



## ***Commentary***

### ***USP 42–NF 37, Second Supplement***

**June 28, 2019**

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.

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

**General Chapter/Section(s):** <797> Pharmaceutical Compounding – Sterile Preparations  
**Expert Committee(s):** Compounding  
**No. of Commenters:** 1705

**Sections:**

1. [Introduction and Scope](#)
  2. [Personnel Training and Evaluation](#)
  3. [Personal Hygiene and Garbing](#)
  4. [Facilities and Engineering Controls](#)
  5. [Certification and Recertification](#)
  6. [Microbiological Air and Surface Monitoring](#)
  7. [Cleaning, Disinfecting, and Applying Sporicidal Agents in Compounding Areas](#)
  8. [Introducing Items Into the SEC and PEC](#)
  9. [Equipment, Supplies, and Components](#)
  10. [Sterilization and Depyrogenation](#)
  11. [Master Formulation and Compounding Records](#)
  12. [Release Inspections and Testing](#)
  13. [Labeling](#)
  14. [Establishing Beyond-Use Dates](#)
  15. [Use of Conventionally Manufactured Products as Components](#)
  16. [Use of CSPs as Components](#)
  17. [SOPs](#)
  18. [Quality Assurance and Quality Control](#)
  19. [CSP Handling, Storage, Packaging, Shipping, and Transport](#)
  20. [Documentation](#)
  21. [Compounding Allergenic Extracts](#)
- [Glossary](#)  
[Appendix](#)

**General Comments**

**Commentary Summary #1:** Several commenters suggested that physician offices should 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. 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. Immediate use CSPs must be administered within 4 hours following the start of preparation. Additionally, preparation per approved labeling is out of the scope of the chapter, as described in *1.4 Preparation Per Approved Labeling*.

**Commentary Summary #2:** Commenter indicated that the chapter is overly prescriptive and interferes with physicians' ability to provide quality care and oversight to patients.

**Response:** Comment not incorporated. The intent of the chapter is to help ensure quality compounded preparations regardless of where and by whom the CSP is compounded. Additionally, the chapter has 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*).

**Commentary Summary #3:** Multiple commenters noted that the chapter requires purchase and adoption of specific goods and services that are provided by present and former committee members, which may represent a commercial conflict of interest.

**Response:** Comment not incorporated. This chapter does not require the procurement of specific goods and services. USP makes reasonable efforts to avoid the existence or appearance of partiality, conflict of interest, or USP endorsement of a particular organization's products or services. Further, expert volunteers must abide by USP's conflict of interest policy and applicable provisions of the [Code of Ethics](#) and the [USP Rules and Procedures of the Council of Experts](#).

**Commentary Summary #4:** Several commenters suggested that the chapter should be presented as recommendations and best practices, but not mandates. Other commenters requested that the chapter be renumbered to a number above 1000 to make it informational.

**Response:** Comment not incorporated. The intent of the chapter is to provide standards to ensure a quality CSP. The chapter has been an official quality standard since 2004. USP has no role in enforcement of compounding chapters. 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.

**Commentary Summary #5:** Several commenters asked whether references to general chapters above 1000 are also requirements.

**Response:** Comment not incorporated. References to general chapters above 1000 are informational.

**Commentary Summary #6:** Commenter suggested calling out <797> as a standalone chapter.

**Response:** Comment not incorporated. The references within <797> are also required if they are to general chapters below 1000.

**Commentary Summary #7:** Several commenters suggested including the rationale and evidence supporting the changes in the chapter. Other commenters requested the additional literature references in the chapter.

**Response:** Comment not incorporated. The standards in the chapter are intended to be best practices based on a combination of available evidence, expertise of the Compounding Expert Committee, and input from stakeholders.

**Commentary Summary #8:** Several commenters recommended that the chapter should only apply to preparation of compounded sterile human drugs and should not pertain to preparations compounded for animal patients. The requirements described in the chapter should be directed towards compounding pharmacy facilities and not dispensers that may be performing some degree of compounding. Commenters

provided several examples of preparations prepared by veterinarians that would be difficult to prepare in a sterile compounding facility [e.g., cleanroom suite or segregated compounding area (SCA)].

**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. The Compounding Expert Committee may consider development of a specific veterinary compounding chapter in the future. 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 veterinary compounding.

**Commentary Summary #10:** Commenter requested that veterinary practitioners should be exempted from the chapter. The commenter further noted that each section should be reviewed and amended as it pertains to the needs of veterinarians and veterinary patients.

**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. The Compounding Expert Committee may consider development of a specific veterinary compounding chapter in the future. 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 veterinary compounding.

**Commentary Summary #11:** Several commenters requested that a statement be added to state that the chapter does not pertain to the administration or dispensing of CSPs to patients in veterinary practice settings.

**Response:** Comment partially 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. The Compounding Expert Committee may consider development of a specific veterinary compounding chapter in the future. 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 veterinary compounding.

**Commentary Summary #12:** Several commenters suggested adding a statement that the chapter is not intended to supersede any state laws regarding compounding in veterinary practices.

**Response:** Comment not incorporated. USP has no role in enforcement of compounding chapters. 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.

**Commentary Summary #13:** Commenter requested addition of language stating that medications prepared for animal patients should be limited to medications prepared for therapeutic purposes. Commenter noted that the statement would help animal research laboratories that prepare sterile medication doses for purposes of primary science research. Many research animals are terminated immediately after the end of the experiment, and the risk of infection is not relevant.

**Response:** Comment not incorporated. The requirements of this chapter are equally relevant to CSPs for human and animal patients. The Compounding Expert Committee may consider development of a specific veterinary compounding chapter in the future. 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 veterinary compounding.

**Commentary Summary #14:** Commenter suggested limiting the scope of the chapter to CSPs prepared for animals that are used for food.

**Response:** Comment not incorporated. The requirements of this chapter are equally relevant to CSPs for humans and animals, regardless of whether the animals are for companionship, performance, or food. 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 animal use.

**Commentary Summary #15:** Commenter noted that the revised standard would prevent the compounding of ophthalmic preparations for conditions such as infectious corneal ulcers, endophthalmitis, and dry eye.

**Response:** Comment not incorporated. All CSPs, regardless of the route of administration, must follow the requirements in the chapter to ensure a quality CSP. The intent of the chapter is to minimize harm to patients that could result from 1) microbial contamination (nonsterility), 2) excessive bacterial endotoxins, 3) variability from the intended strength of correct ingredients, 4) physical and chemical incompatibilities, 5) chemical and physical contaminants, and/or 6) use of ingredients of inappropriate quality.

**Commentary Summary #16:** Commenter noted that the revisions will have unintended consequences for anesthesiologists and recommended that the chapter state that the “one-hour rule” does not apply in operating room or procedure room settings. Additionally, commenter raised the issue of drug shortages and noted that there are requirements in the chapter that would discourage policies to help alleviate drug shortages.

**Response:** Comment not incorporated. The intent of the chapter is to help ensure quality compounded preparations regardless of where the CSP is compounded. Additionally, the chapter provides 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*). Further, provisions for use of conventionally manufactured products as components provide standards for use of

single-dose containers, multiple-dose containers, and pharmacy bulk packages (see 15. *Use of Conventionally Manufactured Products as Components*).

**Commentary Summary #17:** Multiple commenters requested that the chapter should exempt operating room settings from the scope of the chapter. Alternatively, a commenter suggested that the chapter provide more clarity about the distinction between compounding and administration. For example, preparation of a medication for a pending operation should not be considered compounding.

**Response:** Comment partially incorporated. The intent of the chapter is to help ensure quality compounded preparations regardless of where the CSP is compounded. Separate sections were added 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 Compounding Expert Committee will consider developing FAQs in the future to assist in providing additional clarity.

**Commentary Summary #18:** Commenter requested an exemption from the requirements for low-risk, low-volume critical access hospitals in rural areas.

**Response:** Comment not incorporated. The intent of the chapter is to help ensure quality compounded preparations regardless of where the CSP is compounded. Additionally, the chapter provides information to assist with specific types of preparations (e.g. administration, immediate use, and preparation per approved labeling).

**Commentary Summary #19:** Several commenters noted that office-based dermatologists prepare buffered lidocaine in the morning and use it throughout the day to perform office surgeries. Buffered lidocaine is less painful when injected and remains sterile when stored in a needle capped syringe for several days.

**Response:** Comment partially incorporated. Chapter was revised to clarify that administration of medication is out of 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 will evaluate the feasibility of developing a compounded preparation monograph for buffered lidocaine with epinephrine.

**Commentary Summary #20:** Commenter recommended that the chapter should provide an exemption for Mohs surgeons to ensure their ability to prepare buffered or diluted lidocaine and use it for 12 or 24 hours.

**Response:** Comment partially incorporated. Chapter was revised to clarify that administration of medication is out of 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 will evaluate the feasibility of developing a compounded preparation monograph for buffered lidocaine with epinephrine.

**Commentary Summary #21:** Several commenters requested an exemption for compounded preparations to be prepared outside of controlled environments and be stored for at least 12 hours to facilitate patient access. The commenter noted that one

hour is only adequate for some in-office preparations, and that a longer exemption is needed for preparations such as buffered lidocaine with epinephrine.

**Response:** Comment partially incorporated. Chapter was revised to clarify that administration of medication is out of 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 will evaluate the feasibility of developing a compounded preparation monograph for buffered lidocaine with epinephrine.

**Commentary Summary #22:** Commenter suggested that preparations for cutaneous administration (e.g., buffered lidocaine) prepared in an unclassified area should be allowed to be stored for 8 hours.

**Response:** Comment partially incorporated. Chapter was revised to clarify that administration of medication is out of 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 will evaluate the feasibility of developing a compounded preparation monograph for buffered lidocaine with epinephrine.

**Commentary Summary #23:** Commenter suggested reorganizing the chapter to move the *Quality Assurance and Quality Control* section to the beginning of the chapter, and then referring to the specific quality assurance (QA) and quality control (QC) requirements in each subsequent section.

**Response:** Comment not incorporated. The chapter is organized to describe the requirements for quality CSPs. The QA and QC program should take into consideration all of the requirements in the chapter. Additionally, rearranging the chapter may be confusing for users who see information by topics. The outline of the chapter is aligned with <795> *Pharmaceutical Compounding – Nonsterile Preparations*. The Expert Committee will consider revising <1163> *Quality Assurance in Pharmaceutical Compounding* in the future.

**Commentary Summary #24:** Several commenters requested addition of the following statement: “The use of technologies, techniques, materials, and procedures other than those described in this chapter is not prohibited so long as they have been proven to be equivalent or superior with statistical significance to those described herein.”

**Response:** Comment not incorporated. The chapter allows use of sterility testing that is non-inferior to <71> *Sterility Tests* provided that it is validated per <1223> *Validation of Alternative Microbiological Methods. General Notices 6.30 Alternative and Harmonized Methods and Procedures* also allows for alternative methods and procedures to be used, provided that they are validated per <1225> *Validation of Compendial Procedures*. The Expert Committee decided that it would be difficult to determine equivalence or statistical significance for all technologies, techniques, materials, and procedures not defined in the chapter. The Expert Committee may consider future revisions to the chapter to accommodate advancements in technologies, techniques, materials, and procedures.

**Commentary Summary #25:** Commenter suggested that entities should be allowed to perform their own assessments of risk to identify work practices and technologies that are alternative but equivalent to those in the chapter for preventing contamination and ensuring sterility.

**Response:** Comment not incorporated. The chapter allows use of sterility testing that is non-inferior to <71> *Sterility Tests* provided that it is validated per <1223> *Validation of Alternative Microbiological Methods. General Notices 6.30 Alternative and Harmonized Methods and Procedures* also allows for alternative methods and procedures to be used, provided that they are validated per <1225> *Validation of Compendial Procedures*. The Expert Committee decided that it would be difficult to determine equivalence or statistical significance for all technologies, techniques, materials, and procedures not defined in the chapter. The Expert Committee may consider future revisions to the chapter to accommodate advancements in technologies, techniques, materials, and procedures.

**Commentary Summary #26:** Commenter noted that the chapter should not be given a 3-digit number 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.

**Commentary Summary #27:** Several commenters requested that the implementation of the chapter be delayed until clear parameters can be set for establishing extended beyond-use dates (BUDs).

**Response:** Comment not incorporated. The chapter is intended to provide standards to help ensure quality CSPs. The 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.

**Commentary Summary #28:** Several commenters requested that the implementation date for the chapter be delayed to give institutions sufficient time to make necessary changes. The commenter noted that facilities implementing both the revised <797> and <800> *Hazardous Drugs – Handling in Healthcare Settings* need additional time to make changes to their facilities and to fiscally plan for construction services and new equipment. Commenters requested a delay of at least 18 months or at least 24 months.

**Response:** Comment not incorporated. General Chapter <800> has been published since February 2016 and will become official in December 2019. The facility changes in <797> are intended to ensure a quality CSP and to allow for longer and more flexible BUDs based on the criteria described in *14. Establishing Beyond-Use Dates*. Further, the facility and environmental monitoring requirements are similar to those in the existing chapter.

**Commentary Summary #29:** Several commenters requested a delayed implementation date because the scope and scale of the changes within the chapter

can result in a tremendous amount of changes and revisions to current work practices, electronic health records, and policies.

**Response:** Comment not incorporated. The facility changes in <797> are intended to ensure a quality CSP and to allow for longer and more flexible BUDs based on the criteria described in 14. *Establishing Beyond-Use Dates*. Further, the facility and environmental monitoring requirements are similar to those in the existing chapter.

**Commentary Summary #30:** Commenter requested that USP monitor the implementation of the final chapter. The commenter noted that often, standards are implemented and there is no evaluation as to the impact or modifications made based on the results of an evaluation.

**Response:** Comment not incorporated. USP has no role in the enforcement of the compounding chapters. 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. However, USP will survey stakeholders to potentially develop tools, including frequently asked questions (FAQs), to help users implement the standard.

**Commentary Summary #31:** Commenter noted that the chapter does not have provisions that require verification for the presence, correct identity, and correct amount of all ingredients in the finished CSP. The commenter noted that Institute for Safe Medication Practices (ISMP) reported compounding errors should be addressed in the chapter.

**Response:** Comment not incorporated. Quality checks are incorporated throughout the chapter to ensure accuracy and quality of the CSPs (e.g., component selection, release testing, labeling, etc.).

**Commentary Summary #32:** Commenter requested that the chapter discuss errors during pharmacy preparation of parenteral products and admixtures since they have been reported to the ISMP National Medication Errors Reporting Program.

**Response:** Comment not incorporated. Quality checks are incorporated throughout the chapter to ensure accuracy and quality of the CSPs (e.g., component selection, release testing, labeling, etc.). USP will consider future development of a chapter on parenteral nutrition.

**Commentary Summary #33:** Commenter requested more prescriptive procedural guidance (e.g., fingertip sampling, media-fill testing, aseptic technique, donning and doffing procedures).

**Response:** Comment partially incorporated. Gloved fingertip and thumb sampling and media-fill testing are described in *Box 2-1* and *Box 2-2*, respectively. The Expert Committee will consider development of tools and resources for other procedures. Donning and doffing procedures must be determined by the facility and may be dependent on the facility layout and placement of the sink.

