



Commentary

USP–NF 2023 Issue 1

November 1, 2022

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

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

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

General Chapter

<797> Pharmaceutical Compounding – Sterile Preparations

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General Chapter/Section(s): <797> Pharmaceutical Compounding – Sterile Preparations
Expert Committee: Compounding
No. of Commenters: 328

General Comments

Expert Committee-Initiated Change #1: All instances of “compounding space” were changed to “compounding area”.

Expert Committee-Initiated Change #2: Instances of “alcohol-based hand sanitizer” were revised to “alcohol-based hand rub”.

Expert Committee-Initiated Change #3: All instances of “pass-through” were revised to “pass-through chamber”.

Expert Committee-Initiated Change #4: The order when referring to steam, dry heat, or irradiation was reorganized to reflect the order in which the methods of terminal sterilization are recommended.

Comment Summary #1: The commenter recommended including a table of contents as part of the final chapter.

Response: Comment partially incorporated. While a table of contents cannot be added as a part of the chapter, per *USP Style Guide*, a table of contents is included as a part of the *USP–NF* platform.

Comment Summary #2: Commenters indicated the chapter revisions are not necessary.

Response: Comment not incorporated. The chapter was revised to improve clarity and to respond to stakeholder input. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #3: Commenters stated that the revisions limit access to compounded preparations and recommended increasing inspections instead of revising the chapter.

Response: Comment not incorporated. The chapter was revised to improve clarity and to respond to stakeholder input. The standards are based on a combination of available evidence, expertise of the Compounding Expert Committee members, and input from stakeholders. The revisions take into consideration stability and sterility data, the compounding environment, and the financial impact on compounders and patients. The beyond-use dates (BUDs) for Category 1 and Category 2 CSPs in *Table 10* and *Table 11*, respectively, should allow facilities to prepare adequate CSPs for patient needs. The BUDs are intended to minimize the risk of microbial growth in the event of inadvertent contamination, and to allow for patient access to critical therapies.

Comment Summary #4: Commenters indicated there is a lack of scientific evidence provided to support revisions to the standard.

Response: Comment not incorporated. The chapter was revised to improve clarity and to respond to stakeholder input, and the standards are based on a combination of available evidence, expertise of the Compounding Expert Committee (EC), and input from stakeholders. Supplementary materials were developed and are available on the USP website to aid stakeholders in understanding the rationale and evidence for the revisions. The scientific evidence was reviewed at multiple open EC meetings and stakeholder engagement events.

Comment Summary #5: Commenters recommended that the EC consider the financial impact of the new requirements on organizations and patients, particularly in rural and underserved areas.

Response: Comment partially incorporated. BUDs and other requirements in the chapter are based on several considerations, including stability and sterility data, the compounding

environment, and the financial impact on compounders and patients. The intent of the chapter is to help ensure quality compounded preparations regardless of where the CSP (compounded sterile preparation) is compounded.

Comment Summary #6: The commenter recommended that USP work with other organizations to ensure that key terms in the chapter conform to standardized agreed-upon definitions.

Response: Comment not incorporated. The chapter was developed after significant stakeholder input and engagement. The terms in the chapter are defined in the glossary and are consistent with industry terms as they apply to the scope of the chapter.

Comment Summary #7: The commenter suggested that USP include other stakeholders in building quality within compounding, citing the example of providing stricter packaging standards.

Response: Comment not incorporated. The requirements in this chapter were developed based on stakeholder input, available evidence, and the expertise of the EC. This chapter describes the minimum standards to be followed when preparing CSPs and the chapter does not prohibit compounders from implementing stricter requirements than those in the chapter.

Comment Summary #8: The commenter suggested that clear procedures in tables be added to ease compliance.

Response: Comment incorporated. Several tables were added and modified for added clarity.

Comment Summary #9: Several commenters requested a delay in implementation to give institutions sufficient time to make necessary changes.

Response: Comment incorporated. The Expert Committee decided to delay implementation by 1 year to November 1, 2023.

Comment Summary #10: Commenter noted that the chapter should not be given a 3-digit number, should be informational only, and that the chapter is not enforceable unless adopted by regulatory bodies.

Response: Comment not incorporated. General Chapter <797> has been numbered as a 3-digit number since it was developed in 2004. The chapter additionally states that USP has no role in enforcement. Further, pursuant to *General Notices 2.30 Legal Recognition*, assuring compliance with USP standards is the responsibility of regulatory bodies. Accreditation or credentialing organizations may adopt and enforce USP standards.

Comment Summary #11: The commenter requested that <800> be opened for review and modified as it is referenced in the revised <797>.

Response: Comment partially incorporated: References in <800> to <797> will be updated through USP's compendial editorial processes. Also, the CMP EC will consider additional revisions to <800> in the future through USP's normal standard setting process.

Comment Summary #12: Several commenters suggested that physician offices be granted an exemption from the chapter. Commenters noted that numerous preparations are compounded in physician offices (e.g., buffered lidocaine, anesthetics, reconstituted conventionally manufactured products) without adverse events.

Response: Comment not incorporated. The Chapter was revised to clarify that administration of medication is outside the scope of the chapter (*1.2 Administration*). Preparation of compounded sterile preparations (CSPs) for direct and immediate administration to a patient is not subject to the requirements for Category 1 and Category 2 if all of the conditions in *1.3 Immediate Use CSPs* are met. Additionally, preparation per approved labeling is out of the scope of the chapter, as described in *1.4 Preparation Per Approved Labeling*.

Comment Summary #13: Commenter recommended that the chapter should provide an exemption to ensure their ability to prepare buffered or diluted lidocaine and use it for 12 hours and requested USP staff meet to confirm the process of developing a monograph for buffered lidocaine and steps for states to adopt the monograph.

Response: Comment partially incorporated. The chapter was revised to clarify that administration of medication is outside the scope of the chapter (*1.2 Administration*). Preparation of CSPs for direct and immediate administration to a patient is not subject to the requirements for Category 1 and Category 2 if all of the conditions in *1.3 Immediate Use CSPs* are met. Immediate use CSPs must be administered within 4 hours following the start of preparation. The Expert Committee is working to develop a compounded preparation monograph for buffered lidocaine with epinephrine; however, USP has no role in enforcement. Ensuring compliance with the requirements of the chapter or monograph is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #14: A commenter requested that veterinary practitioners compounding within their scope be exempted from the requirements of <797> until a veterinary specific chapter is developed.

Response: Comment not incorporated. The chapter does contain provisions for administration (see *1.2 Administration*), compounding for immediate use (*1.3 Immediate Use CSPs*), and preparation per approved labeling (*1.4 Preparation Per Approved Labeling*). The requirements of this chapter are equally relevant to CSPs for human and animal patients and have been so since the chapter was first developed in 2004. The Compounding Expert Committee is continuing to engage with veterinarians and veterinary practice groups to develop resources and address their unique needs. USP has no role in the enforcement of compounding chapters. Pursuant to *General Notices 2.30 Legal Recognition*, ensuring compliance with USP standards is the responsibility of regulatory bodies. Regulators may choose to enforce the requirements of <797> with respect to veterinarians compounding for animal patients.

Comment Summary #15: Commenter requested clarification regarding areas of regulatory conflict as it applies to veterinarians compounding for animal patients and requested USP rectify and avoid such conflicts.

Response: Comment not incorporated. The Compounding Expert Committee is continuing engagement with veterinarians and veterinary practice groups to develop resources and address their unique needs. USP has no role in the enforcement of compounding chapters. Pursuant to *General Notices 2.30 Legal Recognition*, ensuring compliance with USP standards is the responsibility of regulatory bodies. Regulators may choose to enforce the requirements of <797> with respect to veterinarians compounding for animal patients.

Comment Summary #16: The commenter requested that the chapter be more prescriptive with certain technology, for example the use of technology for documentation.

Response: Not incorporated. The chapter describes the minimum standards to be followed when preparing CSPs and the chapter does not prohibit compounders from going beyond the requirements in the chapter.

Comment Summary #17: The commenter requested that there be a section on repackaging since it is considered compounding.

Response: Comment not incorporated. Repackaging is compounding and must follow all of the requirements in the chapter and therefore does not require a separate section.

Comment Summary #18: The commenter recommended including visual aids from the previous chapter.

Response: Comment not incorporated. Images in previous chapter contained information more specific than the minimum standards described in the chapter and led to erroneous assumptions that those pictured were the only acceptable facility designs.

Comment Summary #19: The commenter suggested adding a section to this chapter specifically for compounding from nonsterile starting ingredients and prohibiting Category 1 CSPs from starting with nonsterile ingredients.

Response: Comment not incorporated. Category 1, 2, and 3 CSPs are distinguished primarily based on the BUD and the environment in which they are compounded. In some critical

situations, Category 1 CSPs may need to be prepared from one or more nonsterile starting ingredient(s). This framework provides a risk-based approach with shorter BUDs for Category 1 CSPs in *Table 12* and longer BUDs for Category 2 CSPs in *Table 13* to help ensure patient access to needed therapies.

1. Introduction and Scope

Expert Committee-Initiated Change #1: Subsections in *Section 1.1* were numbered, and the listed practices were alphabetized.

Expert Committee-Initiated Change #2: A statement was added to *1.4 Preparation Per Approved Labeling* to clarify that <800> has additional recommendation for the preparations of hazardous drugs.

Expert Committee-Initiated Change #3: Text was revised to clarify that handling of blood components and other biological materials must additionally comply with laws and regulations of the applicable regulatory jurisdiction.

Expert Committee-Initiated Change #4: Text was revised for immediate-use CSPs to state that any unused starting component from a single-dose container must be discarded after preparation is complete. (removed “for the individual patient” after “preparation”)

Expert Committee-Initiated Change #5: The word “exact” was removed from the following statement for immediate-use CSPs “unless directly administered by the person who prepared it or administration is witnessed by the preparer, the CSP must be labeled with the names and amounts of all active ingredients, the name or initials of the person who prepared the preparation, and the exact 4-h time period within which administration must begin.”

Comment Summary #20: The commenter indicated more emphasis should be placed on final product verification to ensure CSPs are prepared correctly based on the formulation records.

Response: Comment not incorporated. This is out of scope of the minimum standards of the chapter. Each compounding facility must develop a written training program that describes the required training, the frequency of training, and the process for evaluating the performance of individuals who compound, have direct oversight of compounding personnel, perform in-process checks, final verification, and dispensing of CSPs.

Comment Summary #21: Commenters recommended specifying that the spiking of IV bags is outside the scope of the chapter.

Response: Comment not incorporated. Spiking an IV bag of a conventionally manufactured sterile product without any further manipulation is considered administration rather than compounding. The chapter does contain provisions for administration (see *1.2 Administration*), compounding for immediate use (*1.3 Immediate Use CSPs*), and preparation per approved labeling (*1.4 Preparation Per Approved Labeling*). This information is more specific than the minimum standards described in the chapter, and the EC will consider addressing this topic in supplementary materials.

Comment Summary #22: Commenters indicated it is unclear if reconstituting is compounding or if it falls under *1.4 Preparation Per Approved Labeling*.

Response: Comment not incorporated. The chapter states that reconstituting per approved labeling is not compounding. Preparing a conventionally manufactured sterile product in accordance with the directions in the manufacturer’s approved labeling is out of scope of the chapter if the product is prepared as a single dose for an individual patient, and the approved labeling includes information for the diluent, the resultant strength, the container closure system, and storage time.

Comment Summary #23: The commenter recommended expanding the list of personnel and settings to whom the chapter describes the minimum requirements for preparing CSPs.

Response: Comment not incorporated. The chapter states that the chapter describes the minimum requirements that apply to all persons who prepare CSPs and all places where CSPs are prepared, and states that this includes but is not limited to some examples of personnel and settings affected. This is a topic that may be described in the facility's SOPs.

Comment Summary #24: The commenter recommended clarifying the conditions in which the CSP categories may be compounded when first describing the CSP categories in *Section 1.5*.

Response: Comment not incorporated. Requirements for Category 1, Category 2, and Category 3 CSPs are included throughout the chapter. The chapter states in the introduction and scope that Category 1, Category 2, and Category 3 CSPs are distinguished primarily based on the states of environmental control under which they are compounded, the probability for microbial growth during the time they will be stored, and the time period within which they must be used.

Comment Summary #25: Commenters recommended clarifying that the chapter is not applicable for manufacturing conventionally manufactured products, compounding by manufacturers, and in 503B facilities.

Response: Comment not incorporated. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction. Manufacturers must comply with FDA's current good manufacturing practices (CGMP) and/or laws and regulations of the applicable regulatory jurisdiction. Additional clarification on the application of standards in this chapter is provided in the *USP General Notices*.

Comment Summary #26: Commenters recommended stating that standard anesthesia preparation is considered administration.

Response: Comment not incorporated. The chapter states that administration, for the purposes of the chapter, is the direct application of a sterile product or preparation to a single patient by injecting, infusing, or otherwise providing a sterile product or preparation in its final form, and administration is specified in *1.2 Administration* as being out of scope of the chapter. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #27: The commenter recommended addressing in the chapter the use of CSP workflow automation.

Response: Comment not incorporated. The chapter states that the use of technologies, techniques, materials, and procedures other than those described in the chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose (e.g., *Validation of Alternative Microbiological Methods* (1223) and *Validation of Compendial Procedures* (1225)).

Comment Summary #28: The commenter recommended addressing in the chapter the use of IV automation.

Response: Comment not incorporated. The chapter states that the use of technologies, techniques, materials, and procedures other than those described in the chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose (e.g., *Validation of Alternative Microbiological Methods* (1223) and *Validation of Compendial Procedures* (1225)).

Comment Summary #29: The commenter recommended clarifying use of drug vial optimization and deferring to the manufacturer storage and stability information for CSTDs (closed system transfer devices).

Response: Comment partially incorporated. The text was revised to state that the use of technologies, techniques, materials, and procedures other than those described in the chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose (e.g., *Validation of Alternative Microbiological Methods* (1223) and *Validation of Compendial Procedures* (1225)).

Comment Summary #30: The commenter recommended stating that alternative technologies must perform reproducibly to demonstrate they are fit for use and perform as intended.

Response: Comment incorporated. The text was revised to state that the use of technologies, techniques, materials, and procedures other than those described in the chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose (e.g., *Validation of Alternative Microbiological Methods* (1223) and *Validation of Compendial Procedures* (1225)).

Comment Summary #31: The commenter requested the creation of a sterile compounding automation chapter to provide information and standards for use of IV automation.

Response: Comment partially incorporated. The Compounding Expert Committee will consider development of additional resources to support understanding of the standards. The Compounding Expert Committee will consider the development of a standard related to automation.

Comment Summary #32: Several commenters suggested that the chapter allow sterile compounding technologies (automated technologies as well as specific procedures such as the use of CSTDs) and remove the text that alternative technologies, techniques, and materials may not be used to modify the requirements in the chapter.

Response: Comment partially incorporated. Alternate technologies, techniques, materials, and procedures other than those described in chapter are not prohibited as long as they are noninferior to those described in the chapter and are validated for the intended purpose (e.g., *Validation of Alternative Microbiological Methods* (1223) and *Validation of Compendial Procedures* (1225)).

Comment Summary #33: The commenter indicated that, “The alternative technologies, techniques, or materials must not be used to modify requirements outlined in this chapter (e.g., extending beyond-use dates, the amount of time a single-dose or multiple-dose container may be used, compounding in alternative environments)”, stifles innovation as there are examples where exceptions should be made for extending BUDs, such as CSTDs being able to prevent contamination from infiltrating the vial it is attached to.

Response: Comment partially incorporated. The text was revised to state that the use of technologies, techniques, materials, and procedures other than those described in the chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose (e.g., *Validation of Alternative Microbiological Methods* (1223) and *Validation of Compendial Procedures* (1225)).

Comment Summary #34: Commenters recommended expanding the definition of blood components regarding the chapter statement that handling of blood components must additionally comply with laws and regulations of the applicable regulatory jurisdiction.

Response: Comment not incorporated. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction. The chapter defines blood components as any therapeutic constituent of blood separated by physical or mechanical means (e.g., white cells, red cells, platelets, plasma, serum). It is not intended to include plasma-derived products (e.g., albumin, coagulation factors, immunoglobulins) manufactured under an approved BLA or equivalent.

Comment Summary #35: Commenters recommended clarifying the definition of “other biological materials” regarding the chapter requirements for blood-derived and other biological materials.

Response: Comment not incorporated. The chapter provides an example of other biological materials of autologous serum. Other biological materials are those that are not blood-derived but are derived directly from a patient.

Comment Summary #36: Commenters recommended when compounding activities require the manipulation of a patient’s blood-derived or other biological material, that the manipulations be clearly separated or thoroughly cleaned and disinfected.

Response: Comment not incorporated. To avoid cross-contamination, the manipulations must be clearly separated from other compounding activities and equipment used in CSP preparation activities, and they must be controlled by specific SOPs. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #37: The commenter indicated that repackaging of a sterile product or preparation from its original container into another container should be exempt from adherence to the requirements of the chapter.

Response: Comment not incorporated. Repackaging of a sterile product or preparation from its original container into another container must be performed in accordance with the requirements in the chapter to ensure the product or preparation remains sterile.

Comment Summary #38: The commenter recommended referring to API in bulk form as “bulk drug substance”.

Response: Comment partially incorporated. The use of “API”, “active ingredients”, “drug product, and “bulk drug substance” were reviewed and corrected throughout. A statement was added to the definition of API to state that API is also referred to as “bulk drug substance”, and that a conventionally manufactured drug product is not an API but is typically manufactured from an API(s).

Comment Summary #39: The commenter indicated support for the statement in the chapter that compounding of radiopharmaceuticals is not required to meet the standards in the chapter and is subject to the requirements in *Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging <825>*.

Response: Comment incorporated. Language was maintained to indicate that the compounding of radiopharmaceuticals is not required to meet the standards of the chapter as they are subject to the requirements in <825>.

Comment Summary #40: The commenter indicated support for the statement in the chapter that the handling of sterile hazardous drugs (HDs) must additionally comply with <800>.

Response: Comment incorporated. Language was maintained to indicate that the handling of sterile hazardous drugs must comply with <800>.

Comment Summary #41: The commenter recommended clarifying the definition of a compounding facility.

Response: Comment not incorporated. The chapter describes the minimum requirements that apply to all persons who prepare CSPs and all places where CSPs are prepared. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #42: The commenter recommended including brand names for proprietary bag and vial systems.

Response: Comment not incorporated. All specific brand references have been removed from the chapter.

Comment Summary #43: The commenter recommended clarifying what is meant by “preparing CSPs” as it is unclear if the chapter applies to supervisors who do not actively compound.

Response: Comment incorporated. The chapter requires that facilities that prepare CSPs must develop SOPs for the compounding process and other support activities. Additional information was added for clarity to describe requirements for compounders, the designated person, and personnel with direct oversight of compounding personnel, and personnel who do not compound nor have direct oversight of compounding personnel.

Comment Summary #44: The commenter recommended that only persons entering a sterile compounding area to prepare or check a CSP should meet the requirements in 3. *Personal Hygiene and Garbing* per designated person's discretion.

Response: Comment not incorporated. To maintain the environmental conditions, any person entering a sterile compounding area must meet the requirements in 3. *Personal Hygiene and Garbing*. The designated person(s) may permit accommodations to personnel preparation as long as the quality of the CSP and environment will not be affected.

Comment Summary #45: The commenter recommended adding that products for nebulizer administration must be sterile.

Response: Comment not incorporated. There are situations where preparing products for nebulization is a part of administration.

Comment Summary #46: The commenter recommended adding text to clarify that preparing and infusing commercially prepared IV crystalloid solutions or procuring and injecting unaltered IV medications by a licensed professional at the point of care are common examples of administration and are not considered compounding.

Response: Comment not incorporated. This information is more specific than the minimum standards described in the chapter. The chapter states that administration of medication is out of the scope of the chapter.

Comment Summary #47: The commenter recommended adding specific examples of scenarios that would constitute "administration".

Response: Comment not incorporated. This information is more specific than the minimum standards described in the chapter. The chapter states that administration of medication is out of the scope of the chapter.

Comment Summary #48: Commenters recommended harmonizing the definition of administration with the CDC's Safe Injection Practice to Prevent Transmission of Infections to Patients.

Response: Comment not incorporated. The chapter references the Centers for Disease Control and Prevention (CDC) safe injection practices as an example of standard precautions that apply to administration.

Comment Summary #49: The commenter recommended addressing compounding hazardous drugs for direct and immediate administration.

Response: Comment incorporated. Language was added to clarify that for compounding of CSPs for direct and immediate administration, handling of sterile hazardous drugs (HDs) must additionally comply with <800>.

Comment Summary #50: The commenter recommended incorporating language to preclude compounding hazardous drugs for direct and immediate administration.

Response: Comment not incorporated. Language was added to clarify that for compounding of CSPs for direct and immediate administration, handling of sterile hazardous drugs (HDs) must additionally comply with <800>.

Comment Summary #51: Commenters recommended removing the requirement for personnel compounding CSPs for direct and immediate administration to be trained and demonstrate competency in aseptic processes or specifying that it only applies to pharmacy personnel.

Response: Comment not incorporated. The chapter states that the training and demonstration of competency are as they relate to assigned tasks and the facility's SOPs.

Comment Summary #52: Commenters recommended clarifying if personnel compounding CSPs for direct and immediate administration are required to be trained and demonstrate competency according to the training requirements of the chapter.

Response: Comment not incorporated. The chapter states that the training and demonstration of competency are as they relate to assigned tasks and the facility's SOPs.

Comment Summary #53: The commenter recommended clarifying how immediate-use provisions apply for COVID-19 vaccines.

Response: Comment not incorporated. This information is more specific than the minimum standards described in the chapter. The chapter states that preparing a conventionally manufactured sterile product in accordance with the directions in the manufacturer's approved labeling is out of scope of the chapter if the product is prepared as a single dose for an individual patient, and the approved labeling includes information for the diluent, the resultant strength, the container closure system, and storage time.

Comment Summary #54: The commenter recommended clarifying if garbing is required for personnel preparing CSPs for direct and immediate administration.

Response: Comment not incorporated. The chapter states that aseptic techniques, processes, and procedures are followed, and written SOPs are in place to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, and mix-ups with other conventionally manufactured products or CSPs. This is a topic to be described in the facility's SOPs.

Comment Summary #55: The commenter recommended exempting any additives to a total parenteral nutrition preparation from the requirement that CSPs for direct and immediate administration not involve more than 3 different sterile products.

Response: Comment not incorporated. Two or more of the same sterile components (product) may be used as long as there are not more than three different sterile components (products).

Comment Summary #56: Commenters indicated support for compounding of CSPs for direct and immediate administration not being subject to the requirements for Category 1, Category 2, or Category 3 CSPs when administration begins within 4 hours following the start of preparation.

Response: Comment incorporated.

Comment Summary #57: Commenters indicated that allowing administration within 4 hours following the start of preparation for immediate-use CSPs is too long for immediate-use CSPs.

Response: Comment not incorporated. This statement was rephrased to clarify that when all of the conditions are met, compounding of CSPs for direct and immediate administration is not subject to the requirements for Category 1, Category 2, or Category 3 CSPs. The allowance of up to 4 hours was based on the lag phase of microbial growth.

Comment Summary #58: The commenter recommended changing the requirement for compounding immediate-use CSPs for administration within 4 hours following the start of preparation to 6 or 8 hours for veterinary compounding.

Response: Comment not incorporated. The allowance of up to 4 hours was based on the lag phase of microbial growth.

Comment Summary #59: The commenter indicated support for training requirements being related to their assigned tasks and the facility's SOPs for personnel compounding CSPs for direct and immediate administration.

Response: Comment incorporated.

Comment Summary #60: The commenter recommended clarification regarding how duration of administration may impact the requirement that administration begins within 4 hours following the start of preparation of immediate-use CSPs.

Response: Comment not incorporated. The chapter states that if administration has not begun within 4 hours following the start of preparation, it must be promptly, appropriately, and safely discarded.

Comment Summary #61: Commenters recommended clarifying the meaning of "direct and immediate administration" for compounding immediate-use CSPs.

Response: Comment not incorporated. The Expert Committee found the current description to be sufficient.

Comment Summary #62: The commenter indicated clarification is needed to distinguish 1.3 *Immediate-Use CSPs* from 1.4 *Preparation Per Approved Labeling*.

Response: Comment not incorporated. The chapter states that preparing a conventionally manufactured sterile product in accordance with the directions in the manufacturer's approved labeling is out of scope of the chapter if the product is prepared as a single dose for an individual patient, and the approved labeling includes information for the diluent, the resultant strength, the container closure system, and storage time.

Comment Summary #63: Commenters recommended clarifying what is meant by, "the preparation involves not more than 3 different sterile products", to compound immediate-use CSPs.

Response: Comment not incorporated. "Products" was chosen, rather than "containers", to indicate that two or more of the same sterile components (products) may be used as long as there are not more than three different sterile components (products).

Comment Summary #64: Commenters indicated that there are products used in emergent situations that require more than 3 vials of product, and that more than 2 different sterile products should be allowable to compounding as immediate-use CSPs.

Response: Comment not incorporated. "Products" was chosen, rather than "containers", to indicate that two or more of the same sterile components (products) may be used as long as there are not more than three different sterile components (products).

Comment Summary #65: The commenter recommended incorporating language to limit the number of commercially manufactured sterile packages of sterile products allowed for preparing immediate-use CSPs outside of emergent situations.

Response: Comment not incorporated. There are clinical situations where up to three different sterile components are needed to be combined for administration within 4 hours.

Comment Summary #66: Commenters recommended requiring that to compound immediate-use CSPs, unless administered by the person who prepared it, administration is witnessed by the preparer, and not put down, the CSP must be labeled with the names and amounts of all active ingredients, the name or initials of the person who prepared the preparation, and the exact 4-hour period within which administration must begin.

Response: Comment partially incorporated. The text was revised to state that unless directly administered by the person who prepared it or administration is witnessed by the preparer, the CSP must be labeled with the names and amounts of all active ingredients, the name or initials of the person who prepared the preparation, and the 4-hour period within which administration must begin.

Comment Summary #67: The commenter recommended that National Patient Safety Goal NPSG.01.01.01 standards be incorporated or referenced for immediate-use labeling requirements.

Response: Comment not incorporated. This information is a part of administration and is out of scope of the chapter.

Comment Summary #68: The commenter indicated that a period was incorrectly included after "14" in "Docking of the proprietary bag and vial systems for future activation and administration is considered compounding and must be performed in accordance with this chapter, with the exception of 14. *Establishing Beyond-Use Dates*."

Response: Comment not incorporated. The period after 14 is to indicate a section number per *USP Style Guide*.

Comment Summary #69: Commenters indicated that in 1.4 *Preparation Per Approved Labeling*, it is unclear what constitutes approved labeling.

Response: Comment incorporated. Wording was revised in this section to clarify "approved labeling or supplemental materials provided by the product's manufacturer."

Comment Summary #70: The commenter recommended incorporating language regarding compounding hazardous drugs per approved labeling.

Response: Comment incorporated.

Comment Summary #71: The commenter indicated support for *Section 1.4 Preparation Per Approved Labeling*.

Response: Comment incorporated.

Comment Summary #72: The commenter recommended clarifying that investigational products are outside the scope of the chapter.

Response: Comment not incorporated. The chapter describes the minimum requirements that apply to all persons who prepare CSPs and all places where CSPs are prepared. USP has no role in enforcement. Manufacturers must comply with FDA's current good manufacturing practices (CGMP) and/or laws and regulations of the applicable regulatory jurisdiction.

Comment Summary #73: The commenter indicated that mixing, reconstituting, and other such acts performed in accordance with FDA-approved labeling are only exempt from the requirements of the chapter when the product is prepared as a single dose.

Response: Comment not incorporated. The chapter states that compounding does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling or supplemental materials provided by the product's manufacturer. Preparing a conventionally manufactured sterile product in accordance with the directions in the manufacturer's approved labeling is out of scope of the chapter only if the product is prepared as a single dose for an individual patient, and the approved labeling includes information for the diluent, the resultant strength, the container closure system, and storage time.

Comment Summary #74: The commenter indicated that activities that occur according to the package label should be exempt from the requirements of the chapter, regardless of the number of doses or patients treated, and that the limitation on the immediate-use clause should not apply.

Response: Comment not incorporated. Preparing a conventionally manufactured sterile product in accordance with the directions in the manufacturer's approved labeling is out of scope of the chapter only if the product is prepared as a single dose for an individual patient, and the approved labeling includes information for the diluent, the resultant strength, the container closure system, and storage time. A CSP compounded for direct and immediate administration is not subject to the requirements for Category 1, Category 2, or Category 3 CSPs when all the conditions in *1.3 Immediate-Use CSPs* are met, including that single-dose containers must not be used for more than one patient.

Comment Summary #75: Commenters indicated that docking of proprietary bag and vial systems for future activation and administration should not be considered compounding.

Response: Comment not incorporated. The chapter states that docking of proprietary bag and vial systems for future activation and administration is considered compounding and must be performed in an ISO Class 5 environment in accordance with the chapter, except for *14. Establishing Beyond-Use Dates*. BUDs for proprietary bag and vial systems must not be longer than those specified in the manufacturer's labeling.

Comment Summary #76: The commenter indicated that BUDs assigned for docking of proprietary bag and vial systems for future activation and administration need to be extended to up to 96 hours.

Response: Comment not incorporated. If the proprietary bag and vial system for immediate administration becomes contaminated, it is given before there is time for enough microbial growth to harm the patient. The chapter states that docking of proprietary bag and vial systems for future activation and administration is considered compounding and must be performed in an ISO Class 5 environment in accordance with the chapter, with the exception of *14. Establishing*

Beyond-Use Dates. BUDs for proprietary bag and vial systems must not be longer than those specified in the manufacturer's labeling.

Comment Summary #77: The commenter indicated that docking and activation of proprietary bag and vial systems in accordance with the manufacturer's labeling for immediate administration to an individual patient should be considered compounding.

Response: Comment not incorporated. Docking and activation of proprietary bag and vial systems in accordance with the manufacturer's labeling for immediate administration to an individual patient falls under the definition of preparation per approved labeling.

Comment Summary #78: The commenter recommended requiring that docking of proprietary bag and vial systems for future activation and administration to be performed in accordance with the chapter under controlled conditions.

Response: Comment partially incorporated. The chapter was revised to state that docking of proprietary bag and vial systems for future activation and administration is considered compounding and must be performed in an ISO Class 5 environment in accordance with this chapter, with the exception of *14. Establishing Beyond-Use Dates.* BUDs for proprietary bag and vial systems must not be longer than those specified in the manufacturer's labeling.

Comment Summary #79: Commenters recommended clarifying the environments in which docking of proprietary bag and vial systems for future activation and administration can be performed.

Response: Comment partially incorporated. The chapter was revised to state that docking of proprietary bag and vial systems for future activation and administration must be performed in an ISO Class 5 environment in accordance with this chapter.

Comment Summary #80: The commenter recommended clarifying what approved labeling is required for a proprietary bag and vial system to not be considered compounding.

Response: Comment not incorporated. Docking and activation of proprietary bag and vial systems in accordance with the manufacturer's labeling for immediate administration to an individual patient is not considered compounding and may be performed outside of an ISO Class 5 environment.

Comment Summary #81: The commenter indicated that any sterile vial being punctured should be prepared in an isolator unless used as an immediate-use CSP, regardless of if it is prepared per approved labeling.

Response: Comment not incorporated. Preparing a conventionally manufactured sterile product in accordance with the directions in the manufacturer's approved labeling is out of scope of the chapter if the product is prepared as a single dose for an individual patient, and the approved labeling includes information for the diluent, the resultant strength, the container closure system, and storage time.

Comment Summary #82: The commenter recommended adding clarity regarding assigning BUDs to proprietary bag and vial systems docked outside of an ISO Class 5 environment.

Response: Comment not incorporated. The chapter states that docking of proprietary bag and vial systems for future activation and administration is considered compounding and must be performed in an ISO Class 5 environment in accordance with the chapter, with the exception of *14. Establishing Beyond-Use Dates.* BUDs for proprietary bag and vial systems must not be longer than those specified in the manufacturer's labeling.

Comment Summary #83: The commenter recommended moving the information included in *1.4 Preparation Per Approved Labeling* to beneath the introduction to provide clarity about what is not considered compounding.

Response: Comment not incorporated. Moving this information could lead to misinterpretation of the scope of the chapter.

Comment Summary #84: The commenter recommended adding requirements to *1.4 Preparation Per Approved Labeling* similar to the requirements for immediate-use CSPs.

Response: Comment not incorporated. The Expert Committee finds the current wording of this section to be sufficient.

Comment Summary #85: Commenters recommended removing from *1.5 CSP Categories* that the three categories of CSPs are distinguished by the probability for microbial growth during the time they will be stored, and the time period within which they must be used.

Response: Comment not incorporated. This description was maintained to provide further description of how the three categories of CSPs are distinguished.

Comment Summary #86: The commenter indicated that the conditions under which USP compounded preparation monographs are to be compounded to assign extended BUDs are inconsistent with the chapter language distinguishing the categories of CSPs.

Response: Comment not incorporated. Per *General Notices*, if there is a compounded preparation monograph for a particular CSP formulation, the BUD in the monograph can be assigned if the CSP is prepared according to the monograph and all monograph requirements are met, including sterility testing. The description of how the three categories of CSPs are distinguished was maintained. The Expert Committee will further revise monographs for consistency with the chapter.

Comment Summary #87: The commenter recommended clarifying that the requirements that are not specifically described as applicable to Category 1, Category 2, or Category 3, are applicable to the compounding of all CSPs except under specific conditions described for allergenic extracts and sterile radiopharmaceuticals.

Response: Comment partially incorporated. Allergenic extracts are within the scope of the chapter, but because of certain characteristics of allergenic extracts and allergy practice, preparation of allergenic extract prescription sets is not subject to all the requirements in this chapter that are applicable to other sterile CSPs. The text was revised to state that the requirements that are not specifically described as applicable to Category 1, Category 2, or Category 3, are applicable to the compounding of all CSPs unless the CSP is otherwise described in *1.1 Scope*.

Comment Summary #88: The commenter recommended differentiating CSPs for topical use, CSPs intended for in vitro use, and those for intrathecal use.

Response: Comment not incorporated. The chapter distinguishes three categories of CSPs, primarily based on the state of environmental control under which they are compounded, the probability for microbial growth during the time they will be stored, and the time within which they must be used.

Comment Summary #89: Commenters indicated that the use of a restricted-access barrier system (RABS) validated to maintain ISO 5 air quality in an SCA should be allowed longer BUDs than the limits for Category 1 CSPs.

Response: Comment not incorporated. There is insufficient evidence to support longer BUDs for CSPs compounded in RABS located in an unclassified space. There are instances where microbial growth has been discovered in RABS.

Comment Summary #90: The commenter recommended restricting compounding in an SCA to only nonhazardous CSPs and using only conventionally manufactured sterile starting components.

Response: Comment not incorporated. The chapter allows compounding of nonsterile to sterile CSPs in an SCA.

Comment Summary #91: The commenter recommended clarifying that if one or more starting components is nonsterile that bacterial endotoxin mitigation measures need to be stressed.

Response: Comment partially incorporated. The chapter was revised to state that when compounding with nonsterile starting components, supplies, or equipment, the quality of the components, the effectiveness of the sterilization step, and bacterial endotoxin mitigation

strategies are critical to achieving a sterile preparation that is free from excessive bacterial endotoxins.

Comment Summary #92: Commenters recommended removing Category 3 CSPs.

Response: Comment not incorporated. Category 3 describes CSPs made in a compounding facility that meets additional quality assurance requirements. Category 3 CSPs may be assigned longer BUDs than those set for Category 2 CSPs but not exceeding the limits in *Table 14*, if compounded in accordance with all applicable requirements for Category 3 CSPs in <797>.

Comment Summary #93: The commenter recommended including additional environmental and personnel standards for compounding with nonsterile starting components.

Response: Comment partially incorporated. The chapter was revised to state that when compounding with nonsterile starting components, supplies, or equipment, the quality of the components, the effectiveness of the sterilization step, and bacterial endotoxin mitigation strategies are critical to achieving a sterile preparation that is free from excessive bacterial endotoxins.

