response: Comment not incorporated. The compounding record showed products used were produced July 23, 2018, and August 13, 2018.

Monograph/Section(s): Crospovidone/Identification D
Expert Committee(s): Complex Excipients
No. of Commenters: 0

EC Initiated Change #1: "Sieves" (plural form) were changed to "sieve" (singular form) because only one 63-µm analytical sieve is described in the testing procedure.

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

Comment Summary #1: The commenter indicated that, in their experience, Dabigatran Etexilate Mesilate is slightly hygroscopic in nature and requested relaxing the limit in the test for *Water Determination* from NMT 0.3% to NMT 0.8%.
Response: Comment not incorporated. The limit for *Water Determination* can be considered for revision upon receipt of FDA approved specifications.
Comment Summary #2: The commenter indicated they have tentative approval for Dabigatran Etexilate Capsules and requested increasing the *Water Determination* limit from 0.3% to 0.5%.
Response: Comment not incorporated. The limit for *Water Determination* can be considered for revision upon receipt of FDA approved specifications.
Comment Summary #3: The commenter indicated that acceptance criterion in the test for *Water Determination* is different from what has been approved and recommended revising the acceptance criteria to be consistent with what has been approved.
Response: Comment not incorporated. The limit for *Water Determination* can be considered for revision upon receipt of FDA approved specifications.
Comment Summary #4: The commenter experienced column pressure issues using the column specified in the *PF* 48(4) procedure for *Organic Impurities*. They indicated concern that the injection size is too small, and the flow rate is too high. The commenter asked if the procedure is a UPLC procedure even though the flow rate is so high. The commenter indicated that any adjustments that would need to be made are outside of what is allowed by General Chapter <621>.
Response: Comment not incorporated. The Expert Committee determined that the proposed column and chromatographic conditions are suitable and consistent with the *Organic Impurities* validation data which was performed using UHPLC instrumentation. Use of alternate procedures is discussed in General Notices "6.30. Alternative and Harmonized Methods and Procedures".
Comment Summary #5: The commenter indicated they cannot perform the Limit of Hexyl methane sulfonate by GCMS due to unavailability of the solid phase extraction and nitrogen-

evaporator apparatus. The commenter has developed and validated an in-house method to determine the content of Hexyl methane sulfonate along with other alkyl sulfonates by GCMS.
Response: Comment not incorporated. The Expert Committee noted that the proposal provides a note indicating that Bond Elut Si SPE cartridges are suitable for the analysis. If needed, revision to the monograph can be considered upon the receipt approved specifications. The Expert Committee is interested in a validated analytical procedure which does not require the use of hazardous reagents. Use of alternate procedures is discussed in General Notices "6.30. Alternative and Harmonized Methods and Procedures".
Comment Summary #6: The commenter indicated for the *Organic Impurities* test, they have additional in-house impurities that are not listed in the *PF* 48(4) proposal and observed resolution concerns between their in-house impurities and impurities specified in the in the *PF* 48(4) proposal. In addition, one of their in-house impurities is proposed to FDA to be controlled at 0.15% which is higher than the proposed Unspecified impurity limit of NMT 0.10%. The commenter indicated that they use two in-house impurity procedures that can separate all USP specified impurities and in-house impurities.
Response: Comment not incorporated. The Expert Committee noted that the product referenced by the commenter is not approved by FDA. The Expert Committee may be open to considering the referenced in-house impurities, limits and procedures if such a product were to receive approval from the FDA at a later date. In addition, use of alternate procedures is discussed in General Notices "6.30. Alternative and Harmonized Methods and Procedures".
Comment summary #7: 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 #8: The commenter indicated that in the test for *Organic Impurities* the limit for Dabigatran etexilate related compound B (mesylate salt) is different from what has been approved and recommended to revise the *Acceptance criteria* to be consistent with what has been approved.
Response: Comment incorporated. The limit for Dabigatran etexilate related compound B is increased to NMT 0.25%.
Expert Committee-initiated Change #1: In the test for *Organic Impurities,* the solutions and calculation sections are revised to accommodate using USP Dabigatran etexilate related compound B RS only in the System suitability solution and use of a Relative Response Factor (RRF) for quantitation of Dabigatran etexilate related compound B. The RRF for dabigatran etexilate related compound B is added to Table 3. In addition, the Sensitivity solution is revised to be prepared from the Standard solution rather than Standard stock solution.
Expert Committee-initiated Change #2 The reporting threshold is removed from the test for Limit Hexyl methane sulfonate.

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

Comment Summary #1: A commenter notes that the monograph for Diazepam Compounded Injection, 5 mg/mL may produce a drug product that is essentially a copy of an FDA-approved product. Please see the final guidance for industry Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act (January 2018). FDA recommends using only FDA-approved drug products unless the patient has a specific medical need that cannot be met by

the approved drug products. Because compounded drug products do not go through the drug approval process, they should only be used when an FDA-approved product is not available to meet the medical needs of an individual patient. As stated in the 503A Copies Guidance, under section 503A, they do not consider a drug product to be commercially available if the drug product appears on the FDA Drug Shortage list, however, diazepam sodium is not currently listed on the FDA Drug Shortage list.

Response: Comment not incorporated. The Expert Committee notes that the uses of compounded drug products extend beyond the circumstances listed by the commenter, including circumstances when the drug product is unavailable, such as when it is on shortage, or used outside of the United States.

Comment Summary #2: A commenter has concerns about developing monographs for preparations that may present safety risks (e.g., Diazepam Compounded Injection) given the limited labeling that generally accompanies compounded drug products. FDA-approved diazepam injection products are labeled with a boxed warning regarding risks from concomitant use with opioids; abuse, misuse, and addiction; and dependence and withdrawal reactions.[3] Because of the serious side effects that can occur with the use of this drug, an approved package insert should be available to inform both practitioner and patient of the serious side effects and provide recommendations for appropriate follow up. Such package inserts are not required and will not be available for this compounded drug.

Response: Comment not incorporated. The Expert Committee considered the risks identified, but the cited product labeling suggestions are not directly applicable to compounded preparations.

Comment Summary #3: A commenter notes that there is insufficient detail to appropriately create the 0.1% hydrochloric acid and 0.1% sodium hydroxide solutions. They recommend including the concentration of both hydrochloric acid and sodium hydroxide. Further, they recommend stating the type of sodium hydroxide (i.e., pellets, solution, etc.) to be used.

Response: Comment not incorporated. Concentration and material type information provided in respective USP-NF monographs.

Comment Summary #4: A commenter suggests revising the text to plainly state the type of API used. For example, “In the same container, add Diazepam and…” could be revised to “In the same container, add Diazepam **powder** and…”

Response: Comment incorporated.

Comment Summary #5: A commenter recommends explicitly stating that the Benzyl alcohol used should be parenteral grade for clarity.

Response: Comment incorporated.

Comment Summary #6: A commenter recommends revising the final sentence of the Definition section as follows: “Then pass the solution through the filter and into a sterile glass ~~container~~ **vial with septum and aluminum caps**, discarding the filtrate.”

Response: Comment not incorporated. Final container specified in Packaging and Storage.

Comment Summary #7: A commenter notes that the pH *Acceptance criteria* are given as 6.0-7.0. FDA liaisons to the Compounding Expert Committee note that this is inconsistent with observations of the raw data. They recommend tightening this range to be consistent with the raw data.

Response: Comment partially incorporated. pH range changed to 5.8 – 6.8 based on review of the stability data.

Comment Summary #8: A commenter recommends including <788> Particulate Matter in Injections in the Specific Tests section.

Response: Comment not incorporated. <788> was performed in the stability study but is not required for Specific Testing.

Comment Summary #9: A commenter recommends clarifying the storage conditions. In the Packaging and Storage section, it states that the product should be stored at controlled room

temperature. However, in the Beyond-Use-Date section, it states that the product can be stored at controlled room temperature or in a refrigerator.
Response: Comment incorporated.