**Commentary Summary #34:** Commenter requested that references to <797> in <800> be updated when the revised <797> is published.

**Response:** Comment incorporated. References in <800> to <797> will be updated as appropriate through the General Chapters Dependency process.

**Commentary Summary #35:** Commenter requested that the time periods in the chapter be better defined. For example, commenter requested clarification on whether

monitoring every 6 months means every 180 days or every 6 months as long as it is within the month.

**Response:** Comment not incorporated. The intent of every 6 months is to mean every 180 days. Every 6 months is easier to understand, and facilities will have to determine when to perform their monitoring.

**Commentary Summary #36:** Several commenters requested that the temperature units be denoted throughout the chapter.

**Response:** Comment not incorporated. *General Notices 8.180 Temperatures* specifies that temperature is expressed in centigrade (Celsius). Temperature units are not repeated in the chapter as the unit is defined in the *General Notices* and also in USP's style guide.

**Commentary Summary #37:** Commenter noted that the chapter does not specify the use of a filtering needle when opening an ampule.

**Response:** Comment not incorporated. The chapter does not provide prescriptive requirements for each type of container closure or dosage form. Compounders should follow the manufacturers' labeling information and best practices for using and administering medications from ampules.

**Commentary Summary #38:** Commenter requested that the statement "based on current scientific information and best practices for sterile compounding" be eliminated.

**Response:** Comment incorporated.

**Commentary Summary #39:** Several commenters requested that the chapter address drug vial optimization (DVO). DVO allows the use of closed-system transfer devices (CSTDs) to extend the BUD of single-dose containers.

**Response:** Comment not incorporated. CSTDs are not FDA-cleared for extending BUDs of single-dose containers. An indication for use to prevent microbial ingress requires a microbial ingress test, which immerses the system in microbes and assesses how many microbes are able to gain access to the inside of the container. The Expert Committee does not think there is adequate assurance of sterility to use CSTDs to extend the BUDs of single-dose containers. In addition to assuring sterility, compounders must also consider the physical and chemical stability and container-closure integrity of the single-dose container.

**Commentary Summary #40:** Several commenters requested allowing CSTDs to be used to extend the BUD of single-dose containers based on publications in peer-reviewed literature.

**Response:** Comment not incorporated. The Expert Committee evaluated the peer-reviewed literature on use of CSTDs to extend BUDs. The studies did not perform a microbial ingress test which immerses the system in microbes and assesses how many microbes are able to gain access to the inside of the container. Additionally, there is a study that states that the sterility of the product is not guaranteed. The Expert Committee does not think there is adequate assurance of sterility to use CSTDs to extend the BUDs of single-dose containers. In addition to assuring sterility, compounders must also consider the physical and chemical stability and container-closure integrity of the single-dose container.

**Commentary Summary #41:** Commenter requested changing the use of the term "standards" throughout the chapter to "requirements."

**Response:** Comment not incorporated. The chapter is intended to provide quality standards for preparing CSPs. The standard contains both recommendations and requirements.

**Commentary Summary #42:** Commenter noted that colony forming unit “(cfu)” should be uppercase, “CFU.”

**Response:** Comment not incorporated. The acronym “cfu” is lowercase based on USP’s style guide.

**Commentary Summary #43:** Commenter noted concerns that there may be potential conflicts between the chapter and the FDA Guidance for Industry on *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use*. The commenter specifically noted concerns within the FDA guidance.

**Response:** Comment not incorporated. The chapter does not reference the FDA guidance. Commenter should refer specific comments on the guidance to the agency.

**Commentary Summary #44:** Commenter requested that the standard provide guidance to adopting authorities on how the chapter should be applied to existing facilities. Commenter noted that the facilities must meet the physical environment requirements of <797> at the time of construction, but the adopting authority may require the existing facility be brought into compliance where conditions of the physical environment are deemed to present a distinct and clear risk.

**Response:** Comment not incorporated. The chapter applies to both existing facilities and new facilities. Applicable regulatory bodies are responsible for ensuring compliance with the appropriate standards.

**Commentary Summary #45:** Commenter requested a graphic for testing personnel and guests entering the cleanroom. The commenter noted that visitors and maintenance staff entering the compounding area must be appropriately garbed.

**Response:** Comment partially incorporated. Facilities must have appropriate policies and procedures for authorized personnel entering the compounding area. The chapter was revised to require hand hygiene and garbing for all persons who enter the compounding area.

**Commentary Summary #46:** Commenter recommended limiting the preparation of demonstrably difficult CSPs to manufacturers due to their complexity.

**Response:** Comment not incorporated. Demonstrably difficult is not adequately defined, and limiting specific dosage forms may have unintended consequences for patient access to medications.

**Commentary Summary #47:** Commenter recommended that the heating, ventilation, and air conditioning (HVAC) system must be dedicated and designed to minimize contamination.

**Response:** Comment not incorporated. Dedicated and designed HVAC systems may be ambiguous and subject to different interpretations. The chapter describes specific requirements for facilities and equipment, including HVAC requirements.

**Commentary Summary #48:** Commenter recommended adding a provision for emergency preparations, disasters, or shortages.

**Response:** Comment not incorporated. Emergencies, disasters, and shortages are not in the scope of the chapter. There are other regulatory jurisdictions that may oversee procedures in the event of emergencies and disasters.

## 1. Introduction and Scope

**Commentary Summary #1:** Commenter suggested that the concepts of administration and immediate use be better defined and moved to the section on *Specific Practices*.

**Response:** Comment partially incorporated. New subsections, *1.2 Administration* and *1.3 Immediate Use CSPs*, were created. The concepts were clarified within the new subsections.

**Commentary Summary #2:** Several commenters requested that the section be reorganized to improve clarity on which practices are out of the scope of the chapter.

**Response:** Comment incorporated.

**Commentary Summary #3:** Commenters requested the inclusion of checklists for practices that are out of the scope of the chapter. The commenter suggested that the section can be divided into clear topics with bullets for each of the topics.

**Response:** Comment partially incorporated. The section was reorganized with several new subsections to improve readability and understandability.

**Commentary Summary #4:** Multiple commenters noted that the statement that “preparation of non-hazardous CSPs for administration must follow applicable jurisdictional laws and regulations” is superfluous and should be removed from the chapter.

**Response:** Comment incorporated.

**Commentary Summary #5:** Commenter requested that a statement be added to indicate that preparation of non-hazardous CSPs for administration must be labeled consistent with <7> *Labeling* whenever possible.

**Response:** Comment not incorporated. The statement for labeling “whenever possible” is vague and may be subject to varying interpretation. Further information about labeling of CSPs can be found in *13. Labeling*.

**Commentary Summary #6:** Multiple commenters noted that aseptic technique should apply to “compounding” of any sterile medication and not “preparation” of any sterile medication.

**Response:** Comment not incorporated. Aseptic technique must be followed for preparing and compounding any sterile medication.

**Commentary Summary #7:** Multiple commenters requested a list of criteria for determining aseptic technique. Commenter requested guidance on how to evaluate personnel to ensure that they meet the requirements for aseptic technique. Other commenter requested examples of environment, equipment, and processes required for aseptic technique.

**Response:** Comment not incorporated. Aseptic technique is a process of compounding to minimize contamination. Aseptic technique involves procedures to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, and mix-ups with other products or CSPs. The Expert Committee will consider future resources and tools to describe and define aseptic technique.

**Commentary Summary #8:** Commenter requested moving the requirement for aseptic technique to the beginning of the chapter to make it clear that aseptic technique applies to all sterile medications.

**Response:** Comment incorporated.

**Commentary Summary #9:** Multiple commenters noted that the minimum requirements for aseptic technique should include 1) establishing a clean surface on which to perform mixing that is not directly under or adjacent to an air vent, a window, or foot traffic and 2) performing hand hygiene and vial sanitization.

**Response:** Comment not incorporated. Aseptic technique is a process of compounding to minimize contamination. Aseptic technique involves procedures to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, and mix-ups with other products or CSPs. Techniques may be different based on the type of preparation, the environment, and other factors. The Expert Committee will consider future resources and tools to describe and define aseptic technique.

**Commentary Summary #10:** Commenter recommended adding that “substitution or inclusion of incorrect ingredients” be added to the list of factors that may cause harm to patients.

**Response:** Comment not incorporated. The chapter lists examples of factors that may cause harm to patients. Chemical and physical contaminants may include incorrect ingredients in the CSP.

**Commentary Summary #11:** Commenter noted that “variability from intended strength of correct ingredients” is not adequately addressed in the chapter.

**Response:** Comment not incorporated. Variability from intended strength of correct ingredients has been added to the chapter as an example of a factor that may cause harm to patients. The chapter provides QA and QC principles and other requirements (e.g., master formulation records, compounding records, labeling) that should be in place to minimize harm to patients, including harm due to variability from intended strength of correct ingredients.

**Commentary Summary #12:** Commenter suggested that the factors of “physical and chemical incompatibilities” and “chemical and physical contaminants” that may cause harm to patients be removed because the chapter does not outline any requirements to minimize these risks.

**Response:** Comment not incorporated. The list is intended to provide examples of factors that may cause harm to patients. The chapter provides QA and QC principles and other requirements (e.g., master formulation records, compounding records, labeling) that should be in place to minimize harm to patients.

**Commentary Summary #13:** Commenter requested that the section on factors affecting the risk associated with CSPs include items such as batch size, complexity of compounding, inherent nature of the drug, and length of storage time between compounding and administration.

**Response:** Comment not incorporated. The framework for Category 1 and Category 2 CSPs is based primarily on the BUD and the environment in which it is compounded. Other public comments noted that the factors associated with risks are not exhaustive and the chapter did not provide guidance on how to accommodate for those risks.

**Commentary Summary #14:** Commenter noted the subsection title “CSPs AFFECTED” should be lower case. The small caps may cause misunderstanding.

**Response:** Comment not incorporated. The formatting of the section and subsection titles are based on USP’s style guide.

**Commentary Summary #15:** Commenter recommended specifying that the dosage forms listed are required to be “sterilized in their final container or aseptically produced” instead of noting that they must be sterile.

**Response:** Comment not incorporated. The list of dosage forms is intended to provide an introduction and examples of CSPs that must be sterile. The chapter later describes sterilization processes including terminal sterilization and aseptic processing.

**Commentary Summary #16:** Commenter noted that wound irrigations are not required to be sterile.

**Response:** Comment not incorporated. Irrigations for internal body cavities (i.e. any space that does not normally communicate with the environment) are required to be sterile. Other irrigations such as those for wounds should be sterile (see also FDA Guidance for Industry [Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment](#)).

**Commentary Summary #17:** Commenter requested clarification on whether irrigations for the gastrointestinal tract are required to be sterile.

**Response:** Comment not incorporated. Irrigations for internal body cavities (i.e. any space that does not normally communicate with the environment) are required to be sterile.

**Commentary Summary #18:** Commenter noted that the statement that the chapter applies to all persons who compound should be revised to indicate that it does not apply to immediate use CSPs.

**Response:** Comment not incorporated. The chapter, including the provisions for immediate use, applies to all personnel who prepare CSPs.

**Commentary Summary #19:** Commenter noted that the chapter should not apply to “all persons” and should exclude those administering or preparing immediate use CSPs.

**Response:** Comment partially incorporated. The sections on administration and immediate use CSPs were reorganized into subsections for clarity. The chapter still applies to all persons who prepare CSPs, including those preparing immediate use CSPs.

**Commentary Summary #20:** Commenter requested that ambulatory surgery centers be added to the list of places where the chapter applies.

**Response:** Comment incorporated.

**Commentary Summary #21:** Commenter requested that the chapter clearly define who is the compounder and identify common situations where there are non-pharmacy healthcare professionals who are compounding.

**Response:** Comment not incorporated. The chapter applies to all healthcare practitioners who are compounding. Adding examples of common situations could be misconstrued by users who might think that those are the only situations where compounding is occurring.

**Commentary Summary #22:** Commenter requested that home infusion settings be added to the list of places where the chapter applies.

**Response:** Comment partially incorporated. The chapter applies to infusion facilities.

**Commentary Summary #23:** Commenter noted that the pharmacist-in-charge is ultimately responsible for ensuring compliance with state law.

**Response:** Comment not incorporated. The statement is out of the scope of the chapter. Facilities are responsible for compliance with the laws and regulations of the applicable regulatory jurisdiction.

**Commentary Summary #24:** Commenter requested reorganization of the subsection on *Specific Practices* to clarify the requirements for hazardous drugs (HDs) and radiopharmaceuticals.

**Response:** Comment incorporated.

**Commentary Summary #25:** Commenter requested that reference to standards for HDs and radiopharmaceuticals be moved to earlier in the chapter.

**Response:** Comment incorporated.

**Commentary Summary #26:** Multiple commenters noted that repackaging of sterile products is not sterile compounding and should be removed from the chapter. The commenter further noted that repackaging does not carry the same risks as compounding and does not rise to the level of inclusion in the chapter.

**Response:** Comment not incorporated. Repackaging requires manipulation of sterile products, which carries the risk of inadvertent microbial contamination. Storage of the repackaged products must also take into consideration the physical and chemical stability, sterility, and container-closure integrity. Repackaging must be performed in accordance with the requirements in the chapter.

**Commentary Summary #27:** Commenter noted that the FDA definition of compounding does not include repackaging. Commenter requested harmonization with FDA to exclude repackaging from the scope of the chapter. Repackaging does not carry the same risks as sterile compounding.

**Response:** Comment not incorporated. Repackaging requires manipulation of sterile products, which carries the risk of inadvertent microbial contamination. Storage of the repackaged products must also take into consideration the physical and chemical stability, sterility, and container-closure integrity. Repackaging of sterile products must be performed with aseptic technique and must be performed in accordance with the requirements in the chapter.

**Commentary Summary #28:** Commenter suggested removing FDA Guidance as the sole guidance from the repackaging provision.

**Response:** Comment incorporated.

**Commentary Summary #29:** Commenter requested examples of practices that are considered repackaging. For example, commenter requested clarification on whether repackaging includes transferring medications into syringes.

**Response:** Comment not incorporated. Repackaging includes transferring a sterile product or preparation from its original container into another container (e.g., syringe).

**Commentary Summary #30:** Commenter noted that requiring repackaging to meet <797> requirements for assigning BUD would conflict with FDA guidance on repackaging.

**Response:** Comment not incorporated. Repackaging of sterile products and preparations must be performed in accordance with the requirements of the chapter to minimize the risk of microbial contamination. The FDA Guidance for Industry on [Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing](#)

[Facilities](#) adds that the FDA intends to evaluate the BUDs in the guidance when the revised <797> is published.

**Commentary Summary #31:** Several commenters requested deletion of the statement that a shorter BUD is required for repackaged products and preparations when there is evidence or documentation requiring a shorter BUD.

**Response:** Comment incorporated. However, *14.3 Establishing a BUD for a CSP* specifies that a shorter BUD is required when the stability of the CSP or its components is less than those stated in *Table 10* for Category 1 CSPs and *Table 11* for Category 2 CSPs.