Comment Summary #94: The commenter recommended Category 3 CSPs describe CSPs compounded from nonsterile starting materials, with associated requirements for sterility and endotoxin testing.

Response: Comment not incorporated. The categories were revised to avoid inaccurately conferring a level of risk to a particular CSP without consideration for all factors that influence the quality of that CSP. Renaming the CSP categories as Category 1 and Category 2, distinguished primarily by the conditions under which they are made and the time within which they are used, is intended to be a neutral designation. Category 3 describes CSPs made in a compounding facility that meets additional quality assurance requirements. Category 3 CSPs may be assigned longer BUDs than those set for Category 2 CSPs but not exceeding the limits in *Table 14*, if compounded in accordance with all applicable requirements for Category 3 CSPs in <797>.

Comment Summary #95: The commenter suggested that in veterinary practice, the majority of compounding is performed using FDA approved drugs and poses less risk than compounding from bulk drug stances.

Response: Comment not incorporated. The compounding definition in this chapter includes CSPs made from both drug products as well as bulk drug substances.

Comment Summary #96: The commenter recommended clarifying the conditions in which the CSP categories may be compounded when first describing the CSP categories in *Section 1.5*.

Response: Comment not incorporated. Requirements for Category 1, Category 2, and Category 3 CSPs are included throughout the chapter. The chapter states in the introduction and scope that Category 1, Category 2, and Category 3 CSPs are distinguished primarily based on the states of environmental control under which they are compounded, the probability for microbial growth during the time they will be stored, and the time period within which they must be used.

2. Personnel Training and Evaluation

Expert Committee-Initiated Change #1: The statement was revised in *Box 1. Gloved Fingertip and Thumb Sampling Procedures* and in *Box 2. Media-Fill Testing Procedures*, stating to, “Handle and store samples to avoid contamination and prevent condensate from dropping onto the agar during incubation and affecting the accuracy of the CFU reading (e.g., invert containers)”.

Expert Committee-Initiated Change #2: Language was revised to clarify that designated person(s) are responsible for creating and implementing a training program for personnel and

for ensuring that compounders, personnel who have direct oversight of compounders, and personnel who perform restocking or cleaning and disinfection duties are initially trained and qualified by demonstrating knowledge and competency in maintaining the quality of the sterile compounding environment before being allowed to perform their job functions independently.

Expert Committee-initiated Change #3: Text was revised to clarify that when performing a media-fill test, simulate the most difficult and challenging aseptic compounding procedures encountered by the person replacing all the components used in the CSPs with soybean-casein digest media. (added “aseptic”).

Expert Committee-initiated Change #4: *Box 1* was revised from “Store media devices appropriately” to “Handle and store media devices to avoid contamination...”

Comment Summary #97: The commenter requested that a statement be added to this section to clarify that training for immediate use does not require a physical manipulation or manual aseptic fill process to determine competency.

Response: Comment not incorporated. This information is more specific than the minimum standards described in the chapter. The chapter states that the training and demonstration of competency are as they relate to assigned tasks and the facility’s SOPs.

Comment Summary #98: Commenters requested that the ongoing competency evaluation for Category 1 and Category 2 CSPs be every 12 months, instead of every 6 months, except for personnel that have not compounded in 6 or more months.

Response: Comment not incorporated. Training and Competency in Principles and Practices is required every 12 months for compounders and those that oversee compounding personnel. The aseptic competency and garbing competency are every 6 months for Category 1 and Category 2 CSPs. Personnel are the biggest source of contamination, and the EC determined that this frequency of personnel monitoring helps ensure continued, consistent, and proper performance to support the assignment of the BUDs in *Table 12* and *Table 13* for Category 1 and Category 2 CSPs, respectively.

Comment Summary #99: The commenter stated support for the proposed training requirements for personnel only performing immediate-use compounding.

Response: Comment incorporated.

Comment Summary #100: The commenter suggested clarifying whether or not training requirements apply when a compounding robot is exclusively used to compound.

Response: Comment not incorporated. Not all compounding robots are the same, some may still require operator entry and manipulation. This is more specific than the minimum standards described in this chapter. Additionally, the chapter allows the use of technologies as long as they are noninferior to those described in the chapter and are validated for the intended purpose.

Comment Summary #101: Several commenters suggested specifying that the designated person must ensure that any person who enter the sterile compounding area maintain the quality of the environment (to allow that person to be escorted, for example) as opposed to requiring that any personnel who enter be trained.

Response: Comment partially incorporated. Detail was added to this section to clarify the training requirements for compounders, those who oversee compounding, personnel who restock or clean and disinfect the sterile compounding area, personnel who perform in-process checks or final verification, personnel who only compound immediate-use CSPs, and others (maintenance personnel, certifiers, contractors, etc.).

Comment Summary #102: Several commenters recommended that the action level in *Table 1* for after media-fill testing be >3 for consistency.

Response: Comment incorporated.

Comment Summary #103: Several commenters request clarification on the training requirements for those that have direct oversight of compounding and suggested defining oversight in an FAQ.

Response: Comment partially incorporated. Oversight was added to the glossary and a table was added to *Section 2* to clarify the training requirements for various personnel.

Comment Summary #104: The commenter recommended specifying that media fill tests need to simulate the most challenging aseptic procedures and not all procedures such as presterilization steps.

Response: Comment incorporated.

Comment Summary #105: Commenters requested clarifying the difference between the every 12 months competency assessment and the every 6 month competency assessment, as well as the initial and ongoing competency assessments.

Response: Comment incorporated. A table was added to clarify the minimum frequencies for personnel training and evaluation.

Comment Summary #106: Several commenters requested changing the frequency of media-fill testing with post gloved fingertip and thumb sampling and surface sampling from every 6 months to annually for personnel compounding Category 1 and Category 2 CSPs.

Response: Comment not incorporated. Media-fill testing is an objective way to demonstrate aseptic practices, and this must be performed to assess personnel proficiency in compounding. The chapter is intended to provide the minimum standard to help ensure the quality of CSPs. The chapter requires media-fill testing with post gloved fingertip and surface sampling at least every 6 months. Personnel are the biggest source of contamination, and the EC determined that this frequency of personnel monitoring helps ensure continued, consistent, and proper performance to support the assignment of the BUDs in *Table 12* and *Table 13* for Category 1 and Category 2 CSPs, respectively.

Comment Summary #107: The commenter recommended establishing a risk-based approach to training as opposed to a set annual training and competency assessment.

Response: Comment not incorporated. Personnel are the biggest source of contamination, and this frequency of personnel monitoring helps ensure continued, consistent, and proper performance.

Comment Summary #108: The commenter suggested that the training program “must” equip personnel with the appropriate knowledge, not “should”.

Response: Comment incorporated.

Comment Summary #109: Commenters requested clarifying which core competencies require didactic training versus observational competency.

Response: Comment not incorporated. Personnel must both complete training and be able to demonstrate knowledge of principles and competency of skills, initially and every 12 months in at least the listed core competencies.

Comment Summary #110: The commenter requested that a chart of required competencies, required methods of demonstrating competency and frequencies be added.

Response: Comment incorporated.

Comment Summary #111: The commenter requested citing examples of how each core competency can be assessed.

Response: Comment not incorporated. The chapter requires that each compounding facility develop a written training program that describes the training, the frequency of training and the process for evaluating the performance of personnel. SOPs should specify the training required for assigned tasks.

Comment Summary #112: Commenters requested deleting “written or electronic testing must be completed”.

Response: Comment incorporated.

Comment Summary #113: The commenter requested deleting the term “apyrogenicity” from *Section 2.1 Demonstrating Knowledge and Competency of Core Skills*, as that is only relevant if performing sterility testing.

Response: Comment partially incorporated. The text was amended to say “(and apyrogenicity if compounding with nonsterile components).”

Comment Summary #114: The commenter requesting maintaining “independently” in the following sentence: “Before beginning to compound CSPs independently...”, as its removal would be detrimental to new practitioners in training.

Response: Comment incorporated.

Comment Summary #115: The commenter requested that *Table 1* include “Should personnel have excursions on hand monitoring, the person should repeat the garb assessment.”

Response: Comment not incorporated. *Table 1* is the action levels for gloved fingertip and thumb sampling. The text in this section states that a failure in any portion of the evaluation constitutes an overall failure of the aseptic manipulation competency.

Comment Summary #116: The commenter requested clarification on what to do in case of failure of the aseptic competency.

Response: Comment not incorporated. The text in this section states that a failure in any portion of the evaluation constitutes an overall failure of the aseptic manipulation competency. The designated person(s) and the facility’s SOP should determine the appropriate corrective action, depending on the failure and the personnel.

Comment Summary #117: Commenters requested requiring additional actions in case of a failure of aseptic competency, such as a root cause analysis be performed for turbid broth, along with species identification, a triplicate repeat, and additional training.

Response: Comment not incorporated. The chapter requires that the results of the evaluation and corrective action be documented and does not require identification of species. The chapter is a minimum standard, and facilities may choose to identify species and must perform corrective action. However, personnel may not compound Category 1, 2, or 3 CSPs independently, or have direct oversight of compounding personnel until they successfully pass the aseptic manipulation competency. The designated person(s) and the facility’s SOP should determine the appropriate corrective action, depending on the failure and the personnel.

Comment Summary #118: Several commenters requested clarification on what training is required for pharmacists that verify the final CSP but do not compound.

Response: Comment incorporated. Training requirements have been clarified in the text and two tables have been added to clarify the type and frequency of training for various personnel.

Comment Summary #119: The commenter requested that a designated person be allowed an authorized representative for certain situations.

Response: Comment incorporated.

Comment Summary #120: Commenter requested clarification on what qualifications are required for a designated person.

Response: Comment not incorporated. The chapter outlines the responsibilities of the designated person(s). Facilities must determine the appropriate qualifications. This information is more specific than the minimum standards described in the chapter.

Comment Summary #121: Commenters request data be included in the chapter to support that an increased frequency of garbing competency will improve patient safety, and suggest that an annual evaluation is sufficient.

Response: Comment partially incorporated. This information is more specific than the minimum standards in the chapter. The chapter was revised to improve clarity and to respond to stakeholder input. The standards are based on a combination of available evidence, expertise of the Compounding Expert Committee, and input from stakeholders, and take into consideration stability and sterility data, the compounding environment, and the financial impact on

compounders and patients. Personnel are the main source of contaminants, and a frequency of every 6 months for the garbing competency for compounders helps assure continued proper hand hygiene and garbing procedures. The text was changed to allow designated person(s) and personnel who oversee compounding personnel to perform the competency every 12 months.

Comment Summary #122: The commenter suggested that nonsterile to sterile compounding should meet the same requirements as Category 3 compounding.

Response: Comment not incorporated. Category 1, 2, and 3 CSPs are distinguished primarily based on the BUD and the environment in which they are compounded. The chapter describes the minimum standards to be followed when preparing CSPs and the chapter does not prohibit compounders from going beyond the requirements in the chapter.

Comment Summary #123: The commenter stated that the frequency of the garbing evaluation is not in alignment with regulatory expectations for compounders elsewhere.

Response: Comment not incorporated. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #124: The commenter requested that media-fill testing for Category 3 CSPs be every 6 months, instead of every 3 months.

Response: Comment not incorporated. Personnel are the main source of contaminants, and Category 3 CSPs have longer BUDs, which increases the risk of microbial contamination and proliferation, as well as chemical degradation, physical incompatibilities, and the compromising of the container closure system. To address these risks and maintain a higher state of environmental control, additional requirements must be met if compounding Category 3 CSPs. A frequency of every 3 months for the garbing competency helps assure continued proper hand hygiene and garbing procedures.

Comment Summary #125: The commenter requested that Category 1 CSPs have less frequent media fill testing than Category 2 CSPs due the shorter BUDs.

Response: Comment not incorporated. Category 1 CSPs are compounded under the least controlled environmental conditions. Personnel are the biggest source of contamination, and the EC determined that this frequency of personnel monitoring helps ensure continued, consistent, and proper performance to support the assignment of the BUDs.

Comment Summary #126: The commenter requested that identification down the genus level for failure of media-fill testing should not be required for Category 1 CSPs.

Response: Comment not incorporated. The chapter states that microbial identification of the cfu is not required for media-fill testing.

Comment Summary #127: Several commenters requested that surface sampling of the direct compounding area not be required after media-fill testing.

Response: Comment not incorporated. Surface sampling is included as part of the aseptic manipulation competency to demonstrate the ability to stage properly and compound without contaminating the direct compounding area.

Comment Summary #128: The commenter suggested clarifying whether manufacturer incubation recommendations may be used if they differ from USP recommendations.

Response: Comment not incorporated. The chapter specifies and requires specific incubation temperatures, as the EC has determined they are the appropriate incubation temperatures and times to ensure optimal recovery of microorganism.

Comment Summary #129: The commenter requested that the media-fill section clarify that the aseptic manipulation competency must be passed prior to “independently” compounding, to align with *Section 2.1 Demonstrating Knowledge and Competency of Core Skills*.

Response: Comment incorporated.

Comment Summary #130: The commenter requested clarification on whether the three garbing and hand hygiene successful completions must be in succession.

Response: Comment incorporated.

Comment Summary #131: The commenter stated that *Box 1. Gloved Fingertip and Thumb Sampling Procedures* to be overly prescriptive and suggested allowing sampling by “appropriate means.”

Response: Comment not incorporated. The procedures are intended to provide guidance for appropriate sampling techniques and appropriate incubation temperatures and times to ensure optimal recovery of microorganism.

Comment Summary #132: The commenter requested removing the requirement of Gloved Fingertip and Thumb sampling from the garbing assessment.

Response: Comment not incorporated. The Gloved Fingertip and Thumb Sampling is a means to assess that personnel are able to successfully garb and don gloves without contamination.

Comment Summary #133: The commenter requested removing the requirement for documentation of the starting temperature of each incubation period.

Response: Comment not incorporated. The starting temperature must be recorded to ensure it is within range.

Comment Summary #134: The commenter requested the addition of the word “initial” to gloved fingertip and thumb sampling, to differentiate between the initial and subsequent sampling done inside an ISO Class 5 PEC.

Response: Comment partially incorporated. The subsequent Gloved Fingertip and Thumb sampling that is done inside an ISO Class 5 PEC is part of the aseptic manipulation competency, and it is done following the media-fill test. The initial gloved fingertip and thumb sampling is part of the garbing competency. The text was revised to clarify “Gloved fingertip and thumb sampling must be performed on both hands and inside of an ISO Class 5 PEC immediately following the media fill test.”

Comment Summary #135: The commenter suggested requiring that an observation of poor technique during media fill test be considered a failure of the competency, even if there is no growth upon incubation.

Response: Comment not incorporated. Failure of the media-fill test is determined by visible turbidity or other visual growth in the media on or before the end of the incubation period. This chapter is a minimum standard and facilities may enforce more stringent requirements.

Comment Summary #136: The commenter requested clarification as to why incubation of Gloved fingertip samples at 20°–25° for an additional 5 days was required, as the higher temperature would kill bacteria that thrive at room temperature.

Response: Comment not incorporated. Gloved fingertip sampling devices should be incubated at a temperature of 30°–35° for no less than 48 hours and then at 20°–25° for no less than 5 additional days to help ensure adequate recovery of potential microorganisms. The EC did not find evidence that bacteria would be killed at higher temperatures.

Comment Summary #137: The commenter requested clarifying that the Gloved fingertip test after garbing must be done before the application of IPA.

Response: Comment incorporated.

Comment Summary #138: The commenter requested recommending microbial identification of the CFU after gloved fingertip and thumb sampling to know whether the isolate was a skin or dirt organism.

Response: Comment not incorporated. Growth that exceeds the action levels in the table is considered a failure. The chapter is a minimum standard and facilities may choose to enforce more stringent requirements.

Comment Summary #139: Multiple commenters noted that the incubation times and temperatures for gloved fingertip and thumb sampling and media-fill testing are different. Commenters noted that the incubation temperatures and times should be consistent for both gloved fingertip and thumb sampling and media-fill testing.

Response: Comment partially incorporated. Gloved fingertip and thumb samples must be incubated at a high temperature (30°–35°) and then a low temperature (20°–25°) to allow for readability. Lower temperatures facilitate growth of micrococcus and staphylococcus, while higher temperatures encourage the growth of other microorganisms. Media-fill samples must be incubated at 20° -25° and 30° -35° for a minimum of 7 days at each temperature band to detect a broad spectrum of microorganisms. The order of incubation temperatures must be described in the facility's SOPs.

Comment Summary #140: The commenter requested that addition garbing samples be required for those preparing Category 3 CSPs.

Response: Comment not incorporated. This chapter is a minimum standard and facilities may choose to enforce more stringent requirements.

Comment Summary #141: The commenter recommended adding text to specify that sampling paddles not be inverted.

Response: Comment not incorporated. The text requires handling and storing of samples to avoid contamination and lists the example of inverted containers.

Comment Summary #142: A commenter requested changing text from initiate the media fill test "before the expiration date of the media" to "by" the expiration date of the media.

Response: Comment incorporated.

Comment Summary #143: The commenter requested removing the requirement for a visual observation of the media-fill test for subsequent media-fills after the initial evaluation.

Response: Comment not incorporated. Visual observation is a key component of ensuring proper aseptic technique to reduce the risk of contamination.

Comment Summary #144: The commenter requested adding surface sampling as the last step in *Box 2*.

Response: Comment not incorporated. *Box 2* describes procedures specifically for media-fill testing.

Comment Summary #145: The commenter suggested that the instructions in *Box 2* are unclear as to whether the incubation temperatures listed are for media-fill samples only or include Gloved Fingertip samples as well, and recommended separating with a comma.

Response: Comment partially incorporated. The third bullet was separated into two bullets and additional clarification was added to the paragraphs above *Box 2*.

Comment Summary #146: Commenters requested clarification on the number of people in a cleanroom suite or SCA during the simulated media-fill, and recommended removing number of people in cleanroom suite as the number of people in the anteroom do not impact media-fill testing in the PEC.

Response: Comment incorporated. Text was changed from "Number of personnel in the cleanroom suite" to "Number of people in the buffer room or SCA."

Comment Summary #147: The commenter requested that the elements listed as requirements for a media-fill simulation, such as simulating the number of aseptic additions or transfers, be a recommendation and not a requirement, as not all factors may be captured at all times.

Response: Comment not incorporated. The media-fill test must simulate the most difficult and challenging aseptic compounding procedures encountered by the person in order to properly assess competency.

Comment Summary #148: The commenter stated that the acceptance criteria for gloved fingertip sampling should be 0 CFUs, as a sterile product cannot be released when contamination is identified on the compounder's gloved hands.

Response: Comment not incorporated. Compounding involves handling ingredients, components, and equipment that may be nonsterile or the outer surfaces of components may not be sterile, and IPA is not a sterilant, so there may be growth on the gloved fingertip test. The action level after garbing is >0 CFUs, and post media-fill testing, the action level is >3.

Comment Summary #149: Several commenters requested clarification on the action levels for surface sampling done as part of the aseptic manipulation and what constitutes a failure.

Response: Comment not incorporated. The chapter states that surface sampling of the direct compounding area must occur in accordance with the requirements in *6.3 Monitoring Surfaces for Viable Particles*.

Comment Summary #150: The commenter requested clarification on whether failure of the surface sampling post media fill requires identification of the microorganism to the genus level.

Response: Comment not incorporated. The chapter states that surface sampling of the direct compounding area must occur in accordance with the requirements in *6.3 Monitoring Surfaces for Viable Particles*, which requires attempting to identify microorganisms to the genus level.

Comment Summary #151: Commenters noted that the broad scope of training requirements may be misinterpreted to apply to anesthesiology departments and requested clarification, as they do not consider their duties in the operating room to fall under compounding.

Response: Comment partially incorporated. *Section 2* was revised to clarify specific training requirements for compounders, those who oversee compounding, and other personnel. Tables were added to further clarify the training requirements per type of personnel and the frequency of training. Additionally, Chapter was revised to clarify that administration of medication is out of the scope of the chapter (*1.2 Administration*). Preparation of compounded sterile preparations (CSPs) for direct and immediate administration to a patient is not subject to the requirements for Category 1 and Category 2 if all of the conditions in *1.3 Immediate Use CSPs* are met. Additionally, preparation per approved labeling is out of the scope of the chapter, as described in *1.4 Preparation Per Approved Labeling*. Activities out of scope of the chapter would not be considered compounding and would not require abiding by the training requirements in the chapter.

Comment Summary #152: The commenter request removing the requirement of documenting the training of outside vendors and other departments.

Response: Comment partially incorporated. Documentation of training is required, but *Section 2* was revised to clarify specific training requirements for compounders, those who oversee compounding, and other personnel. Tables were added to further clarify the training requirements per type of personnel and the frequency of training. Excepting compounders, designated person(s) and personnel with direct oversight of compounding, all other personnel's training must be defined per facility SOPs.

Comment Summary #153: Several commenters requested an accommodation for vendors, cleaners, and other isolated instances of entry into the compounding area and requested alternate strategies to mitigate the risk of contamination in these cases.

Response: Comment incorporated. *Section 2* was revised to clarify specific training requirements for compounders, those who oversee compounding, and other personnel. Tables were added to further clarify the training requirements per type of personnel and the frequency of training. Excepting compounders, designated person(s) and personnel with direct oversight of compounding, all other personnel's training must be defined per facility SOPs.

Comment Summary #154: The commenter requested adding a table to clarify the requirements of the aseptic manipulation competency, including type of sample, incubation temperature, incubation duration and action level.

Response: Comment partially incorporated. The addition of *Table 2* clarifies the initial training and competency requirements. The chapter describes the specifics of the aseptic competency testing in *Box 1*, *Box 2*, and *Box 6*.

3. Personal Hygiene and Garbing

Expert Committee-initiated Change #1: A statement was added that “food (including mints, gum, etc.) and drinks must not enter anterooms, buffer rooms, or segregated compounding areas.

Expert Committee-initiated Change #2: To accommodate various facility designs, a statement was added that the required garb (in addition to the manner of storage and order of garbing) must be determined by the facility and documented in the facility’s SOPs.

Expert Committee-initiated Change #3: “When preparing Category 1 CSPs, all garb must be donned within the perimeter of the SCA” was changed to “When preparing Category 1 CSPs, all garb must be donned just prior to entering the perimeter of the SCA.”

Expert Committee-initiated Change #4: The text was clarified that gowns may be reused, when Compounding Category 1 and Category 2 CSPs, within the same shift if the gown is maintained in a classified area or “adjacent to, or within, the SCA” in a manner that prevents contamination.

Expert Committee-initiated Change #5: The garbing requirements in 3.3 were revised from “If the facility compounds Category 3 CSPs, additional garbing requirements must be continuously met.” to “...must be continuously met in the buffer room in which Category 3 CSPs are prepared.”

Comment Summary #154: The commenter requested clarification on whether chronic medical issues such as eczema would preclude a person from compounding CSPs.

Response: Comment not incorporated. This information is more specific than the minimum standards described in the chapter. The chapter states that the designated person may permit accommodations to personnel preparation as long as the quality of the CSP and environment will not be affected.

Comment Summary #155: Commenters noted an error in the “rate of 10⁶” and recommended changing to 10⁶.

Response: Comment incorporated.

Comment Summary #156: Commenters requested additional detail on the types of jewelry and cosmetics prohibited, or staff that are unable to remove jewelry or permanent cosmetics such as eyelash extensions.

Response: Comment not incorporated. The designated person may permit accommodations to personnel preparation as long as the quality of the CSP and environment will not be affected. Accommodations must be documented.

Comment Summary #157: The commenter requested clarification on what covering would suffice to meet the requirement to “cover any jewelry that cannot be removed.”

Response: Comment not incorporated. The facility and/or designated person(s) must determine the appropriate method to cover jewelry that cannot be removed to minimize contamination to the environment and the CSP. The type of cover would depend on the individual (e.g., consideration of skin allergies) and the type and size of the jewelry (e.g., transdermal implant).

Comment Summary #158: The commenter requested addressing the prohibition of food and drink the cleanroom.

Response: Comment incorporated.

Comment Summary #159: The commenter requested requiring that accommodations to personnel preparation made by the designated person be documented prior to the initial occurrence and reviewed once yearly or as needed.

Response: Comment not incorporated. This chapter is a minimum standard and facilities may enforce more stringent requirements.

Comment Summary #160: The commenter requested clarification on the frequency required of reviewing the accommodations to personnel preparation.

Response: Comment not incorporated. This information is more specific than the minimum standards of the chapter and must be described in the facility SOPs.

Comment Summary #161: The commenter requested clarifying that the designated person may permit accommodations “of the activities listed in *Section 3.1*” to avoid ambiguity as to the broadness of accommodations the designated person(s) may make.

Response: Comment incorporated. The text was revised to clarify that the designated person(s) may make accommodations “to personnel preparation”.

Comment Summary #162: Commenters requested adjusting the statement prohibiting the use of refillable containers of soap for hand hygiene, as it would leave few options in managing staff with allergies or requested accommodations to the primary soap.

Response: Comment incorporated.

Comment Summary #163: A comment requested clarification that a sponge side of a scrub brush may be used, as long as the brush side is not.

Response: Comment not incorporated. The expert committee finds the language sufficiently clear that the prohibition is only for the brush.

Comment Summary #164: The commenter suggested that all persons entering a compounding area must wash hands up to the elbows and not just those that are compounding.

Response: Comment not incorporated. The chapter states that any person entering a compounding area where Category 1, Category 2, or Category 3 CSPs are prepared must wash hands and forearms up to the elbows with soap and water before initiating compounding activities.

Comment Summary #165: The commenter requested clarification on whether or not touchless refillable soap containers may be used.

Response: Comment partially incorporated. While the Expert Committee did not address touchless containers specifically, the text was revised to clarify that disposable soap containers must not be refilled or topped off.

Comment Summary #166: The commenter suggested revising “piercings that could interfere with the effectiveness of garbing” to “visible piercings above the neck or on the hands and wrists” as “interfere” is subjective.

Response: Comment not incorporated. The Expert Committee found the current description to be sufficient. The designated person(s) may permit accommodations. USP has no role in enforcement. That is the jurisdiction of the applicable regulatory body.

Comment Summary #167: The commenter suggested that the requirement to apply sterile 70% IPA to gloves before entering the PEC every time is burdensome and recommended it be changed to “routinely”.

Response: Comment incorporated. The text was revised to “Application of sterile 70% IPA to gloves must occur immediately before compounding and regularly throughout the compounding process.”

Comment Summary #168: The commenter requested eliminating the use of sterile gloves over gloves in a compounding aseptic containment isolator (CACI), as it decreases dexterity.

Response: Comment not incorporated. Sterile gloves must be worn when compounding CSPs to reduce the risk of contamination due to the inherent bioburden in nonsterile gloves.

Comment Summary #169: The commenter requested clarifying that sleeves must be low particulate and sterile, as gloves must be sterile and the sleeves has a much greater surface area than a glove.

Response: Comment incorporated. The text that all low-lint outer garb must be sterile was clarified with “including the use of sterile sleeves over gauntlet sleeves when a RABS is used.”

Comment Summary #170: The commenter recommended that low-lint garb “should” be sterile, not “must”.

Response: Comment not incorporated. This requirement is for compounding Category 3 CSPs, and the bioburden in nonsterile garb increases the risk of contamination. In order to assign the longer BUDs for Category 3 CSPs, more stringent requirements must be followed.

Comment Summary #171: The commenter requested that disposable gowns be allowed to be reused up to manufacturer specifications if maintained in an ISO-certified anteroom.

Response: Comment not incorporated. This requirement is for compounding Category 3 CSPs. In order to assign the longer BUDs for Category 3 CSPs, more stringent requirements must be followed to reduce the risk of contamination and microbial proliferation.

Comment Summary #172: The commenter requested that body parts that are difficult to cover (ears, forehead) with garbing be excluded from the requirement that exposed skin is not allowed in the buffer room.

Response: Comment not incorporated. The chapter specifically states that face and neck must be covered. This requirement is for compounding Category 3 CSPs. In order to assign the longer BUDs for Category 3 CSPs, more stringent requirements must be followed to reduce the risk of contamination and microbial proliferation, especially as human shedding is the main source of contamination.

Comment Summary #173: The commenter requested defining what a validated laundry cycle is and suggested the Hospital Laundry Accreditation Counsel.

Response: Comment not incorporated. The chapter requires that laundered garb be laundered and resterilized with a validated cycle. The facilities' SOPs must describe this process. Multiple organizations may offer guidelines, so references to a specific organization were removed.

Comment Summary #174: The commenter requested clarification on whether low-lint garb was intentional and suggested removing the low-lint requirement.

Response: Comment not incorporated. Low-lint garb is required to reduce particulate count and reduce the risk of contamination.

Comment Summary #175: The commenter requested adding to the Category 3 CSP garbing requirements that the facility SOPs must describe the sterilization procedure for reusing goggles and other reusable equipment.

Response: Comment incorporated.

Comment Summary #176: The commenter suggested that "All low-lint garb must be sterile" might mean that other garb does not need to be sterile and recommended changing to "All garb must be sterile", or adding that reusable garb must be sterilized before use.

Response: Comment partially incorporated. Text was changed to all low-lint outer garb must be sterile, and a bullet was added to clarify that facility SOPs must describe the disinfection procedures for reusable equipment.

Comment Summary #177: The commenter requested that different facility designs may make it difficult to meet the requirement that doffing and donning garb not occur in the anteroom or the SCA at the same time.

Response: Comment incorporated. The text was edited to "Donning and doffing should not occur in the same area at the same time."

Comment Summary #178: The commenter requested requiring the use of coveralls in place of gowns for all sterile compounding.

Response: Comment not incorporated. This chapter is a minimum standard, and facilities and regulators may choose to enforce more stringent requirements.

Comment Summary #179: The commenter suggested that "all low-lint garb must be sterile" may be misinterpreted to mean that scrubs must be sterile which is overly burdensome.

Response: Comment incorporated. Text was revised to clarify "All low-lint outer garb must be sterile".

Comment Summary #180: The commenter requested adding “to minimize contamination” to the sentence “The manner of storage designed to minimize contamination and order of garbing must be determined by the facility and documented in the facility’s SOPs.”

Response: Comment not incorporated. The Expert Committee finds the current wording of this statement to be sufficient.

Comment Summary #181: The commenter noted that the garbing requirements are not in alignment with current industry practice and regulatory expectations for compounders elsewhere, and suggested requiring eye coverings, requiring that all garb for all categories be sterile and to disallow reuse of garb.

Response: Comment not incorporated. USP has no role in enforcement. This chapter is a minimum standard and facilities and regulators may choose to enforce additional requirements.

Comment Summary #182: The commenter noted that while reusing gowns is allowed if the gown is stored within the perimeter of the SCA, it contradicts the requirement that garbing is to occur prior to stepping over the perimeter line.

Response: Comment incorporated. When preparing Category 1 CSPs, all garb must be donned within the perimeter of the SCA” was changed to “When preparing Category 1 CSPs, all garb must be donned just prior to entering the perimeter of the SCA.”

Comment Summary #183: Commenters requested clarifying that shoe covers not be donned within the perimeter of the SCA, and excluded from the statement that all garb must be donned within the perimeter of the SCA.

Response: Comment partially incorporated. The EC removed the text “When preparing Category 1 CSPs, all garb must be donned within the perimeter of the SCA.” The chapter states “Garb must be donned and doffed in an order that reduces the risk of contamination. The required garb, manner of storage, and order of garbing must be determined by the facility and documented in the facility’s SOPs. When preparing Category 2 or Category 3 CSPs, all garb should be donned in a classified area before entering the buffer room”

Comment Summary #184: The commenter requested either prohibiting the laundering and reuse of garb when compounding Category 1 and Category 2 CSPs, or requiring that laundering be validated for these categories.

Response: Comment not incorporated. The Expert Committee found the financial impact of such a requirement to be burdensome. This chapter is a minimum standard, and facilities and regulators may enforce additional requirements.

Comment Summary #185: The commenter stated that requiring that all garb be donned within the perimeter of the SCA for Category 1 CSPs conflicts with <800>, which requires that a second pair of shoe covers be donned before entering the C-SEC.

Response: Comment incorporated. The EC removed the text “When preparing Category 1 CSPs, all garb must be donned within the perimeter of the SCA.” The chapter states “Garb must be donned and doffed in an order that reduces the risk of contamination. The required garb, manner of storage, and order of garbing must be determined by the facility and documented in the facility’s SOPs. When preparing Category 2 or Category 3 CSPs, all garb should be donned in a classified area before entering the buffer room”

Comment Summary #186: The commenter requested an exception to the Category 3 garbing requirements when robotic enclosures are used to prepare CSPs.

Response: Comment not incorporated. There are variations in robotic enclosures that would make such an exception a high contamination risk. Some may still require operator entry and manipulation. Further, the chapter states that the use of technologies, techniques, materials, and procedures other than those described in the chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose (e.g., *Validation of Alternative Microbiological Methods* (1223) and *Validation of Compendial Procedures* (1225)).

Comment Summary #187: The commenter noted support for the requirement that if compounding an HD, appropriate PPE must be worn in accordance with <800>.

Response: Comment incorporated.

Comment Summary #188: Commenters requested revising the requirement to follow the manufacturer's instructions for the volume of alcohol-based hand sanitizer to use, as this does not take into account anatomical variations that may require more or less volume.

Response: Comment incorporated.

Comment Summary #189: The commenter requested allowing the use of air dryers to dry hands.

Response: Comment not incorporated. Air dryers must not be used due to the risk of creating air turbulence and circulating contamination to the compounding area. The Expert Committee determined that hand dryers are not as effective in drying hands. The chapter specifies that hands and forearms must be dried with low-lint disposable towels or wipers.

Comment Summary #190: The commenter requested the removal of the requirement to use a nail cleaner.

Response: Comment not incorporated. The Expert Committee decided that debris can be under nails and must be removed using a nail cleaner.

Comment Summary #191: The commenter requested removing the word "visible" from "remove visible debris from underneath fingernails under warm running water using a disposable nail cleaner.", as this infers that a nail cleaner is not required if debris is not visible.

Response: Comment partially incorporated. The text was revised to "Clean underneath fingernails under warm running water using a disposable nail cleaner."

Comment Summary #192: The commenter recommended adding statements for handling PPE shortages.

Response: Comment not incorporated. This information is more specific than the minimum standards described in the chapter.

Comment Summary #193: The commenter requested clarification on if gowns with a closed neck means that the neck need to be completely covered, or just the chest.

Response: Comment partially incorporated. For Category 1 and Category 2 CSPs, the examples listed were changed to "gown or coverall"). For Category 3 CSPs, the chapter specifically states that the neck must be covered.

Comment Summary #194: The commenter requested clarification on the glove requirements for RABs and whether the sterile gloves must be inside the gauntlet gloves or worn on the outside of gauntlet gloves.

Response: Comment not incorporated. The chapter states that if using a RABS (i.e., a CAI or CACI), disposable gloves should be worn inside the gloves attached to the RABS sleeves. Sterile gloves must be worn over the gloves attached to the RABS sleeve

Comment Summary #195: The commenter suggested that hand washing sinks should be located in an ISO-classified anteroom in order to minimize ingress of contaminants.

Response: Comment not incorporated. The chapter allows the sink that is used for hand hygiene to be placed either inside or outside of the anteroom, in facilities with a cleanroom suite, to accommodate various facility designs.

Comment Summary #196: Commenters noted that a reference in *Section 3.2 to Box 3* should be *Box 4*.

Response: Comment incorporated.

Comment Summary #197: The commenter recommended spelling out "seconds" instead of the abbreviation "s".

Response: Comment not incorporated. Abbreviations are used as required per *USP Publication Style Guide*.

Comment Summary #198: The commenter requested that <800> references should include the chapter name.

Response: Comment not incorporated. References are per the *USP Publications Style Guide*.

Comment Summary #199: The commenter requested adding examples of cosmetics that must not be used.

Response: Comment not incorporated. The listed cosmetics are examples and not an all-inclusive list. Accommodations may be permitted by the designated person(s) and must be documented.