Monograph/Section(s): 1,2-Distearoyl-Sn-Glycero-3-Phosphocholine/Multiple sections
Expert Committee(s): Complex Excipients
No. of Commenters: 1

Comment Summary #1: The commenter requested to change the wording in the Identity by Fatty Acid Composition from: “The areas of peaks present in the Blank sample solution chromatogram…” to “The peaks present in the Blank sample solution chromatogram…” for better accuracy.
Response: Comment incorporated.
Comment Summary #2: The commenter requested to consider an appropriate or compatible %RSD requirement that will support the Assay limit and minimize the chance of Assay failure.
Response: Comment not incorporated. The procedure implemented a calibration curve approach which gives a more accurate determination due to the non-linear nature of the detector. The data collected supports compliance with the Assay limit and suggested that the RSD requirement is appropriate. The Expert Committee will consider a revision upon available data and information received.
Comment Summary #3: The commenter requested to change the concentration of USP 1,2-Distearoyl-sn-Glycero-3-Phosphocholine RS from “0.08 g/mL” to “0.08 mg/mL” in the impurity standard stock solution in the Organic Impurities.
Response: Comment incorporated. The concentration was a typo.
Comment Summary #4: The commenter requested that specific solvents should not be specified in the monograph due to the dependency of residual solvents on the manufacturing process in the Limits of Ethanol and Acetone test, instead residual solvents should meet ICH limit, which is default expectation per USP General Notice on Residual Solvents and <467>. The commenter indicated that if a solvent is not included in the ICH, manufacturers should set a limit with appropriate justifications.
Response: Comment partially incorporated by expanding the specification limit (5000ppm for both acetone and ethanol).
Comment Summary #5: The commenter requested the removal of the requirement to test for yeasts and molds in the Microbial Enumeration Tests ⟨61⟩ and Tests for Specified Microorganisms ⟨62⟩, suggesting that testing for total aerobic bacteria is sufficient.
Response: Comment not incorporated. The limit is a general requirement in <1111>. The requirement for Yeasts and Molds can normally be achieved, and it is also in accordance with the typical applications this article is used for.

Monograph/Section(s): Dronabinol Capsules/Organic Impurities
Expert Committee: Small Molecules 3
No. of Commenters: 1

Comment Summary #1: The commenter indicated that in the test for *Organic Impurities* the impurity profile includes Specified unidentified impurity 1”, “Specified unidentified impurity 2”, and “Specified unidentified impurity 3” with no chemical names and structures. They noted that identification of impurities by relative retention time is not specific and that unidentified impurities with acceptance criteria higher than ICH Q3B identification thresholds pose challenges and ambiguity for users to identify the impurities and demonstrate method equivalency if they wish to adopt alternative methods. The commenter recommended providing additional clarity by including impurity names and structures in the monograph.

Response: Comment partially incorporated. The test for *Organic Impurities* is removed. A new test may be proposed in the future.
Comment summary #2: The commenter recommended removing the reporting threshold in the test for *Organic Impurities* as it will vary based on product-specific factors.
Response: Comment not incorporated. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

Monograph/Section(s): Dutasteride Capsules/Organic Impurities
Expert Committee: Small Molecules 5
No. of Commenters: 1

Comment summary #1: The commenter indicated that the acceptance criteria for "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 not incorporated. The proposed acceptance criteria represent the widest approved limits available to USP. If needed a future revision can be considered upon receipt of approved specifications and supporting data.
Comment summary #2: The commenter recommended removing the "reporting thresholds" in the test for *Organic Impurities* as they will vary based on product-specific factors.
Response: Comment not incorporated. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.
Comment summary #3: The commenter requested clarity on control of impurities between the currently official monographs for Dutasteride and Tamsulosin hydrochloride Capsules and the proposed monograph for Dutasteride Capsules in *PF* 49(4).
The two monographs have the same *Organic Impurities* procedure. However, the monograph for Dutasteride and Tamsulosin hydrochloride Capsules does not specify any impurities and only controls "Any unspecified degradation products and Total degradation products". The proposed monograph for Dutasteride Capsules lists several specified impurities.
Response: Comment not incorporated. Depending on the product development steps/timeline, it is possible to have differences in impurity specifications. The proposed acceptance criteria are consistent with the sponsor's approved specifications**.**

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

Comment summary #1: The commenter indicated that the *Identification* section should include an acetate confirmation test.
Response: Comment not incorporated. The Expert Committee indicated that since this compound is not a salt, there is no counter-ion. Therefore, it would be inappropriate to include the acetate confirmation test.
Comment summary #2: The commenter recommended removing the "reporting threshold" in the test for *Organic Impurities* as it will vary based on product-specific factors.
Response: Comment not incorporated. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

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

Comment Summary #1: A commenter notes that the monograph for Famotidine Compounded Injection may produce a drug product that is essentially a copy of an FDA approved product, as described in the final guidance document entitled "Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act." FDA recommends using only FDA-approved drug products unless the patient has a specific medical need (e.g., an allergy) that cannot be met by the approved drug products.
Response: Comment not incorporated. The Expert Committee notes that the uses of compounded drug products extend beyond the circumstances listed by the commenter, including circumstances when the drug product is unavailable, such as when it is on shortage, or used outside of the United States.
Comment Summary #2: A commenter notes that the final preparation does not contain a preservative. As such, they suggest that the definition be updated to clearly state that it contains no preservative.
Response: Comment not incorporated. The "Packaging and Storage" section indicates to package in single-dose containers. The commercial product does not state that it is preservative-free.
Comment Summary #3: A commenter notes the official monograph for Famotidine Injection includes language to indicate that the product should be diluted prior to administration. The current proposal for the compounded product does not include a similar directive. If the compounded product should also be diluted prior to administration, they recommend including this directive in the monograph and revising the labeling section to state such, similar to the Famotidine Injection monograph.
Response: Comment incorporated. The "Labeling" section was revised to state, "Label to indicate the *Beyond-Use Date* and that the Injection is to be diluted with a suitable parenteral vehicle prior to administration."
Comment Summary #4: A commenter suggests revising the text to plainly state the type of API and excipients used. For example, "Dissolve Famotidine, Aspartic Acid, and Mannitol in approximately…" could be revised to "Dissolve Famotidine powder, Aspartic Acid powder, and Mannitol powder in approximately…"
Response: Comment partially incorporated. Formulations other than powder would be acceptable for aspartic acid and mannitol. Monograph text revised to state, "Dissolve *Famotidine powder*, *Aspartic Acid*, and *Mannitol* in approximately 360 mL of Vehicle."
Comment Summary #5: A commenter notes the assay acceptance criteria range is given as 90.0%-110.0%. This is inconsistent with our understanding of the data.
Response: Comment not incorporated. The Expert Committee bases its acceptance criteria on existing USP monographs and expert opinion, not solely on laboratory testing criteria.
Comment Summary #6: A commenter suggests revising the current statement as follows: "Label it to state the Beyond-Use Date." They further direct the committee to comment #3 above for additional considerations regarding the labeling section criteria.
Response: Comment not incorporated. The labeling section is consistent with existing USP stylistic practices.

Monograph/Section(s): Fentanyl Citrate Compounded Injection
Expert Committee: Compounding Expert Committee
No. of Commenters: 1

Comment Summary #1: A commenter notes that the monograph for Fentanyl Citrate Compounded Injection, 50 µg/mL may produce a drug product that is essentially a copy of an FDA-approved product. Please see the final guidance for industry Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act (January 2018). FDA recommends using only FDA-approved drug products unless the patient has a specific medical need that cannot be met by the approved drug products. Because compounded drug products do not go through the drug approval process, they should only be used when an FDA-approved product is not available to meet the medical needs of an individual patient. However, they recognize that fentanyl citrate injection is currently on the FDA Drug Shortage list.
Response: Comment not incorporated. The Expert Committee notes that the uses of compounded drug products extend beyond the circumstances listed by the commenter, including circumstances when the drug product is unavailable, such as when it is on shortage, or used outside of the United States.
Comment Summary #2: A commenter has concerns about developing monographs for preparations that may present safety risks (e.g., Fentanyl Citrate Compounded Injection) given the limited labeling that generally accompanies compounded drug products. FDA-approved fentanyl citrate injection products are labeled with a boxed warning regarding the risk of addiction, abuse, and misuse; life threatening respiratory depression; cytochrome P450 3A4 interactions; and risks from concomitant use with benzodiazepines or other CNS depressants. Because of the serious side effects that can occur with the use of this drug, an approved package insert should be available to inform both practitioner and patient of the serious side effects and provide recommendations for appropriate follow up. Such package inserts are not required and will not be available for this compounded drug.
Response: Comment not incorporated. The Expert Committee considered the risks identified, but the cited product labeling suggestions are not directly applicable to compounded preparations.
Comment Summary #3: A commenter suggests revising the text throughout the monograph to plainly state the type of API used. For example, “Fentanyl (as fentanyl citrate)” could be revised to “Fentanyl (as fentanyl citrate **powder**)” and “Dissolve Fentanyl in sufficient Vehicle…” could be revised to “Dissolve Fentanyl (**as fentanyl citrate powder**) in sufficient Vehicle…”
Response: Comment incorporated.
Comment Summary #4: A commenter suggests clarifying the quantities to be used for fentanyl and fentanyl citrate, as follows: “5000 µg (7855 µg of **fentanyl citrate**).”
Response: Comment incorporated.
Comment Summary #5: A commenter notes that the weight of Fentanyl Citrate, USP is based on the anhydrous basis. To aid the compounder, they suggest including calculations for conversion of monohydrate forms to anhydrous powder. Providing the calculations used to support the monograph will ensure consistency and protect the public from potential calculation errors. This will help ensure mistakes in dosing are not made.
Response: Comment not incorporated. The Compounding Expert Committee considers incorporating example calculations on a case-by-case basis.
Comment Summary #6: The pH *Acceptance criteria* range is given as 4.0-7.5. A commenter notes that this is inconsistent with observations of the raw data. They recommend tightening this range to be consistent with the raw data.
Response: Comment not incorporated. pH range adopted from Fentanyl Citrate Injection monograph.
Comment Summary #7: The pH *Acceptance criteria* range is given as 4.0-7.5. A commenter notes that this is inconsistent with observations of the raw data. They recommend tightening this range to be consistent with the raw data.