**Commentary Summary #32:** Several commenters suggested that a shorter BUD is required for repackaged products and preparations only when there is federal documentation.

**Response:** Comment not incorporated. The statement on BUD assignment for repackaging was removed. However, *14.3 Establishing a BUD for a CSP* specifies that a shorter BUD is required when the stability of the CSP or its components is less than those stated in *Table 10* for Category 1 CSPs and *Table 11* for Category 2 CSPs.

**Commentary Summary #33:** Commenter requested deletion of references to FDA Guidance documents as it could create a potential regulatory conflict. The commenter noted that FDA Guidance documents are not legally binding, and they reflect the agency's current thinking on a topic.

**Response:** Comment incorporated.

**Commentary Summary #34:** Commenter recommended referencing current and final FDA guidance documents.

**Response:** Comment not incorporated. References to FDA Guidance documents were removed from the chapter.

**Commentary Summary #35:** Commenter requested the ability to extend BUDs for repackaged products or preparations when there are studies available.

**Response:** Comment not incorporated. Repackaging must also take into consideration the physical and chemical stability, sterility, and container-closure integrity. The Expert Committee will consider development of new resource(s) to assist compounders in extending BUDs for Category 2 CSPs. The resources may include criteria for validated, stability-indicating assays and testing for sterility, endotoxins, container-closure integrity, and particulate matter. The resource(s) are intended to guide correct interpretation and application of test results.

**Commentary Summary #36:** Commenter suggested that longer BUDs should be allowed for repackaged products if there is published evidence in a peer-reviewed medical journal demonstrating stability.

**Response:** Comment not incorporated. Repackaging must also take into consideration the physical and chemical stability, sterility, and container-closure integrity. The Expert Committee will consider development of new resource(s) to assist compounders in extending BUDs for Category 2 CSPs. The resources may include criteria for validated stability-indicating assays and testing for sterility, endotoxins, container-closure integrity, and particulate matter. The resource(s) are intended to guide correct interpretation and application of test results.

**Commentary Summary #37:** Commenter noted that the provisions for allergenic extracts should also include "testing dilutions."

**Response:** Comment not incorporated. The term testing dilutions is not defined and the chapter is intended to address compounding of allergenic extracts as described under *Specific Practices* and *21. Compounding Allergenic Extracts*.

**Commentary Summary #38:** Commenter suggested that the provisions for allergenic extracts should apply to compounding for an individual patient.

**Response:** Comment incorporated.

**Commentary Summary #39:** Multiple commenters requested clarification on the characteristics that distinguish allergenic extracts from Category 1 and Category 2 CSPs.

**Response:** Comment not incorporated. The provisions for allergenic extracts in *21. Compounding Allergenic Extracts* state that patients must be maintained on a maintenance dose of prepared allergenic extracts for a period of time longer than the BUDs specified for Category 1 and Category 2. Longer BUDs are required for prescription sets to achieve effective therapy. Furthermore, allergenic extracts are preserved, and the preparation is additionally described in FDA Guidance on [Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application](#).

**Commentary Summary #40:** Multiple commenters requested that “simple” be removed from the bullet describing the criteria for determining whether the provisions in *21. Compounding Allergenic Extracts* apply.

**Response:** Comment incorporated.

**Commentary Summary #41:** Commenter requested that “added substances” be changed to “sterile diluents” in the bullet describing the criteria for determining whether the provisions in *21. Compounding Allergenic Extracts* apply.

**Response:** Comment not incorporated. “Added substances” is a broader term that includes sterile diluents.

**Commentary Summary #42:** Commenter requested that “disinfected” be removed from the bullet describing stoppers under the criteria for determining whether the provisions in *21. Compounding Allergenic Extracts* apply.

**Response:** Comment incorporated.

**Commentary Summary #43:** Commenter noted that handling of blood components must be held to jurisdictional standards and guidelines such as the Centers for Disease Control and Prevention (CDC) Biosafety in Microbiological and Biomedical Laboratories (BMBL).

**Response:** Comment partially incorporated. Blood components must comply with jurisdictional standards and guidelines. The reference to BMBL guidelines was removed. Compliance with BMBL guidelines would be required if they were referenced in applicable jurisdictional standards and guidelines.

**Commentary Summary #44:** Commenter requested the addition of a statement indicating that compliance with <825> *Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging* should be regarded as compliance with <797>. Commenter noted that many state regulatory bodies include reference to <797> in their laws and/or regulations, and upon adoption of <825>, there will likely be delays as regulatory boards update their documents to replace references to <797> with those to <825>.

**Response:** Comment not incorporated. General Chapters <797> and <825> are intended to be separate chapters, and compliance with one chapter does not suggest compliance with the other. Both chapters will be published in June 2019 with an official date of December 2019. Pursuant to *General Notices 2.30 Legal Recognition*, assuring compliance with USP standards is the responsibility of regulatory bodies.

**Commentary Summary #45:** Commenter requested language to specify who can have oversight of the compounding facility (e.g., a pharmacist).

**Response:** Comment not incorporated. Oversight responsibilities should be determined by the facility, and facilities must take into consideration the laws and regulations of the applicable regulatory jurisdiction.

**Commentary Summary #46:** Commenter noted that <797> should address HDs that are excreted in urine, stool, sweat, and saliva.

**Response:** Comment not incorporated. Handling of HDs is addressed in <800>. General Chapter <800> does provide examples of the potential for exposure based on the handling activity, and *18. Medical Surveillance* provides actions that may be taken to monitor and track exposure of personnel to HDs.

**Commentary Summary #47:** Commenter requested removal of references to <800>. Commenter also requested removal of any reference to negative pressure requirements. Commenter noted that isolators and personal protective equipment (PPE) provide adequate protection for personnel against drug contamination and exposure to HDs.

**Response:** Comment not incorporated. General Chapter <800> was published with the intent to protect personnel and the environment from HD contamination. General Chapter <800> describes facility, equipment, and personnel containment standards to minimize the risk of exposure to HDs. All HD handling information was removed from <797>, and a reference was added to <800> for information on handling HDs.

**Commentary Summary #48:** Commenter requested adding implantable pellets as an example of dosage forms that must be sterile.

**Response:** Comment not incorporated. Implants are required to be sterile. The list is not intended to be an exhaustive list. Providing specific examples may cause confusion about whether non-listed dosage forms are required to be sterile.

**Commentary Summary #49:** Commenter requested that a definition for infusion be added to the chapter.

**Response:** Comment not incorporated. Injections, including infusions, are intended to provide examples of dosage forms that are required to be sterile.

**Commentary Summary #50:** Commenter noted that the CDC Safe Injection Practices to Prevent Transmissions of Infections to Patients does not provide guidance on administration. Commenter recommended referencing “standard precautions, such as the CDC safe injection practices.”

**Response:** Comment incorporated.

**Commentary Summary #51:** Several commenters requested clarifications on “special considerations” for compounding of biological products.

**Response:** Comment partially incorporated. The statement on special considerations for biological products was removed from the chapter and a provision for blood-derived and other biological materials was added.

**Commentary Summary #52:** Commenter requested deletion of the statement that compounding using biologic products requires special consideration because these products are particularly susceptible to microbial growth and chemical and physical degradation.

**Response:** Comment incorporated.

**Commentary Summary #53:** Multiple commenters noted that the concept of designated person should be introduced at the beginning of the chapter.

**Response:** Comment incorporated.

**Commentary Summary #54:** Commenter requested that reference to the designated person should consistently refer to “designated person(s)” to emphasize that this may be one or more persons.

**Response:** Comment incorporated.

**Commentary Summary #55:** Multiple commenters noted that the duties of the designated person should be listed in a separate box.

**Response:** Comment not incorporated. The designated person is responsible and accountable for the performance and operation of the facility and personnel in the preparation of CSPs and for performing other functions as described in the chapter. Providing a comprehensive list of duties of a designated person may run the risk that certain facility-specific duties are not accounted for.

**Commentary Summary #56:** Commenter requested that the requirements for administration be organized in a bulleted list to improve clarity.

**Response:** Comment partially incorporated. Administration was placed in a separate subsection. Additional requirements for administration were eliminated from the chapter since administration is out of the scope of the chapter.

**Commentary Summary #57:** Multiple commenters requested that information on administration be reorganized and separated from other parts of the chapter to improve clarity.

**Response:** Comment incorporated.

**Commentary Summary #58:** Multiple commenters requested that administration be defined as the direct application of a sterile medication and requested removal of the requirement that it be “direct and immediate.” Commenter noted that some regulators may interpret immediate to mean administration within 1 hour.

**Response:** Comment incorporated.

**Commentary Summary #59:** Commenter requested that the term “application” be removed in terms of describing administration.

**Response:** Comment partially incorporated. The section was clarified to provide examples of application, including but not limited to injecting, infusing, or otherwise providing a sterile medication in its final form to a single patient.

**Commentary Summary #60:** Commenter noted that the provisions for administration should not go beyond the CDC’s safe injection practices.

**Response:** Comment incorporated.

**Commentary Summary #61:** Commenter noted that the CDC safe injection practices do not provide guidance on “hang times” and the frequency of changing tubing and bags for continuous infusions.

**Response:** Comment not incorporated. Administration is out of the scope of the chapter. Healthcare practitioners should refer to other references for information on hang times and frequency of changing tubing and bags for continuous infusions.

**Commentary Summary #62:** Commenter requested removal of the exemption for administration. CSPs must either be prepared as an immediate use CSP or be required to meet all of the requirements in the chapter to ensure quality CSPs.

**Response:** Comment partially incorporated. Administration is the practice of medicine and it is out of the scope of the chapter. A section on immediate-use CSPs has been added to the chapter.

**Commentary Summary #63:** Commenter requested specifying that administration occurs outside of a cleanroom suite.

**Response:** Comment not incorporated. The chapter specifies that administration is out of the scope of the chapter (*see 1.2 Administration*).

**Commentary Summary #64:** Several commenters recommended clarification that the administration provision applies to administration of single-dose containers and multiple-dose containers.

**Response:** Comment not incorporated. Administration, referring to the direct application of a sterile medication, is out of the scope of the chapter regardless of whether the medication is a single-dose container or a multiple-dose container.

**Commentary Summary #65:** Commenter requested a limit on the number of ingredients and containers that may be combined under the administration provision.

**Response:** Comment not incorporated. Administration, referring to the direct application of a sterile medication, is out of the scope of the chapter. Criteria for preparation of immediate use CSPs are further described in *1.3 Immediate Use CSPs*.

**Commentary Summary #66:** Commenter noted that administration needs to have proper documentation and labeling requirements to ensure aseptic technique.

**Response:** Comment not incorporated. Administration, referring to the direct application of a sterile medication, is out of the scope of the chapter. Criteria for preparation of immediate use CSPs and preparation per approved labeling are further described in *1.3 Immediate Use CSPs* and *1.4 Preparation Per Approved Labeling*, respectively.

**Commentary Summary #67:** Several commenters recommended that since administration is out of the scope of the chapter, the chapter should not describe administration. Commenters noted that the requirement for administration to begin within 1 hour of starting the preparation should be eliminated.

**Response:** Comment partially incorporated. The administration provision was added to distinguish between administration and compounding. The requirement for beginning administration within 1 hour of preparation was eliminated.

**Commentary Summary #68:** Commenter requested addition of language stating that administration of medication is part of the practice of medicine and may only be performed by physicians or by delegation from a physician. The commenter noted that this applies to physician anesthesiologists who may delegate administration to nurses, nurse anesthetists, anesthesiologist assistants, or other assistants. Further, the commenter suggested language that states that administration includes the preparation of medication as required by the individual needs of the patient (e.g., drawing up medication, reconstituting, diluting, and mixing sterile components).

**Response:** Comment not incorporated. Chapter was revised to clarify that administration of medication is out of 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. Additionally, preparation per approved labeling is out of the scope of the chapter, as described in *1.4 Preparation Per Approved Labeling*.

**Commentary Summary #69:** Commenter noted that withdrawing of doses is within the scope of the chapter, and users must refer to *15. Use of Conventionally Manufactured Products as Components*.

**Response:** Comment partially incorporated. Administration is out of the scope of the chapter as described in *1.2 Administration*. However, use of conventionally manufactured products as components in CSPs is described in *15. Use of Conventionally Manufactured Products as Components*.

**Commentary Summary #70:** Commenter suggested that administration should be within the scope of the chapter. Otherwise, compounding would be required to be performed by nurses with no training in CSP processing.

**Response:** Comment not incorporated. Administration is out of the scope of the chapter. Facilities should provide proper training for all personnel who may be preparing and/or administering drugs. Further, the chapter refers to CDC's safe injection practices for administration.

**Commentary Summary #71:** Commenter noted that administration should additionally follow the manufacturer's or compounder's labeling.

**Response:** Comment not incorporated. Administration is out of the scope of the chapter.

**Commentary Summary #72:** Commenter requested the addition of a provision to allow for immediate use CSPs to be administered within 1 hour.

**Response:** Comment partially incorporated. Immediate use CSPs must meet all of the criteria described in *1.3 Immediate Use CSPs*, including the requirement that administration begin within 4 hours following the start of preparation.

**Commentary Summary #73:** Commenter noted that compounding outside of a primary engineering control (PEC) is only permissible when the CSP is immediately administered to a patient.

**Response:** Comment incorporated. A provision for immediate use CSPs was added to the chapter.

**Commentary Summary #74:** Commenter requested that the chapter clarify all practices that must be followed to prevent breaches in infection control. The commenter noted that there are several examples of outbreaks in outpatient settings where providers have performed sterile compounding without the use of any PEC. Many clinical practices additionally prepare multiple syringes at the start of the day to prepare for procedures. Examples of unsafe practices include: failure to follow aseptic technique, use of a single-dose vial to prepare a CSP for more than one patient outside of a PEC, use of a single needle and syringe to serially enter medication containers, and batch preparation of multiple syringes to be administered throughout the day or even on the following day(s).

**Response:** Comment partially incorporated. A provision for immediate use CSPs was added to the chapter. A CSP may only be prepared outside of a PEC for immediate use if all of the criteria in the chapter are met. The Expert Committee decided that it would not be feasible to list all the potential breaches that may occur in practice settings. Healthcare practitioners must follow aseptic technique, and written procedures must be 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.

**Commentary Summary #75:** Commenter requested the creation of a provision for immediate use to include a limited number of punctures and information on the sterile products that may be used.

**Response:** Comment partially incorporated. Provisions for immediate use CSPs were added to the chapter, including specific criteria related to aseptic processes, evidence-based information for physical and chemical stability, number of sterile products, use of single-dose containers, when administration must begin, and labeling.

**Commentary Summary #76:** Commenter requested the addition of a section on immediate use CSPs for preparations that may need to be prepared immediately in patient care areas.

**Response:** Comment incorporated.

**Commentary Summary #77:** Commenter requested that parenteral nutrition not be allowed to be prepared as an immediate use CSP.

**Response:** Comment partially incorporated. Immediate use CSPs must meet all of the criteria described in *1.3 Immediate Use CSPs*, including the requirement that the CSP not involve more than three different sterile products.