Comment Summary #200: The commenter requested adding more details and examples about various cosmetics and piercings in an FAQ.

Response: Comment not incorporated. The Expert Committee finds the current wording of this section to be sufficient for the purposes of a chapter that is a minimum standard, but will consider discussing additional examples in supplementary materials.

Comment Summary #201: The commenter noted that the handwashing requirement for 30 seconds may be unsafe for veterinarians practicing outdoors in colder climates.

Response: Comment not incorporated. Handwashing is required to maintain quality CSPs and reduce contamination risk and is not a new requirement from the current standard.

Comment Summary #202: The commenter noted that requiring that all garb be donned in a classified area before entering the buffer room is not workable and suggested adding language to specify that shoe covers be donned when crossing the line of demarcation.

Response: Comment not incorporated. The order of garbing must be determined by the facility and documented in the facility's SOP. The chapter states that garb must be donned and doffed in an order that reduces the risk of contamination.

Comment Summary #203: The commenter requested clarification on whether all low-lint garments may be reused within the same shift, for Category 1 and Category 2 CSPs, or if this only applies to gowns.

Response: Comment not incorporated. The chapter states that gowns may be reused within the same shift if compounding Category 1 and Category 2 CSPs, if the gown is maintained in a classified area or inside the perimeter of an SCA, and specifies that garb, except for gowns, cannot be reused and must be discarded or laundered before reuse.

Comment Summary #204: The commenter requested clarifying that when compounding Category 3 CSPs, only the outer coverall must be sterile, to clarify that a nonsterile hair bouffant may be worn prior to entry into the anteroom and prior to donning the sterile coverall.

Response: Comment partially incorporated. The text was revised to clarify that all low-lint "outer" garb must be sterile.

Comment Summary #205: The commenter noted a conflict between requiring that all garb must be donned within the perimeter of the SCA and that a sink is not permitted in the SCA, as this would not allow for hand washing after garbing.

Response: Comment incorporated. The order of garbing must be determined by the facility and documented in the facility's SOP. The chapter states that garb must be donned and doffed in an order that reduces the risk of contamination.

Comment Summary #206: The commenter requested that for Category 3 CSPs, sterile coveralls be specifically required, as a gown would not be sufficient unless pant legs or scrubs were sterile.

Response: Comment partially incorporated. Coveralls are not specifically required, but the text was revised to clarify that all low-lint "outer" garb must be sterile. The chapter states that exposed skin is prohibited in the buffer room and that the face and neck must be covered.

Comment Summary #207: Commenters suggested changing the "should" to a "must" in the statement "When preparing Category 2 or Category 3 CSPs, all garb should be donned in a classified area before entering the buffer room."

Response: Comment not incorporated. The order of garbing and the location of where garbing occurs (e.g., anteroom, buffer room, or SCA) must be determined by the facility and documented in the facility's SOP. The order of garbing and location where garbing occurs would depend on the type of garbing used (e.g., sterile gowns) and the placement of the sink (e.g., if the sink is located inside or outside of the anteroom).

Comment Summary #208: Commenters requested clarifying that the face and neck must be covered by "goggles, sterile coverall, or face shield" in the buffer room where Category 3 CSPs are compounded, to allow for the use of face shields for people who wear glasses.

Response: Comment not incorporated. The chapter does not specify how the exposed skin must be covered, just that exposed skin is not allowed in the buffer room where Category 3 CSPs are compounded, and that the face and neck must be covered. The chapter states that the required garb, manner of storage, and order of garbing must be determined by the facility and documented in the facility's SOPs.

Comment Summary #209: The commenter requested requiring two pairs of sterile gloves for those preparing Category 3 CSPs and including an example of how to properly don sterile garb.

Response: Comment not incorporated. This chapter is a minimum standard, and facilities may implement additional requirements. Additionally, the chapter states that the required garb, manner of storage, and order of garbing must be determined by the facility and documented in the facility's SOPs.

Comment Summary #210: The commenter requested that the use of sterile garb and the prohibition of exposed skin in the buffer room be required for Category 2 CSPs, in addition to Category 3 CSPs.

Response: Comment not incorporated. The garbing requirements listed in the chapter are intended to provide a practical approach for compounding, which is different from cGMP requirements. The chapter is intended to provide the minimum standard to ensure quality CSPs. However, facilities may additionally require individuals to adhere to more stringent garbing requirements, such as sterile garb.

Comment Summary #211: The commenter noted that the use of low-lint full gowns, shoe covers, head covers, masks and gloves in all instances of compounding is not possible in many veterinary settings.

Response: Comment not incorporated. The chapter does contain provisions for administration (see *1.2 Administration*), compounding for immediate use (*1.3 Immediate Use CSPs*), and preparation per approved labeling (*1.4 Preparation Per Approved Labeling*). Additionally, the chapter has been revised from the current standard to allow for more flexibility in garbing procedures. The requirements of this chapter are equally relevant to CSPs for human and animal patients. The Compounding Expert Committee is continuing engagement with veterinarians and veterinary practice groups to develop resources and address their unique needs.

4. Facilities and Engineering Controls

Expert Committee-initiated Change #1: CAI and CACI were defined at first usage.

Expert Committee-initiated Change #2: Rust was added as an example of damage that surfaces should be resistant to.

Expert Committee-initiated Change #3: "Particulates" was changed to "particles".

Expert Committee-initiated Change #4: The text was revised to clarify that in a cleanroom suite, a minimum differential positive pressure of 0.020-inch water column is required between each "adjacent" ISO classified area.

Expert Committee-initiated Change #5: The text was revised to clarify that a visible perimeter must define the SCA, but the term "boundary" was removed for clarity. Additionally, it was

clarified that the area within 1 m of the PEC should be dedicated for only sterile compounding, and the use of “perimeter” was corrected throughout the chapter to align with these changes.

Expert Committee-initiated Change #6: The following was removed: “If compounding is not performed daily, cleaning and disinfecting of the sink(s) must be completed before initiating hand hygiene and garbing” and replaced with “Surfaces of the sink(s) must be cleaned and disinfected each day of use, and a sporicidal disinfectant must be applied at least monthly.”

Expert Committee-initiated Change #7: *Section 4.2* was reformatted with subsections for clarity.

Expert Committee-initiated Change #8: Text was revised to clarify that in a facility with an SCA design, a hand-washing sink must be placed not closer than 1 m to the PEC and may be either inside the SCA or in close proximity to the SCA.

Comment Summary #212: Commenters requested requiring 20 HEPA-filtered ACPH from the HVAC in the ceiling for ISO-8 spaces with no provision for supplementary air sources. Other commenters noted that PECs may require repair, so ACPH independent of PECs allows for continuity of care.

Response: Comment not incorporated. A PEC may provide ACPH, but the chapter states that 15 ACPH must come from the HVAC in the ceiling for an ISO Class 8 room. The EC found that prohibiting ACPH from PECs is too restrictive, and that it is the responsibility of the facility to meet the requirement in the chapter for the total ACPH requirement for the corresponding ISO Class. This chapter is a minimum standard and facilities and regulators may enforce additional requirements.

Comment Summary #213: The commenter requested clarification on how temperature readings would impact the need for a change in ACPH.

Response: Comment partially incorporated. “Effects of temperature” removed from the factors that influence ACPH. The EC found that while temperature would have an impact on microbial growth and proliferation, there is not an overall significant impact on ACPH requirements.

Comment Summary #214: The commenter noted that <800> allows the C-PEC to contribute 100% of the total ACPH, contradicting <797> which requires that specific levels of ACPH come from the HVAC through HEPA filters in the ceiling. This would result in expensive renovations for facilities relying on the C-PEC, which may not always be possible.

Response: Comment not incorporated. <800> states that sterile compounding must follow standards in <797>. ACPH requirements in <800> are based on where the C-PEC is located (C-SCA or ISO-7 buffer room), and whether sterile or nonsterile compounding is occurring.

Comment Summary #215: The commenter noted that, for clarity, the word “absence” should be replaced with “presence” in the following: “Air returns in the cleanroom suite must be low on the wall unless a visual smoke study demonstrates an absence of stagnant airflow where particulate will accumulate.”

Response: Comment partially incorporated. “absence” was maintained, but the text was revised to remove “where particulate will accumulate.”

Comment Summary #216: Commenters requested removing the exception to the requirement for air returns to be low on the wall if a smoke study demonstrates an absence of stagnant airflow.

Response: Comment not incorporated. The chapter provides flexibility to facilities that may not be able to locate air returns on the walls. Facilities can have air returns that are not low on the wall if a visual smoke study can demonstrate an absence of stagnant airflow where particulate will accumulate.

Comment Summary #217: The commenter requested clarification on whether a smoke study and environmental monitoring are needed anytime there is a change that affects the quality of the room, or if that only applies when there are not air returns low in the wall.

Response: Comment not incorporated. The Expert Committee finds the current wording of this statement to be sufficiently clear in stating that “this smoke study”, referring to the smoke study done if air returns are not low on the wall.

Comment Summary #218: The commenter requested clarifying that the “clean” side of an anteroom is where the anteroom is exited into the buffer room.

Response: Comment not incorporated. Chapter states that the clean side is the area closest to the buffer room.

Comment Summary #219: The commenter noted support for the incorporation of requirements to prevent hazardous drug contamination.

Response: Comment incorporated.

Comment Summary #220: The commenter noted that certification for CVEs, BSCs and CACIs used for presterilization procedures should be required every 12 months and not every 6 months, as powder containment is not related to sterility.

Response: Comment not incorporated. Presterilization procedures can affect the air quality and ISO requirement for the buffer room, so certification every 6 months is appropriate. Additionally, stakeholders have previously requested that the frequency be changed from 12 months to 6 months.

Comment Summary #221: The commenter recommended removing the chapter references to the Controlled Environment Testing Association (CETA) *Certification Guide for Sterile Compounding Facilities* for procedures to certify a compounding area.

Response: Comment incorporated. The EC has removed all references to professional organizations from the chapter and has concluded that the chapter sufficiently outlines the requirements for certification. The revised text clarifies that a compounding area used to compound Category 1, Category 2, or Category 3 CSPs must first be independently certified using the requirements in this chapter, and when applicable, manufacturer specifications.

Comment Summary #222: The commenter noted disagreement with the removal of the CETA reference and requested that USP provide specific standards for evaluation and certification of PECs and SECs.

Response: Comment not incorporated. The EC has removed all references to professional organizations from the chapter and has concluded that the chapter sufficiently outlines the requirements for certification. The revised text clarifies that a compounding area used to compound Category 1, Category 2, or Category 3 CSPs must first be independently certified using the requirements in this chapter, and when applicable, manufacturer specifications.

Comment Summary #223: The commenter requested revising the “should” to a “must” in the recommendation that furniture, equipment and materials in a classified area or SCA should be low-shedding and easily cleaned and disinfected.

Response: Comment not incorporated. The Expert Committee supports this practice but finds its requirement overly prescriptive. This chapter is a minimum standard and facilities may enforce more stringent requirements.

Comment Summary #224: The commenter requested clarification on whether the sink needs to be cleaned on a Monday morning if left in a clean state over the weekend.

Response: Comment partially incorporated. The text has been revised to “surfaces of the sink must be cleaned and disinfected each day of use”.

Comment Summary #225: The commenter requested that the SCA be required to be a dedicated room instead of an area with a visible perimeter.

Response: Comment not incorporated. The SCA design is intended to provide flexibility to facilities preparing Category 1 CSPs with shorter BUDs. This chapter is a minimum standard and facilities may enforce more stringent requirements.

Comment Summary #226: Several commenters requested an allowance for Category 2 CSPs to be compounded in an isolator or SCA and noted that a RABS is able to maintain ISO-5 conditions in an unclassified space.

Response: Comment not incorporated. The Expert Committee has not found validated evidence that a RABS is able to provide sterility for longer BUDs in an SCA beyond those for Category 1 CSPs. The SCA provides a flexible approach for facilities that do not have a cleanroom suite to provide needed medications for patients. The risk associated with using an unclassified SCA is mitigated by facility design requirements described in the chapter and the shorter BUDs.

Comment Summary #227: The commenter requested that the requirement for “no turbulence or refluxing at any critical sites for a robotic enclosure” be extended to apply to all PECs.

Response: Comment not incorporated. The chapter states that “HEPA-filtered air must be supplied by the PEC at a velocity sufficient to sweep particles away from critical sites and maintain unidirectional airflow during operations. Proper design, control, and use minimizes turbulence and creation of eddies or stagnant air in the PEC.” The Expert Committee also noted that this is a requirement assessed during certification of all PECs.

Comment Summary #228: The commenter requested clarification as to why a robotic enclosure requires a smoke study every 6 months if no changes were made to the enclosure.

Response: Comment not incorporated. The chapter states that this is to ensure that the RABS is properly integrated into the facility and that compounders understand how to utilize the unidirectional airflow to maintain first air in the DCA.

Comment Summary #229: Commenters requested that dynamic airflow smoke pattern test be performed only if there are changes to the area or alternation in the configuration of the room that could affect air quality.

Response: Comment not incorporated. Performing a dynamic smoke pattern test only in the situations described above may be too infrequent to detect any potential issues. Further, the frequency of performing dynamic smoke pattern tests aligns with the frequency of recertification (see 5. *Certification and Recertification*).

Comment Summary #230: Multiple commenters requested clarifying that not all “preparation” for the compounding of CSPs must be done in an ISO Class 5 or better PEC, that this should only apply to aseptic processing and that presterilization (preparation) procedures should be excluded.

Response: Comment partially incorporated. The word “prepared” was changed to “compounded” in the following: “Category 1, Category 2, and Category 3 CSPs must be compounded in an ISO Class 5 or better PEC. If compounding only Category 1 CSPs, the PEC may be placed in an unclassified SCA.”

Comment Summary #231: Several commenters requested clarifying that two separate PECs are not required if there is only occasional nonsterile compounding for hazardous drugs.

Response: Comment not incorporated. <797> states that if the PECs used for sterile and nonsterile compounding are placed in the same room, they must be placed at least 1 meter apart. The chapter describes the minimum requirements for placement of PECs for compounding non-HD CSPs. For compounding HDs, refer to <800>.

Comment Summary #232: A number of commenters requested clarification that “nonsterile preparations” in the following text refers to presterilization procedures: “If the PECs used for sterile and nonsterile compounding are placed in the same room, they must be placed at least 1 meter apart.”

Response: Comment partially incorporated. Presterilization was added as an example in parentheses.

Comment Summary #233: The commenter requested defining “equipment” as it relates to the requirement that a smoke study must be repeated whenever a change is made to the placement of equipment...that affects the quality of the air.”

Response: Comment not incorporated. The EC found that the text is sufficiently clear that the smoke study must be repeated whenever a change is made that affects the quality of the air and lists as examples HVAC alternations or change of HEPA filter units.

Comment Summary #234: The commenter requested that the requirement that sterile compounding facilities be designed to provide a well-lighted and comfortable environment be changed to a recommendation, because while they agree with the requirement, the referenced <1066> is a guidance document and not compendially applicable.

Response: Comment not incorporated. The EC maintains that a well-lighted and comfortable environment is required to ensure comfortable conditions for compounding personnel. The reference to “see *Physical Environments that Promote Safe Medication Use* <1066>” does not make <1066> compendially applicable. Compendial applicability is described in the *General Notices*.

Comment Summary #235: The commenter requested allowing tacky mats on the dirt side of the anteroom to trap dust and prevent it from entering the buffer room.

Response: Comment not incorporated. Tacky mats are often a source of contamination and must not be placed in an ISO classified area. Further, the area around the tacky mat is difficult to clean.

Comment Summary #236: A number of commenters requested exceptions to the requirement that inlaid ceiling panels must be caulked around each panel to seal them to the support frame. Commenters requested allowing a gasketed system, or weighted panels, or other forms of secured tiles.

Response: Comment not incorporated. The EC found that other methods of sealing the panels do not suffice to maintain the quality of the environment. Additionally, several stakeholders previously requested that sealing the panels be limited to caulking around each panel.

Comment Summary #237: The commenter requested that an “integral decontamination system” be defined as it relates to the elements of a pharmaceutical isolator, as there are multiple standards for the integral decontamination system and better clarification is required to ensure compliance.

Response: Comment not incorporated. This information is more specific than the minimum standards described in the chapter. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #238: The commenter requested recommending, not requiring, that a line of demarcation separate the clean and dirty sides of an anteroom, to allow for various facility designs.

Response: Comment not incorporated. The chapter allows for various facility designs, including the use of two separate anterooms. Otherwise, a line of demarcation must separate the clean and dirty sides to provide guidance for personnel when garbing and moving materials to and from the buffer room.

Comment Summary #239: The commenter requested clarification on the activities allowed or prohibited on the dirt vs the clean side of the line of demarcation, specifically as it related to where specific garbing must occur.

Response: Comment not incorporated. The chapter states that the order of garbing and the location of where garbing occurs (e.g., anteroom, buffer room, or SCA) must be determined by the facility and documented in the facility’s SOP. The order of garbing and location where garbing occurs would depend on the type of garbing used (e.g., sterile gowns) and the placement of the sink (e.g., if the sink is located inside or outside of the anteroom).

Comment Summary #240: Several commenters requested prohibiting nonsterile compounding, even in a separate PEC placed 1 meter apart, in the same cleanroom where sterile compounding is taking place.

Response: Comment not incorporated. This allowance was maintained to allow for presterilization procedures, and the text was revised to list presterilization procedures as an example of nonsterile compounding that may take place in a cleanroom. Presterilization procedures must be performed in at least an ISO Class 8 environment to reduce the risk of contamination to the CSP.

Comment Summary #241: The commenter requested clarification on what testing (e.g. particle count studies) would suffice to meet the requirement that the PECs used for sterile and nonsterile compounding placed in the same room are sufficiently effective to maintain ISO-7 classification.

Response: Comment not incorporated. Maintaining the proper ISO-7 classification is part of the routine certification and recertification under dynamic conditions, as described in *Section 5. Certification and Recertification*.

Comment Summary #242: Commenters requested that the subsection “Facilities preparing Category 2 or Category 3 CSPs from nonsterile starting components”, which requires that presterilization procedures be done in an isolator, should be removed, as *Section 9.1 Equipment* allows for assessing whether handling components requires an isolator.

Response: Comment not incorporated. Presterilization procedures could generate airborne particles that negatively affects the quality of the environment, so when done as part of compounding, these activities must be done in an ISO Class 8 environment or better and must be performed in a single-use containment glove bag, CVE, BSC or CACI to minimize the risk of airborne contamination. *Section 9.1* requires that all weighing, measuring, and manipulating components be evaluated to determine if it must be done in a PEC or other closed system processing device, and references *Section 4.2*, which specifies that when these activities are done as part of presterilization procedures for compounding Category 2 and Category 3, then they must be done in a single-use containment glove bag, CVE, BSC or CACI.

Comment Summary #243: Commenters requested that removing the statement “For placement of a pharmaceutical isolator used for the preparation of HDs, see <800>”, as <800> does not reference “pharmaceutical isolators”.

Response: Comment incorporated. Statement was removed.

Comment Summary #244: The commenter requested expanding the range for negative-pressure rooms, as -0.01 to -0.03 is too restrictive for many facilities.

Response: Comment not incorporated. The chapter requires that in a cleanroom suite, a minimum differential positive pressure of 0.020-inch water column is required between adjacent ISO-classified areas (e.g., between the buffer room and anteroom). The pressure differential between the anteroom and the unclassified area must not be less than 0.020-inch water column. The upper limit of negative pressure in <800> is intended to minimize the risk that contamination will be pulled in from lower-air-quality to higher-air-quality environments.

Comment Summary #245: Commenters requested clarifying why a daily review of the results of a pressure monitoring device is required and suggested that reviewing trends over a few days is more helpful than one point in time, especially when the continuous monitoring device in use has an alarm. Further, it was noted that boards of pharmacy are interpreting the section to include daily documentation of RABS as there is a pressure differential between the transfer and compounding chamber.

Response: Comment not incorporated. The Expert Committee determined that there should still be daily review of the pressure in the classified areas to ensure that the pressure is maintained at the appropriate level during compounding activities. Further, it states that “Where pressure differentials are required, a pressure differential monitoring device must be used...”. USP has

no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #246: The commenter requested that the pressure differential between the buffer room and anteroom be specifically required, and not listed as an e.g. in the following “In a cleanroom suite, a minimum differential positive pressure of 0.02-inch water column is required between each ISO classified area (e.g., between the buffer room and anteroom).”

Response: Comment not incorporated. The EC determined that the language was sufficiently clear in describing a pressure cascade between each adjacent ISO-classified area, and between the anteroom and the unclassified area.

Comment Summary #247: The commenter requested clarifying whether the data on a continuous pressure differential monitoring device must have a system for saving the continuously logged data, or whether recoding the value on a different pressure gauge once daily meets the requirements. The commenter requested specifying that the data must be downloaded and reviewed at least once daily.

Response: Comment not incorporated. The EC finds that the text is sufficiently clear in stating that “Where pressure differentials are required, a pressure differential monitoring device must be used to continuously monitor the pressure differentials.

The quantitative results from the pressure monitoring device must be reviewed and documented at least daily on the days when compounding is occurring.” The chapter is a minimum standard, and facilities and regulators may enforce additional requirements.

Comment Summary #248: The commenter noted that the requirement to clean the sink before initiating hand hygiene and garbing if compounding is not performed daily is logistically difficult, as it would require donning garb to clean the sink, then doff and don again to perform hand hygiene.

Response: Comment incorporated. The statement was revised to “Surfaces of the sink(s) must be cleaned and disinfected each day of use, and a sporicidal disinfectant must be applied at least monthly.”

Comment Summary #249: The commenter noted that the requirement that the sink must not be located inside the perimeter of the SCA compromises garbing and hand hygiene practices, and instead to allow it to be located in the SCA but at least 1 meter away from the PEC.

Response: Comment incorporated. The text was revised to “In a facility with an SCA design, a hand-washing sink must be placed not closer than 1 m to the PEC and may be either inside the SCA or in close proximity to the SCA.”

Comment Summary #250: The commenter noted that hand-washing sinks should be exclusively placed on the clean side of the anteroom.

Response: Comment not incorporated. The EC maintains that if the sink is located inside the anteroom, it may be placed on either the clean side or the dirty side of the anteroom, to allow for various facility designs. This chapter is a minimum standard, and facilities may enforce additional requirements.

Comment Summary #251: The commenter requested requiring that the sink in a cleanroom suite be within the anteroom.

Response: Comment not incorporated. The EC maintains that in facilities with a cleanroom suite, the sink used for hand hygiene may be placed either inside or outside of the anteroom to accommodate various facility designs.

Comment Summary #252: The commenter requested adding the temperature and humidity requirements of an SCA, in addition to those listed for a cleanroom suite.

Response: Comment not incorporated. The listed temperature and humidity ranges are recommendations and not requirements. Stakeholders have noted difficulties in maintaining certain temperatures and relative humidity in unclassified SCAs. Facilities must determine the appropriate temperature and relative humidity for the compounding area.

Comment Summary #253: Several commenters requested that the required temperature and humidity be instead listed as a range of acceptable temperature. Commenters noted concerns that the cleanroom suite temperature, at 20° and below, is out of the range of storage temperatures for most medication

Response: Comment not incorporated. The listed temperature and humidity ranges are recommendations and not requirements. Facilities must determine the appropriate temperature and relative humidity for the compounding area. Further, facilities may adjust the cleanroom temperature to allow for storage of medications.

Comment Summary #254: The commenter requested adding that the use of professional calibration of temperature and humidity monitoring devices suffices as verification of accuracy of the equipment.

Response: Comment not incorporated. This detail is more specific than the minimum standards in this chapter. The chapter requires that the temperature and humidity monitoring devices be verified for accuracy at least every 12 months, or as required by the manufacturer. The chapter does not describe how the verification must occur. Further, the EC finds that calibration may be more burdensome than verification.

Comment Summary #255: Multiple commenters requested an upper limit for temperature and humidity requirements in the cleanroom suite.

Response: Comment not incorporated. The chapter recommends a temperature of 20° or lower and a relative humidity below 60%. Facilities must determine the appropriate temperature and relative humidity for the compounding area, which can be verified through microbial air and surface sampling.

Comment Summary #256: Commenters requested clarifying that temperature and humidity readings must be documented only on days that compounding occurs.

Response: Comment not incorporated. The chapter allows for either daily documentation of the readings, or storage in a continuous recording device that is retrievable. The readings must be reviewed as described in the facility's SOPs.

Comment Summary #257: The commenter noted that the temperature and humidity requirements are not in alignment with regulatory expectations for compounders elsewhere.

Response: Comment not incorporated. The listed temperature and humidity ranges are recommendations and not requirements. Facilities must determine the appropriate temperature and relative humidity for the compounding area. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #258: The commenter requested that we add "higher than the recommendations in this chapter" to this statement: "The ACPH may need to be higher to maintain the required ISO classification...".

Response: Comment not incorporated. The Expert Committee finds the current wording of this statement to be sufficient.

Comment Summary #259: The commenter requested that the word "can" be changed to "may" in the following: "Only Category 1 CSPs can be compounded in an SCA.", as may dictates permission.

Response: Comment incorporated.

Comment Summary #260: The commenter requested separating the text discussing pressure-differential monitoring systems from the paraph preceding it as it is a separate topic.

Response: Comment incorporated.

Comment Summary #261: The commenter requested consolidating all the boxes on *Table 3* that state "ISO Class 7 positive-pressure buffer room with an ISO Class 8 positive-pressure anteroom."

Response: Comment not incorporated. The EC maintained the table for added clarity.

Comment Summary #262: The commenter requested reformatting the bullet points describing ACPH to match.

Response: Comment incorporated.

Comment Summary #263: A compounder requested adding a provision for new technology regarding “the buffer room must not contain plumbed water sources”, as some newer technology such as hazardous compounding robots require water sources.

Response: Comment not incorporated. The Expert Committee decided that the additional descriptions are too prescriptive. Further, the chapter states that the use of technologies, techniques, materials, and procedures other than those described in the chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose (e.g., *Validation of Alternative Microbiological Methods* (1223) and *Validation of Compendial Procedures* (1225)). Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #264: The commenter requested clarifying if weighing and measuring of nonsterile products needs to be done in an ISO Class 8 space or per facility SOPs.

Response: Comment not incorporated. The chapter specifies that these procedures must be completed in an ISO Class 8 or better environment.

Comment Summary #265: The commenter noted that the text should be revised to require a change of garb after presterilization procedures are complete, prior to performing aseptic manipulation.

Response: Comment not incorporated. The EC found that this might be overly prescriptive and burdensome to compounders. The chapter does require that presterilization procedures be done in a CVE, BSC, CACI or a single use containment glove bag to minimize the risk of airborne contamination. This chapter is a minimum standard, and facilities and regulators may enforce additional requirements.

5. Certification and Recertification

Expert Committee-initiated Change #1: The phrase “It is important to place special emphasis on certifying the ISO Class 5 areas” was deleted from the text for conciseness and clarity.

Comment Summary #266: The commenter requested clarifying why dynamic airflow smoke pattern tests only apply to a PEC and not the SEC.

Response: Comment not incorporated. The dynamic airflow smoke test that is described in this section must be done initially to certify a classified area and every 6 months in a PEC is to demonstrate unidirectional airflow over and away from the preparation. The EC did not intend this to be completed for the SEC, unless as specified in *Section 4.2.1 Types of SECs and design*, which states that a smoke study must be conducted if air returns are not low on the wall, or whenever there is change to the placement of equipment within the room or other alteration that affects the quality of the air.

Comment Summary #267: The commenter requested clarification on whether HEPA filter factory testing done before publication of this chapter is required to be retrieved.

Response: Comment not incorporated. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #268: The commenter requested specifying a number for an acceptable air velocity.

Response: Comment not incorporated. The air velocity cannot be specified as it is dependent on HEPA filters and other factors. This is determined during the certification process.

Comment Summary #269: The commenter requested requiring recertification after corrective action has been taken in response to out-of-range results, to ensure that the corrective action is effective.

Response: Comment not incorporated. Corrective action depends on the specific out of range result. Re-certification of the entire room may not be required. The chapter requires that data collected in response to corrective actions must be reviewed to confirm that the actions taken have been effective.

Comment Summary #270: The commenter requested removing the phrase “It is important to place special emphasis on certifying the ISO Class 5 areas.”

Response: Comment incorporated.

Comment Summary #271: Commenters requested including a requirement for smoke studies of the ISO-classified SECs, regardless of location of air returns.

Response: Comment not incorporated. The EC determined that the current requirements are sufficient and this might be too prescriptive for compounders. This chapter is a minimum standard, and facilities and regulators may enforce additional requirements.

Comment Summary #272: Commenters requested clarifying the meaning of “largest number of personnel and highest complexity” as it related to dynamic operating conditions for the airflow smoke pattern test.

Response: Comment not incorporated. Dynamic operating conditions is defined as Conditions in the compounding area in which operating personnel are present and simulating or performing compounding. The definition also recommends that the conditions should reflect the largest number of personnel and highest complexity of compounding expected during routine operations as determined by the designated person(s). The procedures to be used during dynamic operating conditions must be facility-specific.

Comment Summary #273: Multiple commenters noted that dynamic airflow smoke pattern test should be required only initially and when there are changes to the facility, and not every 6 months.

Response: Comment not incorporated. A dynamic airflow smoke pattern test must be performed initially and every 6 months. Performing it only in the event of a move or in anticipation of airflow changes is too infrequent to capture functionality issues in a timely manner.

Comment Summary #274: The commenter requested requiring that documentation of personnel present during the dynamic airflow smoke test also include documenting the number of certifying personnel as that affects the total bioburden.

Response: Comment not incorporated. This chapter is a minimum standard, and facilities may enforce additional requirements.

Comment Summary #275: The commenter recommended merging “A monitoring program for total airborne particles must be developed and implemented to measure the performance of the engineering controls that are being used to provide the specified levels of air cleanliness (e.g., in the ISO Class 5 PEC and ISO Class 7 and 8 rooms)” with “This monitoring program must include total airborne particle count testing in all classified areas during dynamic operating conditions at least every 6 months,” to clarify that it is the same test.

Response: Comment incorporated. The new statement is “Total airborne particle count testing must be conducted in all classified areas during dynamic operating conditions at least every 6 months to measure the performance of the engineering controls that are being used to provide the specified levels of air cleanliness (e.g., in the ISO Class 5 PEC and ISO Class 7 and 8 rooms).”

Comment Summary #276: The commenter suggested revising the sentence “It is imperative that all engineering control equipment function as designed and that the levels of total airborne particles remain within acceptable limits during compounding” to clarify avoid implying that the compounder must monitor during the preparation of every CSP.

Response: Comment incorporated. The text was revised to “The engineering control equipment function must function as designed to ensure that the levels of total airborne particles remain within acceptable limits during compounding (see *Table 4*).

Comment Summary #277: The commenter requested requiring recertification every 3 months, as 6 months is inadequate to assess environmental control.

Response: Comment not incorporated. The EC found that this may be overly burdensome to compounders. This chapter is a minimum standard, and facilities and regulators may enforce additional requirements.

6. Microbiological Air and Surface Monitoring

Expert Committee-initiated Change #1: Subsections of 6.2 *Monitoring Air Quality for Viable Airborne Particles* and 6.3 *Monitoring Surfaces for Viable Particles* were numbered for ease of navigation and to improve clarity.

Expert Committee-initiated Change #2: An exception was added to the surface sampling of a PEC used to prepare Category 3 CSPs to address self-enclosed robotic devices. “Additionally, surface sampling must be conducted within the PEC used to prepare Category 3 CSPs, at the end of each batch before cleaning and disinfection occurs, *unless a self-enclosed robotic device is used. When a self-enclosed robotic device is used as the PEC to prepare Category 3 CSPs, surface sampling must be conducted at least once daily at the end of compounding operations, before cleaning and disinfection occurs.*”

Expert Committee-initiated Change #3: The term “device” was revised to either sampling device or media device throughout the text for clarity.

Expert Committee-initiated Change #4: The statement was revised in *Box 5. Active Air Sampling Procedures for Viable Airborne Monitoring* and in *Box 6. Surface Sampling Procedures*, stating to, “Handle and store samples to avoid contamination and prevent condensate from dropping onto the agar during incubation and affecting the accuracy of the CFU reading (e.g., invert containers)”.

Expert Committee-initiated Change #5: Language was revised for clarity to state, “It is important that personnel are trained and competent in air and surface sampling procedures to ensure accurate and reproducible sampling.”

Expert Committee-initiated Change #6: An instance of “must” was revised to be “should” for the statement, “When conducted, surface sampling should be performed at the end of a compounding activity or shift but before the area has been cleaned and disinfected”, to consider certification personnel.

Comment Summary #278: The commenter requested adding clarification on including procedures for the review of sampling data in the facility’s SOPs.

Response: Comment not incorporated. Chapter states that facilities must develop and implement written procedures for air and surface monitoring, and that all procedures, test results, and corrective actions must be documented, and the records must be maintained.

Comment Summary #279: The commenter requested that specific ISO standards be referenced for surface sampling.

Response: Comment not incorporated. The action levels for surface sampling are outlined in *Table 8*.

Comment Summary #280: The commenter noted that monthly viable air sampling tests are more important than surface sampling, as surface sampling almost always consists of skin flora, whereas air sampling is affected by various factors.

Response: Comment not incorporated. Surface sampling is useful for evaluating facility cleaning and handling procedures, work surface cleaning and disinfecting procedures and personnel competency in work practices such as cleaning and disinfecting.

Comment Summary #281: The commenter indicated that monthly viable air sampling should only be required if there are repeated failures in surface sampling.

Response: Comment not incorporated. For entities compounding Category 1 and Category 2 CSPs, viable air sampling must be completed at least every 6 months. For entities compounding any Category 3 CSPs, this must be completed within 30 days prior to the commencement of any Category 3 compounding and at least monthly thereafter regardless of the frequency of compounding Category 3 CSPs.

Comment Summary #282: The commenter stated that volumetric air sampling should be performed on a quarterly basis at minimum, to ensure that weather changes have no effect on the HVAC, and alerts personnel to issues in a timely manner.

Response: Comment not incorporated. The expert committee supports more frequent monitoring, but many commenters noted that more frequent monitoring is burdensome and impractical for many facilities. This chapter is a minimum standard, and facilities and regulators may implement additional or more stringent requirements.

Comment Summary #283: The commenter noted that initial and air and surface monitoring must be conducted under both static and dynamic conditions, to help identify whether personnel or the environment is the reason for excursions.

Response: Comment not incorporated. The expert committee supports more frequent monitoring, but many commenters noted that more frequent monitoring is burdensome and impractical for many facilities. This chapter is a minimum standard, and facilities and regulators may implement additional or more stringent requirements.

Comment Summary #284: The commenter requested clarifying if changing HEPA filters qualifies as servicing of equipment that requires air sampling.

Response: Comment not incorporated. *Section 4* lists change of HEPA filter units as an example of activities that affect the quality of the air and would require environmental monitoring.

Comment Summary #285: Multiple comments requested clarification on what activities require viable air sampling, for example changing filters or caulking a small area or pass-through chamber. Others suggested adding examples in supplementary documents or FAQs.

Response: Comment not incorporated. The specific activities are situational and depend on whether or not the air quality and environment are affected.

Comment Summary #286: The commenter requested that the action level for air sampling be changed from > 1 cfu to =1 cfu, as the PEC must be free of any contamination.

Response: Comment not incorporated. This chapter is a minimum standard, and facilities and regulators may implement additional or more stringent requirements.

Comment Summary #287: The commenter suggested adding a range for incubation, such as 48-72 hours, or 5-7 days, as samples left in the incubator can dry out.

Response: Comment not incorporated. The chapter is a minimum standard, but the EC will consider addressing additional best practices for incubation in supplementary materials.

Comment Summary #288: The commenter requested clarifying the number of sampling sites required per PEC or room.

Response: Comment not incorporated. The number of sampling sites per classified area must be determined by the facility SOPs. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #289: The commenter requested that CFU counts be considered as a cumulative count and not a per plate count for each ISO classified space. The commenter also requested reducing the action levels for ISO Class 8 to align with the surface sampling limits.