Response: Comment not incorporated. pH range adopted from Fentanyl Citrate Injection monograph.
Comment Summary #8: In the Labeling section, a commenter recommends stating that the product should be labeled to indicate the route of administration, including whether it can be administered intrathecally based on endotoxin content.
Response: Comment incorporated.

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

Comment Summary #1: The commenter recommended that in the *Chemical Information* section one of the names for flurbiprofen was revised and recommended including "(±)-" sign in the revised name.
Response: Comment not incorporated. The "(±)-" indicates that the compound does not have optical rotation but is not required because this can be inferred from the chemical name. The proposed name "Sodium 2-(2-fluoro-[1,1'-biphenyl]-4-yl) propionate dihydrate" is consistent with IUPAC. USP is phasing out the plus/minus symbol for consistency.
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 #1: The commenter indicated concerns in the test for *Organic Impurities* with the proposed specification reduction of Related Compound A from 1.5% to 0.15%.
Response: Comment not incorporated. The commenter indicated that the *Acceptance criteria* is no longer a concern. The Expert Committee indicated that, if needed, a future revision can be considered upon receipt of approved specifications and supporting data.

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

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 that during method verification of the *Organic Impurities* procedure published in *PF* 48(4), that the method was found feasible and the relative retention times of all Impurities were observed as mentioned in monograph. The commenter indicated that the baseline was found not stable with an inconsistent hump observed between 16 and 18 minutes. The commenter recommends inclusion of a delayed injection time of 20 minutes which results in satisfactory baseline.
Response: Comment not incorporated. The chromatographic system for the *Organic Impurities* procedure was not modified as part of the *PF* 48(4) proposal. In addition, the validation data supporting the inclusion of the external standard approach shows that a suitable baseline was achieved. *General Chapter* <621> provides guidance on system equilibration and parameters that can be modified.

Comment summary #3: The commenter requested guidance regarding when to use relative response factor (RRF) values in the monograph versus their internally calculated RRF values. The commenter provided the results of their internal RRF value verification and noted concern that the RRF values of 5-Chlorohydrochlorothiazide and Hydrochlorothiazide dimer should not be 1.0.
Response: Comment incorporated. The commenter's observation regarding the RRF values in the currently official USP-NF monograph for Hydrochlorothiazide supports the proposed revision that updated RRF values for all the specified impurities.

Monograph/Section(s): Hydrocortisone Compounded Oral Suspension
Expert Committee: Compounding Expert Committee
No. of Commenters: 1

Comment Summary #1: A commenter recommends the following revision to the text: in the preparation of Hydrocortisone Compounded Oral Suspension 2 mg/mL section: "Transfer contents stepwise and quantitatively to a calibrated container using **no less than 3** rinses of Vehicle A."
Response: Comment not incorporated. The CMP EC based compounding directions on what was used in the underlying study and what would be beneficial to compounders that would use the CPM in practice.
Comment Summary #2: A commenter recommends the following revision to the text: In the preparation of Hydrocortisone Compounded Oral Suspension 1mg/mL section: "Perform this step two times to completely rinse the mortar. Mix well by vortexing on a vortex mixer, then sonicating in an ultrasonic bath for 5 minutes to remove any air bubbles. Bring the volumetric flask to final volume…"
Response: Comment not incorporated. The USP Compounding Expert Committee has not included this information in other Compounded Preparation Monographs. Additionally, the stability study confirms that the formula meets assay requirements using traditional compounding techniques that do not include vortexing or sonication.
Comment Summary #3: A commenter recommends the following revision to the text: In the preparation of Hydrocortisone Compounded Oral Suspension 20mg/mL section: "Perform this step two times to completely rinse the mortar. **Mix well by vortexing on a vortex mixer, then sonicating in an ultrasonic bath for 5 minutes to remove any air bubbles.** Bring the volumetric flask to final volume…"
Response: Comment not incorporated. The USP Compounding Expert Committee has not included this information in other Compounded Preparation Monographs. Additionally, the stability study confirms that the formula meets assay requirements using traditional compounding techniques that do not include vortexing or sonication.
Comment Summary #4: A commenter notes the newly proposed formulations state to use SuspendIt, a proprietary suspending agent manufactured by PCCA, Houston, Texas, as the vehicle. They have concerns with using proprietary excipients when there is no information about the identity of the excipient provided in the monograph. The commenter recommends that the ingredients in the proprietary excipients be provided so that the identity of the excipients is understood by the public. It is important that the public has information that will help them understand the risks and benefits associated with the use of a drug product, including any excipients in the drug product
Response: Comment not incorporated. USP is unable to disclose the requested information but notes that the information can be obtained directly from the manufacturer.

Monograph/Section(s): Hydroxypropyl Betadex/Limit of Betadex, Propylene Glycol, and Other Related Substances
Expert Committee(s): Complex Excipients
No. of Commenters: 1

Comment Summary #1: The commenter requested to list a temperature for the detector (Differential refractometer) or indicate "a suitable constant temperature", or add a notice in the general chapter <621> that -will include "If a temperature is not listed, use a constant temperature between 20-40 C for differential refractometer detectors".
Response: Comment not incorporated. This test is not part of the proposed revision. The expert committee will consider a future revision based on available data and information.

Monograph/Section(s): Isoproterenol Hydrochloride/ Multiple sections
Expert Committee: Small Molecules 5
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 indicated that the specifications in their FDA approved application are outside the range in the monograph proposal.
Response: Comment not incorporated. The commenter did not provide sufficient information for the Expert Committee to consider changes to the monograph. A future revision can be considered upon receipt of approved specifications and supporting data.
Comment summary #3: The commenter recommended for the Microbiological Examination of Nonsterile Products <61> & <62> limits of: Total Aerobic Microbial Count (cfu/g): 10^3; Total Combined Yeasts/Molds Count (cfu/g): 10^2.
Response: Comment not incorporated. Comment is out of scope for this proposal. There are not any tests in the official monograph or *PF* proposal for Microbiological examination.

Monograph/Section(s): Ketamine Hydrochloride Compounded Injection
Expert Committee: Compounding Expert Committee
No. of Commenters: 1

Comment Summary #1: A commenter notes that they have general concerns regarding the potential safety issues associated with compounded ketamine products and the communication of the risks to patients due to compounded products being exempt from section 502(f)(1) concerning the labeling of drugs with adequate directions for use. Ketamine is a schedule III-controlled substance and has the potential for abuse and dependence. While FDA-approved ketamine for injection does not contain a boxed warning, it is contraindicated in patients for whom a significant elevation of blood pressure would constitute a serious hazard and the label contains several warnings regarding the risk of hemodynamic instability, emergence reactions, respiratory depression, pediatric neurotoxicity, drug-induced liver injury, and increase in cerebrospinal fluid pressure. They have published a compounding risk alert warning patients and health care providers about the potential risks associated with compounded ketamine products.
Response: Comment not incorporated. The Expert Committee considers safety issues with regards to compounding. The Expert Committee notes that the uses of compounded drug