**Commentary Summary #78:** Commenter requested additional clarification and parameters on when CSPs may be prepared as an immediate use CSP.

**Response:** Comment incorporated.

**Commentary Summary #79:** Commenter requested that the chapter retain the “1-hour” rule, whereby CSPs prepared in unclassified areas must be administered within 1 hour of initiating compounding. Commenter noted that this is critical to minimize the risks to patients if there is contamination during the preparation process and to prevent outbreaks associated with batch preparation.

**Response:** Comment partially incorporated. Provisions for administration and immediate use CSPs are further clarified in *1.2 Administration* and *1.3 Immediate Use CSPs*.

**Commentary Summary #80:** Commenter requested language to advise users that risks of microbial contamination may be greater with immediate use compounding or if the CSP is not prepared under Category 1 or Category 2 requirements.

**Response:** Comment not incorporated. Immediate use CSPs are subject to all of the criteria described in the chapter and must be administered within a shorter amount of time than the BUDs for Category 1 or Category 2 CSPs.

**Commentary Summary #81:** Commenter requested that the term “immediate” be defined throughout the chapter.

**Response:** Comment not incorporated. The term “immediate” is intended to describe a short period of time.

**Commentary Summary #82:** Multiple commenters noted that the provision for immediate use should be limited to emergency situations only to prevent untrained individuals from compounding. The commenter noted that unless it is an emergency situation, CSPs must be prepared in an International Organization for Standardization (ISO) Class 5 PEC.

**Response:** Comment not incorporated. Certain medications need to be compounded and administered immediately to patients. These may be for routine procedures or emergency situations. Facilities should implement training requirements for all relevant personnel. Additionally, the immediate use CSP provision lists specific criteria that must be met, including aseptic processes.

**Commentary Summary #83:** Commenter requested additional training and qualification requirements for personnel preparing CSPs in patient care areas for immediate use.

**Response:** Comment not incorporated. The chapter provides specific criteria that must be met when preparing immediate use CSPs, including aseptic processes. Facilities should implement training requirements for all personnel.

**Commentary Summary #84:** Commenter suggested that pooling of multiple containers of drugs and biologics should be excluded from the definition of compounding.

**Response:** Comment not incorporated. The mixing of multiple containers of drugs and biologics may be performed as an immediate use CSP if all of the criteria in the chapter are met. One of the criteria for immediate use CSPs is that the preparation is limited to not more than three different sterile products.

**Commentary Summary #85:** Commenter requested clarification on the number or types of components that can be used under the immediate use provision.

**Response:** Comment incorporated. One of the criteria under the immediate use provision specifies that not more than three different sterile components may be used, and if any container is a single-dose container, it must be discarded after preparation for the individual patient is complete.

**Commentary Summary #86:** Commenter requested clarification on how many times a single-dose container may be punctured.

**Response:** Comment incorporated. A single-dose container to prepare an immediate use CSP may only be used for an individual patient and must be discarded after preparation. Otherwise, if the single-dose container is entered and punctured only in ISO Class 5 or cleaner air, the provisions in *15.1 Use of Conventionally Manufactured Single-Dose Containers* apply.

**Commentary Summary #87:** Commenter recommended that preparation “must” be performed in accordance with evidence-based information for physical and chemical compatibility. Commenter noted that this needs to be a “must” requirement and not a “should” recommendation.

**Response:** Comment not incorporated. Information on physical and chemical compatibility is not always available for each preparation. Compounders should refer to any evidence-based information whenever possible.

**Commentary Summary #88:** Commenter requested additional criteria around immediate use CSPs, noting that the risk of microbial contamination is greater if a CSP is not prepared as a Category 1 or Category 2 CSP. Commenter recommended

additional requirements for hand hygiene, preparation in a clean space away from potential sources of contaminants, and discarding of single-dose containers after preparation for an individual patient.

**Response:** Comment partially incorporated. Immediate use CSPs are required to be administered within 4 hours of beginning preparation to mitigate risks of inadvertent contamination. Immediate use CSPs must be prepared under aseptic processes. Aseptic technique involves procedures to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, and mix-ups with other products or CSPs. The Expert Committee will consider developing future resources and tools to describe and define aseptic technique.

**Commentary Summary #89:** Several commenters requested that the definition for compounding be harmonized with FDA's definition. For example, reconstitution of medications should not be considered compounding.

**Response:** Comment incorporated.

**Commentary Summary #90:** Several commenters requested that information about preparation according to manufacturer's approved labeling be moved to a separate section.

**Response:** Comment incorporated.

**Commentary Summary #91:** Commenter noted that preparation of FDA-approved products according to their FDA-approved labeling should not be subject to the requirements in the chapter.

**Response:** Comment incorporated.

**Commentary Summary #92:** Commenter requested clarification that preparation of conventionally manufactured sterile products in accordance with approved labeling should be exempt from the requirements of the chapter only when prepared for an individual patient.

**Response:** Comment incorporated.

**Commentary Summary #93:** Multiple commenters noted that preparation per approved labeling must follow the requirements of the chapter to promote patient safety. Commenter requested that the provision exempting preparation per approved labeling be removed from the chapter.

**Response:** Comment not incorporated. Preparation per approved labeling for a single dose for an individual patient and where the approved labeling contains specific information is out of the scope of the chapter. Otherwise, preparation is subject to the requirements in the chapter. The provision is consistent with the FDA definition for compounding, which excludes preparation consistent with labeling.

**Commentary Summary #94:** Commenter suggested that preparation per approved labeling must follow the requirements in the chapter because the approved labeling does not provide information on personnel training, facility and engineering controls, and labeling. Preparation per approved labeling should not be exempted from the requirements in the chapter in order to promote patient safety.

**Response:** Comment not incorporated. Preparation per approved labeling for a single dose for an individual patient and where the approved labeling contains specific information is out of the scope of the chapter. Otherwise, preparation is subject to the requirements in the chapter. The provision is consistent with the FDA definition for compounding, which excludes preparation consistent with labeling. The FDA approval

process includes review of the labeling information to help ensure that conventionally manufactured products are appropriately prepared.

**Commentary Summary #95:** Commenter requested additional requirements for preparation of conventionally manufactured products in accordance with manufacturer's approved labeling. Specifically, the commenter noted that preparation per approved labeling still requires labeling, records, and aseptic technique.

**Response:** Comment partially incorporated. Preparation per approved labeling is out of scope of the chapter. However, preparation per approved labeling must be for a single dose for an individual patient, and the approved labeling must contain specific information. Otherwise, preparation is subject to the requirements in the chapter.

**Commentary Summary #96:** Commenter requested more clarification of the difference between reconstitution (e.g., preparation according to package insert) and compounding.

**Response:** Comment incorporated.

**Commentary Summary #97:** Multiple commenters noted that preparation of a conventionally manufactured sterile product in accordance with the manufacturer's labeling is not compounding irrespective of whether the product is prepared for an individual patient or multiple patients.

**Response:** Comment not incorporated. Batch preparation of several conventionally manufactured sterile products increases the risk of inadvertent contamination because of the number of manipulations. Preparation of conventionally manufactured sterile products for multiple patients must be performed in accordance with the chapter.

**Commentary Summary #98:** Commenter noted that "reconstitution" is ambiguous in relation to preparation according to manufacturer-approved labeling and recommended clarification.

**Response:** Comment incorporated.

**Commentary Summary #99:** Multiple commenters noted that conventionally manufactured sterile products prepared in accordance with directions contained in approved labeling must be administered within 1 hour.

**Response:** Comment not incorporated. The preparation of a conventionally manufactured sterile product must follow the directions contained in the approved labeling. The approved labeling may have different requirements for when the drug has to be administered.

**Commentary Summary #100:** Commenter requested that preparation per approved labeling should only be permitted in situations where patient care would be compromised if there was a delay in treatment. The commenter noted that otherwise, the provision would allow conventionally manufactured products to be prepared in uncontrolled environments by individuals who are not trained.

**Response:** Comment not incorporated. Preparation per approved labeling is out of the scope of the chapter regardless of whether the medication is given under routine procedures or in an emergency situation. The FDA approval process includes review of the labeling information to help ensure that conventionally manufactured products are appropriately prepared. The facility should provide adequate training for all personnel who prepare and administer medications.

**Commentary Summary #101:** Commenter requested clarification of a “single patient” in the context of preparation per approved labeling. The commenter noted that this could be interpreted to mean one CSP for one patient or multiple CSPs for one patient.

**Response:** Comment incorporated. Chapter was clarified to state that preparation per approved labeling is out of the scope of the chapter if the conventionally manufactured sterile product is prepared as a single dose for an individual patient.

**Commentary Summary #102:** Commenter requested the addition of language stating that preparation of a conventionally manufactured sterile product that deviates from the approved labeling is required to meet the requirements in the chapter.

**Response:** Comment not incorporated. The chapter states that preparation of a conventionally manufactured sterile product in accordance with the manufacturer’s approved labeling is out of the scope of the chapter. Any deviation from the approved labeling is required to meet the standards in the chapter.

**Commentary Summary #103:** Commenter noted that the language for preparation of conventionally manufactured sterile products per approved labeling prohibits off-label preparation of CSPs. The commenter indicated that the labeling of many older medications does not undergo timeline updates, and compounders need the flexibility to deviate from the approved labeling.

**Response:** Comment not incorporated. The chapter states that preparation of a conventionally manufactured sterile product in accordance with the manufacturer’s approved labeling is out of the scope of the chapter. Deviation from the approved labeling is permitted. However, preparation that is different from the approved labeling is required to meet the standards in the chapter.

**Commentary Summary #104:** Commenter requested clarification that preparation of a conventionally manufactured product, including both HDs and non-HDs, in accordance with the approved labeling is out of the scope of the chapter.

**Response:** Comment not incorporated. General Chapter <800> is made compendially applicable through reference in <797>. A referenced USP General Chapter applies only in so far as the USP General Chapter referencing it applies. Thus only activities under the scope of <797> would be subject to the HD handling requirements specified in <800>. According to <797>, preparation of a conventionally manufactured sterile product is out of the scope of the chapter if specific conditions are met. Thus, this practice would also be out of the scope of <800>. The Compounding Expert Committee will consider an FAQ to clarify the compendial applicability of <800>.

**Commentary Summary #105:** Commenter requested that a cross-reference be added to *15. Use of Conventionally Manufactured Products as Components* because users will not read the remainder of the chapter otherwise.

**Response:** Comment not incorporated. Users must read the entire chapter. Preparation per approved labeling is separate from use of conventionally manufactured products as described in *15. Use of Conventionally Manufactured Products as Components*.

**Commentary Summary #106:** Commenter requested that the chapter provide guidance on assigning a BUD for conventionally manufactured products that are prepared per approved labeling.

**Response:** Comment not incorporated. The preparation of a conventionally manufactured sterile product must follow the directions contained in the approved

labeling. The approved labeling may have different requirements for how long the drug may be stored. Further, *15. Use of Conventionally Manufactured Products as Components* provides additional information on use of conventionally manufactured products.

**Commentary Summary #107:** Commenter requested clarification that preparation of proprietary bag and vial systems (e.g., docking and activation) should not be considered compounding as long as they are assembled using aseptic technique and stored for future use.

**Response:** Comment partially incorporated. Docking and activation of a proprietary bag and vial system in accordance with the manufacturer's labeling for immediate administration to an individual patient is not considered compounding. However, docking a proprietary bag and vial system for future activation is considered compounding and must be performed in accordance with the chapter, with the exception of establishing a BUD. Batch preparation of several proprietary bag and vial systems and prolonged storage increases the risk of inadvertent contamination and microbial proliferation. Thus, batch preparation must be done in accordance with the chapter.

**Commentary Summary #108:** Commenter requested that the list of examples of proprietary bag and vial systems be provided in alphabetical order to eliminate any potential perception of bias.

**Response:** Comment incorporated.

**Commentary Summary #109:** Several commenters requested longer BUDs (e.g., 72 or 96 hours) for docking of proprietary bag and vial systems for future activation and administration.

**Response:** Comment not incorporated. The BUDs for proprietary bag and vial systems must not be longer than those specified in the manufacturer's labeling.

**Commentary Summary #110:** Commenter noted that excluding from compounding the practice of docking and activation of proprietary bag and vial systems for immediate administration to an individual patient would promote assembly in the patient care areas. The commenter noted that this practice deviates from pharmacy practice standards and recommendations.

**Response:** Comment not incorporated. Docking and activation of proprietary bag and vial systems for immediate administration to an individual patient is not compounding. Facilities may determine where docking and activation may occur, and facilities may additionally prohibit docking and activation in patient care areas.

**Commentary Summary #111:** Commenter requested additional language to specify that docking and activation of proprietary bag and vial systems requires aseptic technique. Commenter additionally recommended that docking of the proprietary bag and vial system for future activation and administration must be performed in an ISO Class 5 environment and the BUD should be established as described by the manufacturer.

**Response:** Comment not incorporated. The chapter states that aseptic technique is required for the preparation of any sterile medication. Docking of a proprietary bag and vial system for future activation and administration must be performed in accordance with the chapter, which includes requirements in addition to an ISO Class 5 PEC.

**Commentary Summary #112:** Multiple commenters noted that docking and activation of proprietary bag and vial systems requires aseptic technique. At a minimum, this should include establishing a clean surface that is not directly under or adjacent to an air vent, window, or traffic. The commenter noted that this requires hand hygiene and vial sanitization.

**Response:** Comment not incorporated. The chapter states that aseptic technique is required for the preparation of any sterile medication.

**Commentary Summary #113:** Several commenters noted that docking and activation of proprietary bag and vial systems should be excluded from compounding regardless of whether it is immediately administered or stored for future use.

**Response:** Comment not incorporated. Docking and activation of proprietary bag and vial systems for immediate administration to an individual patient is not considered compounding. However, manipulation of several units and/or storage of docked units for future use may increase the risk for microbial contamination and proliferation because of the number of manipulations and prolonged storage.

**Commentary Summary #114:** Commenter requested that the requirements for docking and activating proprietary bag and vial systems for immediate use be separated from the requirements for docking the systems for future use.

**Response:** Comment partially incorporated. A new subsection was added for proprietary bag and vial systems, and key terms were italicized for emphasis.

**Commentary Summary #115:** Commenter requested adding Vial2Bag as an example of a proprietary bag and vial system.

**Response:** Comment not incorporated. Example systems were provided for informational purposes and not intended to provide a list of every device on the market. Additionally, some systems may only be intended for immediate administration and not for docking and future activation.

**Commentary Summary #116:** Commenter requested a time limit for immediate administration of a docked and activated proprietary bag and vial system.

**Response:** Comment not incorporated. The intent of the term immediate administration is to prevent storage of a docked and activated proprietary bag and vial system.

**Commentary Summary #117:** Commenter requested that docked and activated proprietary bag and vial systems be administered immediately at the “point of care.”

**Response:** Comment not incorporated. Point of care is not well defined.

**Commentary Summary #118:** Commenter requested clarification on whether the BUD on the manufacturer’s labeling for proprietary bag and vial systems may be changed.