Response: Comment not incorporated. If two sampling media devices are collected at a single location, all recovered growth on each must be documented and action levels applied to each sampling media device separately. Air and surface sampling have different action levels but

they are sampling different aspects of the classified area. The action levels are consistent with the previous version of <797>.

Comment Summary #290: The commenter noted that the sentence that “samples must be incubated in an incubator at temperatures that will promote growth of bacteria and fungi” contradicts the specific incubation parameters in *Box 5*, as it implies that organizations may decide their own temperatures.

Response: Comment incorporated. The sentence was revised to “Samples must be incubated in an incubator at the temperatures listed in *Box 5*.”

Comment Summary #291: The commenter recommended requiring that facilities re-perform the viable air monitoring to ensure that corrective actions have resolved out of range levels.

Response: Comment incorporated. The text was revised to, “The corrective action plan must be documented and should include resampling of failed areas to confirm corrective action was successful.”

Comment Summary #292: The commenter suggested that the requirement that an attempt must be made to identify microorganisms recovered from air sampling to the genus level is unclear as to what “an attempt” means, and this will likely be used to justify failure to identify microorganisms. It would also make it impossible to meet the requirement that the corrective action plan be dependent on the cfu and the microorganism recovered.

Response: Comment not incorporated. Previous commenters have noted difficulty or concerns with practicality to require identification of every cfu encountered, and there are times when the microorganism cannot be identified.

Comment Summary #293: The commenter noted that the text was unclear as to whether growth from air sampling on two plates is assessed cumulatively against the action levels, or if each plate is assessed separately.

Response: Comment incorporated. The text was clarified that if two sampling media devices are collected at a single location, all recovered growth on each must be documented and action levels applied to each sampling media device separately.

Comment Summary #294: The commenter suggested that requiring air monitoring monthly if compounding Category 3 CSPs is expensive and should only be required monthly if there has been a surface sample monitoring issue or sterility testing failure, as this would be a great additional measure to ensure high air quality when there has been an out of specification result.

Response: Comment not incorporated. The Expert Committee decided that air sampling for Category 3 CSPs is required monthly to capture enough data points to identify trends and demonstrate that the quality of the environment is able to be achieved and maintained. The additional requirements for Category 3 CSPs must be met in order to allow for the longer BUDs.

Comment Summary #295: The commenter recommended removing the word “plate” from *Table 5*, as plates are not the only device that is used with air samplers. Other commenters requested consistency in the terms used to describe sampling devices, and reserve the term “device” for plates, paddles, contact slides, etc.

Response: Comment incorporated. The terms have been changed throughout the chapter and are referred to as either media devices or sampling devices.

Comment Summary #296: The commenter recommended requiring that incubator temperatures be reviewed during incubation at least on a daily basis and not just daily on the days the compounding facility is open.

Response: Comment not incorporated. Comments have previously noted that they are not open daily and may not be able to monitor incubation temperatures daily. This chapter is a minimum standard, and facilities may implement additional or more stringent requirements and document these in facility SOPs.

Comment Summary #297: The commenter noted that entities compounding Category 3 CSPs should require continuous monitoring of air samples to know that the environment is controlled.

Additionally, compounders cannot put the sampling device in the PEC while compounding without disrupting unidirectional air flow, BUDs should not exceed those of Category 2 CSPs.

Response: Comment not incorporated. Other commenters have indicated that increased monitoring is burdensome, impractical, and cost-prohibitive. The Expert Committee supports more frequent monitoring. This chapter is a minimum standard and entities may implement additional or more stringent requirements. Additionally, the Expert Committee has identified a need for BUDs to extend beyond those of Category 2 CSPs, and facilities that compound Category 3 CSPs must meet additional requirements at all times to ensure the quality of the environment.

Comment Summary #298: The commenter requested requiring the identification of organisms for any growth on air sampling, regardless of cfu count. Otherwise, it is not possible to identify highly pathogenic organisms in lower counts. The commenter also requested discussing highly pathogenic organisms in the text.

Response: Comment not incorporated. ISO Class 7 and ISO Class 8 areas are permitted to have some level of viable particles (see *Table 5*). Commenters in the past have noted that it is too burdensome to require identification of all microorganisms. Further, most microorganisms are potentially pathogenic if they contaminate CSPs. The term highly pathogenic may be interpreted differently among users.

Comment Summary #299: The commenter requested removing the requirement that an attempt must be made to identify organisms to the genus level if levels measured during viable air sampling exceed action level, as this is costly and time-consuming.

Response: Comment not incorporated. This is only required when the levels exceed action levels. Facilities should obtain the assistance of a microbiologist for identifying microorganisms to the genus level. Not every single cfu may be required to be identified. For example, there may be several cfu that have similar morphology and can be visually identified as the same microorganism without separate identification steps.

Comment Summary #300: The commenter noted concern about the availability of tools required for the monthly surface sampling. Other commenters noted that this frequency is impractical due to the time it takes to receive a surface sample test result from a vendor. Others recommended the frequency be changed to quarterly instead of monthly, or using a sliding scale frequency, starting at every 3 months, increasing to monthly in case of failure and decreasing to every 6 months for consistent negative results.

Response: Comment not incorporated. The Expert Committee decided to require surface sampling monthly, and viable air sampling every 6 months for entities compounding Category 1 and Category 2 CSPs. Surface sampling is useful for evaluating facility cleaning and handling procedures, work surface cleaning and disinfecting procedures and personnel competency in work practices such as cleaning and disinfecting. This frequency also allows for assessment and identification of trends over time, given that changes in staffing, environment, etc.

Comment Summary #301: The commenter requested specifying that an SCA is not a classified area and does not require viable air sampling.

Response: Comment not incorporated. The SCA is defined in the glossary as an area not required to be classified.

Comment Summary #302: Commenters requested removing the requirement for surface sampling at the end of a shift and noted that specifying surface sampling at the end of a compounding activity suffices, as it may be confusing to identify when to conduct surface sampling with overlapping shifts in a 24/7 facility. It also would require that certifiers stay until the end of a shift, making scheduling sampling times difficult.

Response: Comment incorporated. The statement was revised from a “must” to a “should”: “When conducted, surface sampling should be performed at the end of a compounding activity or shift but before the area has been cleaned and disinfected.”

Comment Summary #303: The commenter requested additional information on what is required for the initial environmental sampling.

Response: Comment not incorporated. Facility SOPs must describe the details of the initial environmental sampling beyond that provided in the chapter.

Comment Summary #304: The commenter suggested that environmental monitoring requirements for Category 3 CSPs should be more stringent, specifically that surface sampling after compounding should be performed in the cleanroom suite and not only in the PEC.

Response: Comment not incorporated. The chapter requires, for Category 3 CSPs, that surface sampling of all classified area and pass-through chambers occur prior to assigning a BUD longer than those in *Table 13* and at least weekly. In addition to this, surface sampling of the PEC must occur at the end of each batch. Other commenters have noted difficulties in implementing more frequent surface sampling. This chapter is a minimum standard, and facilities may implement additional or more stringent requirements.

Comment Summary #305: The commenter noted that the proposed viable air monitoring is inadequate to assess a state of control for Category 1 and Category 2 CSPs, and the twice yearly monitoring does not provide adequate data points to conduct trends. The commenter also noted a lack of increased frequency for nonsterile to sterile compounding.

Response: Comment not incorporated. Other commenters have noted difficulties in implementing more frequent surface sampling. This chapter is a minimum standard, and facilities may implement additional or more stringent requirements.

Comment Summary #306: The commenter requested removing pass-through chambers from the areas where surface sampling must be conducted, as they are not required to be classified. Others noted that it is unclear what action level to use to assess unclassified pass-through chambers.

Response: Comment not incorporated. The EC noted that unclassified pass-through chambers are often a source of contamination, and surface sampling can identify trends and provide verification of proper cleaning procedures of the pass-through chamber.

Comment Summary #307: The commenter requested clarification on the frequency of monitoring if Category 3 CSPs are rarely compounded.

Response: Comment not incorporated. The chapter states that the more stringent requirements for compounding Category 3 CSPs apply at all times where Category 3 CSPs are compounded, regardless of whether or not they are compounded on a given day.

Comment Summary #308: Commenters noted an error in the action levels for surface sampling for ISO Class 5 stating 3. The action level should be >3.

Response: Comment incorporated.

Comment Summary #309: The commenter requested an action level of 1 CFU for surface sampling, as that is consistent with regulatory requirements internationally.

Response: Comment not incorporated. USP has no role in enforcement. This chapter is a minimum standard, and regulators may choose to enforce additional or more stringent requirements.

Comment Summary #310: A number of commenters requested that the bullet specifying surface sampling of frequently touched surfaces be clarified that the frequently touched surface needs to be evaluated for risk, as not every such surface can be sampled, for example the gowning bench would not provide sufficient data.

Response: Comment partially incorporated. The text was revised from each classified area must be sampled, including...frequently touched surfaces”, to “Each classified area, including each room and the interior of each ISO Class 5 PEC and pass-through chambers connecting to classified areas, must be sampled for microbial contamination using a risk-based approach. Samples should be taken from the following classified areas:...”

Comment Summary #311: The commenter requested adding corrective action if data trends indicate a sudden increase, even if it is below the action level.

Response: Comment not incorporated. The chapter states to “Evaluate cfu counts against the action levels in *Table 6*, and examine counts in relation to previous data to identify adverse results or trends.” Further, the chapter specifies that the investigation, part of the corrective action, should include an evaluation of trends.

Comment Summary #312: The commenter requested specifying that the surface sample collected in conjunction with the media-fill test is to be taken in the DCA, as the sample location is not clear.

Response: Comment incorporated.

Comment Summary #313: The commenter requested adding pass-through chambers as a site to surface sample in the list of recommended areas:

Response: Comment partially incorporated. The list is of specific surfaces in classified areas. Pass-through chambers may not be classified, so they are included in the text above this list: “Each classified area, including each room and the interior of each ISO Class 5 PEC and pass-through chambers connecting to classified areas, must be sampled for microbial contamination using a risk-based approach.”

Comment Summary #314: The commenter requested adding “including SCA locations” to the “staging or work areas near the PEC” as a location that requires surface sampling.

Response: Comment not incorporated. The text requires that surface sampling must occur in each classified area, and the referenced list is a list of surfaces within a classified area or pass-through chamber connecting to a classified area.

Comment Summary #315: The commenter requested clarifying whether the cleanroom may be used while awaiting retesting in the case of growth exceeding action levels for surface sampling.

Response: Comment not incorporated. The EC determined that this is too prescriptive, as this would depend on several factors, including the location of the out of specification result. Facility SOPs must determine the proper corrective action. The chapter states that the corrective action plan must be dependent on the cfu count and the microorganism recovered. Some examples of corrective action include process or facility improvements, personnel training, cleaning and disinfecting, or HEPA filter replacement and/or repair. The extent of the investigation should be consistent with the deviation and should include an evaluation of trends. The corrective action plan must be documented.

Comment Summary #316: A comment recommended removing the statement from *Box 6* to “remove residue from the surface using sterile 70% IPA”, as sterile IPA is not a cleaning agent, and the text above *Box 6* requires cleaning and disinfecting after sampling.

Response: Comment incorporated. The text was revised to “After sampling, clean and disinfect the sampled area to remove residue from the surface.”

Comment Summary #317: A comment suggested allowing the option of surface sampling or finger touch plates within the PEC used to prepare Category 3 CSPs.

Response: Comment not incorporated. The EC determined that finger touch plates are logistically impractical, in that for example, they may require a second person in the room that would also have to garb. Surface sampling provides better data on work surface cleaning and disinfecting procedures and personnel competency in such work practices. This chapter is a minimum standard, and facilities may choose to implement additional or more stringent requirements.

Comment Summary #318: The commenter noted that the sentence that “samples must be incubated in an incubator at temperatures that will promote growth of bacteria and fungi” contradicts the specific incubation parameters in *Box 6*, as it implies that organizations may decide their own temperatures.

Response: Comment incorporated. The sentence was revised to “Samples must be incubated in an incubator at the temperatures listed in *Box 6*.”

Comment Summary #319: The commenter requested allowing samples to be incubated outside of an incubator if room temperature is required.

Response: Comment not incorporated. Samples must be incubated in an incubator to ensure maintenance of incubation temperatures and to minimize the risk of inadvertent contamination.

Comment Summary #320: The commenter requested removing pH from the following requirement for surface sampling: “COAs from the manufacturer must verify that the sampling media devices meet the expected growth promotion, pH, and sterilization requirements” to be consistent with the requirements for viable air sampling.

Response: Comment partially incorporated. pH was added as a requirement to the COAs for media devices for air sampling.

Comment Summary #321: The commenter requested adding that pass-through chambers must also be surface sampled when compounding Category 3 CSPs, to maintain consistency with Category 1 and Category 2 CSP requirements.

Response: Comment incorporated.

Comment Summary #322: The commenter noted that, “The interior of the PEC and the equipment contained in it” is unclear as to whether every IV workflow device within the PEC would need to be surface sampled.

Response: Comment partially incorporated. The text was clarified that each classified area, including each room and the interior of each PEC, and pass-through chambers to classified areas must be sampled. The list of recommended sampling locations within classified areas was revised to “Equipment contained within the PEC.”

Comment Summary #323: The commenter requested clarifying that surface sampling only needs to occur in classified areas where aseptic processing occurs, and since the likelihood of microbial proliferation from ingredients and components during pre-sterilization procedures is low (due to sterilization).

Response: Comment not incorporated. Surface sampling data is required in classified spaces to ensure all processes and procedures for maintain the environment are adequate.

Comment Summary #324: The commenter requested that the action level for surface sampling be changed from > 3 cfu to > 1 cfu, as the PEC must be free of any contamination.

Response: Comment not incorporated. This chapter is a minimum standard, and facilities and regulators may implement additional or more stringent requirements. The proposed action levels for surface sampling are consistent with the existing standard and other industry guidance. Previous commenters have noted concerns that lowering the action levels may require more frequent identification of microorganisms.

Comment Summary #325: A number of commenters requested clarification on what constituted a frequently touched surface for the purposes of surface sampling.

Response: Comment not incorporated. The specific sampling locations must be facility specific and must be documented in the facility’s monitoring program.

Comment Summary #326: The commenter requested removing the requirement for surface sampling as part of the aseptic manipulation, as it does not reduce the likelihood of microbial contamination since the DCA is sanitized between each preparation lot.

Response: Comment not incorporated. Surface sampling is included as part of the aseptic manipulation competency to demonstrate the ability to stage properly and compound without contaminating the direct compounding area. Surface sampling also demonstrates the ability to properly clean and sanitize the environment and that cleaning and sanitizing agents are effective.

Comment Summary #327: Several commenters requested removing the requirement of surface sampling upon completion of each batch of Category 3 CSPs, as the other additional requirements for this category suffice to provide information on the environmental quality.

Response: Comment not incorporated. The Expert Committee determined that surface sampling after each batch is less burdensome than requiring gloved fingertip and thumb sampling after each batch. Surface sampling demonstrates the ability to stage properly and compound without contaminating the direct compounding area, and is required to reduce the risk of microbial proliferation given the longer BUDs for Category 3 CSPs.

Comment Summary #328: The commenter requested removing the surface sampling requirement after a batch if <71> testing is performed.

Response: Comment not incorporated. <71> testing does not replace or ensure proper personnel staging of the DCA and proper compounding technique. Surface sampling demonstrates the ability to stage properly and compound without contaminating the direct compounding area, and is required to reduce the risk of microbial proliferation given the longer BUDs for Category 3 CSPs.

Comment Summary #329: The commenter noted that “Surface sampling must also be conducted in conjunction with media-fill testing” is unclear as to whether it implies sampling the entire facility or cleanroom every time a media-fill test is conducted.

Response: Comment incorporated. The text was revised to clarify that “Surface sampling *in the DCA* must also be conducted in conjunction with media-fill testing...”.

Comment Summary #330: The commenter requesting limiting surface sampling to monthly if robotic technology is used.

Response: Comment not incorporated. Due to longer BUDs allowed for Category 3 CSPs, additional requirements must be met, including more frequent environmental monitoring to ensure that the environment is maintained in a state of control. This applies to robotic technology. A statement was added that for a self-enclosed robotic device, surface sampling at the end of a batch is not required, and instead must be conducted at least once daily at the end of compounding operations, before cleaning and disinfection.

Comment Summary #331: The commenter requested not requiring surface samples at the end of each batch if IV robots are used, and instead require continuous monitoring of viable air, or performing media fill during or after the batch.

Response: Comment partially incorporated. A statement was added to clarify that for a self-enclosed robotic device, surface sampling at the end of a batch is not required, and instead must be conducted at least once daily at the end of compounding operations, before cleaning and disinfection.

Comment Summary #332: Several commenters noted that the following statement is confusing and must be rephrased: “For entities compounding Category 1 and Category 2 CSPs, surface sampling of all classified areas and pass-through chambers connecting to classified areas for microbial contamination must be conducted at least monthly.”

Response: Comment incorporated. “for microbial contamination” was removed.

7. Cleaning, Disinfecting, and Applying Sporicidal Disinfectants and Sterile 70% IPA

Expert Committee-Initiated Change #1: The section was restructured and renumbered to improve clarity.

Expert Committee-Initiated Change #2: The title was revised for *Table 10. Minimum Frequency for Cleaning and Disinfecting Surfaces and Applying Sporicidal Disinfectants in Classified Areas and in the SCA.*

Expert Committee-Initiated Change #3: Revisions were made to clarify that sterile 70% IPA is used.

Expert Committee-Initiated Change #4: The description of “cleaning agent” was revised.

Expert Committee-Initiated Change #5: Language was added to clarify the requirements for disinfecting with an EPA-registered disinfectant (or equivalent for entities outside the US). Additionally, a statement was added to clarify that once opened, sterile cleaning and disinfecting agents and supplies (e.g., closed containers of sterile wipers) and sterile 70% IPA may be reused for a time period specified as by the manufacturer and/or described in the facility written SOPs.

Comment Summary #333: Commenters indicated that the structure of the table representing the minimum frequencies for cleaning and disinfecting surfaces and applying sporicidal disinfectants in classified areas and within the perimeter of the SCA is unclear and overwhelming. Some commenters recommended splitting the table into more than one, such as for Category 1 and 2 CSPs and a separate table for Category 3 CSPs.

Response: Comment partially incorporated. The table of minimum frequencies for cleaning, disinfecting, and applying sporicidal disinfectants in classified areas and in the SCA was reformatted, and the processes included in the table were moved to the chapter text for clarity.

Comment Summary #334: The commenter recommended removing the requirement that cleaning and disinfecting must be completed before initiating compounding.

Response: Comment incorporated. The chapter states the minimum frequencies for cleaning, disinfecting, and applying sporicidal disinfectants in classified areas and in the SCA, and was revised to not specify when during the day this must be done. This is a topic that may be described in the facility’s SOPs.

Comment Summary #335: Commenters recommended that cleaning and disinfecting should be done daily on days when compounding occurs before compounding, and indicated there should be consistent verbiage between cleaning and disinfecting.

Response: Comment partially incorporated. The chapter states the minimum frequencies for cleaning, disinfecting, and applying sporicidal disinfectants in classified areas and in the SCA, and was revised to not specify when during the day this must be done. This is a topic that may be described in the facility’s SOPs. The table of minimum frequencies for cleaning, disinfecting, and applying sporicidal disinfectants in classified areas and in the SCA was reformatted, and the processes included in the table were moved to the chapter text for clarity.

Comment Summary #336: Commenters recommended that PEC(s) and equipment inside the PEC(s), and removable work tray of PECs, be cleaned and disinfected daily before compounding, on days when compounding occurs.

Response: Comment partially incorporated. The chapter states the minimum frequencies for cleaning, disinfecting, and applying sporicidal disinfectants in classified areas and in the SCA, and was revised to not specify when during the day this must be done. This is a topic that may be described in the facility’s SOPs. The language was revised to indicate that equipment and all interior surfaces of the PEC is cleaned and disinfected daily on days when compounding occurs and when surface contamination is known or suspected. The language was revised to indicate that the work surface of the removable work tray is cleaned and disinfected on days when compounding occurs, and all surfaces and the area underneath the work tray are cleaned and disinfected monthly.

Comment Summary #337: The commenter recommended stating that if compounding is not performed daily, cleaning and disinfecting must be performed before initiating compounding.

Response: Comment not incorporated. The chapter states the minimum frequencies for cleaning, disinfecting, and applying sporicidal disinfectants in classified areas and in the SCA, and was revised to not specify when during the day this must be done. This is a topic that may be described in the facility’s SOPs.

Comment Summary #338: The commenter recommended adding “daily” as a frequency for cleaning the PEC and equipment inside the PEC within the table showing the minimum frequencies for cleaning and disinfecting surfaces and applying sporicidal disinfectants in classified areas and within the perimeter of the SCA.

Response: Comment incorporated. The text was revised to indicate that equipment and all interior surfaces of the PEC are cleaned daily on days when compounding occurs and when surface contamination is known or suspected.

Comment Summary #339: The commenter indicated it is not clear if cleaning is permitted at the end of the day and disinfecting is permitted at the start of the day. The commenter also indicated that many facilities use one-step products, so the separation of cleaning and disinfecting may be inappropriate for the table of minimum frequency for cleaning and disinfecting surfaces and applying sporicidal disinfectants in classified areas and within the perimeter of the SCA.

Response: Comment not incorporated. The chapter states the minimum frequencies for cleaning, disinfecting, and applying sporicidal disinfectants in classified areas and in the SCA, and was revised to not specify when during the day this must be done. The chapter states that surfaces must be cleaned prior to being disinfected with an EPA-registered disinfectant (or equivalent for entities outside the US) unless an EPA-registered (or equivalent for entities outside the US) one-step disinfectant cleaner is used to accomplish both the cleaning and disinfection in one step.

Comment Summary #340: The commenter recommended it be stated that cleaning must occur before disinfection.

Response: Comment not incorporated. The chapter states that surfaces must be cleaned prior to being disinfected with an EPA-registered disinfectant (or equivalent for entities outside the US) unless an EPA-registered (or equivalent for entities outside the US) one-step disinfectant cleaner is used to accomplish both the cleaning and disinfection in one step.

Comment Summary #341: The commenter recommended including information regarding cleaning under high intake velocity grilles when applicable.

Response: Comment not incorporated. The chapter describes minimum frequencies for cleaning and disinfecting the removable work tray of the PEC, when applicable.

Comment Summary #342: The commenter indicated that it is unclear if a two-step disinfectant must be sterile for cleaning and disinfecting the PEC.

Response: Comment incorporated. The chapter was revised to state that for cleaning and disinfecting the PEC, apply, using a sterile low-lint wiper, a sterile cleaning agent followed by a sterile EPA-registered disinfectant or apply a sterile EPA-registered (or equivalent for entities outside the US) one-step disinfectant cleaner to equipment and all interior surfaces of the PEC.

Comment Summary #343: Commenters recommended that the section titled “Cleaning Supplies” be titled “Cleaning Agents”, and recommended clarifying if supplies and/or agents must be sterile if used inside the PEC, and if they need to be sterile if used outside of the PEC.

Response: Comment partially incorporated. The section was restructured to separately state the requirements for cleaning agents and cleaning supplies.

Comment Summary #344: The commenter indicated that personnel that clean and disinfect ISO 7 and ISO 8 areas, but not ISO 5 areas, should not be required to wear sterile gloves.

Response: Comment not incorporated. Any person entering a compounding area where Category 1, Category 2, or Category 3 CSPs are prepared must be properly garbed, including sterile gloves.

Comment Summary #345: The commenter recommended clarifying if alcohol wipes must be single-use for each vial or can be used as long as they remain wet, and if larger wipes are used if each corner can be used for different vials.

Response: Comment not incorporated. This information is more specific than the minimum standards described in the chapter. The chapter states that once opened, sterile cleaning and disinfecting agents and supplies (e.g., closed containers of sterile wipers) and sterile 70% IPA may be reused for a time period specified as by the manufacturer and/or described in the facility written SOPs.

Comment Summary #346: The commenter recommended clarifying what is meant by the “equivalent” of an EPA-registered cleaning product.

Response: Comment partially incorporated. Language was added to clarify that an EPA-registered disinfectant (or equivalent for entities outside the US) is used.

Comment Summary #347: The commenter recommended alternatives be offered for a facility to execute a verification and validation protocol on cleaning and cleaning effectiveness to achieve the same goals as the cleaning and disinfecting requirements of the chapter with reduced testing.

Response: Comment partially incorporated. The chapter states that the use of technologies, techniques, materials, and procedures other than those described in the chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose (e.g., *Validation of Alternative Microbiological Methods* (1223) and *Validation of Compendial Procedures* (1225)). Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #348: The commenter recommended stating that after cleaning and disinfecting, or after the application of a one-step disinfectant cleaner or sporicidal disinfectant in a PEC, the facility’s SOPs should determine if sterile 70% IPA should or must be applied to remove residue, to clarify the statement.

Response: Comment partially incorporated. Language was revised to clarify that in a PEC, sterile 70% IPA must be applied after cleaning and disinfecting, or after the application of a one-step disinfectant cleaner or sporicidal disinfectant, to remove any residue.

Comment Summary #349: The commenter recommended that PEC(s) and equipment inside the PEC(s), and the removable work tray of the PEC, be disinfected with sterile 70% IPA at a frequency determined by the facility SOPs, rather than every 30 minutes.

Response: Comment not incorporated. During the compounding process sterile 70% IPA must be applied to the horizontal work surface, including any removable work trays, of the PEC at least every 30 min if the compounding process takes 30 min or less. If the compounding process takes more than 30 min, compounding must not be disrupted, and the work surface of the PEC must be disinfected immediately after compounding.

Comment Summary #350: The commenter recommended removing “bottles of 70% sterile IPA” from the statement that, “Once opened, sterile cleaning and disinfecting supplies (e.g., closed containers of sterile wipers, bottles of 70% sterile IPA) may be reused for a time period specified in the facility written SOPs”.

Response: Comment partially incorporated. The statement was revised to state, “Once opened, sterile cleaning and disinfecting agents and supplies (e.g., closed containers of sterile wipers) and sterile 70% IPA may be reused for a time period specified as by the manufacturer and/or described in the facility written SOPs.”

Comment Summary #351: Commenters indicated that the statement, “Mops used in areas where HDs are compounded must be dedicated for use only in those areas”, should not be included in the chapter as the handling of hazardous drugs is described in <800>.

Response: Comment not incorporated. This language was included to describe a particular requirement for mops used in areas where HDs are compounded, as the text describes where floor mops may be used. This subject is not specifically addressed in <800>. *USP <800>* states that cleaning of sterile compounding areas must comply with <797>.

Comment Summary #352: The commenter recommended referring the reader to <800> in addition to the statement that mops used in areas where HDs are compounded must be dedicated for use only in those areas.

Response: Comment not incorporated. This subject is not specifically addressed in <800>. USP <800> states that cleaning of sterile compounding areas must comply with <797>.

Comment Summary #353: The commenter recommended that single-use mop heads must be used, rather than stating that a floor mop may be used in both the buffer and ante-area, but only in that order.

Response: Comment not incorporated. The chapter states that wipers, sponges, pads, and mop heads should be disposable. The text here is included to describe that a floor mop may be used for both the buffer and anteroom, but only in that order.

Comment Summary #354: The commenter recommended that sterile water be added as an appropriate solution for removing visible particles, debris, or residue using sterile, low-lint wipers.

Response: Comment not incorporated. The chapter states to, if necessary, remove visible particles, debris, or residue with an appropriate solution (e.g., Sterile Water for Injection or Sterile Water for Irrigation) using sterile, low-lint wipers. Sterile Water for Injection and Sterile Water for Irrigation are included as examples of appropriate solutions, but this is not an all-inclusive list of appropriate solutions.

Comment Summary #355: The commenter indicated that for cleaning, disinfecting, and applying a sporicidal disinfectant in the PEC, visible particles, debris, or residue should only be required to be removed by water when they are visibly present.

Response: Comment partially incorporated. The language was revised to state, “If necessary, remove visible particles, debris, or residue with an appropriate solution (e.g., Sterile Water for Injection or Sterile Water for Irrigation) using sterile, low-lint wipers.”

Comment Summary #356: The commenter recommended that for cleaning, disinfecting, and applying a sporicidal disinfectant in the PEC, the requirement to remove visible particles, debris, or residue with an appropriate solution (e.g., Sterile Water for Injection or Sterile Water for Irrigation) using sterile, low-lint wipers should be removed due to a disinfecting agent being adequate for removing particles, debris, or residue.

Response: Comment not incorporated. The language was revised to state, “If necessary, remove visible particles, debris, or residue with an appropriate solution (e.g., Sterile Water for Injection or Sterile Water for Irrigation) using sterile, low-lint wipers.”

Comment Summary #357: The commenter recommended removing the boxes describing procedures for cleaning and disinfecting the PEC and procedures for applying a sporicidal disinfectant in the PEC. The commenter indicated that the procedures described are overly specific and restrictive.

Response: Comment not incorporated. The boxes describing these procedures are included to provide a suggested method for cleaning and disinfecting the PEC and for applying a sporicidal disinfectant in the PEC.

Comment Summary #358: Commenters recommended rewording the sentence, “All cleaning, disinfecting, and application of sporicidal disinfectants must be documented according to the facility’s SOPs”, to clarify if facilities must document each use of sporicidal.

Response: Comment not incorporated. The chapter states that this documentation must be described in the facility’s SOPs.

Comment Summary #359: The commenter indicated that due to the diversity of veterinary practice settings, cleaning requirements are unable to be implemented for such practices.

Response: Comment not incorporated. The Compounding Expert Committee is committed to ongoing engagement on the application of these standards to veterinary medicine. USP has no

role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #360: The commenter indicated that the cleaning and disinfecting requirements in the chapter are out-of-date, and that it is unclear what microbiological cultures the requirements are aimed at preventing for a regularly used cleanroom.

Response: Comment not incorporated. The chapter states that a cleaning agent is used for the removal of substances (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces; that a disinfectant is used to destroy fungi, viruses, and bacteria; and that a sporicidal is used to destroy bacterial and fungal spores when used at a sufficient concentration for a specified contact time, and is expected to kill all vegetative microorganisms.

Comment Summary #361: The commenter indicated the chapter revisions regarding cleaning and sanitization requirements are not necessary.

Response: Comment not incorporated. The chapter was revised to improve clarity and to respond to stakeholder input. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #362: The commenter recommended increasing the frequency of applying sporicidal disinfectant to potentially weekly, in lieu of monthly viable air sampling.

Response: Comment not incorporated. The minimum frequencies for applying sporicidal disinfectants in the chapter are in alignment with <1072>. The chapter describes the minimum standards to be followed when preparing CSPs and the chapter does not prohibit compounders from going beyond the requirements in the chapter. A monitoring program for viable airborne particles must be developed and implemented to assess microbiological air quality in all classified areas.

Comment Summary #363: The commenter indicated that floors, walls, ceilings, and doors should not be required to have sporicidal disinfectant applied when no gross soiling has occurred.

Response: Comment not incorporated. The chapter indicates a minimum frequency for applying sporicidal disinfectant monthly to wall(s), door(s), and ceiling(s). The chapter indicates a minimum frequency for applying sporicidal disinfectant to floor(s) monthly for entities compounding Category 1 and/or Category 2 CSPs, and weekly for entities compounding Category 3 CSPs. These frequencies are in alignment with <1072>.

Comment Summary #364: The commenter recommended that sporicidal disinfectants only be applied at the frequency in the chapter when surface or air cultures are showing fungal or bacterial spores above accepted levels.

Response: Comment not incorporated. The minimum frequencies for applying sporicidal disinfectants in the chapter are in alignment with <1072>. The purpose of applying a sporicidal disinfectant is to destroy bacterial and fungal spores when used at a sufficient concentration for a specified contact time, and is expected to kill all vegetative microorganisms. Cleaning, disinfecting, and applying sporicidal disinfectants and sterile 70% IPA help prevent microbial contamination of CSPs from surfaces in classified areas and SCAs.

Comment Summary #365: The commenter recommended the frequency of applying sporicidal disinfectant should be monthly for entities compounding Category 3 CSPs.

Response: Comment not incorporated. The minimum frequencies for applying sporicidal disinfectants in the chapter are in alignment with <1072>. Cleaning, disinfecting, and applying sporicidal disinfectants and sterile 70% IPA help prevent microbial contamination of CSPs from surfaces in classified areas and SCAs. Category 3 describes CSPs made in a compounding facility that meets additional quality assurance requirements in order to assign longer BUDs than those set for Category 2 CSPs, but not exceeding the limits for Category 3 CSPs.

Comment Summary #366: The commenter indicated that sporicidal disinfectants should not be required as simple wiping removes up to 2 log reduction of microorganisms.

Response: Comment not incorporated. The minimum frequencies for applying sporicidal disinfectants in the chapter are in alignment with <1072>.

Comment Summary #367: The commenter indicated that the box reflecting procedures for cleaning and disinfecting the PEC states that the agents are applied to equipment and all interior surfaces of the PEC, while the box reflecting procedures for applying a sporicidal disinfectant in the PEC states that the agent is applied to all surfaces and the area underneath the work tray. The commenter recommended clarifying if interior and exterior surfaces of the PEC are cleaned with a sporicidal disinfectant.

Response: Comment not incorporated. The boxes describing these procedures are included to provide a suggested method for cleaning and disinfecting the PEC and for applying a sporicidal disinfectant in the PEC. The chapter indicates that equipment and all interior surfaces of the PEC are cleaned and disinfected daily on days when compounding occurs and when surface contamination is known or suspected. The chapter indicates that sporicidal disinfectant is applied monthly to PEC(s) and equipment inside the PEC(s) for entities compounding Category 1 and/or Category 2 CSPs, and weekly for entities compounding Category 3 CSPs. When sporicidal disinfectant is applied monthly to PEC(s) for entities compounding Category 1 and/or Category 2 CSPs, and weekly for entities compounding Category 3 CSPs, this includes the interior and exterior of the PEC(s).

Comment Summary #368: The commenter recommended for the box reflecting procedures for applying a sporicidal disinfectant in the PEC, adding the use of vapor phase hydrogen peroxide as an option for applying sporicidal disinfectant.

Response: Comment not incorporated. The box describing the procedure is included to provide a suggested method for applying a sporicidal disinfectant in the PEC. The chapter does not prevent the use of gases. The chapter states that the use of technologies, techniques, materials, and procedures other than those described in the chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose (e.g., *Validation of Alternative Microbiological Methods* (1223) and *Validation of Compendial Procedures* (1225)).

Comment Summary #369: Commenters recommended clarifying, in the box reflecting procedures for cleaning and disinfecting the PEC, if an EPA-registered one-step disinfectant needs to be sterile.

Response: Comment incorporated. The text was clarified to state that using a sterile low-lint wiper, apply a sterile cleaning agent followed by a sterile EPA-registered disinfectant or apply a sterile EPA-registered (or equivalent for entities outside the US) one-step disinfectant cleaner to equipment and all interior surfaces of the PEC.

Comment Summary #370: The commenter recommended clarifying regarding the box reflecting procedures for cleaning and disinfecting the PEC, if an EPA-registered one-step disinfectant needs to be sterile. The commenter recommended that an EPA-registered one-step disinfectant not be required to be sterile.

Response: Comment partially incorporated. The text was clarified to state that using a sterile low-lint wiper, apply a sterile cleaning agent followed by a sterile EPA-registered disinfectant or apply a sterile EPA-registered (or equivalent for entities outside the US) one-step disinfectant cleaner to equipment and all interior surfaces of the PEC.

Comment Summary #371: Commenters recommended clarifying regarding the box reflecting procedures for applying a sporicidal disinfectant in the PEC, if an EPA-registered one-step disinfectant needs to be sterile.

Response: Comment incorporated. The text was revised to state that after cleaning and disinfecting, apply the sterile sporicidal disinfectant using a sterile low-lint wiper to all surfaces and the area underneath the work tray; if the sporicidal disinfectant is a sterile EPA-registered

(or equivalent for entities outside the US) one-step disinfectant sporicidal cleaner, separate cleaning and disinfecting steps are not required.