products extend beyond the circumstances listed by the commenter, including circumstances when the drug product is unavailable, such as when it is on shortage.
Comment Summary #2: A commenter notes that the monograph for Ketamine Hydrochloride Compounded Injection, 100 mg/mL may produce a drug product that is essentially a copy of an FDA-approved product, as described in the final guidance for industry Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act (January 2018) (the 503A Copies Guidance). However, they recognize that ketamine HCl injection is currently on the FDA Drug Shortage list and, as stated in the 503A Copies Guidance, under section 503A they do not consider a drug product to be commercially available if the drug product appears on the FDA Drug Shortage list.
Response: Comment not incorporated. The Expert Committee notes that the uses of compounded drug products extend beyond the circumstances listed by the commenter, including circumstances when the drug product is unavailable, such as when it is on shortage, or used outside of the United States.
Comment Summary #3: A commenter notes that the directions twice state to use a "suitable container" or "sterile containers" during preparation. "Suitable" and "sterile" terms, while helpful, are insufficient descriptions. They recommend clearly stating the type of sterile container (e.g., Type I glass) that was used to support the monograph's criteria and either the specific type of "suitable" container (Type X glass, plastic, etc.) or a list of properties that will deem a container "suitable" for use. The lack of clarity for container types could result in a product unable to adequately maintain the Beyond-Use Date, which could result in potential harm to patients.
Response: Comment partially incorporated. The "Packaging and Storage" section was revised to indicate to package in light-resistant, sterile, glass containers.
Comment Summary #4: A commenter suggests including some information on appropriate storage conditions (length of time, temperature, etc.) for the 0.1 mg/mL Benzethonium Chloride solution before use in the preparation.
Response: Comment not incorporated. This is more prescriptive than the Compounding Expert Committee has been for sub-formulas in CPMs. The BUDs and other conditions described in USP <795> *Pharmaceutical Compounding – Nonsterile Preparations* would apply.
Comment Summary #5: A commenter recommends clearly stating the calculation (ratio) used to determine the amount of Ketamine Hydrochloride from Ketamine Hydrochloride powder to avoid confusion and potential mistakes in dosing that could potentially lead to serious adverse events.
Response: Comment partially incorporated. The proposed monograph already included "Ketamine (as Ketamine Hydrochloride) powder, equivalent to," "10 g (11.5 g of Ketamine Hydrochloride)", which is consistent with existing USP stylistic practices . The Compounding Expert Committee decided to maintain this information as was already included.
Comment Summary #6: A commenter notes the Packaging and Storage section indicates that the product may be stored in a refrigerator, however, the Beyond-Use Date section does not include dating for products stored under refrigeration. As such, they recommend revising the Beyond-Use Date section to include dating for refrigerated preparations based on the scientific studies performed under refrigerated conditions.
Response: Comment incorporated.
Comment Summary #7: A commenter notes the pH *Acceptance criteria* are inconsistent with our observations of the raw data. They recommend revising the *Acceptance criteria* to be consistent with the raw data.
Response: Comment not incorporated. The pH *Acceptance criteria* are based on an average of the data and a suitable window for preparation.

Monograph/Section(s): Lansoprazole Compounded Oral Suspension

Expert Committee: Compounding Expert Committee
No. of Commenters: 1

Comment Summary #1: Commenter recommends that testing for *USP* <60>, <61>, and <62> as well as appearance should be included in this monograph with acceptance criteria in *USP* <1111> to ensure microbiological quality.
Response: Comment not incorporated. The monograph references this information by citing ⟨795⟩ *Pharmaceutical Compounding—Nonsterile Preparations*.
Comment Summary #2: Commenter suggests including information on what the final yield of each preparation should be determined based on the USP study protocol. This would help ensure consistent reproducibility of the compounded preparations.
Response: Comment not incorporated. Providing a final yield would nullify compounders' ability to scale the CPM to their patients' needs as allowed in USP General Notices 5.20.20.1.
Comment Summary #3: Commenter notes that the first preparation states to use "lansoprazole delayed-release capsule(s) equivalent to 300 mg." For clarity, they suggest clarifying how many capsules would be necessary to contain 300 mg.
Response: Comment not incorporated. This current language was chosen to assure the compounder calculates the quantity of API from capsules to reduce medication errors.
Comment Summary #4: Commenter notes the following sentence: "Calculate the required quantity of each ingredient for the total amount to be prepared." This sentence does not appear in other compounding monographs and seems potentially confusing and unnecessary. To be consistent, they recommend deleting the sentence.
Response: Comment incorporated.
Comment Summary #5: Commenter notes that the second and third preparations use "Lansoprazole" as the source of active ingredient. For clarity and to prevent error, they request that USP clarify the ingredients within this monograph as either lansoprazole capsules or lansoprazole powder.
Response: Comment incorporated.
Comment Summary #6: Commenter notes that two preparations specify "Base, PCCA Suspendit q.s. 100mL." For clarity and to be consistent with other preparations, they suggest revising to "Base, PCCA Suspendit, a sufficient quantity to make 100mL."
Response: Comment incorporated.
Comment Summary #7: Commenter notes that for preparations that use PCCA SuspendIt the monograph instructs to "adjust with sodium hydroxide 10% (w/v) aqueous solution to a pH of 8–8.5 with mixing." However, the pH requirements for preparations that use PCCA SuspendIt is 8.25-8.75. They recommend reviewing the data that was part of USP's study protocol to ensure that the pH range under the directions and specific tests adequately represent the study results. Additionally, the sodium bicarbonate solution needs to include an established BUD for the solution.
Response: Comment partially incorporated. The pH range changed to 8.0 -8.5. The USP Compounding Expert Committee does not establish BUDs for stock solutions in its Compounded Preparation Monographs.
Comment Summary #8: Commenter notes the pH and Beyond-Use Date sections refer to "Oral Suspension in Ora-Blend". However, in the DEFINITION section, the vehicle is given as "A mixture of Ora-Blend and Sodium Bicarbonate Injection (8.4%) (1:1), a sufficient quantity to make". They suggest changing the name of the vehicle in the pH and Beyond-Use Date sections to match what is in the DEFINITION section.
Response: Comment partially incorporated. Vehicle names updated to match USP stylistic practices.
Comment Summary #9: Commenter notes that the monograph does not state if *USP* <51> testing was performed utilizing both options mentioned in this monograph for Sodium

Bicarbonate. The monograph states a compounder can use either FDA approved Sodium Bicarbonate Injection or they may compound a Sodium Bicarbonate Solution. If testing was performed, they recommend stating that in the monograph. If it has not been performed, they recommend that it is performed and reflected in the monograph before the monograph becomes official.
Response: Comment not incorporated. Future <51> *Antimicrobial Effectiveness Testing* is prioritized for legacy monographs but not available at this time.
Comment Summary #10: Commenter notes the monograph appears to be using food grade acesulfame potassium as opposed to the *USP-NF* acesulfame potassium. USP standards require the use of *USP-NF* grade excipients to be utilized to produce pharmaceuticals. They recommend this monograph be revised with the use of *USP-NF* acesulfame potassium and appropriate testing be performed.
Response: Comment partially incorporated. The data was reviewed, and the monograph was revised to reference USP Acesulfame potassium NF.
Comment Summary #11: Commenter notes that the packaging and storage requirements have been revised to indicate that the compounded product should be stored in a plastic container. They suggest also providing the size of the container, as the size of the container is critical for allowance of potential extra air space and contact with container closure which may change stability.
Response: Comment not incorporated. The *USP General Notices* allow for scaling of quantities in USP compounded preparation monographs.
Comment Summary #12: A commenter indicated that the monograph uses proprietary ingredients as excipients where there is no information about the identity of the excipient provided the monograph.
Response: Comment not incorporated. Information on the content of commercial vehicles is available from the manufacturer.

Monograph/Section(s): Leucovorin Calcium Compounded Injection
Expert Committee: Compounding Expert Committee
No. of Commenters: 1

Comment Summary #1: A commenter notes that the monograph for Leucovorin Calcium Compounded Injection, 10 mg/mL may produce a drug product that is essentially a copy of an FDA-approved product. Please see the final guidance for industry Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act (January 2018). FDA recommends using only FDA-approved drug products unless the patient has a specific medical need that cannot be met by the approved drug products. Because compounded drug products do not go through the drug approval process, they should only be used when an FDA-approved product is not available to meet the medical needs of an individual patient. However, they recognize that leucovorin calcium injection is currently on the FDA Drug Shortage list.
Response: Comment not incorporated. The Expert Committee notes that the uses of compounded drug products extend beyond the circumstances listed by the commenter, including circumstances when the drug product is unavailable, such as when it is on shortage, or used outside of the United States.
Comment Summary #2: In the Definition section, a commenter recommends including a statement that the product contains no bacteriostat or other preservative.
Response: Comment not incorporated. The “Packaging and Storage” section indicates to package in single-dose containers.
Comment Summary #3: A commenter suggests revising the text in the table to plainly state the type of API used (i.e., revise “Leucovorin calcium” to “Leucovorin calcium powder”).