**Response:** Comment not incorporated. Users must use the BUDs specified on the manufacturer’s labeling of the proprietary bag and vial system.

**Commentary Summary #119:** Commenter noted that a shorter BUD may be required for proprietary bag and vial systems where there is a concern about water vapor transmission when the bag is removed from the protective overwrap.

**Response:** Comment not incorporated. Users should refer to literature, manufacturer labeling, and other resources for assigning BUDs.

**Commentary Summary #120:** Multiple commenters requested that the chapter be reorganized to describe Category 1 and Category 2 in the introduction and combine the tables containing the summary of minimum requirements and BUDs.

**Response:** Comment not incorporated. The table containing minimum requirements for Category 1 and Category 2 CSPs was removed. The introduction describes the concepts of Category 1 and Category 2, and the subsequent sections describe the requirements, including personnel qualifications, buildings and facilities, microbiological air and surface monitoring, release testing, and BUDs.

**Commentary Summary #121:** Multiple commenters suggested that the chapter should prohibit facilities from preparing CSPs from nonsterile starting ingredients. The commenter noted that current and past contamination events were related to nonsterile-to-sterile compounding and that only sterile-to-sterile compounding should be permitted.

**Response:** Comment not incorporated. Contamination events may occur from nonsterile-to-sterile compounding and sterile-to-sterile compounding. The intent of the chapter is to provide quality standards to minimize the risk of contamination. Certain critical CSPs needed for patient care can only be compounded from nonsterile starting ingredients.

**Commentary Summary #122:** Multiple commenters noted that the change from three microbial contamination risk levels (low, medium, and high) to two categories of CSPs (Category 1 and Category 2) brings more stringent requirements for facilities using the BUDs in the current chapter. Other commenters noted that preparation of frozen antibiotics would be more burdensome.

**Response:** Comment not incorporated. The BUDs for Category 1 and Category 2 CSPs allow for equivalent, and in some cases longer, BUDs depending on the criteria described in *14. Establishing Beyond-Use Dates*. Further, the facility and environmental monitoring requirements are similar to those in the existing chapter.

**Commentary Summary #123:** Multiple commenters requested retaining the classifications of low, medium, and high risk level CSPs instead of Category 1 and 2, so that state regulations would not have to be redrafted.

**Response:** Comment not incorporated. The classifications based on risk of microbial contamination were a misnomer and may mislead users to have a false sense of security or sense of added protection in preparing a CSP of a lower risk level. Further, there has been significant confusion about the conditions that would make a CSP low, medium, or high risk level. The use of Category 1 and 2 is intended to simplify the approach and assist compounders in determining the category of CSP based on the BUD and environment in which the CSP was prepared.

**Commentary Summary #124:** Multiple commenters requested the addition of a sentence that prohibits preparing CSPs as Category 1 if there are one or more nonsterile starting ingredients.

**Response:** Comment not incorporated. Category 1 and Category 2 CSPs are distinguished primarily based on the environment in which they are prepared and the assigned BUD. Category 1 CSPs may contain one or more nonsterile starting ingredients provided that appropriate sterilization procedures are applied, the preparation is compounded in an SCA or cleanroom suite, and the preparation has a BUD of 12 hours or less at controlled room temperature or 24 hours or less when refrigerated.

**Commentary Summary #125:** Commenter noted that the change from the three risk levels (low, medium, and high) to two categories (Category 1 and 2) needlessly increases the amount of gloved fingertip and thumb sampling and media-fill testing.

**Response:** Comment not incorporated. The chapter is intended to provide the minimum standard to help ensure the quality of CSPs. The chapter requires gloved fingertip and thumb sampling and media-fill testing at least every 6 months. This frequency of personnel monitoring helps ensure continued, consistent, and proper performance to support the assignment of the BUDs in *Table 10* and *Table 11* for Category 1 and Category 2 CSPs, respectively.

**Commentary Summary #126:** Commenter noted that risk levels should be added for CSPs prepared from only sterile ingredients and those prepared from one or more nonsterile ingredients. Commenter indicated that nonsterile-to-sterile compounding is a unique process and should not be treated in the same manner as sterile-to-sterile compounding.

**Response:** Comment not incorporated. Category 1 and Category 2 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). The Category 1 and Category 2 framework provides a risk-based approach with shorter BUDs for Category 1 CSPs in *Table 10* and longer BUDs for Category 2 CSPs in *Table 11* to help ensure patient access to needed therapies.

**Commentary Summary #127:** Commenter requested the addition of Category 3 for CSPs prepared from one or more nonsterile starting ingredient(s).

**Response:** Comment not incorporated. Category 1 and Category 2 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). The Category 1 and Category 2 framework provides a risk-based approach with shorter BUDs for Category 1 CSPs in *Table 10* and longer BUDs for Category 2 CSPs in *Table 11* to help ensure patient access to needed therapies.

**Commentary Summary #128:** Commenter requested the addition of Category 3 CSPs for eye drops, inhalants, and intramuscular injections that do not carry the same risk of CSPs for intravenous administration.

**Response:** Comment not incorporated. Category 1 and Category 2 CSPs are distinguished primarily based on the BUD and the environment in which they are compounded. Dosage forms, including those listed under *CSPs Affected* have the risk of harming patients if contaminated or improperly prepared.

**Commentary Summary #129:** Commenter requested the addition of Category 3 CSPs for CSPs prepared in closed system automation devices (i.e., robotic PECs). The commenter noted that such systems include an ISO Class 5 environment and robotic processing utilizing barcode verification ingredients, vision systems and gravimetric controls to provide unprecedented accuracy and safety and aseptic compliance.

**Response:** Comment not incorporated. Category 1 and Category 2 CSPs are distinguished primarily based on the BUD and the environment in which they are compounded. Robotic enclosures used as PECs must continue to demonstrate appropriate air and environmental quality requirements and personnel must be trained. USP and the Expert Committee will discuss advances in technology at an upcoming workshop to explore opportunities for future development of standards.

**Commentary Summary #130:** Multiple commenters requested that the BUD for Category 1 CSPs in refrigerated conditions be extended from 24 hours to 48 hours. Commenters noted that the extension would allow hospitals to prepare CSPs for the weekend.

**Response:** Comment not incorporated. The BUDs for Category 1 CSPs are intended to allow preparation in an unclassified SCA. A conservative BUD is assigned based on the risk of microbial contamination and proliferation.

**Commentary Summary #131:** Multiple commenters requested that the BUD for Category 1 CSPs be extended to 24 or 48 hours at controlled room temperature and 4 days in a refrigerator.

**Response:** Comment not incorporated. The BUDs for Category 1 CSPs are intended to allow preparation in an unclassified SCA. A conservative BUD is assigned based on the risk of microbial contamination and proliferation.

**Commentary Summary #132:** Commenter requested that the BUD for Category 1 CSPs be extended to 12 months to allow for flexibility.

**Response:** Comment not incorporated. The BUDs for Category 1 CSPs are intended to allow preparation in an unclassified SCA. A conservative BUD is assigned based on the risk of microbial contamination and proliferation. A BUD of 12 months would exceed the BUDs for Category 2 CSPs and pose a risk of inadvertent microbial contamination and proliferation.

**Commentary Summary #133:** Commenter requested clarifications on the facility requirements for Category 1 and Category 2 CSPs.

**Response:** Comment not incorporated. Requirements for the facility and placement of the PEC are described in *4. Facilities and Engineering Controls* and Table 3.

**Commentary Summary #134:** Commenter suggested restricting the number of CSPs that may be prepared per day in an SCA in order to limit the risk of a large-scale event.

**Response:** Comment not incorporated. Facilities may have different types of PECs and facility designs that can accommodate varying numbers of CSPs to be prepared daily.

**Commentary Summary #135:** Multiple commenters requested for a sub-category of Category 1 CSPs for CSPs that are prepared with fewer than three manipulations. Commenters noted that this subcategory should allow for a BUD of 24 hours at controlled room temperature, 72 hours refrigerated, and 28 days frozen.

**Response:** Comment not incorporated. Category 1 and Category 2 CSPs are distinguished primarily based on the BUD and the environment in which they are compounded. The Category 1 and Category 2 framework provides a risk-based approach with shorter BUDs for Category 1 CSPs in Table 10 and longer BUDs for Category 2 CSPs in Table 11 to help ensure patient access to needed therapies. The BUDs for Category 1 CSPs are intended to allow preparation in an unclassified SCA. A conservative BUD is assigned based on the risk of microbial contamination and proliferation.

**Commentary Summary #136:** Commenter requested clarifying language to state that sterility must be maintained if preparing CSPs with only sterile starting ingredients.

**Response:** Comment incorporated.

**Commentary Summary #137:** Multiple commenters noted that the pagination splits the table describing the minimum requirements for Category 1 and Category 2 CSPs.

**Response:** Comment not incorporated. The table of minimum requirements for Category 1 and Category 2 CSPs was eliminated because it could not address all of the requirements in the chapter. Further, the comments noted some inconsistencies with the Table and the text in the remaining sections of the chapter. Users should refer to the entirety of the chapter for the requirements.

**Commentary Summary #138:** Multiple commenters requested that the table describing the minimum requirements for Category 1 and Category 2 CSPs should include rows to address HDs.

**Response:** Comment not incorporated. HDs are described in <800>. The table of minimum requirements for Category 1 and Category 2 CSPs was eliminated because it could not address all of the requirements in the chapter. Further, the comments noted some inconsistencies with the Table and the text in the remaining sections of the chapter. Users should refer to the entirety of the chapter for the requirements.

**Commentary Summary #139:** Multiple commenters requested that the table describing the minimum requirements for Category 1 and Category 2 CSPs clarify the requirements for personnel requalification every 12 months as well as gloved fingertip and thumb sampling and media-fill testing every 6 months.

**Response:** Comment partially incorporated. Personnel training and competency assessments are described in *2. Personnel Training and Evaluation*. The table of minimum requirements for Category 1 and Category 2 CSPs was eliminated because it could not address all of the requirements in the chapter. Further, the comments noted some inconsistencies with the Table and the text in the remaining sections of the chapter. Users should refer to the entirety of the chapter for the requirements.

**Commentary Summary #140:** Commenter requested that the table of minimum requirements for Category 1 and Category 2 CSPs list all of the initial competencies and evaluations that compounders are required to complete before being allowed to compound. Other commenters requested clarification on the requalification requirements.

**Response:** Comment not incorporated. The table of minimum requirements for Category 1 and Category 2 CSPs was eliminated because it could not address all of the requirements in the chapter. Further, the comments noted some inconsistencies with the Table and the text in the remaining sections of the chapter. Users should refer to the entirety of the chapter for the requirements. Personnel training and evaluation are described in *2. Personnel Training and Evaluation*.

**Commentary Summary #141:** Commenter requested that the table of minimum requirements for Category 1 and Category 2 CSPs include requirements for the secondary engineering control (SEC).

**Response:** Comment not incorporated. The table of minimum requirements for Category 1 and Category 2 CSPs was eliminated because it could not address all of the requirements in the chapter. Further, the comments noted some inconsistencies with the Table and the text in the remaining sections of the chapter. Users should refer to the entirety of the chapter for the requirements.

**Commentary Summary #142:** Commenter requested that the table of minimum requirements for Category 1 and Category 2 CSPs include a list of areas that require microbiological air and surface monitoring.

**Response:** Comment not incorporated. The table of minimum requirements for Category 1 and Category 2 CSPs was eliminated because it could not address all of the requirements in the chapter. Further, the comments noted some inconsistencies with the Table and the text in the remaining sections of the chapter. Users should refer to the entirety of the chapter for the requirements. Standards for microbiological air and surface monitoring are described in 6. *Microbiological Air and Surface Monitoring*.

**Commentary Summary #143:** Commenter requested that the table of minimum requirements for Category 1 and Category 2 CSPs specify the placement of the PEC for Category 2 CSPs.

**Response:** Comment not incorporated. The table of minimum requirements for Category 1 and Category 2 CSPs was eliminated because it could not address all of the requirements in the chapter. Further, the comments noted some inconsistencies with the Table and the text in the remaining sections of the chapter. Users should refer to the entirety of the chapter for the requirements. Requirements for the facility and placement of the PEC are described in 4. *Facilities and Engineering Controls* and Table 3.

**Commentary Summary #144:** Commenter requested that the table of minimum requirements for Category 1 and Category 2 CSPs specify the requirements for recertification of the PEC and SEC.

**Response:** Comment not incorporated. The table of minimum requirements for Category 1 and Category 2 CSPs was eliminated because it could not address all of the requirements in the chapter. Further, the comments noted some inconsistencies with the Table and the text in the remaining sections of the chapter. Users should refer to the entirety of the chapter for the requirements. Requirements for certification and recertification are described in 5. *Certification and Recertification*.

## 2. Personnel Training and Evaluation

**Commentary Summary #1:** Several commenters noted that the chapter should describe training requirements of the supervising pharmacist and specify whether the supervising pharmacist is required to be trained. Several other commenters requested specificity on whether pharmacists or technicians or both have to be trained and qualified.

**Response:** Comment not incorporated. The chapter states that personnel involved in compounding of the CSP must be trained and qualified. The designated person(s) must oversee the training program and must determine who is required to be trained. Training must be based on the job function of the personnel and should be specific to the facility.

**Commentary Summary #2:** Commenter noted the requirement for training personnel every 12 months is unnecessary and may be overly burdensome.

**Response:** Comment not incorporated. Personnel must be trained every 12 months to ensure continued performance and knowledge of sterile compounding principles and practices.

**Commentary Summary #3:** Commenter noted that the training requirements in the chapter are not well-defined and do not provide the academic credentials, experience, or certification of the trainer.

**Response:** Comment not incorporated. The chapter is intended to provide minimum requirements for compounding quality CSPs. The designated person(s) is responsible

for overseeing the training program. The Expert Committee determined that it was too prescriptive to specify the academic credentials, experience, or certifications of the trainer. Further, the chapter is used globally and certain academic credentials and certifications may not be available globally.

**Commentary Summary #4:** Commenters noted that the training program should include all personnel handling CSPs or accessing the compounding area. Other commenters noted that training also applies to non-pharmacy personnel such as certifiers, consultants, and cleaning staff. Other commenters noted that these individuals should be excluded from the training requirements.

**Response:** Comment not incorporated. The chapter is intended to provide minimum requirements for compounding quality CSPs. The designated person(s) is responsible for overseeing the training program. The scope of the training should be tailored to the individual and the facility. Further, it may be onerous to require consultants and cleaning staff to undergo the same training requirements of compounding personnel. The chapter additionally states that other personnel handling CSPs or accessing the compounding area must be trained and demonstrate competency in performing their assigned tasks.

**Commentary Summary #5:** Commenter requested that “annually” be changed to “every 12 months” to emphasize training must be performed every 12 months.

**Response:** Comment incorporated.

**Commentary Summary #6:** Several commenters noted confusion with the term “requalification.” Several commenters suggested that there could be misinterpretation and confusion where requalification is required every 12 months and other competency assessments (e.g., gloved fingertip and thumb sampling and media-fill testing) is required every 6 months.