Comment Summary #372: The commenter recommended that low-lint wipers not be required to be sterile for applying agents for cleaning and disinfecting procedures and for applying sporicidal disinfectant in the PEC.

Response: Comment not incorporated. The concern with nonsterile wipers is the environment in which they are manufactured and what bioburden they may bring to the controlled area.

Comment Summary #373: The commenter recommended removing the requirement that cleaning agents be sterile.

Response: Comment not incorporated. Cleaning, disinfecting and sporicidal agents used within the PEC must be sterile. In classified areas outside of the PEC, sterile cleaning and disinfecting agents should be used.

Comment Summary #374: The commenter recommended removing the statement that cleaning and disinfecting supplies used in the PEC must be sterile.

Response: Comment not incorporated. Cleaning, disinfecting and sporicidal agents used within the PEC must be sterile. In classified areas outside of the PEC, sterile cleaning and disinfecting agents should be used.

Comment Summary #375: The commenter recommended removing the requirement that sporicidal disinfectants be sterile.

Response: Comment not incorporated. Cleaning, disinfecting and sporicidal agents used within the PEC must be sterile. In classified areas outside of the PEC, sterile cleaning and disinfecting agents should be used.

Comment Summary #376: The commenter indicated that disinfectants, cleaners, and/or one-step disinfectant cleaners should be not required to be sterile due to being followed by sterile 70% IPA.

Response: Comment not incorporated. Cleaning, disinfecting and sporicidal agents used within the PEC must be sterile. In classified areas outside of the PEC, sterile cleaning and disinfecting agents should be used.

Comment Summary #377: The commenter recommended removing the requirement that cleaning and disinfecting agents be sterile, and recommended adding to the box reflecting procedures for cleaning and disinfecting the PEC that if an EPA-registered (or equivalent) one-step disinfectant cleaner is used, separate cleaning and disinfecting steps are not required.

Response: Comment not incorporated. Cleaning, disinfecting and sporicidal agents used within the PEC must be sterile. In classified areas outside of the PEC, sterile cleaning and disinfecting agents should be used. The chapter states that surfaces must be cleaned prior to being disinfected with an EPA-registered disinfectant (or equivalent for entities outside the US) unless an EPA-registered (or equivalent for entities outside the US) one-step disinfectant cleaner is used to accomplish both the cleaning and disinfection in one step.

Comment Summary #378: The commenter recommended that nonsterile one-step and sporicidal disinfectants be allowed for use in classified areas outside of the PEC.

Response: Comment not incorporated. In classified areas outside of the PEC, sterile cleaning and disinfecting agents should be used. This is listed in the chapter as a recommendation rather than a requirement. Facilities and regulators may choose to enforce additional or more stringent requirements.

Comment Summary #379: Commenters recommended clarifying whether cleaning and disinfecting supplies used to clean ISO classified areas outside of the PEC are required to be sterile.

Response: Comment not incorporated. The chapter states that in classified areas outside of the PEC, sterile cleaning and disinfecting agents should be used. This is a recommendation rather than a requirement.

Comment Summary #380: The commenter recommended removing the statement that in classified areas outside of the PEC, sterile cleaning and disinfecting agents should be used.

Response: Comment not incorporated. The chapter states that in classified areas outside of the PEC, sterile cleaning and disinfecting agents should be used. This is a recommendation rather than a requirement.

Comment Summary #381: The commenter recommended clarifying if cleaning and disinfecting supplies used to clean ISO classified areas outside of the PEC are required to be sterile, based on the chapter statement that all cleaning and disinfecting supplies (e.g., wipers, sponges, pads, and mop heads) with the exception of tool handles and holders must be low lint.

Response: Comment not incorporated. The chapter states that in classified areas outside of the PEC, sterile cleaning and disinfecting agents should be used. This is a recommendation rather than a requirement.

Comment Summary #382: The commenter recommended adding clarification regarding the statement that once opened, sterile cleaning and disinfecting supplies (e.g., closed containers of sterile wipes, bottles of 70% IPA) may be reused for a time period specified in the facility written SOPs. The commenter indicated the statement implies that opened sterile cleaning and disinfecting supplies can continue to be used for a specified amount of time, but does not indicate where the supplies will need to be stored nor where they can be reused.

Response: Comment partially incorporated. This information is more specific than the minimum standards described in the chapter. The language was revised to clarify that once opened, sterile cleaning and disinfecting agents and supplies (e.g., closed containers of sterile wipers) and sterile 70% IPA may be reused for a time period specified as by the manufacturer and/or described in the facility written SOPs.

Comment Summary #383: The commenter recommended including more information about an appropriate time period that sterile cleaning and disinfecting supplies may be reused for.

Response: Comment partially incorporated. This information is more specific than the minimum standards described in the chapter. The language was revised to clarify that once opened, sterile cleaning and disinfecting agents and supplies (e.g., closed containers of sterile wipers) and sterile 70% IPA may be reused for a time period specified as by the manufacturer and/or described in the facility written SOPs.

Comment Summary #384: The commenter recommended that guidance be provided in the chapter or in subsequent notices regarding how sterile compounding facilities should handle common shortages of supplies that occur periodically.

Response: Comment partially incorporated. This information is more specific than the minimum standards described in the chapter. The Compounding Expert Committee previously posted the “USP Response to Shortages of Garb and Personal Protective Equipment (PPE) for Low- and Medium-Risk Sterile Compounding During COVID-19 Pandemic. The Expert Committee will consider future resources to support understanding of the standards.

Comment Summary #385: The commenter recommended removing the statements that, “In classified areas outside of the PEC, sterile cleaning and disinfecting agents should be used”, and “Wipers, sponges, pads (not used in a PEC), and mop heads should be disposable”.

Response: Comment not incorporated. While cleaning, disinfecting and sporicidal agents used within the PEC must be sterile, in classified areas outside of the PEC, sterile cleaning and disinfecting agents should be used. Wipers, sponges, pads, and mop heads should be disposable.

Comment Summary #386: The commenter recommended specifying that cleaning and disinfecting supplies used in the PEC must be sterile, “where appropriate”, or adding in the exception of small quantity sterile packs of low-lint wipes.

Response: Comment not incorporated. Cleaning, disinfecting and sporicidal agents used within the PEC must be sterile. The concern with nonsterile wipers is the environment in which they are manufactured and what bioburden they may bring to the controlled area.

Comment Summary #387: The commenter recommended removing the requirement that disinfecting agents and disinfecting pre-wetted wipes be sterile.

Response: Comment not incorporated. Cleaning, disinfecting and sporicidal agents used within the PEC must be sterile. In classified areas outside of the PEC, sterile cleaning and disinfecting agents should be used.

Comment Summary #388: The commenter requested clarifying if cleaning and disinfecting both have to happen daily before compounding if PEC will not be in use, and noted inconsistency with this issue in *Table 8*.

Response: Comment partially incorporated. The table was reformatted for clarity, and the frequency for cleaning and disinfecting was clarified to be daily on days when compounding occurs and when surface contamination is known or suspected. Sterile 70% IPA must additionally be applied immediately before compounding.

Comment Summary #389: Several commenters requested removing the requirement that cleaning and disinfecting agents within the PEC must be sterile. Some commenters cited confusion on whether cleaning agents mixed with sterile water would be considered sterile. Other commenters requested information on the rationale regarding sterile cleaning solutions, citing concern about increased costs.

Response: Comment not incorporated. The chapter states that when diluting concentrated cleaning agents for use in the PEC, sterile water must be used, and specifies that sterile agents should be used in classified areas outside the PEC. The concern with nonsterile cleaning agents is the environment in which they are manufactured and what bioburden they may bring to the PEC.

Comment Summary #390: The commenter noted that the use of “should” in the recommendation that sterile agents should be used in classified areas outside the PEC may be a high-cost burden if regulators enforce this as a requirement.

Response: Comment not incorporated. This statement is a recommendation, and not a requirement. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #391: The commenter noted that requiring the application of sterile 70% IPA to the work surface every 30 minutes if the compounding process takes 30 minutes or less (*Table 8*) is unnecessarily prescriptive and difficult to implement as many small batches may be compounded across work sessions which are typically longer than 30 minutes.

Response: Comment incorporated.

Comment Summary #392: A number of commenters requested clarification and noted that the language in *Section 7.2* is unclear, as it recommends that sterile cleaning supplies used in the PEC must be sterile. It also states that sterile agents should be used in areas outside of the PEC, but does not specify that for inside the PEC. However, *Box 7* explicitly states that sterile wipers and sterile cleaning agents must be used inside the PEC. Commenter requested clarification on when sterile supplies vs sterile agents must or should be used.

Response: Comment incorporated. Sterile cleaning and disinfecting agents must be used within the PEC, and should be used in classified areas outside of the PEC. The headings and content of the subsections of *Section 7* were divided into *Agents* and *Supplies*, and the text was rearranged for clarity.

Comment Summary #393: The commenter requested that Category 1 and Category 2 CSPs be exempted from the requirement that sterile cleaning and disinfecting agents be used in the PEC, if manufactured under Good Manufacturing Practices.

Response: Comment not incorporated. Compounding activities conducted under <797> are not subject to GMP requirements. Sterile cleaning and disinfecting agents are required within the PEC to reduce the risk of microbial contamination from the bioburden introduced by nonsterile cleaning agents.

Comment Summary #394: The commenter noted that while disinfectants must be sterile for use in the PEC, the text suggests that if using an EPA-registered one-step disinfectant, it is not required to be sterile.

Response: Comment incorporated. The text was revised to state “sterile EPA-registered disinfectant or apply a sterile EPA-registered (or equivalent for entities outside the US) one-step disinfectant cleaner to equipment and all interior surfaces of the PEC.”

Comment Summary #395: The commenter requested clarifying the time period within which sterile cleaning products may be used and discarded.

Response: Comment incorporated. This statement was added: “Once opened, sterile cleaning and disinfecting agents and supplies (e.g., closed containers of sterile wipers) and sterile 70% IPA may be reused for a time period specified as by the manufacturer and/or described in the facility written SOPs.”

8. Introducing Items into the SEC and PEC

Comment Summary #396: Commenters recommended including clarification regarding the requirement that before any item is introduced into the clean side of anteroom(s) it must be wiped with a sporicidal disinfectant, EPA-registered disinfectant, or sterile 70% IPA using low-lint wipers by personnel wearing gloves, for when medications are passed into the buffered area from the anteroom. The commenters recommended clarifying if gloves need to be donned to pass something into the SEC.

Response: Comment not incorporated. There is increased risk of contamination associated with not wearing gloves when passing something into the SEC. Before any item is introduced into the clean side of anteroom(s), placed into pass-through chamber(s), or brought into the SCA, providing that packaging integrity will not be compromised, it must be wiped with a sporicidal disinfectant, EPA-registered disinfectant, or sterile 70% IPA using low-lint wipers by personnel wearing gloves.

Comment Summary #397: The commenter indicated that the requirement to wipe any item before it is introduced into the clean side of anteroom(s), placed into pass-through(s), or brought inside the perimeter of an SCA with a sporicidal disinfectant should not be required, as a fungicidal disinfectant would be more appropriate as it would remove fungal spores.

Response: Comment not incorporated. There are also risks of contamination from bacterial spores. The chapter states that the item must be wiped with a sporicidal disinfectant, EPA-registered disinfectant, or sterile 70% IPA.

Comment Summary #398: Commenters recommended that the wiping procedure before introducing items into the SEC should not render the product label unreadable, rather than this being a requirement that the wiping procedure must not render the product label unreadable.

Response: Comment incorporated. The text was revised to state that the wiping procedure should not compromise the packaging integrity or render the product label unreadable.

Comment Summary #399: The commenter recommended removing “sterile” as a requirement for low-lint wipers used to wipe items before being introduced into the PEC as opening wipers outside of a PEC renders them nonsterile.

Response: Comment not incorporated. The concern with nonsterile wipers is the environment in which they are manufactured and what bioburden they may bring to the controlled area.

Comment Summary #400: The commenter recommended clarifying if one person is prepping bags in one hood, and another person is compounding in another hood, does the bag need to

be disinfected before bringing into the second hood, and do personnel have to disinfect gloves every time their hands exit the hood even if they are not touching contaminated surfaces.

Response: Comment not incorporated. This information is more specific than the minimum standards described in the chapter. The chapter states that just before any item is introduced into the PEC, it must be wiped with sterile 70% IPA using sterile low-lint wipers and allowed to dry before use. The chapter states that application of sterile 70% IPA to gloves must occur immediately before compounding and regularly throughout the compounding process. This is a topic that may be described in the facility's SOPs.

Comment Summary #401: The commenter recommended removing the statement that, "when sterile items are received in sealed containers designed to keep them sterile until opening, the sterile items may be removed from the covering as the supplies are introduced into the ISO Class 5 PEC without the need to wipe the individual sterile supply items with sterile 70% IPA", due to this statement being unclear and suggesting that packages for sterile items do not have to be wiped before introduction into the PEC.

Response: Comment not incorporated. This statement refers to sterile items received in sealed containers designed to keep them sterile as the items are introduced into the ISO Class 5 PEC, after being removed from the covering. The material of such supplies (e.g., paper) may be damaged if they were to be wiped. The chapter states that critical sites must be wiped with sterile 70% IPA in the PEC to provide both chemical and mechanical actions to remove contaminants.

9. Equipment, Supplies, and Components

Expert Committee-Initiated Change #1: Subsections of *9.3 Components* were numbered for ease of navigation and to improve clarity.

Expert Committee-Initiated Change #2: Clarification was added regarding the COA requirements when APIs are used as a component.

Comment Summary #402: Commenters recommended removing, "Weighing, measuring, or otherwise manipulating components that could generate airborne chemical particles...must be assessed to determine if these activities must be performed in a PEC or other closed system processing device...The process evaluation must be carried out in accordance with the facility's SOPs and the assessment must be documented." The commenters indicated that this text does not describe a requirement other than to perform and document an "assessment", and that the scope of the assessment is unclear. Other commenters requested clarify the scope, measurement, and expected acceptance criteria for the assessment.

Response: Comment partially incorporated. The word "assessed" was revised to be "evaluated". The chapter states that the process evaluation must be carried out in accordance with the facility's SOPs and must be documented.

Comment Summary #403: The commenter recommended removing or moving to the section for facility design and environmental controls, the text stating that weighing, measuring, or otherwise manipulating components that could generate airborne chemical particles must be assessed to determine if these activities must be performed in a PEC or other closed system processing device. The commenter indicated that combining nonsterile ingredients in a clean, air-conditioned lab and placing them in a container to enter the PEC is sufficient, rather than nonsterile ingredients be combined in an ISO Class 8 environment.

Response: Comment not incorporated. This section refers the reader back to the section for facilities preparing Category 2 or Category 3 CSPs from nonsterile starting component(s). If preparing Category 2 or Category 3 CSP from nonsterile component(s), presterilization procedures must be completed in an ISO Class 8 or better environment.

Comment Summary #404: The commenter recommended revising the text stating that weighing, measuring, or otherwise manipulating components that could generate airborne chemical particles must be assessed to determine if these activities must be performed in a PEC or other closed system processing device to be more reflective of the language in the section for facilities preparing Category 2 or Category 3 CSPs from nonsterile starting components.

Response: Comment not incorporated. This section refers the reader back to the section for facilities preparing Category 2 or Category 3 CSPs from nonsterile starting component(s). This language refers to all weighing, measuring, or otherwise manipulating components that could generate airborne chemical particles, whereas 4.2.6 describes specifically the facilities preparing Category 2 or Category 3 CSPs from nonsterile starting components.

Comment Summary #405: The commenter recommended aligning this section with the section for facilities preparing Category 2 or Category 3 CSPs from nonsterile starting components regarding if a containment device should or must be used.

Response: Comment not incorporated. 9.1 *Equipment* refers to all weighing, measuring, or otherwise manipulating components that could generate airborne chemical particles, whereas 4.2.6 describes specifically the facilities preparing Category 2 or Category 3 CSPs from nonsterile starting components.

Comment Summary #406: The commenter recommended that an accuracy assessment of automated compounding devices or other similar equipment should be per manufacturer recommendation and not necessarily daily.

Response: Comment not incorporated. Compounding personnel must conduct an accuracy assessment before the first use of ACDs or other similar equipment and again each day the equipment is used to compound CSPs. For many systems this will be conducted daily or more frequently by the computer system.

Comment Summary #407: The commenter indicated that it is not clear what an accuracy assessment is and why equipment needs to be reevaluated each day the equipment is used. The commenter recommended revising the text to state that personnel must verify the equipment has been calibrated to deliver accurate volumes and is performing within expected specifications, and that personnel must document instances where the equipment cannot be properly calibrated or not performing within specifications.

Response: Comment not incorporated. Compounding personnel must conduct an accuracy assessment before the first use of ACDs or other similar equipment and again each day the equipment is used to compound CSPs. For many systems this will be conducted daily or more frequently by the computer system. Verifying the volumetric accuracy would be a part of an accuracy assessment.

Comment Summary #408: The commenter recommended that the chapter should require the beyond-use date of bulk APIs repackaged into smaller containers to be limited to harmonize with requirements in <7>.

Response: Comment not incorporated. The requirements for this in <7> are regarding dispensing drugs and for variable environmental conditions after dispensing.

Comment Summary #409: The commenter recommended clarifying the statement that supplies in direct contact with the CSP must be sterile and depyrogenated. The commenter indicated that if beakers are used to assist in removing excess diluent, due to shortages of sterile syringes, these supplies are wiped down and sanitized prior to placement in an ISO 5 direct compounding area, but they are not sterilized or depyrogenated.

Response: Comment not incorporated. Supplies in direct contact with the CSP must be sterile and depyrogenated to avoid increased risk of contamination.

Comment Summary #410: The commenter recommended clarifying how long tubing on a TPN machine or repeater pump should be exchanged.

Response: Comment not incorporated. This information is more specific than the minimum standards described in the chapter. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #411: Commenters recommended clarifying if personnel must monitor and document temperature readings for components stored outside the pharmacy.

Response: Comment not incorporated. The chapter states that personnel must monitor temperature in the area(s) where components are stored either manually at least once daily on days that the facility is open or by a continuous temperature recording device to determine whether the temperature remains within the appropriate range. This includes wherever the components are stored within the facility. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #412: The commenter recommended specifying that personnel must monitor temperature where components are required to be stored in refrigerators and freezers, and that automated dispensing systems and medication rooms that store components and final CSPs at room temperature should be considered for monitoring per the facility's SOPs.

Response: Comment not incorporated. Personnel must monitor temperature in the area(s) where components are stored either manually at least once daily on days that the facility is open or by a continuous temperature recording device to determine whether the temperature remains within the appropriate range. This includes wherever the components are stored within the facility. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #413: Commenters recommended clarifying if humidity sensors, pressure monitors, and thermostats must be calibrated or verified for accuracy as recommended by the manufacturer or every 12 months if not specified by the manufacturer.

Response: Comment not incorporated. The chapter states that all monitoring equipment must be calibrated or verified for accuracy as recommended by the manufacturer or every 12 months if not specified by the manufacturer. This includes all monitoring equipment. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #414: The commenter recommended being more inclusive and/or providing more examples of equipment that would require calibration.

Response: Comment not incorporated. The chapter states that all monitoring equipment must be calibrated or verified for accuracy as recommended by the manufacturer or every 12 months if not specified by the manufacturer. Information from monitoring equipment manufacturers may provide further information regarding examples of equipment that would require calibration.

Comment Summary #415: The commenter recommended that APIs must be obtained and manufactured in an FDA-registered facility.

Response: Comment partially incorporated. The text was revised to clarify that in the United States, APIs must be manufactured by an FDA-registered facility, and outside of the United States, APIs must comply with the laws and regulations of the applicable regulatory jurisdiction.

Comment Summary #416: The commenter recommended that APIs in the United States must be obtained from an FDA-registered facility.

Response: Comment partially incorporated. The text was revised to clarify that in the United States, APIs must be manufactured by an FDA-registered facility, and outside of the United States, APIs must comply with the laws and regulations of the applicable regulatory jurisdiction.

Comment Summary #417: The commenter recommended that all components other than APIs be obtained from an FDA-registered facility, if available.

Response: Comment not incorporated. The chapter states that in the United States, all components other than APIs should be manufactured by an FDA-registered facility, and that outside of the United States all components other than APIs must comply with the laws and

regulations of the applicable regulatory jurisdiction. The chapter states that all components other than APIs must comply with the criteria in the *USP–NF* monograph, if one exists.

Comment Summary #418: The commenter recommended that all packages must be reinspected to detect container breaks, looseness of the cap or closure, and deviation from the expected appearance, aroma, or texture of the contents that might have occurred during storage.

Response: Comment partially incorporated. The language was revised to state that all packages must be reinspected to detect container breaks, looseness of the cap or closure, and deviation from the expected appearance, aroma, and/or texture of the contents that might have occurred during storage.

Comment Summary #419: The commenter recommended that when a *USP–NF* monograph does not exist for APIs or components other than APIs, that the acceptance criteria from <1111> for microbiological quality of nonsterile substance for pharmaceutical use should be met, unless otherwise justified.

Response: Comment not incorporated. The chapter describes the minimum standards to be followed when preparing CSPs and the chapter does not prohibit compounders from going beyond the requirements in the chapter.

Comment Summary #420: The commenter recommended adding required standards for using APIs and components other than APIs for which there is no *USP–NF* monograph.

Response: Comment not incorporated. APIs must have a COA that includes the specifications (e.g., compendial requirements for quality) and that test results for the component show that the API meets expected quality. Components other than APIs must be accompanied by documentation (e.g., COA, labeling) that includes the specifications and test results and shows that the component meets the specifications.

Comment Summary #421: The commenter recommended clarifying if a certificate of quality is required for each lot of sterile empty bags used.

Response: Comment not incorporated. This information is more specific than the minimum standards described in the chapter. The chapter states that each lot of commercially available sterile, depyrogenated containers and container closure systems must be accompanied by a COA or other documentation showing conformance with established specifications (i.e., sterility and depyrogenation requirements). Sterile empty bags obtained from suppliers are described as such in the product labeling. The lot number is traceable back to the manufacturer/supplier if any concerns would be identified.

Comment Summary #422: The commenter indicated that the text does not emphasize the importance of sterility assurance level for ready-to-use primary packs and recommended indicating that primary packaging containers and closure systems must be sterile with a demonstrated sterility assurance level of 10^{-6} or better.

Response: Comment not incorporated. The chapter describes the minimum standards to be followed when preparing CSPs and the chapter does not prohibit compounders from going beyond the requirements in the chapter.

Comment Summary #423: The commenter recommended stating that the visual reinspection of sterile components must be performed in a way that does not compromise the sterility of the component that is being inspected.

Response: Comment not incorporated. The chapter states that sterile container closures must be visually reinspected to ensure that they are free from defects that could compromise sterility and that they are otherwise suitable for their intended use. The Compounding Expert Committee concluded that this language was sufficient to describe the requirement.

10. Sterilization and Depyrogenation

Expert Committee-Initiated Change #1: It was clarified that sterilizing filters with labeling that states “for laboratory use only” or a similar statement must not be used for compounding CSPs.

Expert Committee-Initiated Change #2: Language was revised for clarity stating that, “Filtration may not be an option for some compounded preparations, for example preparations with suspended drug particles or emulsions with a significant droplet size.”

Comment Summary #424: The commenter indicated that no change should be made to the current practice for sterilization and depyrogenation requirements.

Response: Comment not incorporated. The chapter was revised to improve clarity and to respond to stakeholder input. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #425: The commenter recommended adding information concerning the use of sterilant gases for decontamination purposes.

Response: Comment not incorporated. The chapter references the <1229> series of chapters. The sterilization method used must sterilize the CSP without degrading its physical and chemical stability (e.g., affecting its strength, purity, or quality) or the packaging integrity.

Comment Summary #426: The commenter recommended clarifying why a PNSU can be applied to a terminally sterilized product.

Response: Comment not incorporated. Terminal sterilization includes compounding with sterile and/or nonsterile starting ingredient(s) and subsequent sterilization with a lethal process intended to achieve a probability of a nonsterile unit (PNSU) of 10^{-6} (e.g., dry heat, steam, irradiation).

Comment Summary #427: Commenters recommended replacing “depyrogenation with “sanitized” in the sentence, “Items that are not thermostable must be depyrogenated by rinsing with sterile, nonpyrogenic water (e.g., Sterile Water for Injection or Sterile Water for Irrigation) and then thoroughly drained or dried immediately before use in compounding.”

Response: Comment not incorporated. Washing and rinsing is an example of depyrogenation.

Comment Summary #428: Commenters indicated an editorial error where the 7 in “107” was meant to be subscripted in the sentence, “Sterilizing filters must be certified by the manufacturer to retain at least 107 microorganisms of a strain of *Brevundimonas diminuta* per square centimeter of upstream filter surface area under conditions similar to those in which the CSPs will be filtered (i.e., pressure, flow rate, and volume filtered).”

Response: Comment incorporated.

Comment Summary #429: The commenter recommended revising “must” to “should” regarding, “Sterilizing filters must be sterile, depyrogenated, have a nominal pore size of 0.22 μm or smaller, and include labeling for pharmaceutical use.”

Response: Comment partially incorporated. The statement was revised to state that sterilizing filters must be sterile, depyrogenated, have a nominal pore size of 0.22 μm or smaller, and be appropriate for pharmaceutical use.

Comment Summary #430: The commenter recommended revising “should” to “must” regarding, “The filter dimensions and the CSP to be sterilized by filtration should permit the sterilization process to be completed without the need for replacement of the filter during the process.”

Response: Comment not incorporated. The filter dimensions and the CSP to be sterilized by filtration should permit the sterilization process to be completed without the need for replacement of the filter during the process.

Comment Summary #431: The commenter recommended that facilities compounding Category 2 or Category 3 CSPs should be required to perform process validation for each unique type of manipulation performed by the facility.

Response: Comment not incorporated. This is a topic that may be described in the facility’s SOPs. The chapter describes the minimum standards to be followed when preparing CSPs and

the chapter does not prohibit compounders from going beyond the requirements in the chapter. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #432: The commenter recommended that the chapter require validation studies for each load size intended for sterilization for terminal sterilization.

Response: Comment not incorporated. The effectiveness of steam sterilization must be verified and documented with each sterilization run or load by using appropriate biological indicators, such as spores of *Geobacillus stearothermophilus* (ATCC 12980, ATCC 7953, or equivalent; see Biological Indicators for Sterilization (1229.5)), and other confirmation methods such as physicochemical indicators (see Physicochemical Integrators and Indicators for Sterilization (1229.9)). The effectiveness of the dry heat sterilization method must be verified and documented with each sterilization run or load using appropriate biological indicators such as spores of *Bacillus atrophaeus* (ATCC 9372; see (1229.5)) and other confirmation methods (e.g., temperature-sensing devices).

Comment Summary #433: The commenter recommended including information regarding using an autoclave and steam sterilization in relation to the chapter requiring that steam supplied be free of contaminants and generated using water per the manufacturer's recommendation.

Response: Comment partially incorporated. The steam supplied must be generated using water per the manufacturer's recommendation.

Comment Summary #434: The commenter recommended including language regarding final containers as the use of ampules should be considered a manufacturing process rather than compounding.

Response: Comment partially incorporated. The text was revised to state that for CSPs, immediately before filling containers that will be steam sterilized, solutions must be passed through a filter with a nominal pore size of not larger than 1.2 µm for removal of particulate matter.

Comment Summary #435: The commenter suggested clarifying if biological indicators and other confirmation methods such as physicochemical indicators and integrators must be used to verify the steam sterilization cycle.

Response: Comment partially incorporated. The effectiveness of steam sterilization must be verified and documented with each sterilization run or load by using appropriate biological indicators, such as spores of *Geobacillus stearothermophilus* (ATCC 12980, ATCC 7953, or equivalent; see *Biological Indicators for Sterilization* (1229.5)), and other confirmation methods such as physicochemical indicators (see Physicochemical Integrators and Indicators for Sterilization (1229.9)).

Comment Summary #436: The commenter recommended that beakers only be depyrogenated in the oven.

Response: Comment partially incorporated. The description in the chapter regarding placing beakers in an autoclave was removed.

11. Master Formulation and Compounding Records

Expert Committee-Initiated Change #1: Language was revised to state that the compounding record must be created to document the compounding process, removing that it must be created to document the, "compounding process or repackaging process".

Comment Summary #437: Commenters recommended clarifying when an MFR is required.

Response: Comment incorporated. An MFR must be created for all CSPs prepared from nonsterile ingredient(s) or CSPs prepared for more than one patient.

Comment Summary #438: Commenters recommended clarifying if non-pharmacy personnel compounding immediate-use CSPs can be excluded from training requirements to document MFRs and CRs.

Response: Comment incorporated. An MFR must be created for all CSPs prepared from nonsterile ingredient(s) or CSPs prepared for more than one patient. The chapter states that the training and demonstration of competency for compounding immediate-use CSPs are as they relate to assigned tasks and the facility's SOPs.

Comment Summary #439: The commenter indicated that an MFR is not needed for immediate-use CSPs used for multiple patients.

Response: Comment not incorporated. An MFR must be created for all CSPs prepared from nonsterile ingredient(s) or CSPs prepared for more than one patient.

Comment Summary #440: The commenter recommended that an MFR include a reference source to support the stability of the CSP only if applicable.

Response: Comment not incorporated. If <797> is used as the reference source, <797> may be included as the reference source on the MFR.

Comment Summary #441: The commenter indicated that all CSPs should have an MFR that might be used in an OP setting.

Response: Comment not incorporated. An MFR must be created for all CSPs prepared from nonsterile ingredient(s) or CSPs prepared for more than one patient.

Comment Summary #442: Commenters indicated that all CSPs should have an MFR and that immediate-use CSPs are not prepared for more than one patient.

Response: Comment not incorporated. An MFR must be created for all CSPs prepared from nonsterile ingredient(s) or CSPs prepared for more than one patient.

Comment Summary #443: The commenter indicated the chapter is unclear if an MFR can be stored in an ACD or workflow management system.

Response: Comment not incorporated. The chapter does not address how the MFR must be stored as long as it meets all of the requirements. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #444: The commenter recommended clarifying if a compounding record must indicate the date and time of the end of the assigned BUD (i.e., DD/MM/YY, time), or the length of the assigned BUD (i.e., 12 hours).

Response: Comment not incorporated. This is a topic that may be described in the facility's SOPs. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #445: The commenter recommended clarifying if a compounding record must indicate the storage requirements for the CSP prior to or after dispensing.

Response: Comment not incorporated. This is a topic that may be described in the facility's SOPs. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #446: Commenters recommended clarifying when a CR is required.

Response: Comment incorporated. A CR must be created for all Category 1, Category 2, and Category 3 CSPs. A CR must also be created for immediate-use CSPs prepared for more than one patient.

Comment Summary #447: Commenters recommended clarifying what constitutes "retrievable" when compounding records are stored electronically.

Response: Comment partially incorporated. All required documentation for a particular CSP (e.g., MFR, CR, and release inspection and testing results) must be readily retrievable for at least 2 years after preparation or as required by laws and regulations of the applicable regulatory jurisdiction or accrediting organization(s), whichever is longer.

Comment Summary #448: Commenters indicated that all CSPs should have a CR and that immediate-use CSPs are not prepared for more than one patient.

Response: Comment not incorporated. A CR must be created for all Category 1, Category 2, and Category 3 CSPs. A CR must also be created for immediate-use CSPs prepared for more than one patient.

Comment Summary #449: The commenter recommended clarifying if the information required to be included on compounding records be placed on the prescription, medication order, or labels.

Response: Comment not incorporated. This is a topic that may be described in the facility's SOPs. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #450: The commenter recommended clarifying during what parts of the process and in what locations the documentation of compounding should occur.

Response: Comment not incorporated. This information is more specific than the minimum standards described in the chapter. This is a topic that may be described in the facility's SOPs. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #451: Commenters recommended the compounding record include the date of preparation of CSP, and time for a Category 1 CSP, rather than the date and time of preparation for all CSPs.

Response: Comment not incorporated. CRs must include the date and time of preparation of all CSPs.

12. Release Inspections and Testing

Expert Committee-Initiated Change #1: A statement was revised for clarity to state, "Defects that indicate sterility or stability problems must be investigated to determine the cause according to the facility's SOPs."

Comment Summary #452: Commenters indicated regarding the requirement for when a CSP will not be released or dispensed on the day of preparation, a visual inspection must be conducted immediately before it is released or dispensed, that this limits stocking CSPs in automated dispensing cabinets.

Response: Comment not incorporated. Releasing a CSP to the floor is similar to dispensing to a patient, so an additional visual inspection by compounding personnel is not required. Other personnel (i.e., nursing) should be educated to inspect all types of CSPs prior to administration to a patient. This is a topic that may be described in the facility's SOPs.

Comment Summary #453: The commenter recommended clarifying whether technology may be used to perform visual inspections remotely.

Response: Comment not incorporated. This information is more specific than the minimum standards described in the chapter. This is a topic that may be described in the facility's SOPs. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #454: The commenter recommended removing the requirement that the CSP be visually inspected to confirm the CSP and its labeling match the prescription or medication order.

Response: Comment partially incorporated. The language in the chapter was revised to clarify that the CSP label must be visually inspected to confirm that the CSP and its labeling match the prescription or medication order.

Comment Summary #455: The commenter indicated that the use of the term “batch” should not be used within the chapter due to batches only being authorized for anticipatory compounding.

Response: Comment not incorporated. Compounders may prepare multiple CSPs for multiple patients at the same time. The chapter defines batch as more than one CSP prepared as described in the MFR in a single, discrete process, and expected to have uniform character and quality, within specified limits. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #456: The commenter recommended removing the description in the chapter of the additional units that must be compounded to perform sterility testing when the number of CSPs to be compounded in a single batch is less than the number of CSPs needed for testing as specified in <71>, *Table 3*, due to contradicting *USP <71>*.

Response: Comment not incorporated. *USP General Chapter <71> Sterility Tests* falls under the Microbiology Expert Committee and was created for facilities that follow current good manufacturing practices (CGMP). Manufacturers are unlikely to prepare less than 40 items in a batch. This information is provided to be more applicable for compounders.

Comment Summary #457: The commenter recommended incorporating a statement to describe whether in-house sterility testing is permissible and at what percentage.

Response: Comment not incorporated. The chapter does not specify by whom the sterility testing must be performed. This information is more specific than the minimum standards described in the chapter. This is a topic that may be described in the facility’s SOPs. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #458: Commenters indicated that the maximum batch size for all CSPs requiring sterility testing being limited to 250 final yield units is too large an amount.

Response: Comment not incorporated. The limit of 250 final yield units is based on *USP <71> Table 3*, which provides the minimum number of items to be tested in relation to the number of items in the batch. This table specifies that 10 containers are to be tested for quantities greater than 100 to up to 500 containers, leading the Compounding Expert Committee to specify 250 as the maximum batch size for CSPs requiring sterility testing.

Comment Summary #459: Commenters indicated that the maximum batch size for all CSPs requiring sterility testing being limited to 250 final yield units is too limited an amount, seems to be an arbitrary amount, and recommended removing the batch size limitation.

Response: Comment not incorporated. The limit of 250 final yield units is based on *USP <71> Table 3*, which provides the minimum number of items to be tested in relation to the number of items in the batch. This table specifies that 10 containers are to be tested for quantities greater than 100 to up to 500 containers, leading the Compounding Expert Committee to specify 250 as the maximum batch size for CSPs requiring sterility testing. *USP General Chapter <71> Sterility Tests* falls under the Microbiology Expert Committee and was created for facilities that follow current good manufacturing practices (CGMP). <797> sets a minimum standard for quality assurance that encompasses a wide variety of practice sites. These quality assurance parameters are not intended for outsourcing facilities or pharmaceutical manufacturers, as they were created to accommodate the equipment and processes normally performed by 503A facilities. The risk of contaminating a CSP increases as the batch size increases, particularly for manual processes. For example, equipment limitations (such as the size of a PEC) may only permit a portion of a large batch to be packaged in one continuous process. Smaller batches reduce the potential for operator error due to fatigue. The process of sterility testing leads to destruction of the CSP used in testing, as the container closure system has to be breached, and therefore not all units within a batch can be tested for sterility. Sterility testing does not guarantee that an entire batch is sterile, only the units tested. Contamination within a batch may

not be uniformly distributed across all units. The probability of detecting contamination during sterility testing decreases as batch size increases, and risk for unidentified contamination increases.