Response: Comment incorporated.
Comment Summary #4: To aid the compounder, a commenter recommends including the calculations used to determine the amount of Leucovorin calcium powder based on salt conversion and the potency obtained from the API's certification of analysis.
Response: Comment not incorporated. The Compounding Expert Committee considers incorporating example calculations on a case-by-case basis.
Comment Summary #5: Leucovorin calcium may be harmful or fatal if given intrathecally. As such, a commenter recommends revising the Labeling section as follows "**Label to indicate for intravenous or intramuscular use only – fatal if given by other routes. Label to indicate it is for use in a single patient only**. Label to indicate the Beyond-Use Date." This language is similar to that found in the labeling requirement for the Vincristine Injection, USP monograph and aligns with current regulatory guidelines for minimizing medication errors via container labels and carton labeling design.
Response: Comment partially incorporated. Labeling states to indicate for intravenous or intramuscular use only.

Monograph/Section(s): Lidocaine Hydrochloride Compounded Injection
Expert Committee: Compounding Expert Committee
No. of Commenters: 1

Comment Summary #1: A commenter notes that the monograph for Lidocaine Hydrochloride Compounded Injection, 20 mg/mL may produce a drug product that is essentially a copy of an FDA-approved product. Please see the final guidance for industry Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act (January 2018). FDA recommends using only FDA-approved drug products unless the patient has a specific medical need that cannot be met by the approved drug products. Because compounded drug products do not go through the drug approval process, they should only be used when an FDA-approved product is not available to meet the medical needs of an individual patient. However, they recognize that lidocaine hydrochloride injection is currently on the FDA Drug Shortage list and, as stated in the final guidance for industry Compounded Drug Products That are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act (January 2018), under section 503A They do not consider a drug product to be commercially available if the drug product appears on the FDA Drug Shortage list.
Response: Comment not incorporated. The Expert Committee notes that the uses of compounded drug products extend beyond the circumstances listed by the commenter, including circumstances when the drug product is unavailable, such as when it is on shortage, or used outside of the United States.
Comment Summary #2: A commenter notes the following statement: "Prepare 1% sodium hydroxide solution as follows (see Pharmaceutical Compounding—Nonsterile Preparations <797>)." USP <797> refers to sterile preparations. For accuracy, they recommend revising this reference.
Response: Comment incorporated. Reference changed to "Pharmaceutical Compounding-Sterile Preparations <797>."
Comment Summary #3: For clarity, a commenter suggests clarifying the type of sodium hydroxide (pellets, etc.) that should be used.
Response: Comment not incorporated. The Compounding Expert Committee does not clarify the type of materials for non-active ingredients.
Comment Summary #4: A commenter notes that there is insufficient detail to appropriately create the 1% hydrochloric acid and 1% sodium hydroxide solutions. They recommend including the concentration of both the hydrochloric acid and the sodium hydroxide used.

Response: Comment not incorporated. Concentration and material type information provided in respective USP-NF monographs.
Comment Summary #5: For clarity, a commenter suggests revising the text throughout the monograph to plainly state the type of API used (i.e., revise "Lidocaine hydrochloride monohydrate" to "Lidocaine hydrochloride monohydrate powder").
Response: Comment incorporated.
Comment Summary #6: For clarity, a commenter suggests revising the text as follows: "Adjust the solution to a pH of 5.3 to 6.3 with 1% sodium hydroxide solution **(or 1% hydrochloric acid solution, as needed to achieve the correct pH)**."
Response: Comment incorporated.
Comment Summary #7: To aid the compounder, a commenter recommends including the calculations used to determine the API (Lidocaine hydrochloride monohydrate).
Response: Comment not incorporated. The Compounding Expert Committee considers incorporating example calculations on a case-by-case basis.
Comment Summary #8: The *Assay Acceptance criteria* range is given as 90.0%-110.0%. This is inconsistent with observations of the raw data. A commenter recommends tightening this range to be consistent with the raw data.
Response: Comment not incorporated. The Expert Committee bases its *Acceptance criteria* on existing USP monographs and expert opinion, not solely on laboratory testing criteria.
Comment Summary #9: A commenter recommends including <788> Particulate Matter in Injections in the Specific Tests section.
Response: Comment not incorporated. <788> was performed in the stability study but is not required for Specific Testing.
Comment Summary #10: A commenter notes that the Packaging and Storage section states to "Package in tight, light-resistant, sterile, multiple-dose, Type I glass vials." This is inconsistent with the packaging recommendations in the received data. They recommend revising this section to be consistent with the recommendations in the study.
Response: Comment not incorporated. Stability study data supports multi-dose usage of this preparation.
Comment Summary #11: For consistency with the marketed approved product, Lidocaine Hydrochloride Injection, a commenter recommends revising the Labeling section as follows: "**Label to indicate the product is not for epidural or caudal use**. Label it to state the *Beyond-Use Date*."
Response: Comment incorporated.

Monograph/Section(s): Lidocaine and Tetracaine Compounded Cream
Expert Committee: Compounding Expert Committee
No. of Commenters: 1

Comment Summary #1: A commenter has concerns regarding the safety of the compounded drug product and the communication of the risks to patients due to compounded drug products being exempt from section 502(f)(1) concerning the labeling of drugs with adequate directions for use. They have published two public health advisories regarding the potential hazards of using topical anesthetics.
Response: Comment not incorporated. The Expert Committee considered the risks identified, but the cited product labeling suggestions are not directly applicable to the compounded preparations.
Comment Summary #2: A commenter notes that the proposed monograph title is inconsistent with what was balloted and approved in April 2023 by the USP Nomenclature and Labeling Expert Committee. They recommend revising the title to be consistent with what was approved, as follows: "Lidocaine and Tetracaine Compounded ~~Topical~~ Cream."

Response: Comment incorporated.
Comment Summary #3: For clarity, a commenter suggests revising the text throughout the monograph to plainly state the type of API used. For example, “Lidocaine” and “Tetracaine” could be revised to “Lidocaine **powder**” and “Tetracaine **powder**.” Further, “Add the Lidocaine and Tetracaine into a glass mortar…” could be revised to “Add the Lidocaine **powder** and Tetracaine **powder** into a glass mortar…”
Response: Comment incorporated.
Comment Summary #4: To aid the compounder, a commenter suggests including calculations for the APIs on the anhydrous basis. Providing the calculations used to support the monograph will ensure consistency and protect the public from potential calculation errors. This will help ensure mistakes in dosing are not made.
Response: Comment not incorporated. The Compounding Expert Committee considers incorporating calculation examples on a case-by-case basis.
Comment Summary #5: The formulation states to use Emollient cream, a proprietary based manufactured by PCCA, Houston, Texas, as the vehicle. A commenter has concerns with using proprietary excipients when there is no information about the excipient's identity provided in the monograph. They recommend that the ingredients in the proprietary excipients be provided so that the public understands their identity. It is important that the public has information that will help them understand the risks and benefits associated with the use of the drug product, including any excipients in the drug product.
Response: Comment not incorporated. USP is unable to disclose the requested information but notes that the information can be obtained directly from the manufacturer.
Comment Summary #6: A commenter recommends including USP <61> *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* and <62> *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms* in the Specific Tests section.
Response: Comment not incorporated. Requiring compliance with USP <60>, USP <61>, and USP <62> would not be consistent with the requirements in USP <795> *Pharmaceutical Compounding – Nonsterile Preparations.*
Comment Summary #7: The Packaging and Storage section states that the final preparation should be stored at controlled room temperature but the Beyond-use-Date section states that the preparation can be stored in a refrigerator or at controlled room temperature. A commenter recommends clarifying the storage conditions.
Response: Comment incorporated.

Monograph/Section(s): Locust Bean Gum/Multiple Sections
Expert Committee(s): Complex Excipients
No. of Commenters: 1

Comment Summary #1: The commenter requested to change the wording the Definition to correct errors and avoid the word “natural”:

a. revising the sentence “Locust Bean Gum is a nature-derived ingredient from the seed of the leguminous carob tree (Ceratonia siliqua). These are mainly the ground endoscope of the seeds from Ceratonia siliqua L. (Fam. Fabaceae, also known as Leguminosae).” to “Locust Bean Gum is (the flour) obtained by grinding the endosperms of seeds of the carob tree Ceratonia siliqua L. (Fam. Fabaceae, also known as Leguminosae).”
b. revising the sentences “These high-molecular-weight polysaccharides have a molecular weight range of 50,000 to 3,000,000.” and “Locust Bean Gum has an overall ratio of mannose to lactose in the range of 3.4: 1 to 4.2: 1. The galactomannan content in this

material is NLT 70.0% and NMT 90.0%." to "It consists chiefly of high molecular weight hydrocolloidal polysaccharides having a molecular weight range of 50,000 to 3,000,000. The galactomannan content in this material is NLT 70.0% and NMT 90.0% and the ratio of mannose to galactose is in the range of 3.4:1 to 4.2:1."