**Response:** Comment incorporated. Revised the section to clarify that training must occur every 12 months and competency assessment must be performed at the frequencies described in the chapter. The term “requalification” was removed from the chapter.

**Commentary Summary #7:** Commenter stated that the section on reevaluation, retraining, and requalification is confusing and redundant of information in the subsequent subsections.

**Response:** Comment incorporated. The section on reevaluation, retraining, and requalification was eliminated. Information on competency assessments and frequencies are incorporated in the subsequent subsections.

**Commentary Summary #8:** Commenter suggested that the section on reevaluation, retraining, and requalification should be reorganized and separated by written and observed demonstration components. The commenter noted that the information should be placed in bulleted form and to provide subheadings to promote readability.

**Response:** Comment partially incorporated. The section on reevaluation, retraining, and requalification was eliminated. Information on competency assessments and frequencies is incorporated in the subsequent subsections.

**Commentary Summary #9:** Commenter noted that supervisor oversight should be required to ensure that personnel are appropriately evaluated, trained, and qualified.

**Response:** Comment partially incorporated. A designated person must oversee the training of personnel.

**Commentary Summary #10:** Commenter suggested that the requalification requirements specify that gloved fingertip sampling is intended to confirm the ability to aseptically garb and media-fill testing is intended to confirm the ability to aseptically compound.

**Response:** Comment not incorporated. The section on reevaluation, retraining, and requalification was eliminated. Information on competency assessments and frequencies is incorporated in the subsequent subsections.

**Commentary Summary #11:** Commenter noted that the requalification requirements apply to “compounding personnel” while the competency assessments in the subsequent sections apply to “all compounding personnel.” Commenter noted that competency assessments should apply to only “compounding personnel.”

**Response:** Comment partially incorporated. The section on reevaluation, retraining, and requalification was eliminated. Information on competency assessments and frequencies is incorporated in the subsequent subsections. Competency assessments apply to “all compounding personnel.”

**Commentary Summary #12:** Commenter noted that the retraining and requalification requirements for cleaning and disinfecting in conjunction with changes in cleaning and disinfecting procedures imply that personnel do not have to be trained if changes are not made. Others requested clarification on what types of changes require training. Commenters requested that a frequency be specified for requalifying personnel while others stated that training should be every 12 months.

**Response:** Comment not incorporated. The section on reevaluation, retraining, and requalification was eliminated. Information on training personnel on cleaning and disinfecting is described in *7. Cleaning and, Disinfecting, and Applying Sporicidal Agents in Compounding Areas*. Personnel must be trained to perform cleaning and disinfecting activities as described in the standard operating procedures (SOPs). The facility-specific training program should determine the frequency of training.

**Commentary Summary #13:** Multiple commenters noted that personnel should be trained in appropriate compounding principles and practices “as relevant to and defined by each entity.”

**Response:** Comment not incorporated. The chapter specifies that 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 involved in preparing CSPs. The training program must be specific to the personnel and the facility, and the designated person(s) is responsible for overseeing the training program.

**Commentary Summary #14:** Commenter requested clarification on whether the training program can be based on one procedure or multiple procedures.

**Response:** Comment not incorporated. The chapter specifies that 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 involved in preparing CSPs. The training program must be specific to the personnel and the facility, and the designated person(s) is responsible for overseeing the training program.

**Commentary Summary #15:** Several commenters recommended that the training program “must” equip personnel with the appropriate knowledge and train them on the required skills to perform their assigned tasks.

**Response:** Comment not incorporated. The designated person(s) is responsible for overseeing the training program. It would be difficult to encompass all of the knowledge and skill requirements in a training program. For example, troubleshooting unanticipated problems would be difficult to include in training programs.

**Commentary Summary #16:** Commenter requested that the training and evaluation of personnel must be documented.

**Response:** Comment incorporated.

**Commentary Summary #17:** Commenter noted that training and observations may be performed by the designated person(s) or an assigned trainer.

**Response:** Comment incorporated.

**Commentary Summary #18:** Commenter noted that facilities should follow their institution’s guidelines to determine whether personnel pass or fail reevaluations.

**Response:** Comment not incorporated. The chapter states that the designated person(s) must oversee the training program which includes the process for evaluating the performance of individuals.

**Commentary Summary #19:** Multiple commenters noted that requirements for requalification after failure should be distinguished between new staff (hired within the last 6 months) and tenured staff.

**Response:** Comment not incorporated. The section on reevaluation, retraining, and requalification was eliminated. Information on competency assessments and frequencies are incorporated in the subsequent subsections.

**Commentary Summary #20:** Several commenters noted that personnel who failed competency assessment should be permitted to continue to compound. The designated person(s) must identify the cause of the failure and determine appropriate retraining requirements. The commenter noted that personnel competency assessments require incubation times for up to 2 weeks and if personnel are not able to compound at this time, it could undermine public safety.

**Response:** Comment incorporated. The requirement that personnel pass reevaluation in the deficient areas before they can resume sterile compounding was eliminated from the chapter. However, the chapter does require that evaluation and corrective actions in the event of failure must be documented.

**Commentary Summary #21:** Multiple commenters suggested that an incubator is not necessary for room temperature incubation.

**Response:** Comment not incorporated. An incubator ensures that the temperature is consistent and accurate.

**Commentary Summary #22:** Multiple commenters noted that personnel who fail competency assessments should be permitted to continue compounding CSPs with lower BUDs (e.g., Category 1 BUDs).

**Response:** Comment partially incorporated. Personnel preparing Category 1 and Category 2 CSPs must successfully complete competency assessment. The requirement that personnel pass reevaluation in the deficient areas before they can resume sterile compounding was eliminated from the chapter. However, the chapter does require that evaluation and corrective actions in the event of failure must be

documented. The designated person(s) and the facility's SOP should determine the appropriate corrective action, depending on the failure and the personnel.

**Commentary Summary #23:** Multiple commenters noted that personnel who fail written testing be re-educated on missed questions to ensure that they are fully educated on all matters.

**Response:** Comment not incorporated. Each facility must have a training program which describes the process for evaluating the performance of individuals. The facility should determine appropriate corrective action depending on the failure and the personnel.

**Commentary Summary #24:** Multiple commenters noted that compounders who have not compounded in more than 3 months should be requalified in all the core competencies before resuming compounding duties. Other commenters noted that requalification should only be required if the pause is more than 12 months.

**Response:** Comment not incorporated. The requirements that personnel be requalified if they have not compounded in more than 6 months was eliminated from the chapter. Each facility must have a training program that describes the required training, frequency of training, and process for evaluating for performance.

**Commentary Summary #25:** Several commenters recommended removing the requirement for requalifying personnel after a pause in compounding.

**Response:** Comment incorporated.

**Commentary Summary #26:** Commenter requested clarification on the requirements for requalifying personnel after a pause in compounding. For example, whether the personnel have to complete three initial gloved fingertip and thumb samplings or one gloved fingertip and thumb sample.

**Response:** Comment not incorporated. The requirement that personnel be requalified if they have not compounded in more than 6 months was eliminated from the chapter. Each facility must have a training program that describes the required training, frequency of training, and process for evaluating for performance.

**Commentary Summary #27:** Commenter noted that the designated person(s) may not always be able to identify the cause of failure of competency assessments.

**Response:** Comment incorporated. Requirement for the designated person(s) to identify the cause of failure was removed from the chapter.

**Commentary Summary #28:** Multiple commenters noted that requalification must be performed in "at least" the core competencies specified in the chapter. Commenters noted that there may be other requirements and that the addition would emphasize that the core competencies in the chapter is a minimum level practice.

**Response:** Comment not incorporated. The chapter is intended to be the minimum standard. Further, *2.1 Demonstrating Proficiency in Core Competencies* specifies that competency must be demonstrated *in at least* the listed competencies.

**Commentary Summary #29:** Commenter noted that "hand-on demonstration of skills" should be changed to "hands-on observed demonstration of skills" to better define it as an observational evaluation.

**Response:** Comment not incorporated. The requirement for "hands-on demonstration of skills" was removed from the chapter. Competency assessments are described in subsequent sections.

**Commentary Summary #30:** Multiple commenters noted that competency must be demonstrated “at least” every 12 months. Commenter noted that the addition of “at least” will encourage more frequent testing.

**Response:** Comment not incorporated. The chapter is intended to be the minimum standard. Facilities may perform competency assessments more frequently than specified in the chapter.

**Commentary Summary #31:** Commenter noted that the core competency should include knowledge of compatibility and stability.

**Response:** Comment not incorporated. The chapter is intended to provide a list of minimum competencies that must be demonstrated every 12 months. Depending on the personnel job function, the facility may have additional requirements for competency evaluations.

**Commentary Summary #32:** Commenter noted that competency can be demonstrated through written testing and/or through hands-on demonstration of skills. Commenter indicated that competency can be evaluated through both testing and demonstration, or through either option.

**Response:** Comment partially incorporated. Personnel must still complete written or electronic testing as well as competency assessment as described in the preceding subsections.

**Commentary Summary #33:** Multiple commenters noted that not all personnel are required to demonstrate all of the competencies listed in the chapter.

**Response:** Comment not incorporated. The chapter is intended to provide a list of minimum competencies that must be demonstrated by compounding personnel. The competencies are important in ensuring that personnel can continue to compound quality CSPs. Further, the training program must be specific to the personnel and the facility and the designated person(s) is responsible for overseeing the training program.

**Commentary Summary #34:** Commenter noted that all compounders and all individuals who are responsible for validating personnel must complete training.

**Response:** Comment not incorporated. Each facility must develop a training program that is specific for the personnel, facility, and types of CSPs prepared. The designated person(s) is responsible for overseeing the training. The needs of each facility must be determined by the individual facility and designated person(s).

**Commentary Summary #35:** Multiple commenters suggested deletion of the word “independently” when stating that all personnel must complete training and demonstrate knowledge before beginning to prepare CSPs independently. Commenter noted that the statement implies that a compounder may compound before completing any training as long as they are supervised by another compounder.

**Response:** Comment not incorporated. The intent of the statement is to ensure initial training of personnel before any compounding is performed. The designated person(s) is responsible for overseeing the training program which may include observation and hands-on practice with a trainer.

**Commentary Summary #36:** Commenter suggested that “theoretical” be eliminated when describing principles and proficiencies for sterile compounding.

**Response:** Comment incorporated.

**Commentary Summary #37:** Comment requested examples be provided for each of the competencies listed in the chapter.

**Response:** Comment not incorporated. The minimum core competencies are intended to provide specific training considerations. However, the training program must be specific to the personnel and the facility and the designated person(s) is responsible for overseeing the training program.

**Commentary Summary #38:** Commenter noted that the list of core competencies should be organized in a table form with dates on when the competencies must be demonstrated.

**Response:** Comment not incorporated. The minimum competencies are listed in bullets and must be demonstrated every 12 months.

**Commentary Summary #39:** Multiple commenters requested further clarifications on the list of competencies. Commenter requested clarification on cleaning and disinfection competencies. Other commenters requested clarifications on principles of movement of materials and personnel within the compounding facility.

**Response:** Comment not incorporated. The minimum core competencies are intended to provide specific training considerations. However, the training program must be specific to the personnel and the facility and the designated person(s) is responsible for overseeing the training program. For example, while cleaning and disinfecting is described in 7. *Cleaning, Disinfecting, and Applying Sporicidal Agents in Compounding Areas*, training should be based on the facilities' SOPs. Similarly, movement of materials is described in 8. *Introducing Items into the SEC and PEC*.

**Commentary Summary #40:** Commenter requested that calculations be removed from the list of competencies. Other commenters requested that General Chapter <1160> *Pharmaceutical Calculations in Pharmacy Practice* be referenced in the list of competencies.

**Response:** Comment not incorporated. Competency in necessary calculations must be demonstrated to ensure quality CSPs. The training program must be tailored to the facility and the types of CSPs prepared. Further, <1160> is intended to be an informational chapter that may or may not include calculations routinely performed by the facility. Facilities may choose to adopt <1160> as a resource for training personnel.

**Commentary Summary #41:** Commenter noted that use of automated compounding equipment or robotics should be included in the list of competencies.

**Response:** Comment not incorporated. Use of equipment is listed as a minimum core competency.

**Commentary Summary #42:** Commenter suggested making allowances for automated compounding devices (ACDs) and robotics.

**Response:** Comment not incorporated. The chapter does not prohibit the use of ACDs or technology that promotes compounded medication safety (e.g., bar coding). Naming specific technology may allow room for misinterpretation. The Compounding Expert Committee may consider developing a chapter about automated devices in the future.

**Commentary Summary #43:** Commenter noted that testing can be written or can be performed electronically.

**Response:** Comment incorporated.

**Commentary Summary #44:** Commenter noted that if the facility only had one person in the compounding operation, that person must obtain training from an appropriate third party and must demonstrate competency initially and annually. In addition, this person must comply with the other requirements in the chapter.

**Response:** Comment partially incorporated. A provision was added for facilities that have only one person in the compounding operation. That person must demonstrate that they have obtained training and have demonstrated competency.

**Commentary Summary #45:** Commenter requested clarification of the requirements for “maintaining the quality of the environment.”

**Response:** Comment not incorporated. The training program must be developed by the facility and must be tailored to the environment and types of CSPs prepared. Examples of principles for maintaining the quality of the environment include personnel preparation and introducing items into the PEC and SEC, which are described in the chapter.

**Commentary Summary #46:** Commenter noted that there are three types of personnel in a compounding facility: 1) designated person(s), 2) compounding personnel, and 3) all others who handle but do not prepare CSPs. Commenter requested clarification on the training requirements for each type of personnel.

**Response:** Comment not incorporated. Each facility must develop a training program that is specific for the personnel, facility, and types of CSPs prepared. The designated person(s) is responsible for overseeing the training. The needs of each facility must be determined by the individual facility and designated person(s). For example, facilities that have only one person in the compounding operation would be required to fulfill all of the duties of the three types of personnel described by the commenter.

**Commentary Summary #47:** Multiple commenters requested clarification on the requirement for “hands-on demonstration of skill” and whether this includes competency assessments described in subsequent sections.

**Response:** Comment partially incorporated. The requirement for “hands-on demonstration of skills” was removed from the chapter.

**Commentary Summary #48:** Commenter noted that compounding activities should be observed on a periodic or monthly basis. Commenter noted that daily observations would be difficult for small, low staff facilities.

**Response:** Comment not incorporated. The chapter does not require routine visual observations of compounding activities.

**Commentary Summary #49:** Commenter noted that the chapter does not describe the competency assessments required. The commenter noted that if competency assessments are not described in the standard, it would be unenforceable.

**Response:** Comment not incorporated. Competency assessments are described in subsequent subsections including *2.2 Demonstrating Competency in Garbing and Hand Hygiene* and *2.3 Competency Testing in Aseptic Manipulation*.

**Commentary Summary #50:** Multiple commenters noted that knowledge and proficiency may be demonstrated during normal work practices as long as the observation and qualified demonstrations are documented.

**Response:** Comment not incorporated. Each facility must develop a training program that includes training requirements, observations, and documentation.