Comment Summary #460: Commenters recommended that the maximum batch size for all CSPs requiring sterility testing be limited to 500 final yield units.

Response: Comment not incorporated. The limit of 250 final yield units is based on *USP* <71> *Table 3*, which provides the minimum number of items to be tested in relation to the number of items in the batch. This table specifies that 10 containers are to be tested for quantities greater than 100 to up to 500 containers, leading the Compounding Expert Committee to specify 250 as the maximum batch size for CSPs requiring sterility testing. <797> sets a minimum standard for quality assurance that encompasses a wide variety of practice sites. These quality assurance parameters are not intended for outsourcing facilities or pharmaceutical manufacturers, as they were created to accommodate the equipment and processes normally performed by 503A facilities. The risk of contaminating a CSP increases as the batch size increases, particularly for manual processes.

Comment Summary #461: Commenters recommended that batch sizes should be based on testing results and media-fills.

Response: Comment not incorporated. The limit of 250 final yield units is based on *USP* <71> *Table 3*, which provides the minimum number of items to be tested in relation to the number of items in the batch. This table specifies that 10 containers are to be tested for quantities greater than 100 to up to 500 containers, leading the Compounding Expert Committee to specify 250 as the maximum batch size for CSPs requiring sterility testing. *USP* General Chapter <71> *Sterility Tests* falls under the Microbiology Expert Committee and was created for facilities that follow current good manufacturing practices (CGMP). <797> sets a minimum standard for quality assurance that encompasses a wide variety of practice sites. These quality assurance parameters are not intended for outsourcing facilities or pharmaceutical manufacturers, as they were created to accommodate the equipment and processes normally performed by 503A facilities. The risk of contaminating a CSP increases as the batch size increases, particularly for manual processes. For example, equipment limitations (such as the size of a PEC) may only permit a portion of a large batch to be packaged in one continuous process. Smaller batches reduce the potential for operator error due to fatigue. The process of sterility testing leads to destruction of the CSP used in testing, as the container closure system has to be breached, and therefore not all units within a batch can be tested for sterility. Sterility testing does not guarantee that an entire batch is sterile, only the units tested. Contamination within a batch may not be uniformly distributed across all units. The probability of detecting contamination during sterility testing decreases as batch size increases, and risk for unidentified contamination increases.

Comment Summary #462: Commenters recommended removing the maximum batch size for CSPs requiring sterility testing and referring compounder to adhere to *USP* <71> batching and testing requirements.

Response: Comment not incorporated. *USP* General Chapter <71> *Sterility Tests* falls under the Microbiology Expert Committee and was created for facilities that follow current good manufacturing practices (CGMP). <797> sets a minimum standard for quality assurance that encompasses a wide variety of practice sites. These quality assurance parameters are not intended for outsourcing facilities or pharmaceutical manufacturers, as they were created to accommodate the equipment and processes normally performed by 503A facilities.

Comment Summary #463: The commenter recommended clarifying how the maximum batch size for CSPs requiring sterility testing applies for compounding with IV robots.

Response: Comment not incorporated. This information is more specific than the minimum standards described in the chapter. This is a topic that may be described in the facility's SOPs.

The chapter states that the maximum batch size for all CSPs requiring sterility testing must be limited to 250 final yield units. The chapter states that the use of technologies, techniques, materials, and procedures other than those described in the chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose (e.g., *Validation of Alternative Microbiological Methods* (1223) and *Validation of Compendial Procedures* (1225)). Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #464: The commenter recommended revising the maximum batch size for CSPs requiring sterility testing to not apply when certain conditions are met, including sterility testing being modified to test 5% of the batch size with samples taken throughout compounding of the batch, CSPs are compounded using a validated automated compounding device, and CSPs are subjected to validated terminal sterilization procedures.

Response: Comment not incorporated. Sterility testing does not guarantee that an entire batch is sterile, only the units tested. Contamination within a batch may not be uniformly distributed across all units. The probability of detecting contamination during sterility testing decreases as batch size increases, and risk for unidentified contamination increases.

Comment Summary #465: The commenter recommended exempting CSPs prepared via a validated automation process from batch size limitations.

Response: Comment not incorporated. The chapter states that the maximum batch size for all CSPs requiring sterility testing must be limited to 250 final yield units. The chapter states that the use of technologies, techniques, materials, and procedures other than those described in the chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose (e.g., *Validation of Alternative Microbiological Methods* (1223) and *Validation of Compendial Procedures* (1225)). Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #466: The commenter recommended incorporating an exception that single-dose packaged Category 3 CSPs compounded in a batch consisting of single units need not be sterility tested provided that the compounder complies with all other conditions applicable to Category 3 CSPs.

Response: Comment not incorporated. There are risks of contamination with bacterial endotoxins. While sterility testing can only guarantee the units tested are sterile, it can help notify personnel of contamination before affecting as many patients. Single-dose containers do not eliminate the risk of contamination.

Comment Summary #467: The commenter indicated the chapter revisions regarding bacterial endotoxin testing are not necessary.

Response: Comment not incorporated. The requirements regarding bacterial endotoxin testing were developed in response to patient safety concerns. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #468: The commenter recommended incorporating an option for alternative endotoxin testing requirements specifically applicable to batches consisting of a single unit of a single-dose packaged Category 3 injectable CSP.

Response: Comment not incorporated. The use of technologies, techniques, materials, and procedures other than those described in the chapter is not prohibited as long as they are noninferior to those described in the chapter and validated for the intended purpose (e.g., *Validation of Alternative Microbiological Methods* <1223> and *Validation of Compendial Procedures* <1225>).

Comment Summary #469: The commenter recommended revising the requirement that CSPs for nonhuman species must not exceed the endotoxin limit calculated as described in <85> based on the weight of the target animal unless a different limit is scientifically supported, to

specify that CSPs for nonhuman species must not exceed the endotoxin limit calculated as described in <85> based on the largest recommended dose and average weight of the target animal unless a different limit is scientifically supported.

Response: Comment partially incorporated. CSPs for nonhuman species must not exceed the endotoxin limit calculated as described in (85) based on the largest recommended dose and weight (or average weight for more than a single animal) of the target animal species unless a different limit is scientifically supported.

Comment Summary #470: The commenter indicated that endotoxin testing should be required for all Category 2 and Category 3 CSPs.

Response: Comment not incorporated. Bacterial endotoxin testing is required for Category 2 injectable CSPs compounded from one or more nonsterile component(s) and assigned a BUD that requires sterility testing and Category 3 injectable CSPs compounded from one or more nonsterile component(s). The purpose of the bacterial endotoxins test is to ensure the source material does not contain excessive endotoxins and ensure any mitigation steps that were performed are adequate. The chapter describes the minimum standards to be followed when preparing CSPs and the chapter does not prohibit compounders from going beyond the requirements in the chapter.

Comment Summary #471: The commenter recommended incorporating requirements that bacterial endotoxin mitigations measures be implemented when compounding drug products. These recommended requirements include if raw materials are not suitable for intended use, the COA must report endotoxin testing and bioburden testing, and requirements for testing the raw materials and calculating the total amount of endotoxin levels are within safety levels for the intended use of final preparation.

Response: Comment not incorporated. This information is more specific than the minimum standards described in the chapter. The chapter describes the minimum standards to be followed when preparing CSPs and the chapter does not prohibit compounders from going beyond the requirements in the chapter. The Expert Committee will consider future resources to support understanding of the standards.

13. Labeling

Expert Committee-Initiated Change #1: The required information to be included in the labeling on the CSP was revised from individually stating “any applicable special handling instructions” and “any applicable warning statements”, to state that the labeling on the CSP must display the information, as applicable.

Expert Committee-Initiated Change #2: Language was revised for clarification and harmonization with <795> to state that labeling on the CSP must display, as applicable, the compounding facility name and contact information if the CSP is to be sent outside of the facility or healthcare system in which it was compounded.

Expert Committee-Initiated Change #3: The statement, “All labels must also comply with laws and regulations of the applicable regulatory jurisdiction” was removed as it was redundant from the statement earlier in the section, “All labeling must be in compliance with laws and regulations of the applicable regulatory jurisdiction”.

Comment Summary #472: The commenter recommended removing the requirement that the labeling on the CSP should indicate that the preparation is compounded.

Response: Comment not incorporated. The labeling on the CSP should indicate that the preparation is compounded.

Comment Summary #473: The commenter recommended revising the requirement that the labeling on the CSP should indicate that the preparation is compounded, to state that the

labeling on the CSP should indicate that the preparation is compounded in a sterile environment.

Response: Comment not incorporated. The labeling on the CSP should indicate that the preparation is compounded.

Comment Summary #474: The commenter recommended revising the requirement that the labeling on the CSP should indicate that the preparation is compounded, to state that the labeling on the CSP should indicate that the preparation is compounded when space permits or when leaving a facility for which its use is intended.

Response: Comment not incorporated. The labeling on the CSP should indicate that the preparation is compounded.

Comment Summary #475: The commenter recommended allowing the label on each immediate container of the CSP to display if it is a multiple-dose container, a statement stating such, when space permits.

Response: Comment not incorporated. If a CSP is in a multiple-dose container, the label on each immediate container of the CSP must display a statement stating such.

Comment Summary #476: Commenters recommended the label on each immediate container of the CSP must display the storage conditions.

Response: Comment not incorporated. The label on each immediate container of the CSP must display storage conditions if other than controlled room temperature.

Comment Summary #477: The commenter recommended the label on each immediate container of the CSP display the active ingredient(s) or unique name where such can be easily found (e.g., multivitamin injections).

Response: Comment not incorporated. The label on each immediate container of the CSP must display the active ingredient(s) and their amount(s), activity(ies), or concentration(s).

Comment Summary #478: The commenter recommended removing the statement, “All labels must also comply with laws and regulations of the applicable regulatory jurisdiction”, as this is redundant from the statement earlier in the section, “All labeling must be in compliance with laws and regulations of the applicable regulatory jurisdiction”.

Response: Comment incorporated.

Comment Summary #479: Commenters recommended allowing the route of administration be included in the labeling for the CSP rather than the label on each immediate container.

Response: Comment incorporated.

Comment Summary #480: The commenter recommended the label on each immediate container of the CSP display the BUD or expiration date.

Response: Comment not incorporated. The label on each immediate container of the CSP must display the BUD.

Comment Summary #481: The commenter recommended the label on each immediate container of the CSP display the species of the patient.

Response: Comment not incorporated. There are instances where anticipatory batches are prepared for more than one species. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

14. Establishing Beyond-Use Dates

Expert Committee-Initiated Change #1: Subsections of *14.2 Parameters to Consider in Establishing a BUD* and *14.4 Additional Requirements for Category 3 CSPs* were numbered for ease of navigation and to improve clarity.

Expert Committee-Initiated Change #2: The order of information described for *14.2.1* was revised to help improve clarity.

Expert Committee-Initiated Change #3: Instances of “1 day” were revised to state “24 h”.

Expert Committee-Initiated Change #4: Language was revised for clarity stating that compounders must consider parameters that may affect “quality”.

Expert Committee-Initiated Change #5: Language was revised to clarify that each time a Category 3 CSP is prepared, it is sterility tested and meets the requirements of <71> or a validated alternative method that is noninferior to <71> testing.

Comment Summary #482: The commenter recommended clarifying the specificity required for frozen CSPs requiring container closure integrity testing.

Response: Comment not incorporated. The chapter states that if a CSP will be stored in a frozen state, the container closure system must be able to withstand the physical stress (i.e., without breaking or cracking) during storage in a freezer.

Comment Summary #483: The commenter indicated that the BUD limits will negatively impact the frequency with which veterinarians will need to dispose of medications and purchase new inventory.

Response: Comment not incorporated. If there is a compounded preparation monograph for a particular CSP formulation, the BUD in the monograph can be assigned if the CSP is prepared according to the monograph and all monograph requirements are met, including sterility testing. The Compounding Expert Committee is committed to ongoing engagement on the application of these standards to veterinary medicine.

Comment Summary #484: The commenter recommended updating the BUD terminology to include administration time.

Response: Comment not incorporated. The chapter states that administration of medication is out of scope of the chapter. The chapter states that the BUD is not intended to limit the time during which the CSP is administered (e.g., infused).

Comment Summary #485: The commenter recommended clarifying if stability data established from a 503b compounded product can be used as justification for stability to use the corresponding Category 2 BUD limit if all factors remain the same (e.g., storage temperature, concentration, container closure, etc.).

Response: Comment not incorporated. Personnel will not have access to all of the information to ensure all factors are the same. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #486: The commenter recommended a twelve-hour exemption from compliance with the chapter’s standards to allow buffered lidocaine to be prepared in advance of patient visits.

Response: Comment not incorporated. The Monograph Development Subcommittee of the Compounding Expert Committee is committed to ongoing review of compounded monographs that address health needs.

Comment Summary #487: Commenters recommended revising the definition of BUD in the table comparing the definition of BUD with expiration date, to clarify that it is either the date, or hour and date, after which a CSP must no longer be stored prior to administration. Commenters recommended revising the description in the chapter to state that each CSP label must state the date, or the hour and date, beyond which the preparation must no longer be stored prior to administration and must be discarded (i.e., the BUD).

Response: Comment not incorporated. The chapter states that the BUD is not intended to limit the time during which the CSP is administered (e.g., infused). The chapter defines “beyond-use date (BUD)” as the date, or hour and the date, after which a CSP must not be used, stored, or transported, and clarifies that the date is determined from the date and time the preparation is compounded. The chapter states that administration of medication is out of scope of the chapter.

Comment Summary #488: The commenter recommended clarifying that the BUD is the latest time that infusion/administration must begin by, and that infusion time is not part of the BUD.

Response: Comment not incorporated. The chapter states that the BUD is not intended to limit the time during which the CSP is administered (e.g., infused). The chapter states that administration of medication is out of scope of the chapter.

Comment Summary #489: The commenter recommended the BUD include the date and hour, rather than the date, or hour and date, after which a CSP must not be used.

Response: Comment not incorporated. The chapter defines “beyond-use date (BUD)” as the date, or hour and the date, after which a CSP must not be used, stored, or transported, and clarifies that the date is determined from the date and time the preparation is compounded. For CSPs with assigned longer BUDs, including only the date for the BUD may be appropriate. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #490: The commenter recommended revising the description of BUD in *14. Establishing Beyond-Use Dates* to remove the word “used” to clarify that administration is not included in the BUD.

Response: Comment not incorporated. The chapter states that the BUD is not intended to limit the time during which the CSP is administered (e.g., infused). The chapter defines “beyond-use date (BUD)” as the date, or hour and the date, after which a CSP must not be used, stored, or transported, and clarifies that the date is determined from the date and time the preparation is compounded. The chapter states that administration of medication is out of scope of the chapter.

Comment Summary #491: The commenter recommended adding administration time as a parameter to consider in establishing a BUD.

Response: Comment not incorporated. The chapter states that administration of medication is out of scope of the chapter. The chapter states that the BUD is not intended to limit the time during which the CSP is administered (e.g., infused).

Comment Summary #492: The commenter recommended adding composition of the closure systems (e.g., type of glass, resin in stopper) as a factor that can impact stability.

Response: Comment partially incorporated. The language was clarified to state that a parameter that may affect quality that must be considered is materials of composition of the container closure system and compatibility of the container closure system with the final preparation (e.g., leachables, interactions, adsorption, and storage conditions).

Comment Summary #493: The commenter recommended stating in *14.2 Parameters to Consider in Establishing a CSP* that extended BUDs be based on relevant and reliable scientific literature or through direct testing.

Response: Comment not incorporated. The chapter states that the BUD assigned to a Category 3 CSP must be supported by stability data obtained using a stability-indicating analytical method that is able to distinguish the active ingredient from its degradants and impurities and quantify the amount of the active ingredient.

Comment Summary #494: The commenter recommended including requirements for completing a stability-indicating assay.

Response: Comment not incorporated. This information is more specific than the minimum standards described in the chapter. The Compounding Expert Committee will consider development of additional resources to support understanding of the standards. The Compounding Expert Committee will consider the development of a standard related to stability-indicating methods.

Comment Summary #495: The commenter indicated support for the addition of more clear requirements on CSP stability studies.

Response: Comment incorporated. The Expert Committee will consider future resources and stakeholder engagement sessions to support understanding of the standards.

Comment Summary #496: The commenter recommended clarifying what BUD to assign in the absence of stability data for the exact concentration of a CSP.

Response: Comment not incorporated. The chapter states that BUDs for CSPs must be established in accordance with *Table 12* for Category 1 CSPs, *Table 13* for Category 2 CSPs, and *Table 14* for Category 3 CSPs, and that a shorter BUD must be assigned when the stability of the CSP or its components is less than the hours or days in the applicable BUD Limit table. In the absence of stability data for the CSP, the maximum allowable BUD limit listed in the chapter must not be exceeded.

Comment Summary #497: The commenter recommended clarifying how to apply stability studies for Category 2 CSPs which fall in the category of aseptically processed CSPs prepared from only sterile starting components and not undergoing sterility testing.

Response: Comment not incorporated. The chapter states that BUDs for CSPs must be established in accordance with *Table 12* for Category 1 CSPs, *Table 13* for Category 2 CSPs, and *Table 14* for Category 3 CSPs, and that a shorter BUD must be assigned when the stability of the CSP or its components is less than the hours or days in the applicable BUD Limit table. In the absence of stability data for the CSP, the maximum allowable BUD limit listed in the chapter must not be exceeded.

Comment Summary #498: The commenter recommended clarifying how to apply existing stability data in the instance of varying components, techniques, and container closure integrity testing.

Response: Comment not incorporated. Stability requirements for Category 3 CSPs include that the CSP be prepared according to the exact formulation (API and other ingredients of identical grade and procedures) from which the stability data are derived, packaged and stored in a container closure of the same materials of composition as that used in the study, and the analytical method validated based on characteristics such as those described in <1225>. The Compounding Expert Committee has developed tools posted on the USP website to provide further information regarding the requirements for a stability-indicating assay method.

Comment Summary #499: The commenter recommended incorporating edits to clarify that sterilization methods only impact Category 2 CSP BUD limits.

Response: Comment not incorporated. The chapter states that these are some of the factors that affect the achievement and maintenance of sterility that BUDs for CSPs are based on. The chapter specifies that the table of BUD Limits for Category 2 CSPs allows for longer BUDs for terminally sterilized CSPs than for aseptically processed CSPs.

Comment Summary #500: Commenters indicated that sterilization method should not be used for assigning BUDs. The commenter noted that pharmacists are not well-trained on sterilization methods or on implementing, validating and monitoring a terminal sterilization program. The commenter noted that sterilization methods should not be used for assigning BUDs, and instead only allowing sterilization by filtration. The commenter indicated that aseptic sterilization and terminal sterilization should not be viewed differently.

Response: Comment not incorporated. The Compounding Expert Committee decided that compounders may prepare CSPs by terminal sterilization or aseptic processing. The chapter states that aseptic processing includes compounding with only sterile starting ingredient(s) or compounding with nonsterile ingredient(s) followed by sterilization by filtration. Terminal sterilization is the preferred method of sterilization, unless the specific CSP or container closure system cannot tolerate terminal sterilization. BUD limits are longer for terminally sterilized CSPs than for aseptically processed CSPs because terminal sterilization using a verified method provides reasonable assurance that a CSP will be sterile. For sterilization, the chapter refers to <1229>.

Comment Summary #501: Commenters recommended incorporating edits to clarify that starting components only impact Category 2 CSP BUD limits, and that colder storage conditions only impact Category 1 and Category 2 BUD limits.

Response: Comment not incorporated. The chapter states that these are some of the factors that affect the achievement and maintenance of sterility that BUDs for CSPs are based on. The chapter specifies that the tables of BUD Limits for Category 1 CSPs and for Category 2 CSPs allow for longer BUDs for CSPs stored in colder conditions than for CSPs stored at controlled room temperature.

Comment Summary #502: The commenter recommended removing the parameter that BUDs be established based on whether or not sterility testing is performed.

Response: Comment not incorporated. While sterility testing is not a preventative measure for microbial growth, the intent is to reduce the risk of patient harm from undetected contamination of CSPs.

Comment Summary #503: The commenter recommended stating that examples of improper thawing methods include defrosting with hot water, microwaves, or heating mats.

Response: Comment not incorporated. There may be instances where a water bath or heating mat may be appropriate. The example given in the chapter of “(e.g., do not heat in a microwave)” is meant to be an example and not an inclusive list of improper thawing mechanisms.

Comment Summary #504: The commenter recommended referring to parenteral nutrition in the table of BUD Limits for Category 2 CSPs to indicate that BUDs should be based on sterility, stability, and compatibility. The commenter also recommended designating a section of <797> to parenteral nutrition.

Response: Comment partially incorporated. Footnotes were added to the BUD limit tables to clarify that a shorter BUD must be assigned when the physical and chemical stability of the CSP is less than the BUD limit stated in the table. The Expert Committee will consider future resources to support understanding of the standards. The Compounding Expert Committee will consider the development of a standard related to parenteral nutrition.

Comment Summary #505: The commenter recommended that in the absence of passing a sterility test, storage periods for parenteral nutrition must not exceed 30 hours at controlled room temperature, and 9 days at a cold temperature.

Response: Comment partially incorporated. The chapter distinguishes three categories of CSPs (Category 1, Category 2, and Category 3) primarily based on the state of environmental control under which they are compounded, the probability for microbial growth during the time they will be stored, and the time period within which they must be used. Footnotes were added to the BUD limit tables to clarify that a shorter BUD must be assigned when the physical and chemical stability of the CSP is less than the BUD limit stated in the table. The Expert Committee will consider future resources to support understanding of the standards. The Compounding Expert Committee will consider the development of a standard related to parenteral nutrition.

Comment Summary #506: The commenter recommended adding a statement regarding the BUDs for CSPs being based primarily on factors that affect the achievement and maintenance of sterility, to include that parenteral nutrition admixtures are unique preparations and the BUDs for parenteral nutrition admixtures must account for sterility and stability/compatibility, with the BUD being whichever is shortest.

Response: Comment partially incorporated. A shorter BUD must be assigned when the stability of any CSP or its components is less than the hours or days stated in the BUD limit tables. Footnotes were added to the BUD limit tables to clarify that a shorter BUD must be assigned when the physical and chemical stability of the CSP is less than the BUD limit stated in the table. The Expert Committee will consider future resources to support understanding of the

standards. The Compounding Expert Committee will consider the development of a standard related to parenteral nutrition.

Comment Summary #507: The commenter indicated that parenteral nutrition be treated separately from standards for other CSPs due to its unique characteristics and the BUDs should be based on sterility, stability, and compatibility.

Response: Comment partially incorporated. A shorter BUD must be assigned when the stability of any CSP or its components is less than the hours or days stated in the BUD limit tables. Footnotes were added to the BUD limit tables to clarify that a shorter BUD must be assigned when the physical and chemical stability of the CSP is less than the BUD limit stated in the table. The Expert Committee will consider future resources to support understanding of the standards. The Compounding Expert Committee will consider the development of a standard related to parenteral nutrition.

Comment Summary #508: The commenter recommended adding language to describe what to do in the situation that infusion time goes beyond the BUD.

Response: Comment not incorporated. The chapter states that the BUD is not intended to limit the time during which the CSP is administered (e.g., infused). The chapter states that administration of medication is out of scope of the chapter.

Comment Summary #509: Commenters indicated that the BUD limits are too restrictive. Commenters indicated that the BUD limits will lead to increased refill frequencies, reduce patient compliance due to increased need for refills, increased administrative burden to facilities, and increased need for additional personnel. Some commenters indicated that no BUD limit should be less than 90 days, or that BUD limits should be one year. Some commenters indicated that the extra shipping required in response to the BUD limits has negative impacts on the environment. Commenters indicated the BUD limits will lead to increased production and testing costs.

Response: Comment not incorporated. The BUD limits are based on several considerations, such as the minimum time periods necessary to perform required tests, CSP chemical and physical stability, the potential for microbial proliferation, the exponential growth rate of microorganisms with increasing temperatures, and the risk of microbial contamination or not achieving and maintaining sterility despite implementation of the requirements in the chapter. The BUD limits are also based on the diversity of practice settings, environments, processes, raw materials, and analytical approaches. If there is a *USP–NF* compounded preparation monograph for the CSP, and the preparation is labeled to indicate that it meets the monograph specifications, the BUD must not exceed the BUD specified in the monograph.

Comment Summary #510: The commenter indicated concern with extending BUDs for drugs compounded without following CGMP requirements.

Response: Comment not incorporated. The chapter describes a minimum standard to be followed when preparing CSPs that encompasses a wide variety of practice sites. The BUD limits are based on several considerations, such as the minimum time periods necessary to perform required tests, CSP chemical and physical stability, the potential for microbial proliferation, the exponential growth rate of microorganisms with increasing temperatures, and the risk of microbial contamination or not achieving and maintaining sterility despite implementation of the requirements in the chapter. The chapter does not prohibit compounders from going beyond the requirements in the chapter.

Comment Summary #511: The commenter indicated that relying on stability studies to support extended BUDs for compounded drugs is not valid for a given product made by a pharmacy because there may be undetermined differences in the active pharmaceutical ingredients and excipients, formulation, compounding process, and packaging of the preparation. The commenter also indicated that regulators would need information outside of the chapter to determine if private analytical methods and studies are suitable for their intended use.

Response: Comment not incorporated. The chapter describes a minimum standard to be followed when preparing CSPs that encompasses a wide variety of practice sites. The EC has taken a risk-based approach to determining the maximum BUD limits to balance the risk of having less information than would be available in a current good manufacturing practices (CGMP) stability study, with the known stability characteristics and acute, personalized needs of patients. The chapter does not prohibit compounders from going beyond the requirements in the chapter.

Comment Summary #512: The commenter recommended that definitions and BUDs need to be aligned with the Food and Drug Administration.

Response: Comment not incorporated. The standards are developed through a process of convening independent experts who share interactive dialogue between USP, independent experts, and a variety of stakeholders who work in and are familiar with the field. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #513: The commenter recommended that lyophilized CSPs stored at any temperature be assigned the same BUD limit as CSPs stored in a freezer.

Response: Comment partially incorporated. The chapter states that the use of technologies, techniques, materials, and procedures other than those described in the chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose.

Comment Summary #514: Commenters recommended that BUDs be extended beyond 180 days with scientific references available to support extensions. Some commenters recommended a limit of 365 days for extending BUDs.

Response: Comment not incorporated. The BUD limits are based on several considerations, such as the minimum time periods necessary to perform required tests, CSP chemical and physical stability, the potential for microbial proliferation, the exponential growth rate of microorganisms with increasing temperatures, and the risk of microbial contamination or not achieving and maintaining sterility despite implementation of the requirements in the chapter. A diversity of practice settings, environments, processes, raw materials, analytical approaches, and few cases in practice which require greater than a 6-month supply resulted in the limit of 180 days. If there is a *USP–NF* compounded preparation monograph for the CSP, and the preparation is labeled to indicate that it meets the monograph specifications, the BUD must not exceed the BUD specified in the monograph.

Comment Summary #515: Commenters indicated that the BUD limit for aseptically processed CSPs is too restrictive due to the costs to the provider and patient. The commenter recommended the BUD limit be 180 days for aseptically processed CSPs.

Response: Comment not incorporated. The BUD limits are based on several considerations, such as the minimum time periods necessary to perform required tests, CSP chemical and physical stability, the potential for microbial proliferation, the exponential growth rate of microorganisms with increasing temperatures, and the risk of microbial contamination or not achieving and maintaining sterility despite implementation of the requirements in the chapter. The BUD limits are also based on the diversity of practice settings, environments, processes, raw materials, and analytical approaches.

Comment Summary #516: The commenter indicated that the BUD limit for injectable CSPs is too restrictive due to costs and burden for the provider and patient. The commenter recommended the BUD limit be 180 days for injectable CSPs.

Response: Comment not incorporated. The BUD limits are based on several considerations, such as the minimum time periods necessary to perform required tests, CSP chemical and physical stability, the potential for microbial proliferation, the exponential growth rate of microorganisms with increasing temperatures, and the risk of microbial contamination or not

achieving and maintaining sterility despite implementation of the requirements in the chapter. The BUD limits are also based on the diversity of practice settings, environments, processes, raw materials, and analytical approaches.

Comment Summary #517: The commenter recommended BUDs be 180 days.

Response: Comment not incorporated. The BUD limits are based on several considerations, such as the minimum time periods necessary to perform required tests, CSP chemical and physical stability, the potential for microbial proliferation, the exponential growth rate of microorganisms with increasing temperatures, and the risk of microbial contamination or not achieving and maintaining sterility despite implementation of the requirements in the chapter. The BUD limits are also based on the diversity of practice settings, environments, processes, raw materials, and analytical approaches. Category 1 and Category 2 CSPs are stratified based on risk elements including compounding process (e.g., aseptic processing or terminal sterilization), the environment in which compounding occurs, and the starting ingredients used for compounding (e.g., nonsterile or sterile). Category 3 establishes BUD limits that are up to double those assigned for Category 2, thus maintaining the same risk stratification. If there is a *USP–NF* compounded preparation monograph for the CSP, and the preparation is labeled to indicate that it meets the monograph specifications, the BUD must not exceed the BUD specified in the monograph.

Comment Summary #518: Commenters recommended aseptically prepared Category 2 CSPs compounded using only sterile ingredients stored in a refrigerator should have a BUD limit of 14 days.

Response: Comment not incorporated. Based on the previous chapter, many compounders were incorrectly considering medium-risk preparations to be low-risk. The BUD limits are based on several considerations, such as the minimum time periods necessary to perform required tests, CSP chemical and physical stability, the potential for microbial proliferation, the exponential growth rate of microorganisms with increasing temperatures, and the risk of microbial contamination or not achieving and maintaining sterility despite implementation of the requirements in the chapter. The BUD limits are also based on the diversity of practice settings, environments, processes, raw materials, and analytical approaches.

Comment Summary #519: Commenters indicated the chapter revisions regarding BUDs are not necessary and that the BUDs should be maintained from the previous chapter.

Response: Comment not incorporated. The chapter was revised to improve clarity and to respond to stakeholder input. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #520: Commenters indicated that colder storage temperatures for longer BUD limits can impact quality and administration of CSPs.

Response: Comment not incorporated. Storage in colder conditions has been shown to slow the growth of most microorganism. The chapter states that the chemical and physical stability of the CSP and its components must be considered when storing in colder conditions. Footnotes were added to the BUD limit tables to clarify that a shorter BUD must be assigned when the physical and chemical stability of the CSP is less than the BUD limit stated in the table.

Comment Summary #521: Commenters indicated that terminal sterilization may impact packing and CSPs that are heat-sensitive.

Response: Comment not incorporated. The chapter states that terminal sterilization is the preferred method of sterilization, unless the specific CSP or container closure system cannot tolerate terminal sterilization. BUD limits are longer for terminally sterilized CSPs than for aseptically processed CSPs because terminal sterilization using a verified method provides reasonable assurance that a CSP will be sterile.

Comment Summary #522: The commenter recommended removing the terminal sterilization requirement for assigning Category 3 BUDs to preserved ophthalmic CSPs and extending the BUD limit for storage at room temperature to 180 days.

Response: Comment not incorporated. Storage in colder conditions has been shown to slow the growth of most microorganism. BUD limits are longer for terminally sterilized CSPs than for aseptically processed CSPs because terminal sterilization using a verified method provides reasonable assurance that a CSP will be sterile.

Comment Summary #523: Commenters indicated that stability studies may be cost-prohibitive for compounders to perform and will impact medication costs.

Response: Comment not incorporated. Evidence to support the physicochemical stability of a CSP may be obtained from any stability-indicating assay method study, either published or unpublished, and is not required to be repeated for each batch as long as the formula, procedures, and container closure systems in the study are exactly the same for the CSP being prepared. The Compounding Expert Committee has developed tools posted on the USP website to provide further information regarding the requirements for a stability-indicating assay method.

Comment Summary #524: The commenter indicated clarification is needed for what data is required, if any, to support assigned BUDs for category 2 CSPs.

Response: Comment not incorporated. The chapter states that the table of BUD Limits for Category 2 CSPs establishes the longest permitted BUDs for Category 2 CSPs. A shorter BUD must be assigned when the stability of the CSP or its components is less than the hours or days stated in the applicable table.

Comment Summary #525: The commenter indicated that sterility testing ophthalmic products and injections is a significant expenditure to assign a BUD of 45 days.

Response: Comment not incorporated. While sterility testing is not a preventative measure for microbial growth, the intent is to reduce the risk of patient harm from undetected contamination of CSPs. The BUD limits are based on several considerations, such as the minimum time periods necessary to perform required tests, CSP chemical and physical stability, the potential for microbial proliferation, the exponential growth rate of microorganisms with increasing temperatures, and the risk of microbial contamination or not achieving and maintaining sterility despite implementation of the requirements in the chapter. The BUD limits are also based on the diversity of practice settings, environments, processes, raw materials, and analytical approaches.

Comment Summary #526: The commenter indicated that requirements for terminal sterilization, endotoxin testing, and sterility testing will lead to significantly increased costs and limited abilities to prepare CSPs.

Response: Comment not incorporated. BUD limits are longer for terminally sterilized CSPs than for aseptically processed CSPs because terminal sterilization using a verified method provides reasonable assurance that a CSP will be sterile. Bacterial endotoxin testing is required for Category 2 injectable CSPs compounded from one or more nonsterile component(s) and assigned a BUD that requires sterility testing and Category 3 injectable CSPs compounded from one or more nonsterile component(s). While sterility testing is not a preventative measure for microbial growth, the intent is to reduce the risk of patient harm from undetected contamination of CSPs.

Comment Summary #527: The commenter indicated that commonly used medications are unable to be autoclaved and the chapter requirements will lead to these medications being replaced by new compounded preparations.

Response: Comment not incorporated. BUD limits are longer for terminally sterilized CSPs than for aseptically processed CSPs because terminal sterilization using a verified method provides reasonable assurance that a CSP will be sterile. The chapter states that the sterilization method

used must sterilize the CSP without degrading its physical and chemical stability or the packaging integrity.

Comment Summary #528: Commenters indicated that the requirement for CSPs prepared with nonsterile materials to undergo endotoxin testing will cause a significant expenditure for providers, patients, and insurance companies.

Response: Comment not incorporated. Bacterial endotoxin testing is required for Category 2 injectable CSPs compounded from one or more nonsterile component(s) and assigned a BUD that requires sterility testing and Category 3 injectable CSPs compounded from one or more nonsterile component(s). The purpose of the bacterial endotoxins test is to ensure the source material does not contain excessive endotoxins and ensure any mitigation steps that were performed are adequate. Bacterial endotoxins entering patients' bloodstreams in sufficient concentrations can cause harmful effects such as fever and septic shock and can be fatal in the most severe cases.

Comment Summary #529: The commenter indicated that testing each ingredient in a CSP to assign a longer BUD is unattainable due to the increased costs this will incur.

Response: Comment not incorporated. Category 3 CSPs have longer BUDs, which increases the risk of microbial contamination and proliferation, as well as chemical degradation, physical incompatibilities, and the compromising of the container closure system. To address these risks and maintain a higher state of environmental control, additional requirements must be met if compounding Category 3 CSPs. Component selection is described in *Section 9.3.1 Component Selection* and applies to all CSP categories.

Comment Summary #530: The commenter recommended longer BUD limits be permitted for CSPs prepared in RABS located in an SCA.

Response: Comment not incorporated. There is insufficient evidence to support longer BUDs for CSPs compounded in RABS located in an unclassified space. There are instances where microbial growth has been discovered in RABS.

Comment Summary #531: The commenter recommended clarifying that aseptically processed CSPs made from one or more nonsterile starting components have already undergone a filtration sterilization process.

Response: Comment not incorporated. The chapter states that aseptic processing includes compounding with only sterile starting ingredient(s) or compounding with nonsterile ingredient(s) followed by sterilization by filtration.