Response: Comment incorporated.

Comment Summary #2: The commenter requested to add appropriate controls or reference standards to facilitate an objective determination of whether the samples meet the *Acceptance criteria* in Identification A and C.

Response: Comment not incorporated. However, the expert committee plans to strengthen the Identification tests A and C and propose them in a future revision upon available data and information.

Monograph/Section(s): Magnesium Sulfate Compounded Injection
Expert Committee: Compounding Expert Committee
No. of Commenters: 1

Comment Summary #1: A commenter notes that the monograph for Magnesium Sulfate Compounded Injection, 500 mg/mL may produce a drug product that is essentially a copy of an FDA-approved product. Please see the final guidance for industry Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act (January 2018). FDA recommends using only FDA-approved drug products unless the patient has a specific medical need that cannot be met by the approved drug products.

Response: Comment not incorporated. The Expert Committee notes that the uses of compounded drug products extend beyond the circumstances listed by the commenter, including circumstances when the drug product is unavailable, such as when it is on shortage, or used outside of the United States.

Comment Summary #2: A commenter suggests revising the text to plainly state the type of API used (i.e., "Magnesium sulfate heptahydrate" could be revised to "Magnesium sulfate heptahydrate powder").

Response: Comment incorporated.

Comment Summary #3: To aid the compounder, a commenter recommends including the calculations used to determine the amount of magnesium sulfate heptahydrate powder based on salt conversion and the potency obtained from the API's certificate of analysis.

Response: Comment not incorporated. The Compounding Expert Committee considers incorporating calculation examples on a case-by-case basis.

Comment Summary #4: A commenter has the following minor editorial comments:

- In the preparation of 10% sulfuric acid solution text, they recommend revising the final sentence as follows: "Pass the solution through the filter and into a sterile glass container., discarding the first 2 mL of the filtrate."
- In the preparation of 10% sodium hydroxide solution text, they recommend revising the final sentence as follows: "Pass the solution through the filter and into a sterile glass ~~container, discarding~~ container, discarding the first 2 mL of the filtrate."

In the preparation of Magnesium Sulfate Compounded Injection, 500 mg/mL text, for clarity, they recommend the following revision "Mix well and adjust t**he pH to 5.5 to 7.0** dropwise with either the 10% **(w/v)** sodium hydroxide solution or **the** 10% (w/v) sulfuric acid solution, **as necessary to obtain the correct pH** the ~~pH to 5.5 to 7.0~~."

Response: Comment incorporated.

Comment Summary #5: A commenter notes that the final directive states to “Pass the solution through a sterile filter of about 0.2-µm pore size and into a sterile container.” They recommend clarifying whether the product should be single use or multi dose.
Response: Comment not incorporated. Compounders may utilize the monograph to make either. Its final use will be determined by testing specified in Pharmaceutical Compounding—Nonsterile Preparations ⟨797⟩.
Comment Summary #6: The Packaging and Storage section states that the final preparation should be stored at controlled room temperature but the Beyond-use-Date section states that the preparation can be stored in a refrigerator or at controlled room temperature. A commenter recommends clarifying the storage conditions.
Response: Comment incorporated.
Comment Summary #7: For consistency with the marketed approved product Magnesium Sulfate Injection, 500 mg/mL, a commenter recommends revising the Labeling section as follows: “**Must dilute before IV use.** Label it to indicate the Beyond-Use Date.”
Response: Comment incorporated.

Monograph/Section(s): Maltitol Solution/Specific Tests
Expert Committee(s): Simple Excipients
No. of Commenters: 1

Comment Summary #1: The commenter requested eliminating Tests for Specific Microorganisms <62> as no requirement is contained in the monograph.
Response: Comment not incorporated. Although the comment is valid, this test is not part of the proposed revision. The expert committee will consider a future revision.

Monograph/Section(s): Metronidazole Compounded Oral Suspension
Expert Committee: Compounding Expert Committee
No. of Commenters: 1

Comment Summary #1: A commenter has concerns about developing monographs for preparations that may present safety risks (e.g., Metronidazole Compounded Oral Suspension) given the limited labeling that generally accompanies compounded drug products. FDA-approved metronidazole oral products are labeled with a boxed warning stating that metronidazole has been shown to be carcinogenic in mice and rats and that use should be reserved for the conditions described in the Indications and Usage section; unnecessary use should be avoided. Because of the serious side effects that can occur with the use of this drug, an approved package insert should be available to inform both practitioner and patient of the serious side effects and provide recommendations for appropriate follow up. Such package inserts are not required and will not be available for this compounded drug.
Response: Comment not incorporated. The Expert Committee considered the risks identified, but the cited product labeling suggestions are not directly applicable to the compounded preparations. . .
Comment Summary #2:
The formulations state to use Suspendit, a proprietary suspending agent manufactured by PCCA, Houston, Texas, as the vehicle. A commenter has concerns with using proprietary excipients when there is no information about the excipient's identity provided in the monograph. They recommend that the ingredients in the proprietary excipients be provided so that the public understands their identity. It is important that the public has information that will help them understand the risks and benefits associated with the use of the drug product, including any excipients in the drug product.

Response: Comment not incorporated. USP is unable to disclose the requested information but notes that the information can be obtained directly from the manufacturer.
Comment Summary #3: A commenter notes that the directions are inconsistent with the donated study. They recommend reviewing the study and revising the text to be consistent.
Response: Comment not incorporated. The USP Compounding Expert Committee does not include information regarding vortexing or sonication in other Compounded Preparation Monographs. Additionally, the stability study confirms that the formula meets assay requirements using traditional compounding techniques that do not include vortexing or sonication.
Comment Summary #4: The *Assay Acceptance criteria* range is given as 90.0%-110.0%. This is inconsistent with observations of the raw data. A commenter recommends tightening this range to be consistent with the raw data.
Response: Comment not incorporated. The Expert Committee bases its acceptance criteria on existing USP monographs and expert opinion, not solely on laboratory testing criteria.
Comment Summary #5: A commenter notes that the pH acceptance criteria are given as 4.6-5.6. This is inconsistent with observations of the raw data. They recommend tightening this range to be consistent with the raw data.
Response: Comment not incorporated. pH range is supported by data from the stability study.
Comment Summary #6: For accuracy, a commenter recommends revising the Appearance section as follows: "~~Pale to light amber~~ Bright yellow suspension"
Response: Comment Incorporated.

Monograph/Section(s): Morphine Sulfate Compounded Suppositories
Expert Committee: Compounding Expert Committee
No. of Commenters: 1

Comment Summary #1: A commenter has concerns about developing monographs for preparations that may present particular safety risks (e.g., Morphine Sulfate Compounded Suppositories) given the limited labeling that generally accompanies compounded drug products. FDA-approved morphine sulfate products are labeled with a boxed warning regarding the risk of addiction, abuse, and misuse; life threatening respiratory depression; neonatal opioid withdrawal syndrome, and risks from concomitant use with benzodiazepines or other CNS depressants.1 Because of the serious side effects that can occur with the use of this drug, an approved package insert should be available to inform both practitioner and patient of the serious side effects and provide recommendations for appropriate follow up. Such package inserts are not required and will not be available for this compounded drug.
Response: Comment not incorporated. The Expert Committee considered the risks identified, but the cited product labeling suggestions are not directly applicable to the compounded preparations.
Comment Summary #2: For clarity, a commenter suggests revising the text throughout the monograph to plainly state the type of API used. For example, "Morphine sulfate pentahydrate" could be revised to "Morphine sulfate pentahydrate powder." Further, "Thoroughly mix the Morphine sulfate pentahydrate and Silica gel…" could be revised to "Thoroughly mix the Morphine sulfate pentahydrate powder and Silica gel..."
Response: Comment incorporated.
Comment Summary #3: A commenter recommends providing the strength of the final Morphine sulfate suppository in the formula.
Response: Comment incorporated.
Comment Summary #4: To aid the compounder, a commenter recommends including text in the directions to describe the following: the temperature used to melt the base, the approximate melt time for the base, clear instructions for use of the mold, and details regarding the type of

wrap (and/or container that should be used. Further, the commenter recommends clarifying whether multiple suppositories can be placed unwrapped in one container.
Response: Comment partially incorporated. Language added to melt base using temperature and melt time specified by Vehicle manufacturer.
Comment Summary #5: A commenter recommends including a Specific Tests section, with requirements/ *Acceptance criteria* for Appearance and pH that are consistent with the raw data.
Response: Comment not incorporated.
Comment Summary #6: A commenter notes it is unclear how the Beyond-Use-Date was determined. They recommend that the raw data be reviewed for applicability.
Response: Not incorporated. The data has already been reviewed and approved by the Compounding Expert Committee.