**Commentary Summary #51:** Commenter noted that the training and competency requirements for other personnel handling CSPs and/or accessing the compounding area should be moved to the introduction of *2. Personnel Training and Evaluation*. Commenter noted that this information could be missed if not reorganized.

**Response:** Comment not incorporated. Training requirements for compounding personnel and other personnel handling CSPs and/or accessing the compounding area are described in *2.1 Demonstrating Proficiency in Core Competencies*. User should read the chapter in its entirety.

**Commentary Summary #52:** Commenter requested step-by-step procedures on how to perform gloved fingertip and thumb sampling inside of a PEC. Commenter requested details on how to transport glove samples from the PEC to the buffer room and how to remove sterile gloves from a restricted-access barrier system (RABS).

**Response:** Comment not incorporated. *Box 2-1* and *Box 2-2* provide procedures for gloved fingertip and thumb sampling and media-fill testing. Facilities should determine and put in place more detailed procedures based on their facility design, type of PEC, and sampling devices used.

**Commentary Summary #53:** Commenter noted that gloved fingertip and thumb sampling and media-fill testing does not prevent contamination. Commenter suggested that a better way to control contamination is to analyze complex activities and those that require a higher number of manipulative interventions with the aim of reducing complexity and the sheer number of manipulations.

**Response:** Comment not incorporated. Gloved fingertip and thumb sampling and media-fill testing are used to assess personnel hand hygiene, garbing, and aseptic technique. These are part of the personnel competency assessments that must be performed in addition to the other requirements in the chapter to ensure quality CSPs. Facilities should assess their compounding procedures to minimize the risk of contamination. However, the Compounding Expert Committee did not feel that reducing complexity or number of manipulations would address all of the different types of CSPs prepared at different facilities.

**Commentary Summary #54:** Commenter noted that the chapter does not provide expectations or criteria for visually observing personnel.

**Response:** Comment not incorporated. Personnel must be visually observed to ensure proper hand hygiene and garbing.

**Commentary Summary #55:** Several commenters requested more frequent monitoring of personnel through gloved fingertip and thumb sampling and media-fill testing (e.g., quarterly) in order to mitigate potential risks to patients due to poor personnel performance.

**Response:** Comment not incorporated. The chapter is intended to provide the minimum standard to help ensure the quality of CSPs. Facilities are required to observe gloved fingertip and thumb sampling and media-fill testing at least every 6 months. Facilities and regulatory bodies may adopt requirements that are different and more stringent than those in the chapter.

**Commentary Summary #56:** Several commenters noted that gloved fingertip and thumb sampling every 6 months is too frequent. Commenter suggested that personnel monitoring every 12 months is sufficient to maintain the safety of CSPs and the protection of public health.

**Response:** Comment not incorporated. The chapter is intended to provide the minimum standard to help ensure the quality of CSPs. The requirement for personnel monitoring every 6 months helps assure continued proper hand hygiene and garbing

procedures. Monitoring every 12 months may be too infrequent to detect potential problems.

**Commentary Summary #57:** Multiple commenters noted that gloved fingertip and thumb sampling must occur “at least” every 6 months. Commenter noted that the addition of “at least” will encourage more frequent testing.

**Response:** Comment not incorporated. The chapter is intended to be the minimum standard. Facilities may perform competency assessments more frequently than specified in the chapter.

**Commentary Summary #58:** Several commenters noted that visual observations of garbing and hand hygiene procedures should be performed annually.

**Response:** Comment not incorporated. The chapter is intended to provide the minimum standard to help ensure the quality of CSPs. The requirement for personnel monitoring every 6 months helps assure continued proper hand hygiene and garbing procedures. Monitoring every 12 months may be too infrequent to detect potential problems.

**Commentary Summary #59:** Multiple commenters noted that gloved fingertip and thumb sampling should be performed every 12 months for Category 1 CSPs and every 6 months for Category 2 CSPs.

**Response:** Comment not incorporated. The chapter is intended to provide the minimum standard to help ensure the quality of CSPs. The requirement for personnel monitoring every 6 months helps assure continued proper hand hygiene and garbing procedures. Personnel must maintain proper hand hygiene and garbing procedures regardless of whether they are compounding a Category 1 or Category 2 CSP. Monitoring every 12 months may be too infrequent to detect potential problems.

**Commentary Summary #60:** Commenter requested that the standard allow for random observations of personnel instead of visual observations every 6 months. Commenter noted that the compounder should be accountable for meeting the chapter requirements daily. Additionally, commenter noted that emphasis should be placed on education assist staff members in being more comfortable with holding others accountable.

**Response:** Comment not incorporated. The chapter is intended to be the minimum standard. Facilities may require additional visual observations as part of their training and evaluation program or as part of their QA and QC program. Facilities should determine and implement appropriate strategies for holding personnel accountable.

**Commentary Summary #61:** Commenter noted that gloved fingertip and thumb sampling should not be required three separate times before a compounder is allowed to independently compound.

**Response:** Comment not incorporated. Gloved fingertip and thumb sampling three separate times helps ensure that personnel are able to garb and perform hand hygiene properly and consistently. This additionally minimizes the risk of false negatives.

**Commentary Summary #62:** Several commenters requested the deletion of “qualified person” for visually observing hand hygiene and garbing procedures as this term is not defined.

**Response:** Comment incorporated.

**Commentary Summary #63:** Commenter requested that the qualified person required for visually observing hand hygiene and garbing procedures compete proper training by internal or external means and has previously demonstrated competency.

**Response:** Comment not incorporated. The requirement for “qualified person” was eliminated from the chapter.

**Commentary Summary #64:** Several commenters noted that gloved fingertip and thumb sampling should be referred to as “gloved fingertip sampling” since thumbs are considered a finger. Other commenters requested clarity that gloved fingertip and thumb sampling includes every finger and thumb on both hands.

**Response:** Comment not incorporated. The Compounding Expert Committee decided that it was important to emphasize that every fingertip and thumb must be sampled.

**Commentary Summary #65:** Commenter suggested that the term “thumb tip” should be used to emphasize that only the tip of the thumb is to be sampled, rather than the entire thumb.

**Response:** Comment not incorporated. “Thumb tip” is not a commonly used term. The Compounding Expert Committee decided that it was important to emphasize that every fingertip and thumb must be sampled.

**Commentary Summary #66:** Commenter noted that there should be a requirement for daily supervision of employees.

**Response:** Comment not incorporated. The designated person(s) is responsible and accountable for the performance and operation of the facility. The facility may determine the requirement for supervision. Requiring daily supervision may be burdensome for facilities that only have one person in the compounding operation.

**Commentary Summary #67:** Commenter noted as incorrect the statement that gloved fingertip and thumb sampling is important because direct touch contamination is the most likely source of microorganisms. Commenter noted that touching any sterile object with gloved hands is not acceptable aseptic technique and must not be allowed.

Commenter additionally indicated that if aseptic technique is followed, no direct touch contamination would be possible because sterile implements would have to be used for such activities.

**Response:** Comment not incorporated. The Compounding Expert Committee decided that direct touch contamination is a likely source of contamination. The statement was removed from the chapter because it did not provide guidance to users and there could be other sources of potential contamination.

**Commentary Summary #68:** Multiple commenters requested that the statement that gloved fingertip and thumb sampling is important because direct touch contamination is the most likely source of microorganisms be clarified to indicate that it only refers to microorganisms on surfaces.

**Response:** Comment not incorporated. The statement was removed from the chapter because it did not provide guidance to users and there could be other sources of potential contamination.

**Commentary Summary #69:** Commenter requested reorganizing the information about competency in garbing and hand hygiene in a table form.

**Response:** Comment not incorporated. Requirements for competency assessments are specified in the chapter. USP will consider developing educational tools in the future to provide additional assistance with understanding of the chapter.

**Commentary Summary #70:** Commenter requested clarification on whether CSPs prepared by a trainee under the direct supervision of a trained person can be released for patient use.

**Response:** Comment not incorporated. The designated person(s) must oversee the training program. The facility's SOPs and/or work practices should provide guidance on whether such CSPs may be released to patients.

**Commentary Summary #71:** Commenter requested clarification that gloved fingertip and thumb sampling must be performed on both hands.

**Response:** Comment incorporated.

**Commentary Summary #72:** Commenter requested revising the text to indicate that gloved fingertip thumb sampling must be performed before preparing their initial operator media-fill qualifications instead of before being allowed to independently compound.

**Response:** Comment not incorporated. The term "initial operator media-fill qualification" may not be easily understood. The subsequent section specifies that media-fill tests must be performed initially and every 6 months thereafter.

**Commentary Summary #73:** Multiple commenters requested clarification on when gloved fingertip sampling is performed in relation to media-fill testing.

**Response:** Comment incorporated. The chapter specifies that subsequent gloved fingertip and thumb sampling must be performed after media-fill tests.

**Commentary Summary #74:** Commenter noted that the action level for gloved fingertip and thumb sampling should be specified as the number of cfu from both hands.

**Response:** Comment incorporated.

**Commentary Summary #75:** Commenter requested that the table for action levels for gloved fingertip and thumb sampling include visual observation of hand hygiene and garbing procedures.

**Response:** Comment not incorporated. The requirements for visual observation are described in the text. The table is intended to provide a summary of the action levels for gloved fingertip and thumb sampling.

**Commentary Summary #76:** Commenter noted that initial competency assessment should include gloved fingertip and thumb sampling three separate and consecutive times. Commenter noted that this ensures that compounders demonstrate mastery of skill and did not pass competency evaluations by chance.

**Response:** Comment not incorporated. The term consecutive may be misinterpreted to mean that compounders must complete testing three times in one day or three times in three consecutive days. The intent of the requirement is to ensure that compounders pass initial competency. However, the designated person(s) must oversee the training program, and the facility and SOP may specify more detailed requirements for personnel training.

**Commentary Summary #77:** Multiple commenters requested clarification on whether all three initial gloved fingertip and thumb sampling procedures must be passed consecutively. For example, commenters noted that if personnel fail the first gloved fingertip and thumb sampling but pass the next two samplings, would the person be required to repeat all three samplings?

**Response:** Comment not incorporated. The chapter is intended to provide the minimum standard. The facility's written training program should address the specifics for evaluation and reevaluation of personnel who failed competency assessments.

**Commentary Summary #78:** Commenter noted that if all three initial gloved fingertip and thumb sampling procedures are performed on the same day, the compounder must exit the cleanroom, perform hand hygiene, and don sterile gloves before sampling again.

**Response:** Comment not incorporated. The chapter specifies that initial gloved fingertip and thumb sampling must be performed after separate and complete hand hygiene and full garbing procedures.

**Commentary Summary #79:** Commenter suggested that initial competency assessments should include two gloved fingertip and thumb samplings after garbing, one sampling after hand hygiene, garbing, and compounding, and one after compounding.

**Response:** Comment not incorporated. The intent of the requirement is to ensure that compounders pass initial competency and demonstrate proper garbing and hand hygiene procedures. Subsequent gloved fingertip and thumb sampling is performed after media-fill testing.

**Commentary Summary #80:** Commenter suggested that it is unnecessary to perform hand hygiene and garbing three separate times to prove initial competency.

**Response:** Comment not incorporated. The intent of the requirement is to ensure that compounders consistently demonstrate proper garbing and hand hygiene procedures. Separate hand hygiene and garbing procedures help ensure that personnel can perform those tasks consistently and properly.

**Commentary Summary #81:** Commenter requested clarification on whether personnel can apply 70% sterile isopropyl alcohol (IPA) on gloves prior to sampling and whether this could cause false negatives.

**Response:** Comment incorporated. *Box 2-1* provides procedures on gloved fingertip and thumb sampling, stating: Do not apply sterile 70% IPA to gloves immediately before touching the sampling device because this could cause a false-negative result.

**Commentary Summary #82:** Multiple commenters requested clarification on whether initial gloved fingertip and thumb sampling must occur during initial training or at every subsequent sampling.

**Response:** Comment not incorporated. Initial gloved fingertip and thumb sampling procedures are only required for new personnel. Subsequent assessments must be performed every 6 months after media-fill testing.

**Commentary Summary #83:** Commenter noted that reference to media-fill testing should be eliminated from the subsection on gloved fingertip and thumb sampling because it causes confusion.

**Response:** Comment not incorporated. Initial gloved fingertip and thumb sampling is performed after hand hygiene and garbing, and subsequent gloved fingertip and thumb sampling is performed after media-fill testing. Reference to media-fill testing was added to clarify the sequence of competency assessments.

**Commentary Summary #84:** Commenter requested adding a reference to 2.3 *Competency Testing in Aseptic Manipulation* when referencing media-fill testing.

**Response:** Comment incorporated.

**Commentary Summary #85:** Multiple commenters noted that initial gloved fingertip and thumb sampling should not be required to be performed in a PEC (including a restricted access barrier system, or RABS). Other commenters noted that initial gloved fingertip and thumb sampling must be required to be performed in a PEC to minimize the risk of inadvertent contamination (e.g., false positives).

**Response:** Comment incorporated. Initial gloved fingertip and thumb sampling may be performed in a classified area or a SCA, including in a PEC. Facilities may determine where to perform initial competency evaluations as part of their overall training program. However, subsequent gloved fingertip and thumb sampling must be performed in a PEC because it is performed after media-fill testing.

**Commentary Summary #86:** Multiple commenters noted that subsequent gloved fingertip and thumb sampling should not be required to be performed in a PEC. Commenters noted that performing gloved fingertip and thumb sampling in the PEC would require compounders to apply sterile IPA on gloves upon entry into the PEC which would increase the risk of false negatives.

**Response:** Comment not incorporated. Subsequent gloved fingertip and thumb sampling must be performed in a PEC because it is performed after media-fill testing. Further, *Box 2-1* states that sterile IPA must not be applied to gloves immediately before touching the sampling plate because this could cause a false-negative result.

**Commentary Summary #87:** Commenter noted that subsequent gloved fingertip and thumb sampling in the PEC implies the requirement for gloves to be donned in the PEC. The commenter noted that donning gloves in the PEC increases the risk of turbulence, particles, and contamination.

**Response:** Comment not incorporated. Subsequent gloved fingertip and thumb sampling must be performed in a PEC because it is performed after media-fill testing. Personnel must follow facility hand hygiene and garbing procedures, perform media-fill testing, and then perform subsequent gloved fingertip and thumb sampling.

**Commentary Summary #88:** Commenter requested clarification on what actions should be taken in the event of failure of competency assessments.

**Response:** Comment not incorporated. Facilities must evaluate the failure and if possible determine the cause of failure and take corrective actions. Actions would be specific to the personnel, facility, and facility's SOPs.

**Commentary Summary #89:** Commenter recommended language to state that gloved fingertip and thumb sampling is "generally" or "typically" performed at the same time as media-fill testing. Commenter noted that these activities should be linked.

**Response:** Comment not incorporated. The chapter specifies that subsequent gloved fingertip and thumb sampling is performed after media-fill testing.

**Commentary Summary #90:** Commenter noted that sterile gloves should not be required if sterile IPA is wiped onto gloves for gloved fingertip and thumb sampling.