Comment Summary #532: The commenter indicated that the table of BUD Limits for Category 2 CSPs is unclear if the BUDs for terminally sterilized CSPs include CSPs prepared from only sterile starting component(s), and/or prepared from one or more nonsterile starting component(s).

Response: Comment not incorporated. The chapter states that terminal sterilization includes compounding with sterile and/or nonsterile starting ingredient(s) and subsequent sterilization with a process intended to achieve a PNSU of 10^{-6} .

Comment Summary #533: The commenter indicated that sterility testing should be required for any CSP assigned a BUD in excess of the BUD limits in the chapter for aseptically processed Category 2 CSPs.

Response: Comment not incorporated. Sterility testing is required for Category 2 CSPs assigned a BUD that required sterility testing, and for all Category 3 CSPs.

Comment Summary #534: Commenters recommended that Category 3 CSPs should be allowed BUD limits of 180 days stored at room temperature, or regardless of storage condition.

Response: Comment not incorporated. Category 1 and Category 2 CSPs are stratified based on risk elements including compounding process (e.g., aseptic processing or terminal sterilization), the environment in which compounding occurs, and the starting ingredients used for compounding (e.g., nonsterile or sterile). Category 3 establishes BUD limits that are up to

double those assigned for Category 2, thus maintaining the same risk stratification. If there is a *USP–NF* compounded preparation monograph for the CSP, and the preparation is labeled to indicate that it meets the monograph specifications, the BUD must not exceed the BUD specified in the monograph. Storage in colder conditions has been shown to slow the growth of most microorganism.

Comment Summary #535: Commenters recommended adding a section on each of the tables for the BUD Limits for Category 2 CSPs and for Category 3 CSPs with longer BUDs for anhydrous formulations. The commenter recommended the longer BUDs be up to 180 days at room temperature storage for Category 3 CSPs. The commenter recommended an additional 30 days for anhydrous Category 2 and Category 3 CSPs at room temperature.

Response: Comment not incorporated. Spores can be present in nonaqueous preparations. Category 1 and Category 2 CSPs are stratified based on risk elements including compounding process (e.g., aseptic processing or terminal sterilization), the environment in which compounding occurs, and the starting ingredients used for compounding (e.g., nonsterile or sterile). Category 3 establishes BUD limits that are up to double those assigned for Category 2, thus maintaining the same risk stratification. The chapter states that that storage in colder conditions has been shown to slow the growth of most microorganisms. The chapter also states that the chemical and physical stability of the CSP and its components must be considered when storing in colder conditions.

Comment Summary #536: The commenter indicated that BUD limits should be different for oil versus aqueous solutions.

Response: Comment not incorporated. Spores can be present in nonaqueous preparations.

Comment Summary #537: The commenter indicated the statement that one day is equivalent to 24 hours due to the limiting factors of IV workflow and CPOE operating systems being unable to not comprehend a 24-hour clock.

Response: Comment not incorporated. The chapter states that the BUD is the date, or hour and the date, after which a CSP must not be used, stored, or transported.

Comment Summary #538: Commenters recommended removing the sentence stating that the BUD limits in the tables are based on the risk of microbial contamination or not achieving and maintaining sterility despite implementation of the requirements in the chapter, as this suggests the chapter requirements are insufficient to achieve or maintain sterility of a CSP.

Response: Comment not incorporated. There is risk of microbial contamination or not achieving and maintaining sterility despite implementation of the requirements in the chapter. The BUD limits are also based on the diversity of practice settings, environments, processes, raw materials, and analytical approaches.

Comment Summary #539: Commenters indicated that aseptically processed CSPs take a significant amount of time for sterility testing before distributing to patients, which will significantly limit the amount of time the patient will have the CSP prior to the assigned BUD. Some commenters indicated that a 30-day BUD limit would cause institutions to seek rapid microbiological methods.

Response: Comment not incorporated. The chapter does not prohibit dispensing a CSP prior to receiving the results of testing as long as the ability to recall the CSP is established. The chapter does not prohibit rapid sterility test methods.

Comment Summary #540: Commenters indicated that a BUD limit of 60 days is too restrictive and arbitrary and will lead to increased workload for compounding personnel, increased costs for patients, will lead to increased shipping and packaging, and will impact access to CSPs. Some commenters recommended increasing BUDs up to 180 days.

Response: Comment not incorporated. The BUD limits are based on several considerations, such as the minimum time periods necessary to perform required tests, CSP chemical and physical stability, the potential for microbial proliferation, the exponential growth rate of

microorganisms with increasing temperatures, and the risk of microbial contamination or not achieving and maintaining sterility despite implementation of the requirements in the chapter. The BUD limits are also based on the diversity of practice settings, environments, processes, raw materials, and analytical approaches. If there is a *USP–NF* compounded preparation monograph for the CSP, and the preparation is labeled to indicate that it meets the monograph specifications, the BUD must not exceed the BUD specified in the monograph.

Comment Summary #541: The commenter recommended extending the BUDs to 60 days for CSPs stored at room temperature and refrigerated, and for terminally sterilized CSPs stored at room temperature. The commenter also indicated that a 30-day BUD limits the ability to dispense a sterility tested 30-day supply.

Response: Comment not incorporated. The chapter does not prohibit dispensing a CSP prior to receiving the results of testing as long as the ability to recall the CSP is established. The chapter does not prohibit rapid sterility test methods. Storage in colder conditions has been shown to slow the growth of most microorganism. The BUD limits are based on several considerations, such as the minimum time periods necessary to perform required tests, CSP chemical and physical stability, the potential for microbial proliferation, the exponential growth rate of microorganisms with increasing temperatures, and the risk of microbial contamination or not achieving and maintaining sterility despite implementation of the requirements in the chapter. The BUD limits are also based on the diversity of practice settings, environments, processes, raw materials, and analytical approaches.

Comment Summary #542: The commenter recommended removing the storage conditions from the table of BUD Limits for Category 3 CSPs and require that the storage conditions be those of the referenced stability study.

Response: Comment not incorporated. Storage in colder conditions has been shown to slow the growth of most microorganism. The chapter states that the chemical and physical stability of the CSP and its components must be considered when storing in colder conditions. Footnotes were added to the BUD limit tables to clarify that a shorter BUD must be assigned when the physical and chemical stability of the CSP is less than the BUD limit stated in the table. Stability requirements for Category 3 CSPs include that the CSP be packaged and stored in a container closure of the same materials of composition as that used in the study.

Comment Summary #543: The commenter recommended removing the table and all references to the table of BUD Limits for Category 3 CSPs and stating that Category 3 CSPs must not be assigned a BUD longer than that supported by a stability-indicating study or 180 days, whichever is shorter.

Response: Comment not incorporated. Storage in colder conditions has been shown to slow the growth of most microorganism. The chapter states that the chemical and physical stability of the CSP and its components must be considered when storing in colder conditions. Footnotes were added to the BUD limit tables to clarify that a shorter BUD must be assigned when the physical and chemical stability of the CSP is less than the BUD limit stated in the table. The BUD limits are based on several considerations, such as the minimum time periods necessary to perform required tests, CSP chemical and physical stability, the potential for microbial proliferation, the exponential growth rate of microorganisms with increasing temperatures, and the risk of microbial contamination or not achieving and maintaining sterility despite implementation of the requirements in the chapter. The BUD limits are also based on the diversity of practice settings, environments, processes, raw materials, and analytical approaches.

Comment Summary #544: The commenter recommended Category 3 BUD limits be revised to be 120 to 180 at any storage temperature or those of the referenced stability study, whichever is lesser.

Response: Comment not incorporated. Storage in colder conditions has been shown to slow the growth of most microorganism. The chapter states that the chemical and physical stability of the CSP and its components must be considered when storing in colder conditions. Footnotes were added to the BUD limit tables to clarify that a shorter BUD must be assigned when the physical and chemical stability of the CSP is less than the BUD limit stated in the table. The BUD limits are based on several considerations, such as the minimum time periods necessary to perform required tests, CSP chemical and physical stability, the potential for microbial proliferation, the exponential growth rate of microorganisms with increasing temperatures, and the risk of microbial contamination or not achieving and maintaining sterility despite implementation of the requirements in the chapter.

Comment Summary #545: Commenters indicated that facilities that have performed stability studies should be permitted to use the corresponding BUD limits. Some commenters indicated the BUDs should be established as the date reflected by stability-indicating assays. Some commenters indicated the BUDs should be established as the date reflected by stability-indicating assays, up to 180 days.

Response: Comment not incorporated. A diversity of practice settings, environments, processes, raw materials, analytical approaches, and few cases in practice which require greater than a 6-month supply resulted in the limit of 180 days. Category 1 and Category 2 CSPs are stratified based on risk elements including compounding process (e.g., aseptic processing or terminal sterilization), the environment in which compounding occurs, and the starting ingredients used for compounding (e.g., nonsterile or sterile). Category 3 establishes BUD limits that are up to double those assigned for Category 2, thus maintaining the same risk stratification. If there is a *USP–NF* compounded preparation monograph for the CSP, and the preparation is labeled to indicate that it meets the monograph specifications, the BUD must not exceed the BUD specified in the monograph.

Comment Summary #546: The commenter recommended USP establish a platform for facilities to share stability data that can be used for establishing BUDs for Category 3 CSPs.

Response: Comment not incorporated. If there is a *USP–NF* compounded preparation monograph for the CSP, and the preparation is labeled to indicate that it meets the monograph specifications, the BUD must not exceed the BUD specified in the monograph. The Monograph Development Subcommittee of the Compounding Expert Committee is committed to ongoing review of compounded monographs that address health needs. Donors are encouraged to participate in the USP Compounded Preparation Monograph Donation Program to assist the subcommittee in continuing to develop compounded monographs that address health needs of vulnerable populations. Stability-indicating analytical methods referenced can be published or unpublished (e.g., in-house data, studies from member-only organizations that have not been published).

Comment Summary #547: Commenters recommended structuring the chapter with Category 1 and Category 2 and limiting BUDs to 90 days, and removing Category 3 CSPs.

Response: Comment not incorporated. Stakeholders have expressed a need to assign longer BUDs than those for Category 2 for patient-specific CSPs when able to add additional quality assurance requirements. Category 3 describes CSPs made in a compounding facility that meets additional quality assurance requirements. Category 3 CSPs may be assigned longer BUDs than those set for Category 2 CSPs but not exceeding the limits in *Table 14*, if compounded in accordance with all applicable requirements for Category 3 CSPs in <797>.

Comment Summary #548: The commenter recommended that the compounding facility must have documentation of the stability study, including all of the compounding steps and sterilization process parameters.

Response: Comment not incorporated. The documentation will be in the master formulation record and compounding record.

Comment Summary #549: Commenters indicated that the requirements for Category 3 are too restrictive to require a BUD limit of 180 days.

Response: Comment not incorporated. Category 3 describes CSPs made in a compounding facility that meets additional quality assurance requirements. A diversity of practice settings, environments, processes, raw materials, analytical approaches, and few cases in practice which require greater than a 6-month supply resulted in the limit of 180 days. If there is a *USP–NF* compounded preparation monograph for the CSP, and the preparation is labeled to indicate that it meets the monograph specifications, the BUD must not exceed the BUD specified in the monograph.

Comment Summary #550: The commenter recommended a BUD limit of 120 days regardless of the sterilization method or storage condition, as long as the BUD is supported by appropriate testing to demonstrate sterility and stability of the CSP.

Response: Comment not incorporated. The BUD limits are based on several considerations, such as the minimum time periods necessary to perform required tests, CSP chemical and physical stability, the potential for microbial proliferation, the exponential growth rate of microorganisms with increasing temperatures, and the risk of microbial contamination or not achieving and maintaining sterility despite implementation of the requirements in the chapter. The BUD limits are also based on the diversity of practice settings, environments, processes, raw materials, and analytical approaches. The chapter states that terminal sterilization is the preferred method of sterilization, unless the specific CSP or container closure system cannot tolerate terminal sterilization. BUD limits are longer for terminally sterilized CSPs than for aseptically processed CSPs because terminal sterilization using a verified method provides reasonable assurance that a CSP will be sterile. Storage in colder conditions has been shown to slow the growth of most microorganism. The chapter states that the chemical and physical stability of the CSP and its components must be considered when storing in colder conditions. Footnotes were added to the BUD limit tables to clarify that a shorter BUD must be assigned when the physical and chemical stability of the CSP is less than the BUD limit stated in the table.

Comment Summary #551: The commenter recommended that BUDs should not be less than 90-120 days if testing suggests the CSP maintains quality up to 180 days.

Response: Comment not incorporated. The BUD limits are based on several considerations, such as the minimum time periods necessary to perform required tests, CSP chemical and physical stability, the potential for microbial proliferation, the exponential growth rate of microorganisms with increasing temperatures, and the risk of microbial contamination or not achieving and maintaining sterility despite implementation of the requirements in the chapter. The BUD limits are also based on the diversity of practice settings, environments, processes, raw materials, and analytical approaches. Category 1 and Category 2 CSPs are stratified based on risk elements including compounding process (e.g., aseptic processing or terminal sterilization), the environment in which compounding occurs, and the starting ingredients used for compounding (e.g., nonsterile or sterile). Category 3 establishes BUD limits that are up to double those assigned for Category 2, thus maintaining the same risk stratification. If there is a *USP–NF* compounded preparation monograph for the CSP, and the preparation is labeled to indicate that it meets the monograph specifications, the BUD must not exceed the BUD specified in the monograph.

Comment Summary #552: The commenter recommended BUD limits be removed for Category 2 and Category 3 CSPs.

Response: Comment not incorporated. The BUD limits are based on several considerations, such as the minimum time periods necessary to perform required tests, CSP chemical and physical stability, the potential for microbial proliferation, the exponential growth rate of microorganisms with increasing temperatures, and the risk of microbial contamination or not

achieving and maintaining sterility despite implementation of the requirements in the chapter. The BUD limits are also based on the diversity of practice settings, environments, processes, raw materials, and analytical approaches. Category 2 CSPs are stratified based on risk elements including compounding process (e.g., aseptic processing or terminal sterilization), the environment in which compounding occurs, and the starting ingredients used for compounding (e.g., nonsterile or sterile). Category 3 establishes BUD limits that are up to double those assigned for Category 2, thus maintaining the same risk stratification. If there is a *USP–NF* compounded preparation monograph for the CSP, and the preparation is labeled to indicate that it meets the monograph specifications, the BUD must not exceed the BUD specified in the monograph.

Comment Summary #553: The commenter indicated that container closure integrity testing should be required at the end of the shelf-life for the BUD.

Response: Comment incorporated. Language was added to the chapter to clarify that for Category 3 CSPs, once for each formulation and for each container closure system in which it will be packaged, the container closure system must be evaluated for and conforms to container closure integrity to the end of the BUD.

Comment Summary #554: The commenter recommended adding language to convey that container closure integrity testing be performed on units that are aged to the longest BUD using the harshest storage conditions (i.e., 6 months at freezer temperature).

Response: Comment not incorporated. The chapter states that for Category 3 CSPs, once for each formulation and for each container closure system in which it will be packaged, the container closure system must be evaluated for and conforms to container closure integrity to the end of the BUD.

Comment Summary #555: The commenter indicated that the statement in the chapter requiring Category 3 CSPs to be packaged and stored in a container closure of the same materials of composition as that used in the study allows the pharmacist to use a stability study using different container closure components than what the CSP will be packaged in. The commenter recommended revising the statement to state that the Category 3 CSP must be packaged and stored in the identical container closure as that used in the study.

Response: Comment not incorporated. This is information that is not included in a package insert.

Comment Summary #556: The commenter recommended clarifying if the testing requirements for Category 3 CSPs that are injections or ophthalmic solutions, and endotoxin testing for certain Category 2 CSPs, must be completed for each instance of compounding.

Response: Comment not incorporated. The chapter states that if the Category 3 CSP is an injection or it is an ophthalmic solution, particulate-matter testing is conducted once per formulation with acceptable results. Bacterial endotoxin testing is required for Category 2 injectable CSPs compounded from one or more nonsterile component(s) and assigned a BUD that requires sterility testing and Category 3 injectable CSPs compounded from one or more nonsterile component(s).

Comment Summary #557: The commenter recommended clarifying the garbing requirements for Category 3 CSPs regarding if the facility primarily prepares Category 2 CSPs, if sterile garbing and gloves are required for all staff entering the compounding area, and if sterile garb is required at all times or only when preparing Category 3 CSPs.

Response: Comment partially incorporated. The chapter was clarified to state that if the facility compounds Category 3 CSPs, additional garbing requirements must be continuously met in the buffer room in which Category 3 CSPs are prepared, and that the additional garbing requirements must be followed in the buffer room where Category 3 CSPs are prepared for all personnel regardless of whether Category 3 CSPs are compounded on a given day. The chapter states that Category 3 garbing requirements apply to all personnel entering the buffer

room where Category 3 CSPs are compounded and apply at all times regardless of whether Category 3 CSPs are being compounded on a given day.

Comment Summary #558: The commenter recommended clarifying how to assign BUDs for nonpreserved multiple-dose containers without manufacturer specifications.

Response: Comment not incorporated. Language was revised to state that the BUD of a multiple-dose, aqueous, nonpreserved CSP intended for topical, including topical ophthalmic, administration may be assigned in accordance with *14.5 Multiple-Dose CSPs*. The chapter states that the requirement for passing antimicrobial effectiveness testing in accordance with <51> is not required for these formulations if the preparation is prepared as a Category 2 or Category 3 CSP, for use by a single patient, and labeled to indicate that once opened, it must be discarded after 24 hours when stored at controlled room temperature, and/or that once opened, it must be discarded after 72 hours when stored under refrigeration.

Comment Summary #559: The commenter recommended that regarding the requirement for any compounded multiple-dose container to be prepared as a Category 2 or Category 3 CSP, that the requirements for adherence to Category 2 requirements be removed if administration occurs within 4 hours.

Response: Comment partially incorporated. A CSP compounded for direct and immediate administration is not subject to the requirements for Category 1, Category 2, or Category 3 CSPs when all of the conditions in *1.3 Immediate-Use CSPs* are met, including that single-dose containers must not be used for more than one patient.

Comment Summary #560: The commenter indicated support for the ability to use bracketed stability studies and antimicrobial effectiveness testing.

Response: Comment incorporated. Language was maintained to state that antimicrobial effectiveness testing may be performed on a low concentration and a high concentration of the active ingredient in the formulation to establish preservative effectiveness across various strengths of the same formulation (e.g., bracketing).

Comment Summary #561: Commenters indicated that BUDs for nonpreserved otic CSPs and nonpreserved topical CSPs should be the same as those for nonpreserved ophthalmic CSPs.

Response: Comment incorporated. Language was revised to state that the BUD of a multiple-dose, aqueous, nonpreserved CSP intended for topical, including topical ophthalmic, administration may be assigned in accordance with *14.5 Multiple-Dose CSPs*. The chapter states that the requirement for passing antimicrobial effectiveness testing in accordance with <51> is not required for these formulations if the preparation is prepared as a Category 2 or Category 3 CSP, for use by a single patient, and labeled to indicate that once opened, it must be discarded after 24 hours when stored at controlled room temperature, and/or that once opened, it must be discarded after 72 hours when stored under refrigeration.

Comment Summary #562: The commenter recommended that BUDs for nonpreserved otic and irrigation CSPs should be the same as those for nonpreserved ophthalmic CSPs.

Response: Comment partially incorporated. Language was revised to state that the BUD of a multiple-dose, aqueous, nonpreserved CSP intended for topical, including topical ophthalmic, administration may be assigned in accordance with *14.5 Multiple-Dose CSPs*. The chapter states that the requirement for passing antimicrobial effectiveness testing in accordance with <51> is not required for these formulations if the preparation is prepared as a Category 2 or Category 3 CSP, for use by a single patient, and labeled to indicate that once opened, it must be discarded after 24 hours when stored at controlled room temperature, and/or that once opened, it must be discarded after 72 hours when stored under refrigeration.

Comment Summary #563: The commenter recommended clarifying if the statement required to be on a multiple-dose nonpreserved aqueous ophthalmic CSP may reflect the required storage conditions, rather than including the exact statement of, “Discard 24 h after first opening when stored at controlled room temperature or after 72 h when stored under refrigeration.”

Response: Comment incorporated. The language was revised to state that the multiple-dose container is not required to pass antimicrobial effectiveness testing if the preparation is prepared as a Category 2 or Category 3 CSP, for use by a single patient, and labeled (in the label or labeling) to indicate that once opened, it must be discarded after 24 h when stored at controlled room temperature and/or that once opened, it must be discarded after 72 h when stored under refrigeration.

Comment Summary #564: The commenter recommended removing the requirement for antimicrobial effectiveness testing due to the chapter also requiring that the container must not be used for longer than 28 days after being initially entered or punctured.

Response: Comment not incorporated. After a multiple-dose CSP container is initially entered or punctured, the multiple-dose container must not be used for longer than the assigned BUD or 28 days if supported by antimicrobial effectiveness testing results on the CSP, whichever is shorter. If <51> testing shows a shorter timeframe is required, then the shorter limit must be assigned. The limit of 28 days after puncture comes from the limits established in <51>. Variations in formulation and container closure system can impact the preservative's and the CSP's solubility, pH, and stability, potentially rendering the CSP active ingredients, or the preservatives, ineffective.

Comment Summary #565: The commenter recommended that after a multiple-dose container is initially entered or punctured, the multiple-dose container not be used for longer than the assigned BUD or 30 days, rather than 28 days.

Response: Comment not incorporated. The limit of 28 days after puncture comes from the limits established in <51>.

Comment Summary #566: The commenter recommended revising the statement that an aqueous multiple-dose CSP must additionally pass antimicrobial effectiveness testing in accordance with <51>, to only apply for Category 2 CSPs that require sterility testing or exceed the BUD limits for Category 2 CSPs, or Category 3 CSPs. The commenter also indicated that the requirement for <51> testing would not be feasible for preparing stock solution syringes prepared individually.

Response: Comment not incorporated. Stock solutions are not considered to be multiple-dose CSP containers. The chapter does not require <51> testing for CSP stock solutions. A multiple-dose CSP must be prepared as a Category 2 or Category 3 CSP, and an aqueous multiple-dose CSP must additionally pass antimicrobial effectiveness testing in accordance with <51>.

Comment Summary #567: The commenter recommended that a multiple-dose container may be used longer than the assigned BUD or 28 days if supported by antimicrobial effectiveness testing.

Response: Comment not incorporated. After a multiple-dose CSP container is initially entered or punctured, the multiple-dose container must not be used for longer than the assigned BUD or 28 days if supported by antimicrobial effectiveness testing results on the CSP, whichever is shorter. If <51> testing shows a shorter timeframe is required, then the shorter limit must be assigned. The limit of 28 days after puncture comes from the limits established in <51>.

Comment Summary #568: The commenter indicated the chapter conflicts regarding the requirement that aqueous multiple-dose CSPs must pass antimicrobial effectiveness testing and stating that after a multiple-dose container is initially entered or punctured, the container must not be used for longer than the assigned BUD or 28 days if supported by antimicrobial effectiveness testing results on the CSP, whichever is shorter.

Response: Comment not incorporated. If <51> testing shows a shorter timeframe is required, then the shorter limit must be assigned. The limit of 28 days after puncture comes from the limits established in <51>.

Comment Summary #569: Commenters indicated that multiple-dose ophthalmic CSPs should be able to follow the same standards for BUD assignments for Category 1 and Category 2 CSPs as the dosage form should not dictate the BUD limit based on the risk of contamination.

Response: Comment not incorporated. The requirements regarding multiple-dose ophthalmic CSPs were developed in response to stakeholder feedback. Multiple-dose CSP containers must be prepared as a Category 2 or Category 3 CSP to reduce the potential for contamination, while this requirement does not apply for unit dose containers.

Comment Summary #570: The commenter indicated that nonpreserved topical ophthalmic CSPs should be able to follow the same standards for BUD assignments for Category 2 CSPs due to the financial and logistical impacts of antimicrobial effectiveness testing.

Response: Comment not incorporated. The requirements regarding multiple-dose ophthalmic CSPs were developed in response to stakeholder feedback. Multiple-dose CSP containers must be prepared as a Category 2 or Category 3 CSP to reduce the potential for contamination, while this requirement does not apply for unit dose containers. After a multiple-dose CSP container is initially entered or punctured, the multiple-dose container must not be used for longer than the assigned BUD or 28 days if supported by antimicrobial effectiveness testing results on the CSP, whichever is shorter. If testing shows a shorter timeframe is required, then the shorter limit must be assigned. The limit of 28 days after puncture comes from the limits established in . Variations in formulation and container closure system can impact the preservative's and the CSP's solubility, pH, and stability, potentially rendering the CSP active ingredients, or the preservatives, ineffective.

Comment Summary #571: The commenter recommended incorporating language to address the use of eye drop bottles with one-way valve technology to prevent contamination and allow for full dating when this technology is utilized.

Response: Comment not incorporated. The chapter states that the use of technologies, techniques, materials, and procedures other than those described in the chapter is not prohibited as long as they are noninferior to those described in the chapter and validated for the intended purpose. The method would need to be validated for the specific CSP formulation. The packaging is not approved for all preparations.

Comment Summary #572: The commenter indicated that new technologies are used for FDA-approved products to allow for preservative-free aqueous ophthalmic products to be in multiple-dose containers and that the lack of information about such technologies in the chapter will limit patient access to nonpreserved multiple-dose ophthalmic CSPs.

Response: Comment not incorporated. The Compounding Expert Committee is not aware of validated studies demonstrating that multiple-dose containers are able to prevent ingress of contaminated air and backflow of solutions, across a broad range of formulations, and during typical patient-use conditions. FDA-approved ophthalmic multiple-dose containers are approved for the specific drug they are designed to contain. Additionally, the chapter has been revised to say that the use of technologies, techniques, materials, and procedures other than those described in the chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose.

Comment Summary #573: Commenters recommended that multiple-dose, nonpreserved, aqueous, ophthalmic formulations not be required to pass antimicrobial effectiveness testing if dispensed in a multiple-dose nonpreserved ophthalmic dropper bottle designed to prevent microbial contamination over the duration of the BUD, instead of being required to discard 24 hours after first opening when stored at controlled room temperature or after 72 hours when stored under refrigeration.

Response: Comment not incorporated. Antimicrobial effectiveness testing is not required if the preparation is prepared as a Category 2 or Category 3 CSP, used by a single patient, and labeled to indicate that it must be discarded after 24 hours when stored at controlled room

temperature, or 72 hours when stored under refrigeration. The Expert Committee is not aware of validated studies demonstrating multiple-dose containers are able to prevent ingress of contaminated air and backflow of solutions, across a broad range of formulations, and during typical patient-use conditions. FDA-approved ophthalmic multiple-dose containers are approved for the specific drug they are designed to contain. Additionally, the chapter has been revised to say that the use of technologies, techniques, materials, and procedures other than those described in the chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose.

Comment Summary #574: The commenter indicated that limiting the use of nonpreserved aqueous ophthalmic CSPs to 72 hours will lead to a significant expenditure for patients and limit access to care due to the limited availability of compounding services that prepare such products.

Response: Comment not incorporated. The requirements for multiple-dose, nonpreserved, aqueous topical, and topical ophthalmic CSPs apply for multiple-dose CSP containers, which are at high risk for microbial proliferation if contaminated during preparation or use. These additional requirements do not apply for unit dose containers.

Comment Summary #575: The commenter requested a separate category for assigning BUDs for CSPs terminally sterilized by e-beam radiation for solid dosage forms, including no batch size limitation and no recommendation for refrigeration or freezing.

Response: Comment not incorporated. The chapter states that the use of technologies, techniques, materials, and procedures other than those described in the chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose.

15. Use of Conventionally Manufactured Products as Components

Comment Summary #576: The commenter indicated that if a conventionally manufactured single-dose vial is entered or punctured only in an ISO Class 5 or cleaner air, the vial should be allowed to be kept outside of the hood in a classified space. The commenter also indicated that a single-dose vial entered or punctured only in an ISO Class 5 or cleaner air should be allowed a different BUD than a CSP prepared in a PEC in an SCA stored at room temperature.

Response: Comment partially incorporated. The language was revised to state that if a single-dose vial is entered or punctured only in an ISO Class 5 or cleaner air, it may be used up to 12 h after initial entry or puncture as long as the labeled storage requirements during that 12 h period are maintained. Use within twelve hours after initial entry or puncture is based on a risk-based approach.

Comment Summary #577: The commenter recommended that a conventionally manufactured single-dose container entered or punctured only in an ISO Class 5 or cleaner air should be used within 6 hours after initial entry or puncture as long as the storage requirements during that 6-hour period are maintained, rather than used within 12 hours, due to the risk of contamination.

Response: Comment not incorporated. Use within twelve hours after initial entry or puncture is based on a risk-based approach. The chapter describes the minimum standards to be followed when preparing CSPs and the chapter does not prohibit compounders from going beyond the requirements in the chapter.

Comment Summary #578: Commenters recommended defining or clarifying the storage requirements for a conventionally manufactured single-dose container after initial entry or puncture. Commenters indicated clarification was needed regarding after a single-dose vial is entered or punctured in an ISO Class 5 or cleaner air, if it must remain in the ISO Class 5 air.

Response: Comment incorporated. The language was revised to state that if a single-dose vial is entered or punctured only in an ISO Class 5 or cleaner air, it may be used up to 12 h after

initial entry or puncture as long as the labeled storage requirements during that 12 h period are maintained.

Comment Summary #579: The commenter recommended clarifying if a conventionally manufactured single-dose vial entered or punctured and sealed in an ISO Class 5 PEC must be stored continuously in ISO Class 5 air or can be stored in ISO Class 7 air for 6 hours.

Response: Comment partially incorporated. The language was revised to state that if a single-dose vial is entered or punctured only in an ISO Class 5 or cleaner air, it may be used up to 12 h after initial entry or puncture as long as the labeled storage requirements during that 12 h period are maintained.

Comment Summary #580: The commenter recommended spelling out the word “hour” versus “h” and hyphenating or not hyphenating the number and hour consistently.

Response: Comment partially incorporated. Hour being referred to as “h” is per the *USP Style Guide*. Hyphenation of number and hour is used correctly per the *USP Style Guide*.

Comment Summary #581: Commenters recommended clarifying that the “use by” time assigned to an entered or punctured single-dose vial used as the source of a CSP ingredient does not require the BUD of the CSP to be limited to that same “use by” time.

Response: Comment partially incorporated. Language was revised to state that the BUD of a CSP must not exceed the shortest remaining expiration date of any of the commercially available starting components. The text was additionally clarified that the final CSP must be assigned a BUD consistent with *Section 14. Establishing Beyond-Use Dates*.

Comment Summary #582: Commenters recommended clarifying that the “use by” time assigned to an entered or punctured multiple-dose vial used as the course of a CSP ingredient does not require the BUD of the CSP to be limited to that same “use by” time.

Response: Comment partially incorporated. Language was revised to state that the BUD of a CSP must not exceed the shortest remaining expiration date of any of the commercially available starting components. The text was additionally clarified that the final CSP must be assigned a BUD consistent with *Section 14. Establishing Beyond-Use Dates*.

Comment Summary #583: The commenter indicated that the chapter statement that, “The alternative technologies, techniques, or materials must not be used to modify requirements outlined in this chapter (e.g., extending beyond-use dates, the amount of time a single-dose or multiple-dose container may be used, compounding in alternative environments)”, stifles innovation regarding the amount of time a single-dose or multiple-dose container may be used.

Response: Comment partially incorporated. The text was revised to state that the use of technologies, techniques, materials, and procedures other than those described in the chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose (e.g., *Validation of Alternative Microbiological Methods* (1223) and *Validation of Compendial Procedures* (1225)).

Comment Summary #584: The commenter indicated that in veterinary practices the majority of compounding is performed using FDA-approved drugs, which poses lesser risk than compounding from bulk drug substances.

Response: Comment not incorporated. Compounding using conventionally manufactured products is within the scope of compounding. Compounding is defined as the process of combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance to create a sterile preparation. While FDA-approved drugs are sterile and stable on their own, when combined with other ingredients the components may no longer be stable or effective. There is risk of contamination when compounding with bulk substances or commercial drugs.

Comment Summary #585: The commenter indicated that standards should be differentiated for veterinary use due to FDA-approved multiple-dose vials for animal use being preserved, while FDA-approved drugs for human use are often not preserved.

Response: Comment not incorporated. Many FDA-approved drugs for human use are also preserved. Sterile compounding is defined as combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance to create a sterile preparation. While FDA-approved drugs are sterile and stable on their own, when combined with other ingredients the components may no longer be stable or effective.

16. Use of CSPs as Components

Expert Committee-Initiated Change #1: Clarification was added to describe a component CSP compared to a final CSP.

Expert Committee-Initiated Change #2: Text was revised for clarity and moved to 14. *Establishing Beyond-Use Dates* regarding assigning BUDs for CSPs prepared from one or more compounded components.

Expert Committee-Initiated Change #3: “Medication” was revised to “preparation” for clarity regarding the statement that a multiple-dose CSP is designed to contain more than one dose of sterile preparation, intended to be entered or punctured multiple times, and usually contains a preservative.

Comment Summary #586: Commenters recommended clarifying that compounded stock solutions may be used in final products with extended dates.

Response: Comment partially incorporated. Language was added to clarify that for CSPs prepared from one or more compounded components the BUD should generally not exceed the shortest BUD of any of the individual compounded components, however, there may be acceptable instances when the BUD of the final CSP exceeds the BUD assigned to compounding components. Language was added to state that the final CSP must be assigned a BUD consistent with the section for establishing beyond-use dates. The chapter states that a component CSP may be used for sterile compounding for up to 12 h or its assigned BUD, whichever is shorter, and any remainder must be discarded. Text was added to clarify that this time limit for entering or puncturing is not intended to restrict the BUD of the final CSP, and refers the reader to the section for establishing beyond-use dates.

Comment Summary #587: The commenter recommended that component CSPs compounded on the day of compounding the final CSP need to be excluded from the requirement that the BUD of a CSP prepared from one or more compounded components may not exceed the shortest BUD of any of the individual starting components.

Response: Comment partially incorporated. Text was added to clarify that there may be acceptable instances when the BUD of the final CSP exceeds the BUD assigned to compounded components (e.g., pH-altering solutions).

Comment Summary #588: Commenters recommended clarifying the meaning of the statement regarding compounded single-dose CSPs and CSP stock solution, that, “the component CSP may be used for sterile compounding for up to 12 h or its assigned BUD, whichever is shorter, and any remainder must be discarded”.

Response: Comment incorporated. Text was added to clarify that this time limit for entering or puncturing is not intended to restrict the BUD of the final CSP, and refers the reader to the section for establishing beyond-use dates.

Comment Summary #589: The commenter recommended stating that the BUD limits in the BUD Limit tables are for final CSPs only, and products given the BUDs in the tables cannot be further manipulated, to help clarify the use times for CSP stock solutions.

Response: Comment partially incorporated. Language was added to clarify that for CSPs prepared from one or more compounded components the BUD should generally not exceed the shortest BUD of any of the individual compounded components, however, there may be acceptable instances when the BUD of the final CSP exceeds the BUD assigned to

compounding components. Language was added to state that the final CSP must be assigned a BUD consistent with the section for establishing beyond-use dates. The chapter states that a component CSP may be used for sterile compounding for up to 12 h or its assigned BUD, whichever is shorter, and any remainder must be discarded. Text was added to clarify that this time limit for entering or puncturing is not intended to restrict the BUD of the final CSP, and refers the reader to the section for establishing beyond-use dates.

Comment Summary #590: The commenter recommended clarifying how to assign a BUD for a reconstituted single-dose vial, including if a reconstituted single-dose vial may be used as a component for multiple CSPs.

Response: Comment not incorporated. This information is more specific than the minimum standards described in the chapter. The chapter states that a single-dose vial may be used up to 12 h after initial entry or puncture as long as the labeled storage requirements during that 12-h period are maintained when the single-dose vial is entered or punctured only in an ISO Class 5 or cleaner air.