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

Comment summary #1: The commenter requested a note in the test for *Organic Impurities* for Nadolol related compound A indicating "if present" or "this is formulation specific impurity" to help justify their approved specification.
Response: Comment not incorporated. The Expert Committee determined that a note was not needed.

Monograph/Section(s): Naltrexone Hydrochloride Compounded Oral Suspension
Expert Committee: Compounding Expert Committee
No. of Commenters: 1

Comment Summary #1: For clarity, a commenter suggests revising the text throughout the monograph to plainly state the type of API used. For example, "Naltrexone Hydrochloride" could be revised to "Naltrexone Hydrochloride powder." Further, "Place Naltrexone Hydrochloride and Steviol glycosides 95% in a mortar…" could be revised to "Place Naltrexone Hydrochloride powder and Steviol glycosides 95% in a mortar…"
Response: Comment Incorporated.
Comment Summary #2: The formulations state to use SuspendIt, a proprietary suspending agent manufactured by PCCA, Houston, Texas, as the vehicle. A commenter has concerns with using proprietary excipients when there is no information about the excipient's identity provided in the monograph. They recommend that the ingredients in the proprietary excipients be provided so that the public understands their identity. It is important that the public has the information that will help them understand the risks and benefits associated with the use of a drug product, including any excipients in the drug product.
Response: Comment not incorporated. USP is unable to disclose the requested information but notes that the information can be obtained directly from the manufacturer.
Comment Summary #3: For clarity, a commenter recommends revising the directions to include exact volumes for each addition (i.e., revise "Add approximately 2% of the final volume…" should be revised to "Add approximately 2% **(2 mL)** of the final volume…" and "Add approximately 30% of the final volume…" should be revised to "Add approximately 30% **(30 mL)** of the final volume…" etc.).
Response: Comment not incorporated. The Compounding Expert Committee uses percentages to allow for scaling of formulation volume, as allowed by USP General Notices.
Comment Summary #4: A commenter notes it is unclear how the proposed assay *Acceptance criteria* were determined. They recommend that the Expert Committee review the raw data and discuss the origin of these criteria to clarify and determine consistency.

Response: Comment not incorporated. The Expert Committee bases its *Acceptance criteria* on existing USP monographs and expert opinion, not solely on laboratory testing criteria.
Comment Summary #5: A commenter notes that the pH *Acceptance criteria* are given as 4.5-5.5. FDA liaisons to the Compounding Expert Committee note that his is inconsistent with our observations of the raw data. They recommend tightening this range to be consistent with the raw data.
Response: Not incorporated. The pH range is consistent with the Compounding Expert Committee's interpretation of the stability data.
Comment Summary #6: A commenter recommends including USP <61> Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests and <62> Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms in the Specific Tests section.
Response: Comment not incorporated. Requiring compliance with USP <60>, USP <61>, and USP <62> would not be consistent with the requirements in USP <795> Pharmaceutical Compounding – Nonsterile Preparations.

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

Comment Summary #1: A commenter indicates the *Assay Acceptance criteria* range is given as 90.0%-110.0% and is inconsistent with observations of the raw data. They recommend tightening this range to be consistent with the raw data.
Response: Comment not incorporated. The *Acceptance criteria* range in the stability study raw data document is listed as "90.0 – 110.0%."
Comment Summary #2: A commenter indicates the pH acceptance criteria range is given as 4.4-5.4 and is inconsistent with observations of the raw data.
Response: Comment not incorporated. The pH *Acceptance criteria* are based on an average of the data and a suitable window for preparation. There were no pH adjustments in the new formulations.
Comment Summary #3: A commenter indicates it is unclear whether the sterility test showed that using membrane filtration for this compounded product was comparable or better than USP <71>**.**
Response: Comment not incorporated. The preparation met the requirements of <71> Sterility Tests as seen in sterility testing raw data.
Comment Summary #4: A commenter indicates that a limit of NMT 0.4 USP Endotoxin Units/mg of phenol is proposed. It is unclear how this limit was determined.
Response: Comment not incorporated. The endotoxin limit may be calculated using criteria specified in <85> Bacterial Endotoxins Test.
Comment Summary #5: A commenter recommends stating that the product should be labeled to indicate the route of administration in the Labeling section**.**
Response: Comment incorporated. Labeling states to indicate the Beyond-Use date and to state not for IV use.

Monograph/Section(s): Polyethylene Glycol 60 Hydrogenated Castor Oil/Chemical Information
Expert Committee(s): Complex Excipients
No. of Commenters: 0

EC Initiated Change #1: Remove CAS# 61788-85-0 because it is broadly used for Polyethylene glycol hydrogenated castor oil products of varied polymer chain lengths, not specific for this monograph.

Monograph/Section(s): Sodium Phosphates Compounded Injection
Expert Committee: Compounding Expert Committee
No. of Commenters: 1

Comment Summary #1: A commenter notes that the monograph for Sodium Phosphates Injection may produce a drug product that is essentially a copy of an FDA-approved product, as described in the final guidance for industry Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act (January 2018) (the 503A Copies Guidance). However, they recognize that sodium phosphates injection is currently on the FDA Drug Shortage list and, as stated in the 503A Copies Guidance, under section 503A they do not consider a drug product to be commercially available if the drug product appears on the FDA Drug Shortage.
Response: Comment not incorporated. The Expert Committee notes that the uses of compounded drug products extend beyond the circumstances listed by the commenter, including circumstances when the drug product is unavailable, such as when it is on shortage, or used outside of the United States.
Comment Summary #2: A commenter suggests including calculations for conversion of monohydrate forms to anhydrous powder if the anhydrous powder is used. Providing the calculations used to support the monograph will ensure consistency and protect the public from potential calculation errors.
Response: Comment not incorporated. Monograph already states, "If anhydrous is not used, waters of hydration should be included in calculating the appropriate amount of sodium phosphates."
Comment Summary #3: A commenter notes that the directions state to "sterilize in an autoclave" as the final step. For clarity, they recommend including the specific autoclave conditions (e.g., 121º for 20m @ 15psi) in the text.
Response: Comment partially incorporated. The language was revised to match the Compounding Expert Committee's decision for a previous monograph, "... and ~~sterilize in an~~ autoclave to achieve terminal sterilization (see *Steam Sterilization of Aqueous Liquids* <1229.2>)."
Comment Summary #4: A commenter notes that the monograph indicates the product should be stored in single-dose glass containers.
Response: Comment incorporated. The monograph continues to state to, "package in single-dose glass containers."
Comment Summary #5: A commenter notes it is unclear how the *Acceptance criteria* for pH were determined. They recommend reviewing the scientific studies upon which this range is based.
Response: Comment not incorporated. The pH *Acceptance criteria* are based on an average of the data and a suitable window for preparation.
Comment Summary #6: A commenter recommends revising the Appearance section as follows: "Clear, colorless solution with no particulates." Sterile products should be free from particulates.
Response: Comment incorporated.
Comment Summary #7: A commenter recommends including testing for USP <51> Antimicrobial Effectiveness Testing, similar to other compounded monographs.
Response: Comment not incorporated. <51> *Antimicrobial Effectiveness Testing* is not required for single-dose CSPs according to <797>.