Comment Summary #591: Commenters recommended clarifying that the “use-by” time assigned to an entered or punctured multiple-dose CSP used as the source of a finished CSP ingredient does not require the BUD of the finished CSP to be limited to that same “use-by” time.

Response: Comment incorporated. The chapter states that after a multiple-dose CSP is initially entered or punctured, the multiple-dose CSP must not be used for longer than the assigned BUD or 28 days, whichever is shorter. Text was added to clarify that this time limit for entering or puncturing is not intended to restrict the BUD of the final CSP, and refers the reader to the section for establishing beyond-use dates.

Comment Summary #592: Commenters recommended clarifying that the “use-by” time assigned to an entered or punctured single-dose CSP or CSP stock solution used as the source of a finished CSP ingredient does not require the BUD of the finished CSP to be limited to that same “use-by” time.

Response: Comment incorporated. The chapter states that a component CSP may be used for sterile compounding for up to 12 h or its assigned BUD, whichever is shorter, and any remainder must be discarded. Text was added to clarify that this time limit for entering or puncturing is not intended to restrict the BUD of the final CSP, and refers the reader to the section for establishing beyond-use dates.

Comment Summary #593: The commenter indicated that limiting the beyond-use date of CSPs prepared from compounded stock solutions will create a burden for compounding for pediatric and neonatal patients.

Response: Comment partially incorporated. The chapter states that a component CSP may be used for sterile compounding for up to 12 h or its assigned BUD, whichever is shorter, and any remainder must be discarded. Text was added to clarify that this time limit for entering or puncturing is not intended to restrict the BUD of the final CSP, and refers the reader to the section for establishing beyond-use dates.

Comment Summary #594: The commenter recommended clarifying that CSPs made using a component CSP may be given a BUD consistent with the Category 1, Category 2, or Category 3 limits set forth in the chapter provided the component CSP is not used for longer than 12 hours or its assigned BUD.

Response: Comment partially incorporated. The chapter states that a component CSP may be used for sterile compounding for up to 12 h or its assigned BUD, whichever is shorter, and any remainder must be discarded. Text was added to clarify that this time limit for entering or puncturing is not intended to restrict the BUD of the final CSP, and refers the reader to the section for establishing beyond-use dates.

Comment Summary #595: Commenters recommended that the BUD of a CSP prepared from one or more compounded components not exceed 12 hours or the shortest BUD of any of the individual starting components, whichever is shorter.

Response: Comment not incorporated. The chapter states that a component CSP may be used for sterile compounding for up to 12 h or its assigned BUD, whichever is shorter, and any remainder must be discarded. Text was added to clarify that this time limit for entering or puncturing is not intended to restrict the BUD of the final CSP, and refers the reader to the section for establishing beyond-use dates. Text was added to clarify that there may be acceptable instances when the BUD of the final CSP exceeds the BUD assigned to compounded components (e.g., pH-altering solutions). There are instances where a compounded component may be used to compound a CSP where the resulting CSP has greater stability due to the dilution of the component CSP, or the final CSP is terminally sterilized and therefore has greater sterility assurance than the component CSP.

Comment Summary #596: The commenter indicated that a BUD of 12 hours for CSPs compounded with single-dose CSPs and CSP stock solutions would be burdensome for inpatient pharmacies. The commenter recommended a minimum BUD of 24 hours for CSPs compounded from single-dose CSPs or CSP stock solution components.

Response: Comment partially incorporated. The chapter states that a component CSP may be used for sterile compounding for up to 12 h or its assigned BUD, whichever is shorter, and any remainder must be discarded. Text was added to clarify that this time limit for entering or puncturing is not intended to restrict the BUD of the final CSP, and refers the reader to the section for establishing beyond-use dates for the final CSP.

Comment Summary #597: Commenters recommended regarding use of compounded single-dose CSPs and CSP stock solutions, that the dating with which it can be used, or its “in-use time” should be used for greater than 12 hours. Some commenters recommended up to 24 hours, some up to at least 48 hours, or to the BUD limits of Category 2 CSPs.

Response: Comment not incorporated. The chapter states that a component CSP may be used for sterile compounding for up to 12 h or its assigned BUD, whichever is shorter, and any remainder must be discarded. Use within twelve hours after initial entry or puncture is based on a risk-based approach. Text was added to clarify that this time limit for entering or puncturing is not intended to restrict the BUD of the final CSP, and refers the reader to the section for establishing beyond-use dates.

Comment Summary #598: The commenter indicated that if there is stability information past 12 hours, and is 24 hours or longer, a final Category 2 CSP syringe prepared using CSP stock solutions should be allowed a BUD of 24 hours.

Response: Comment partially incorporated. The chapter states that a component CSP may be used for sterile compounding for up to 12 h or its assigned BUD, whichever is shorter, and any remainder must be discarded. Use within twelve hours after initial entry or puncture is based on a risk-based approach. Text was added to clarify that this time limit for entering or puncturing is not intended to restrict the BUD of the final CSP, and refers the reader to the section for establishing beyond-use dates.

Comment Summary #599: The commenter recommended clarifying if an ophthalmic drug can be added to a preserved commercially available nonprescription ophthalmic product and be assigned a 28 day BUD.

Response: Comment not incorporated. This information is more specific than the minimum standards described in the chapter. BUDs for CSPs must be established in accordance with the BUD limits for Category 1, Category 2, and Category 3 CSPs. If prepared as a multiple-dose container, the chapter requirements for multiple-dose CSPs would apply.

Comment Summary #600: The commenter recommended that a compounded single-dose CSP or CSP stock solution be used for sterile compounding for up to 6 hours or its assigned BUD, whichever is shorter, rather than used within 12 hours.

Response: Comment not incorporated. Use within twelve hours after initial entry or puncture is based on a risk-based approach. The chapter describes the minimum standards to be followed when preparing CSPs and the chapter does not prohibit compounders from going beyond the requirements in the chapter.

Comment Summary #601: The commenter recommended adding that for a CSP stock solution, as a Category 2 CSP, the stock solution CSP may be used for sterile compounding up to its assigned BUD, when any remainder must be discarded.

Response: Comment not incorporated. The chapter states that a component CSP may be used for sterile compounding for up to 12 h or its assigned BUD, whichever is shorter, and any remainder must be discarded. Use within twelve hours after initial entry or puncture is based on a risk-based approach.

Comment Summary #602: Commenters recommended clarifying that component CSPs or stock solutions may be given BUDs consistent with those in *Section 14* until they are first used to prepare other preparation, at which point a 12-hour BUD must be applied to the component CSP or stock solution. The commenter recommended clarifying that the final CSP produced from the component CSP should have a BUD of no longer than the BUD assigned to the component CSP, or shorter if the storage conditions change warranting a shorter BUD in accordance with *Section 14*.

Response: Comment partially incorporated. Language was added to clarify that for CSPs prepared from one or more compounded components the BUD should generally not exceed the shortest BUD of any of the individual compounded components, however, there may be acceptable instances when the BUD of the final CSP exceeds the BUD assigned to compounding components. Language was added to state that the final CSP must be assigned a BUD consistent with the section for establishing beyond-use dates. The chapter states that a component CSP may be used for sterile compounding for up to 12 h or its assigned BUD, whichever is shorter, and any remainder must be discarded. Text was added to clarify that this time limit for entering or puncturing is not intended to restrict the BUD of the final CSP, and refers the reader to the section for establishing beyond-use dates.

Comment Summary #603: The commenter recommended adding regarding use of compounded single-dose CSPs and CSP stock solutions, that the resulting final CSP may be assigned a BUD not exceeding the limits for Category 1, Category 2, or Category 3 CSPs. The commenter also recommended including that repackaging of a single-dose CSP or CSP stock solution into unit of use doses will follow the chapter recommendations regarding repackaging.

Response: Comment partially incorporated. The chapter states that a component CSP may be used for sterile compounding for up to 12 h or its assigned BUD, whichever is shorter, and any remainder must be discarded. Text was added to clarify that this time limit for entering or puncturing is not intended to restrict the BUD of the final CSP, and refers the reader to the section for establishing beyond-use dates. The chapter states that repackaging of a sterile product or preparation from its original container into another container must be performed in accordance with the requirements in the chapter.

Comment Summary #604: The commenter recommended clarifying the storage requirements after initial entry or puncture for single-dose CSP vials to be used as a component.

Response: Comment not incorporated. The chapter states that when a compounded single-dose CSP or CSP stock solution is used as a component to compound additional CSPs, the original compounded single-dose CSP or CSP stock solution must be entered or punctured in ISO Class 5 or cleaner air and must be stored under the conditions upon which its BUD is based (e.g., refrigerator or controlled room temperature). The chapter also states the

component CSP may be used for sterile compounding for up to 12 h or its assigned BUD, whichever is shorter, and any remainder must be discarded.

Comment Summary #605: Commenters indicated clarification is needed regarding if the 12 h that a CSP stock solution may be used up to for sterile compounding starts once the stock solution is compounded, or after first entry or puncture.

Response: Comment not incorporated. The chapter states that the original compounded CSP stock solution must be entered or punctured in ISO Class 5 or cleaner air and must be stored under the conditions upon which its BUD is based (e.g., refrigerator or controlled room temperature). The chapter states that a component CSP may be used for sterile compounding for up to 12 h or its assigned BUD, whichever is shorter, and any remainder must be discarded, indicating that the 12 h is after initial entry or puncture.

Comment Summary #606: The commenter recommended if the CSP follows aseptic procedures and BUD limits for Category 2 CSPs with no sterility testing, removing the requirement that multiple-dose CSPs used as components must meet the criteria for antimicrobial effectiveness testing. The commenter also indicated that the requirement for <51> testing would not be feasible for preparing stock solution syringes prepared individually.

Response: Comment not incorporated. Stock solutions are not considered to be multiple-dose CSP containers. The chapter does not require <51> testing for CSP stock solutions. Multiple-dose CSPs are required to meet the criteria for antimicrobial effectiveness testing and the chapter requirements for multiple-dose CSPs. After a multiple-dose CSP is initially entered or punctured, the multiple-dose CSP must not be used for longer than the assigned BUD or 28 days, whichever is shorter. The limit of 28 days after puncture comes from the limits established in <51>. Text was added to clarify that this time limit for entering or puncturing is not intended to restrict the BUD of the final CSP, and refers the reader to the section for establishing beyond-use dates.

Comment Summary #607: The commenter recommended including clear guidance for compounding with a CSP stock solution, including example dilutions, for neonatal and pediatric patients. The commenter also recommended including a subset within the section to allow for stock solution syringes to be dated and used under the BUD limits of Category 2 CSPs with no sterility testing requirement.

Response: Comment partially incorporated. This information is more specific than the minimum standards described in the chapter. The chapter states that a component CSP may be used for sterile compounding for up to 12 h or its assigned BUD, whichever is shorter, and any remainder must be discarded. Text was added to clarify that this time limit for entering or puncturing is not intended to restrict the BUD of the final CSP, and refers the reader to the section for establishing beyond-use dates.

Comment Summary #608: The commenter recommended clarifying if a 503B manufactured product, such as a stock solution, is considered to be a CSP or a conventionally manufactured product.

Response: Comment not incorporated. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction. Manufacturers must comply with FDA's current good manufacturing practices (CGMP) and/or laws and regulations of the applicable regulatory jurisdiction. Additional clarification is provided in the *General Notices*.

17. SOPs

Comment Summary #609: Commenters recommended clarifying if the designated person changes between the review cycles of the SOPs, does the new designated person need to complete the review again immediately or wait until the next review is due.

Response: Comment not incorporated. This information is more specific than the minimum standards described in the chapter. This is a topic that may be described in the facility's SOPs.

Comment Summary #610: The commenter recommended revising the chapter requirement that any "changes or alterations" to an SOP be made only by a designated person(s) and must be documented, to state that any "revisions" to an SOP be made only by a designated person(s) and be documented. This recommendation is to harmonize with the chapter requirement that "revisions" to SOPs be communicated to all personnel involved in these processes and procedures.

Response: Comment not incorporated. The language as chosen is deemed to more closely reflect the intent. Revisions to SOPs must be communicated, while minor changes may not need to be communicated but do need to be made only by a designated person(s) and be documented.

Comment Summary #611: Commenters recommended revising the chapter requirement that SOPs be reviewed at least every 12 months, to every 24 months or every 3 years.

Response: Comment not incorporated. SOPs must be reviewed initially and at least every 12 months by the designated person(s) to ensure that they reflect current practices, and the review must be documented.

Comment Summary #612: The commenter recommended revising the requirement that corrective actions be documented, to the corrective actions be documented and dated.

Response: Comment not incorporated. This is a topic that may be described in the facility's SOPs. The chapter describes the minimum standards to be followed when preparing CSPs and the chapter does not prohibit compounders from going beyond the requirements in the chapter.

Comment Summary #613: The commenter indicated that the chapter requirement for personnel to report any problems, deviations, failures, or errors to the designated person(s) may stifle reporting and recommended this be revised from "must" to "should".

Response: Comment partially incorporated. The chapter was revised to state that all compounding personnel must be trained to report any problems, deviations, failures, or errors to the designated person(s).

18. Quality Assurance and Quality Control

Expert Committee-Initiated Change #1: Language was revised to harmonize with the comparable section in <795>.

Comment Summary #614: Commenters indicated that clarification is needed about if written QA and QC programs must establish a system for evaluation of adverse drug events or non-drug events (e.g., personnel eating and drinking in the anteroom).

Response: Comment not incorporated. The chapter states that designated person(s) must ensure that the facility has formal, written QA and QC programs that establish a system of evaluation of complaints and adverse events. This would include adverse drug events and non-drug events.

Comment Summary #615: Commenters indicated that the appropriate investigations and corrective actions included in a facility's written QA and QC program should be directed at failed sterility testing and/or endotoxin testing. The commenter indicated that it should not be necessary for a facility to have formal written QA and QC programs for routine Category 1, Category 2, and immediate-use CSP inspections before dispensing or administration.

Response: Comment not incorporated. The chapter states that designated person(s) must ensure that the facility has formal, written QA and QC programs that establish a system of appropriate investigations and corrective actions. The facility may define the appropriate investigations and corrective actions in the facility's SOPs.

Comment Summary #616: The commenter recommended clarifying what is meant by “the overall QA and QC program” and when the program must be reviewed.

Response: Comment not incorporated. The chapter states that the overall QA and QC program must be reviewed at least once every 12 months by the designated person(s). The facility may describe when the review of the program occurs in the facility SOPs, as long as it occurs at least once every 12 months. The chapter defines quality assurance as a system of procedures, activities, and oversight that ensure that the compounding process consistently meets quality standards. The chapter defines quality control as the sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the CSP. A quality assurance program is guided by written procedures that define responsibilities and practices that ensure compounded preparations are produced with quality attributes appropriate to meet the needs of patients and health care professionals.

Comment Summary #617: The commenter recommended that a QA and QC program be reviewed at appropriate intervals, rather than reviewed at least once every 12 months.

Response: Comment not incorporated. The overall QA and QC program must be reviewed at least once every 12 months by the designated person(s).

Comment Summary #618: The commenter indicated that CSPs required to be sterility and/or bacterial endotoxin tested should not be dispensed until negative results are received.

Response: Comment not incorporated. The facility may dispense or administer a CSP before the results of release testing are known as long as the ability to recall the CSP is established.

Comment Summary #619: The commenter recommended revising the requirement that facilities have procedures in place to immediately notify the prescriber of a failure of specifications with the potential to cause patient harm, to also require the affected patient be notified.

Response: Comment partially incorporated. Language in this section and in the comparable section in <795> was revised for harmonization. Language was added stating that if investigation into an adverse event reveals a quality problem with a CSP that is likely to affect other patients, those patients and prescribers potentially affected must be informed.

Comment Summary #620: The commenter recommended adding a statement that the designated person(s) must review all adverse event reports as part of the QA and QC programs.

Response: Comment not incorporated. The chapter states that a designated person(s) must review all complaints to determine whether the complaint indicates a potential quality problem with the CSP.

Comment Summary #621: The commenter recommended that a record of a complaint should include the affected patient’s species.

Response: Comment not incorporated. This information is often retrievable from patient files as needed. The chapter describes the minimum standards to be followed when preparing CSPs and the chapter does not prohibit compounders from going beyond the requirements in the chapter. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #622: The commenter recommended that adverse event reporting include requirements for SOPs and written and retrievable records. The commenter recommended the records should also include to the extent that the information is known, the name and strength of the CSP and the assigned internal identification number (e.g., prescription, order, or lot number) and species.

Response: Comment not incorporated. The chapter states that complaint records should include, to the extent that the information is known, the name and strength of the CSP and the assigned internal identification number (e.g., prescription, order, or lot number). Regarding the species of the affected patient, this information is often retrievable from patient files as needed.

The chapter describes the minimum standards to be followed when preparing CSPs and the chapter does not prohibit compounders from going beyond the requirements in the chapter. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

19. CSP Handling, Storage, Packaging, Shipping, and Transport

Expert Committee-Initiated Change #1: Text was added to specify that results of temperature readings must be documented in a temperature log per facility SOPs or stored in the continuous temperature recording device to clarify that while monitoring must be done each day, such as with in-range thermometers when the pharmacy is closed, the readings must be documented in a log according to the facility's SOPs or stored in a continuous temperature recording device.

Comment Summary #623: The commenter recommended clarifying if "personnel" includes all hospital staff or just 503B pharmacy personnel, regarding the chapter requirement that personnel who will be handling, storing, packaging, and transporting CSPs within the facility must be trained in accordance with the relevant SOPs, and the training must be documented.

Response: Comment not incorporated. The chapter states that personnel within the facility who will be performing the listed activities must be trained in accordance with the relevant SOPs and that the training must be documented. Processes and techniques for handling, storing, packaging, and transporting CSPs must be outlined in the facility's SOPs. Regarding being applicable to 503B pharmacy personnel, USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction. Manufacturers must comply with FDA's current good manufacturing practices (CGMP) and/or laws and regulations of the applicable regulatory jurisdiction. Additional clarification is provided in the *General Notices*.

Comment Summary #624: The commenter recommended clarifying if the section applies to storage of CSPs on the hospital units outside of the pharmacy.

Response: Comment not incorporated. The chapter states that to help ensure that CSP quality is maintained during storage at the compounding facility, personnel must monitor conditions in the storage areas. This includes wherever the CSP is stored within the facility. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #625: The commenter recommended that only for components requiring refrigeration or only compounding facilities (e.g., pharmacies) be required to monitor room, refrigerator, and freezer temperatures where components are stored.

Response: Comment partially incorporated. The chapter states that personnel must monitor conditions in the storage areas to help ensure that CSP quality is maintained during storage at the compounding facility. A controlled temperature area must be established and monitored to ensure that the temperature remains within the appropriate range for the CSP, and the temperature must be monitored each day, either manually or by a continuous recording device. The language was revised to state that the results of the temperature readings must be documented in a temperature log per facility SOPs or stored in the continuous temperature recording device and must be retrievable.

Comment Summary #626: The commenter indicated that the statement, "In some cases, the CSP must be packaged in a special container (e.g., a cooler) to protect it from temperature fluctuations", is unclear as it does not specify what "some cases" refers to and does not clearly address refrigerated or frozen CSPs. The commenter recommended stating that CSPs requiring refrigerated or frozen storage must be packaged in a container (e.g., a cooler) that is able to maintain the required storage temperature.

Response: Comment not incorporated. The facility or compounders may determine storage requirements for the CSPs and the means to meet them. The text states that the facility must select appropriate shipping containers and packaging materials based on the product specifications, information from vendors, and the mode of transport.

Comment Summary #627: The commenter recommended clarifying if the section applies to transporting of CSPs only outside of the facility or including within the facility. The commenter also recommended clarifying if CSP labeling would need to include warnings (e.g., “Do not send via pneumatic tube system”) if the section applies to transporting CSPs within the facility.

Response: Comment not incorporated. The chapter states that compounding personnel must select modes of transport that are expected to deliver properly packed CSPs in an undamaged, sterile, and stable condition. This includes wherever the CSP is transported, in and out of the facility. The chapter states that when shipping or transporting CSPs that require special handling, personnel must include specific handling instructions on the exterior of the container.

20. Documentation

Comment Summary #628: The commenter recommended removing the requirement that documentation must include receipt of components.

Response: Comment not incorporated. This information can assist personnel to retrieve information regarding when and which components were received. Documentation must include receipt of components.

Comment Summary #629: The commenter recommended revising the chapter requirement that compounding records for a particular CSP be readily retrievable for at least 3 years after preparation, to 2 years.

Response: Comment incorporated. All required documentation for a particular CSP (e.g., MFR, CR, and release inspection and testing results) must be readily retrievable for at least 2 years after preparation or as required by laws and regulations of the applicable regulatory jurisdiction or accrediting organization(s), whichever is longer.

21. Compounding Allergenic Extracts

Expert Committee-Initiated Change #1: It was clarified that all interior surfaces of the PEC and all work surfaces in the allergenic extract compounding area where direct compounding is occurring must be cleaned and disinfected each day of use before compounding occurs, rather than described as “daily”.

Expert Committee-Initiated Change #2: A box describing the requirements for compounding records for individual allergenic extract prescription sets was removed, and the reader referred to *Box. 10 Compounding Records*.

Expert Committee-Initiated Change #3: “Sanitizing agents” was revised to be “disinfecting agents”.

Comment Summary #630: The commenter recommended clarifying whether all dilutions of allergenic extracts performed in a provider’s office is subject to the chapter requirements.

Response: Comment not incorporated. The standards for compounding allergenic extracts, described in *21. Compounding Allergenic Extracts*, are applicable regardless of where the allergenic extract is compounded when the compounding process involves transfer via sterile needles and syringes of conventionally manufactured sterile allergen products and appropriate conventionally manufactured sterile added substances; and manipulations are limited to penetrating stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile vials.

Comment Summary #631: The commenter requested the chapter address whether dilution of allergen extracts is within nursing scope of practice.

Response: Comment not incorporated. The standards for compounding allergenic extracts, described in *21. Compounding Allergenic Extracts*, are applicable regardless of where the allergenic extract is compounded when the compounding process involves transfer via sterile needles and syringes of conventionally manufactured sterile allergen products and appropriate conventionally manufactured sterile added substances; and manipulations are limited to penetrating stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile vials.

Comment Summary #632: The commenter recommended adding a statement indicating that allergens that are immediate-use will not need to meet the requirements for allergenic extract prescription sets and will be subject to the standards described in *1.3 Immediate-Use CSPs*.

Response: Comment not incorporated. Because of certain characteristics of allergenic extracts and allergy practice, preparation of allergenic extract prescription sets is not subject to all of the requirements in the chapter that are applicable to other sterile CSPs. However, the chapter does not prohibit compounders from going beyond the requirements in the chapter. The chapter does not prohibit allergenic extracts from being prepared for immediate-use when all the requirements are met for compounding CSPs for direct and immediate administration.

Comment Summary #633: The commenter requested removing *21. Compounding Allergenic Extracts* and creating a separate standard for compounding allergenic extract prescription sets.

Response: Comment not incorporated. The decision to describe the standards for compounding allergenic extracts as a specific practice within <797> was in response to stakeholder input and allergist experts. Allergenic extracts are described as a subset of compounding described in a separate section.

Comment Summary #634: The commenter recommended allowing allergenic extract vials to be multiple-dose and still allow a 1-year BUD limit.

Response: Comment not incorporated. Multiple-dose vials have increased risk of contamination. Compounding allergenic extracts is per individual patient prescription set only. The Compounding Expert Committee has received feedback from stakeholders that small variations for allergenic extract prescription sets can lead to anaphylaxis and the smallest amount possible needs to be made all at once to avoid variations.

Comment Summary #635: The commenter recommended clarifying if allergenic extracts can be compounded at bedside.

Response: Comment not incorporated. Compounding allergenic extracts is per individual patient prescription set only.

Comment Summary #636: The commenter indicated that for personnel qualifications for compounding allergenic extract prescription sets, the requirement that personnel who fail competency evaluations must successfully pass reevaluations in the deficient area(s) before they can resume compounding of allergenic extract prescription sets is more stringent than the personnel qualification requirements for compounding other CSPs. The commenter indicated that personnel qualifications for personnel compounding other CSPs does not require a reevaluation in the event of a failure.

Response: Comment not incorporated. Personnel compounding other CSPs are required to successfully complete evaluations, which would require reevaluations in the event of a failure. The language is more explicit regarding personnel qualifications for compounding allergenic extract prescription sets due to this preparation not being subject to all of the requirements in the chapter that are applicable to other sterile CSPs.

Comment Summary #637: The commenter recommended clarifying the definition of expertise in allergen immunotherapy.

Response: Comment not incorporated. The Compounding Expert Committee has received feedback from allergist experts that indicated support for the language as described in the chapter.

Comment Summary #638: The commenter indicated that the personnel qualifications for compounding allergenic extract prescription sets should have the same gloved fingertip and thumb sampling frequency as required for Category 1 and 2 CSPs.

Response: Comment not incorporated. Because of certain characteristics of allergenic extracts and allergy practice, preparation of allergenic extract prescription sets is not subject to all of the requirements in the chapter that are applicable to other sterile CSPs.

Comment Summary #639: The commenter indicated that the chapter references media-fill testing procedures for other CSPs in relation to compounding allergenic extract prescription sets, but the media-fill testing procedures referenced specifies that a surface sample is collected in the DCA Of the PEC, and not all those compounding allergenic extracts will be using a PEC.

Response: Comment incorporated. A statement was added to the chapter to clarify that if compounding outside of a PEC, the post-media-fill surface sample is not required.

Comment Summary #640: The commenter recommended that the minimum garb requirements for personnel compounding allergenic extract prescription sets apply only when mixing within an ISO Class 5 PEC, and that low-lint booties be added to this list of minimum garb requirements.

Response: Comment not incorporated. The minimum garb requirements described in 21.2 *Personnel Hygiene and Garbing for Compounding Allergenic Extract Prescription Sets* apply when compounding in an ISO Class 5 PEC or in a dedicated allergenic extract compounding area. Because of certain aspects of dedicated allergenic extract compounding area design, low-lint booties were not included as a minimum garb requirement. The chapter describes the minimum standards to be followed when preparing CSPs and the chapter does not prohibit compounders from going beyond the requirements in the chapter.

Comment Summary #641: The commenter recommended clarifying where the compounding process for allergenic extract prescription sets is required to occur.

Response: Comment not incorporated. The chapter states that the compounding process must occur in an ISO Class 5 PEC, or in a dedicated allergenic extract compounding area. The chapter defines an allergenic extract compounding area as a designated space, area, or room that is not required to be classified, with a visible perimeter that is suitable for preparation of allergenic extract prescription sets.

Comment Summary #642: The commenter recommended specifying that when possible, ceilings with the perimeter of the AECA must be cleaned and disinfected when visibly soiled and when surface contamination is known or suspected.

Response: Comment not incorporated. Ceilings within the perimeter of the AECA must be cleaned and disinfected when visibly soiled and when surface contamination is known or suspected.

Comment Summary #643: The commenter recommended specifying that only on days when compounding occurs in an AECA, that all work surfaces in the AECA where direct compounding is occurring must be cleaned and disinfected daily.

Response: Comment incorporated. In an AECA, all work surfaces in the AECA where direct compounding is occurring must be cleaned and disinfected each day of use before compounding begins and when surface contamination is known or suspected.

Comment Summary #644: The commenter recommended that lyophilized individual patient allergenic extract prescription sets prepared as Category 3 CSPs and intended to remain lyophilized until the time of administration be assigned BUDs matching those for allergenic extracts prepared under the requirements of 21. *Compounding Allergenic Extracts*.

Response: Comment not incorporated. The BUD for the prescription set must be no later than the earliest expiration date of any allergenic extract or any diluent that is part of the prescription set, and the BUD must not exceed 1 year from the date the prescription set is mixed or diluted. The BUD provisions for allergenic extracts are aligned with the [FDA Guidance on Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application](#).

Comment Summary #645: The commenter recommended adding a requirement that once initially entering or puncturing an allergenic extract multiple-dose container, the container must not be used for more than 28 days unless otherwise specified by the manufacturer on the labeling.

Response: Comment not incorporated. Compounding allergenic extracts is per individual patient prescription set only.

Comment Summary #646: The commenter indicated that a BUD of 1 year from the date of mixing or diluting an allergenic extract prescription set is too long.

Response: Comment not incorporated. Because of certain characteristics of allergenic extracts and allergy practice, preparation of allergenic extract prescription sets is not subject to all of the requirements in the chapter that are applicable to other sterile CSPs. The BUD for the prescription set must be no later than the earliest expiration date of any allergenic extract or any diluent that is part of the prescription set, and the BUD must not exceed 1 year from the date the prescription set is mixed or diluted. The BUD provisions for allergenic extracts are aligned with the [FDA Guidance on Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application](#).

Glossary

Expert Committee-Initiated Change #1: Minor editorial changes were made.

Expert Committee-Initiated Change #2: The definition for “Active pharmaceutical ingredient (API)” was revised for clarity and harmonized with <795>.

Expert Committee-Initiated Change #3: A definition was added for “Alcohol-based hand rub”.

Expert Committee-Initiated Change #4: A definition was added for “Assigned trainer” and harmonized with <795>.

Expert Committee-Initiated Change #5: The definition for “Batch” was revised for clarity.

Expert Committee-Initiated Change #6: The definition for “Beyond-use date (BUD)” was revised for clarity and harmonized with <795>.

Expert Committee-Initiated Change #7: A definition for “Biological safety cabinet (BSC)” was added and harmonized with <795>.

Expert Committee-Initiated Change #8: The definition for “Cleaning” was revised for clarity and harmonized with <795>.

Expert Committee-Initiated Change #9: The definition for “Cleaning agent was revised for clarity and harmonized with <795>.

Expert Committee-Initiated Change #10: The definition for “Containment ventilated enclosure (CVE)” was clarified to be a non-ISO classified full or partial enclosure.

Expert Committee-Initiated Change #11: The definition of “Conventionally manufactured product” was revised to say, “an application approved by the applicable national regulatory agency”, as this is a globally used chapter.

Expert Committee-Initiated Change #12: A definition for “Containment glove bag” was added and harmonized with <795>.

Expert Committee-Initiated Change #13: The definition for “Designated person(s)” was revised for clarity and harmonized with <795>.

Expert Committee-Initiated Change #14: A definition for “Label” was added and harmonized with <795>.

Expert Committee-Initiated Change #15: A definition for “Labeling” was added and harmonized with <795>.

Expert Committee-Initiated Change #16: A definition was added for “Oversight”.

Expert Committee-Initiated Change #17: The definition for “Perimeter” was revised for clarity.

Expert Committee-Initiated Change #18: The definition for “Segregated compounding area (SCA)” was revised for clarity.

Expert Committee-Initiated Change #19: The definition for “Specification” was revised to not include “an API”, as “component” includes active ingredients.

Expert Committee-Initiated Change #20: The definition for “Sterilizing-grade membranes” was revised to “Sterilizing-grade filter” to reflect the more common term used in industry.

Expert Committee-Initiated Change #21: The definition for “Workflow management system” was revised to be, “Technology comprised of hardware and/or software that allows for automation to assist in the verification of components of, and preparation of, CSPs and to document components and processes.”

Comment Summary #647: The commenter recommended clarifying the definition for “batch” to include distribution for multiple patients and not multiple CSPs for a single patient pursuant to a single prescription.

Response: Comment not incorporated. A batch of CSPs can be compounded for a single patient. The chapter defines “batch” as more than one CSP prepared as described in the MFR in a single, discrete process, and expected to have uniform character and quality, within specified limits.

Comment Summary #648: Commenters recommended that the definition for “beyond-use date (BUD)” should state that it is the date and time after which a CSP must no longer be stored prior to administration and must be discarded (i.e., the BUD), and recommending clarifying if administration is included in the BUD.

Response: Comment not incorporated. The chapter states that the BUD is not intended to limit the time during which the CSP is administered (e.g., infused). The chapter defines “beyond-use date (BUD)” as the date, or hour and the date, after which a CSP must not be used, stored, or transported, and clarifies that the date is determined from the date and time the preparation is compounded. The chapter states that administration of medication is out of scope of the chapter.

Comment Summary #649: The commenter recommended revising the definition for “beyond-use date (BUD)” to remove the word “used” to clarify that administration is not included in the BUD.

Response: Comment not incorporated. The chapter states that the BUD is not intended to limit the time during which the CSP is administered (e.g., infused). The chapter defines “beyond-use date (BUD)” as the date, or hour and the date, after which a CSP must not be used, stored, or transported, and clarifies that the date is determined from the date and time the preparation is compounded. The chapter states that administration of medication is out of scope of the chapter.

Comment Summary #650: The commenter recommended clarifying the definition for “beyond-use date (BUD)” to express how to label an appropriate beyond-use date when considering the BUD limits, stability of a preparation, and the chapter stating that administration is out of scope of the chapter.

Response: Comment not incorporated. The chapter states that the BUD is not intended to limit the time during which the CSP is administered (e.g., infused). The chapter defines “beyond-use date (BUD)” as the date, or hour and the date, after which a CSP must not be used, stored, or transported, and clarifies that the date is determined from the date and time the preparation is

compounded. Labeling procedures must be followed as described in the facility's SOPs to prevent labeling errors and CSP mix-ups. The label on the immediate container of the CSP must display prominently and legibly the BUD.

Comment Summary #651: The commenter recommended that the definition for "compounded sterile preparation (CSP)" should refer to other resources for applicable information for pharmaceutical industry.

Response: Comment not incorporated. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction. Manufacturers must comply with FDA's current good manufacturing practices (CGMP) and/or laws and regulations of the applicable regulatory jurisdiction.

Comment Summary #652: Commenters recommended clarifying the definition of "compounding" to differentiate it from "administration".

Response: Comment not incorporated. The chapter defines "compounding" as the process of combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance to create a sterile preparation. The chapter states that for the purposes of the chapter, "administration" means the direct application of a sterile product or preparation to a single patient by injecting, infusing or otherwise providing a sterile product or preparation in its final form, and clarifies that administration of medication is out of the scope of the chapter.

Comment Summary #653: The commenter recommended the definition of "compounding" be harmonized with the definition from the Food and Drug Administration regarding if repackaging is considered compounding.

Response: Comment not incorporated. The chapter defines "compounding" as the process of combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance to create a sterile preparation. The chapter defines "repackaging" as the act of removing a sterile product or preparation from its original primary container and placing it into another primary container, usually of smaller size without further manipulation. USP has no role in enforcement. Ensuring compliance with the requirements of the chapter is the responsibility of the applicable regulatory jurisdiction.

Comment Summary #654: Commenters recommended adding a definition of "immediate-use CSP" to the glossary.

Response: Comment not incorporated. All of the requirements included in *1.3 Immediate-Use CSPs* is significant to define the term "immediate-use CSP".

Comment Summary #655: The commenter recommended that the definition for "laminar airflow system (LAFS)" should clarify that it is placed within a buffer room or SCA.

Response: Comment partially incorporated. The chapter defines "laminar airflow system" as a device or zone within a buffer room that provides an ISO Class 5 or better air quality environment for sterile compounding, and the system provides a unidirectional HEPA-filtered airflow.

Comment Summary #656: The commenter indicated that the chapter does not define "preparation" nor "medication" and requested clarification on the use of these terms in comparison with the term "drug".

Response: Comment partially incorporated. The use of "medication" and "product" were reviewed and corrected for clarity and accuracy throughout the chapter. A sterile medication is not always a drug (i.e., flush, IV bag, bacteriostatic water, diluent). The chapter defines a compounded sterile preparation as a preparation intended to be sterile that is created by combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance.

Comment Summary #657: The commenter recommended that the definition for “workflow management system” should include that they are used in assessing or helping practitioners to assess dose accuracy.

Response: Comment not incorporated. The chapter describes a minimum standard to be followed when preparing CSPs that encompasses a wide variety of practice sites. The chapter does not prohibit compounders from going beyond the requirements in the chapter. Not all workflow management systems have the same abilities. The chapter defines “workflow management system” as technology comprised of hardware and/or software that allows for automation to assist in the verification of components of, and preparation of, CSPs and to document components and processes.