Monograph/Section(s): Sorafenib Tosylate/Organic Impurities
Expert Committee: Small Molecules 3
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 indicated that the RRF for Di(chlorotrifluoromethyl)phenylurea appears to be a typo and requested USP to evaluate and correct.
Response: Comment incorporated. The RRF values for Di(chlorotrifluoromethyl)phenylurea and Sorafenib diarylbiuret analog were switched in the *PF* proposal. The RRF values are corrected to 0.52 for Di(chlorotrifluoromethyl)pheny and 2.5 for Sorafenib diarylbiuret analog consistent with the validation data.
Comment summary #3: The commenter recommended retaining the disregard information for Tolenesulphonic acid (RRT 0.07). i.e. "Disregard toluenesulphonic acid at a relative retention time of 0.07. [NOTE—Toluenesulphonic acid is the counter ion of sorafenib and is present in the chromatogram of the Sample solution.]"
Response: Comment not incorporated. Tolenesulphonic acid (RRT 0.07) is only listed in the Relative retention time, Table 2, under System suitability including the note "The relative retention times in *Table 2* are provided as information that could aid in peak assignment". For additional information, refer to the frequently-asked-questions section of the USP.ORG website under the Organic Impurities topic: https://www.usp.org/frequently-asked-questions/organic-impurities

Monograph/Section(s): Terbinafine Compounded Oral Suspension
Expert Committee: Compounding Expert Committee
No. of Commenters: 1

Comment Summary #1: Commenter notes that the monograph states to use Lamisil 250 mg tablets, Sandoz, Titusville, NJ. This manufacturer does not appear in the Orange Book and thus the tablets may not be available in the US market. There is an entry for Lamisil 250 mg from Novartis Pharmaceuticals Corporation, but this entry is currently listed in the discontinued section of the Orange Book. It is therefore unclear whether Sandoz Pharmaceuticals is marketing another company's drug product or if this drug product is only approved outside of the United States (US). It is also unclear whether compounders will be able to obtain this necessary drug product to create the oral suspension.
Response: Comment not incorporated. The Compounding Expert Committee is currently working on a document that addresses the substitution of unavailable drug product components in Compounded Preparation Monographs.
Comment summary #2: Commenter states that the study upon which this monograph is based tested the product in Ora-Sweet and OraPlus; it does not reference Ora-Blend as a vehicle used. As such, the use of Ora-Blend for this product is unclear. If Ora-Blend is to be included in the formulation, a commenter recommends providing details on the vehicle, including stability and beyond-use-dating for the Expert Committee's review.
Response: Comment not incorporated. The manufacturer of Ora-Blend has confirmed it is equivalent to a 1:1 mixture of Ora-Plus and Ora-Sweet.

Comment summary #3: A commenter recommends including USP <61> Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests and <62> Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms in the Specific Tests section
Response: Comment not incorporated. Requiring compliance with USP <60>, USP <61>, and USP <62> would not be consistent with the requirements in USP <795> Pharmaceutical Compounding – Nonsterile Preparations.
Comment summary #4: A commenter recommends including requirements for Appearance in the Specific Tests section
Response: Comment not incorporated. Appearance was not noted as part of the stability study the monograph is based upon.

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

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 in the test for *Organic Impurities,* difficulty in meeting the %RSD requirement for Leflunomide Related compound A indicating results greater than 5.0%. The commenter recommends USP to adopt their in-house procedure for the content of Leflunomide Related compound A.
Response: Comment partially incorporated. The Expert Committee determined based on supporting data to widen the *System Suitability* %RSD requirement for Leflunomide Related compound A from NMT 5.0% to NMT 10.0%.
Comment summary #3: The commenter indicated that they are in compliance with the *PF* 48(5) proposal.
Response: Comment acknowledged.
Expert Committee-initiated Change #1: In the *Assay*, under Sample solution, the article is revised to be capitalized, i.e., Teriflunomide.

Monograph/Section(s): Teriflunomide Tablets/Organic Impurities
Expert Committee: Small Molecules 4
No. of Commenters: 1

Comment summary #1: The commenter indicated that acceptance criteria for "Teriflunomide Related Compound B" and "Any unspecified degradation product" 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 *Teriflunomide Related Compound B* is widened to NMT 0.5% and the acceptance criteria for *Any unspecified degradation prod*uct is widened to NMT 0.2%. Additionally, the acceptance criteria for *Total degradation products* is widened 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.
Expert Committee-initiated Change #1: The *System Suitability* %RSD requirement for *Leflunomide Related compound A* is widened from NMT 5.0% to NMT 10.0%.

Monograph/Section(s): Tobramycin/Multiple Sections
Expert Committee: Small Molecules 1
No. of Commenters: 4

Comment summary #1: The commenter indicated that for the tests for *Identification B*, *Assay* and *Organic Impurities* the CAD method in the *PF* Tobramycin monograph has four interference peaks in the blank chromatogram, and it is unclear if this is due to the instrument or reagents. The peaks were not present in a previous CAD method used in their laboratory.
Response: Comment not incorporated. Based on these and other comments received across the Tobramycin monograph family proposed in *PF* 49(1), the Expert Committee determined that the proposed changes to *Identification B*, *Assay* and *Organic Impurities* should be cancelled, and the currently official tests are retained.
Comment summary #2: The commenter indicated the S/N for standard solution A in the *Organic Impurities* method is sometimes not sufficient, and it is difficult to reach the required sensitivity during experiments.
Response: Comment not incorporated. Based on these and other comments received across the Tobramycin monograph family proposed in *PF* 49(1), the Expert Committee determined that the proposed changes to *Identification B*, *Assay* and *Organic Impurities* should be cancelled, and the currently official tests are retained.
Comment summary #3: The commenter suggested in the test for *Organic Impurities,* using a direct external standard method instead of a linearity standards curve series for calculation if possible
Response: Comment not incorporated. Based on these and other comments received across the Tobramycin monograph family proposed in *PF* 49(1), the Expert Committee determined that the proposed changes to *Identification B*, *Assay* and *Organic Impurities* should be cancelled, and the currently official tests are retained.
Comment summary #4: Commenters indicated that the specifications in their approvals are outside the range proposal in the monograph.
Response: Comment not incorporated. Based on these and other comments received across the Tobramycin monograph family proposed in *PF* 49(1), the Expert Committee determined that the proposed changes to *Identification B*, *Assay* and *Organic Impurities* should be cancelled, and the currently official tests are retained.
Comment summary #5: The commenter requested that USP extend comments deadline by at least 6 months and to move target official date to at least 1 year beyond normal target timeline of 01 August 2024 to allow sufficient time for CAD instrument purchases and identifying contractors and avoid potential compliance issues.
Response: Comment not incorporated. Based on these and other comments received across the Tobramycin monograph family proposed in *PF* 49(1), the Expert Committee determined that the proposed changes to *Identification B*, *Assay* and *Organic Impurities* should be cancelled, and the currently official tests are retained.
Comment summary #6: The commenter requested for the test for *Organic Impurities,* changes to the method conditions such as the test sample solution concentration because the 0.1% limit of quantification of the proposed method for impurities is not adequate to control impurities to the reporting threshold of 0.05 % required by ICH Q3A guidance.
Response: Comment not incorporated. Based on these and other comments received across the Tobramycin monograph family proposed in *PF* 49(1), the Expert Committee determined that

the proposed changes to *Identification B*, *Assay* and *Organic Impurities* should be cancelled, and the currently official tests are retained.
Comment summary #7: The commenter requested changes to method conditions for the test for *Organic Impurities* to achieve robust separation of all impurities.
Response: Comment not incorporated. Based on these and other comments received across the Tobramycin monograph family proposed in *PF* 49(1), the Expert Committee determined that the proposed changes to *Identification B*, *Assay* and *Organic Impurities* should be cancelled, and the currently official tests are retained.
Comment summary #8: The commenter requested the proposed linear calibration function for the *Organic impurities* and *Assay* be replaced with a log-log function.
Response: Comment not incorporated. Based on these and other comments received across the Tobramycin monograph family proposed in *PF* 49(1), the Expert Committee determined that the proposed changes to *Identification B*, *Assay* and *Organic Impurities* should be cancelled, and the currently official tests are retained.
Comment summary #9: The Commenter indicated the method is not suitable for *Assay* and *Organic Impurity* determination from Tobramycin API because of the high uncertainty (high RSD) in Assay and low signal to noise (lower than 10) in Organic Impurities.
Response: Comment not incorporated. Based on these and other comments received across the Tobramycin monograph family proposed in *PF* 49(1), the Expert Committee determined that the proposed changes to *Identification B*, *Assay* and *Organic Impurities* should be cancelled, and the currently official tests are retained.

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

Comment summary #1: The commenter indicated that in the test for *Limit of Tolnaftate Related Compound D*, the limit for Tolnaftate Related Compound D may not be appropriate for a public standard. They recommend adding a footnote stating that this impurity possesses a structural alert for mutagenicity and a different limit may be appropriate based on ICH M7 guidelines.
Response: Comment incorporated. The test for *Limit of Tolnaftate Related Compound D* is removed. A new test may be proposed in the future once a more robust strategy regarding the potential mutagenicity of Tolnaftate related compound D *(N*,3-Dimethylaniline) is developed.
Comment summary #2: The commenter recommended removing the “reporting threshold” in the test for *Organic Impurities* as it will vary based on product-specific factors.
Response: Comment not incorporated. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.
Expert Committee-initiated Change #1: A note is added to the test for *Organic Impurities* as follows: [Note —This method is not intended for the control of tolnaftate related compound D (*N*,3-Dimethylaniline).]