**Response:** Comment not incorporated. Sterile gloves are required for compounding and for gloved fingertip and thumb sampling. Sterile gloves help minimize the bioburden in the PEC during compounding. Further, sterile gloves should be used during gloved fingertip and thumb sampling to ensure appropriate hand hygiene and garbing procedures and to ensure that personnel can maintain the sterility of the gloves during garbing procedures.

**Commentary Summary #91:** Commenter requested a note be added to gloved fingertip and thumb sampling to emphasize to users that skin should not be exposed inside of the ISO Class 5 PEC.

**Response:** Comment not incorporated. Hand hygiene and garbing requirements are described in 3. *Personal Hygiene and Garbing*. The additional statement would be out of place and may lead to confusion.

**Commentary Summary #92:** Several commenters noted that gloved fingertip and thumb sampling in a RABS may be performed using the sterile glove attached to the RABS. Commenters noted that a sterile glove should not be required to be placed over the gloves attached to the RABS' sleeves.

**Response:** Comment not incorporated. Sterile gloves must be placed over the gloves attached to RABS sleeves to minimize the bioburden in the PEC and the risk of contamination.

**Commentary Summary #93:** Commenters noted that gloved fingertip and thumb sampling in a pharmaceutical isolator may be performed using the sterile glove attached to the pharmaceutical isolator. Commenters noted that a sterile glove should not be required to be placed over the gloves in the pharmaceutical isolator because an automated decontamination cycle is used prior to compounding. Further, the commenter noted that over gloving increases the risk of contamination after the isolator is decontaminated.

**Response:** Comment not incorporated. Sterile gloves must be placed over the gloves attached to pharmaceutical isolator to minimize the bioburden in the PEC and the risk of contamination.

**Commentary Summary #94:** Several commenters requested the addition of a statement "as there is risk the in the transport and introduction of sterile gloves into these products [RABS and pharmaceutical isolators], care must be taken to ensure that the sterility of the sterile gloves and cleanliness of air inside the chamber is maintained."

**Response:** Comment not incorporated. During hand hygiene and garbing procedures, personnel must ensure maintenance of sterile gloves and air quality in the PEC, regardless of the type of PEC used.

**Commentary Summary #95:** Commenter noted that compounding aseptic containment isolators (CACIs) and compounding aseptic isolators (CAIs) should be eliminated because CAIs and CACIs are not isolators.

**Response:** Comment not incorporated. PEC types including CAIs, CACIs, and pharmaceutical isolators are described in 4. *Facilities and Engineering Controls*. Further, the chapter notes that a CAI or CACI is not a pharmaceutical isolator.

**Commentary Summary #96:** Commenter noted that gloved fingertip and thumb sampling should not be required for pharmaceutical isolators if the pharmaceutical isolator is properly cleaned, disinfected, and decontaminated.

**Response:** Comment not incorporated. Gloved fingertip and thumb sampling is used as a means to assess initial and continued personnel competency in hand hygiene and garbing procedures. Personnel competency in hand hygiene and garbing must be evaluated regardless of the type of PEC used.

**Commentary Summary #97:** Multiple commenters noted that the term gauntlet gloves should be changed to gloves attached to the RABS sleeve.

**Response:** Comment incorporated.

**Commentary Summary #98:** Commenter noted that commercial gloved fingertip and thumb sampling kits only require incubation for 48 hours to 72 hours.

**Response:** Comment not incorporated. Gloved fingertip and media-fill 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.

**Commentary Summary #99:** Commenter requested allowing for sampling devices to be incubated in “split phases” to allow for use in an incubator and subsequent storage at ambient room temperature.

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

**Commentary Summary #100:** Multiple commenters noted that the procedures in *Box 2-1* for gloved fingertip and thumb sampling should be examples. The commenter noted that there are alternative valid processes for gloved fingertip and thumb sampling.

**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.

**Commentary Summary #101:** Multiple commenters noted that the action level for initial gloved fingertip and thumb sampling should be represented as > 0 cfu instead of ≥ 1 cfu so that the table is consistent with subsequent text.

**Response:** Comment incorporated.

**Commentary Summary #102:** Commenter noted that the sampling procedures should state that the sampling device must be large enough to accommodate for rolled finger and thumb pads

**Response:** Comment not incorporated. *Box 2-1* is intended to provide procedures for performing gloved fingertip and thumb sampling. Selection of appropriate devices should be done by the facility.

**Commentary Summary #103:** 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 not 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 test samples are incubated at a low temperature (20°–25°) and then at a high temperature (30°–35°) to detect a broad spectrum of microorganisms. The incubation time and temperatures for media-fill test samples are consistent with [FDA Guidance for Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practices](#).

**Commentary Summary #104:** Multiple commenters noted that the incubation for gloved fingertip and thumb sampling should only be required for one temperature at 30°–35° for a shorter amount of time (48 to 72 hours) to eliminate the need to purchase multiple incubators.

**Response:** Comment not incorporated. Gloved fingertip and thumb samples must be incubated at a high temperature (30°–35°) and then at 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. The incubation conditions must be sufficient to detect a broad range of microorganisms.

**Commentary Summary #105:** Commenter noted that incubation at a higher temperature first may inhibit the growth of organisms and cause false negatives. Commenter recommended that the incubation temperatures be revised to incubate at the lower temperature and then at a higher temperature. Lower temperatures facilitate growth of micrococcus and staphylococcus, while higher temperatures encourage the growth of other microorganisms.

**Response:** Comment not incorporated. Incubating at the lower temperature first may compromise the recovery of Gram-positive cocci that are often associated with humans.

**Commentary Summary #106:** Commenter suggested that gloved fingertip and thumb samples may be stored at ambient room temperature conditions, outside of an incubator if temperatures are monitored daily.

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

**Commentary Summary #107:** Commenter noted that trypticase soy agar (TSA) is not an ideal growth media and the addition of neutralizing additives does not improve nutrition properties. Commenter noted that TSA without additives would be a more appropriate media.

**Response:** Comment not incorporated. TSA with neutralizing agents is intended to be an example of microbial growth agar. Facilities may use other general growth agar that supports both bacterial and fungal growth.

**Commentary Summary #108:** Commenter requested clarification on whether the procedures in *Box 2-1* are requirements or recommendations. Commenter noted that the distinction is important for regulators to enforce the procedures.

**Response:** Comment not incorporated. *Box 2-1* is intended to provide procedures on gloved fingertip and thumb sampling. The procedural box provides examples of different microbial growth agar that may be used. The incubation temperatures and times are specified as part of the required procedures.

**Commentary Summary #109:** Commenter noted that the procedures for gloved fingertip and thumb sampling should specify that samples must be collected from each finger and thumb on both hands.

**Response:** Comment incorporated.

**Commentary Summary #110:** Several commenters noted that the incubation temperatures and times specified by the manufacturer should be used instead of those described in *Box 2-1*.

**Response:** Comment not incorporated. The incubation temperatures and times may vary depending on the type of sample. The incubation conditions must be sufficient to detect a broad range of microorganisms.

**Commentary Summary #111:** Commenter noted that the incubation conditions should align with those in General Chapter <1116> *Microbiological Control and Monitoring of Aseptic Processing Environments*.

**Response:** Comment not incorporated. Gloved fingertip and thumb sampling is not described in <1116>. The incubation conditions in *Box 2-1* are consistent with the recommendations in <1116> which state that “incubating at the lower temperature first may compromise the recovery of Gram-positive cocci that are important because they are often associated with humans.”

**Commentary Summary #112:** Commenter noted that the gloved fingertip and thumb sampling device does not need to be labeled with the time of sampling. Commenter noted that the time the sampling device is placed in the incubator should be recorded and not the time of sampling.

**Response:** Comment not incorporated. The time of sampling and time of incubation should be similar. The time noted of sampling is a more accurate reflection of the incubation conditions.

**Commentary Summary #113:** Commenter noted that incubation at two temperatures for the times specified in *Box 2-1* risks drying out the plates. The commenter noted that the incubation conditions are inadequate and prevent compounders from adjusting their sampling procedures.

**Response:** Comment not incorporated. Stakeholders requested specificity in the incubation conditions. The incubation conditions must be sufficient to detect a broad range of microorganisms.

**Commentary Summary #114:** Commenter noted the total number of cfu per hand should be recorded for gloved fingertip and thumb sampling. Commenter noted that it is not necessary to record the number of cfu per hand.

**Response:** Comment not incorporated. Documentation of cfu per hand helps ensure comprehensive and accurate assessments especially since one sampling device is required per hand. Further, such records may assist in evaluations and corrective actions in the event of failure.

**Commentary Summary #115:** Commenter noted that not all sampling devices may be inverted without affecting the integrity of the medium.

**Response:** Comment incorporated.

**Commentary Summary #116:** Commenter noted that *Box 2-1* should specify that a certificate of analysis (COA) must be obtained from the supplier of the growth media to state that the media will support the growth of microorganisms.

**Response:** Comment not incorporated. *Box 2-1* is intended to provide procedural information for gloved fingertip and media testing. A COA must be obtained for media-fill test media as described in *2.3 Competency Testing in Aseptic Manipulation*.

**Commentary Summary #117:** Several commenters noted that the action level of 0 cfu for initial gloved fingertip and thumb sampling is inconsistent with the action level of 3 cfu for subsequent gloved fingertip and thumb sampling. Other commenters noted that the action level for initial and subsequent gloved fingertip and thumb sampling should be 0 cfu.

**Response:** Comment not incorporated. Initial gloved fingertip and thumb sampling is performed immediately after hand hygiene and garbing procedures and is expected to

have 0 cfu. Subsequent gloved fingertip and thumb sampling is performed after media-fill testing and thus may have  $\leq 3$  cfu from both hands.

**Commentary Summary #118:** Several commenters noted that the action level of 0 cfu should be used for both initial and subsequent gloved fingertip and thumb sampling.

**Response:** Comment not incorporated. Initial gloved fingertip and thumb sampling is performed immediately after hand hygiene and garbing procedures and is expected to have 0 cfu. Subsequent gloved fingertip and thumb sampling is performed after media-fill testing and thus may have  $\leq 3$  cfu from both hands.

**Commentary Summary #119:** Commenter noted that the action levels are inappropriate because zero recovery does not mean sterile nor does it mean uncontaminated. The commenter additionally noted that the limit of detection of microbiological growth methods is on the order of 10 cfu, and the variability of these methods is on the order of 0.3 to 0.5 log.

**Response:** Comment not incorporated. The action levels for gloved fingertip and thumb sampling are intended to provide an objective means to assess initial and continued personnel competency in hand hygiene and garbing procedures.

**Commentary Summary #120:** Commenter noted that subsequent sampling can be performed after media-fill testing or after compounding. The commenter noted that some facilities may adopt best practices and perform random or ongoing gloved fingertip and thumb sampling more frequently than every 6 months.

**Response:** Comment not incorporated. Incorporation of additional testing in the table of action levels may cause confusion and may imply a requirement to perform more frequent sampling. The chapter is intended to provide the minimum standard to help ensure the quality of CSPs. Facilities may perform sampling more frequently than described in the chapter.

**Commentary Summary #121:** Commenter noted that the table of action levels for gloved fingertip and thumb sampling should specify that subsequent sampling is required three separate times.

**Response:** Comment not incorporated. Subsequent gloved fingertip and thumb sampling must be performed once after media-fill testing. Only initial gloved fingertip and thumb sampling is required to be performed three separate times.

**Commentary Summary #122:** Multiple commenters requested clarifying when media-fill testing and gloved fingertip and thumb testing must occur.

**Response:** Comment incorporated.

**Commentary Summary #123:** Commenter noted that that the table of action levels for gloved fingertip and thumb sampling should include where the sampling is to be done.

**Response:** Comment not incorporated. The table is intended to provide a summary of the action levels for gloved fingertip and thumb sampling. The sampling procedures are described in the subsequent sections of the chapter.

**Commentary Summary #124:** Commenter noted that the table of action levels for gloved fingertip and thumb sampling should specify that all fingertips must be sampled. The commenter noted that unless fingertips are specified, compounders may not sample all four fingertips and thumb.

**Response:** Comment not incorporated. The table is intended to provide a summary of the action levels for gloved fingertip and thumb sampling. The sampling procedures are described in the subsequent sections of the chapter.

**Commentary Summary #125:** Several commenters noted that media-fill testing every 6 months is too frequent. Commenter suggested that personnel monitoring every 12 months is sufficient to maintain the safety of CSPs and the protection of public health.

**Response:** Comment not incorporated. The chapter is intended to provide the minimum standard to help ensure the quality of CSPs. The requirement for personnel monitoring every 6 months helps assure continued good aseptic technique. Monitoring every 12 months may be too infrequent to detect potential problems.

**Commentary Summary #126:** Commenter requested clarifying whether media-fill testing must be performed for each hood.

**Response:** Comment not incorporated. The facility's SOPs should describe how many media-fill tests must be performed and for how many hoods.

**Commentary Summary #127:** Multiple commenters noted that media-fill testing every 6 months is too infrequent. Commenter recommended periodic or quarterly media-fill testing.

**Response:** Comment not incorporated. The chapter is intended to be the minimum standard. Facilities may perform competency assessments more frequently than specified in the chapter.

**Commentary Summary #128:** Multiple commenters noted that media-fill testing must be performed initially before compounders should be allowed to independently prepare CSPs.

**Response:** Comment incorporated.

**Commentary Summary #129:** Multiple commenters suggested removing the phrase "after successful completion of hand hygiene and garbing competency evaluation" when describing when to perform media-fill testing because it could delay initial competency assessment. Commenters noted that media-fill testing can be performed while awaiting incubation of gloved fingertip and thumb sampling.

**Response:** Comment incorporated.

**Commentary Summary #130:** Commenter noted that personnel must not be allowed to prepare CSPs for patient use until all competency assessments are successfully completed.

**Response:** Comment partially incorporated. The section was revised to state that media-fill testing must be performed initially and every 6 months thereafter.

**Commentary Summary #131:** Commenter noted the media-fill tests must be performed to confirm that gloves remain constantly clean throughout the compounding process.

**Response:** Comment not incorporated. The chapter states that media-fill testing is used to assess sterile technique and related practices which includes maintaining sterility of the gloves.

**Commentary Summary #132:** Multiple commenters suggested that the media-fill test should mimic the most complex compounding procedure performed by the facility. The commenter noted that simulating the most manipulations or the largest size batch is not a good use of resource and incubators may not have sufficient room to store all of the items.

**Response:** Comment incorporated.

**Commentary Summary #133:** Commenter suggested removing the requirement that media-fill tests must simulate the most difficult and challenging compounding procedures performed “during a work shift.”

**Response:** Comment incorporated.

**Commentary Summary #134:** Commenter requested additional language stating that facilities may use their ACD to perform media-fill testing if they prepare a large volume of total parenteral nutrition.

**Response:** Comment not incorporated. Media-fill test must simulate the most difficult and challenging compounding procedures and processing conditions encountered by the person. The simulation may include use of ACDs.

**Commentary Summary #135:** Commenter noted that it would be difficult for large institutions to customize the most complex compounding scenarios for each and every compounder and/or location. Commenter noted that facilities should be allowed to create a representative process that challenges the compounders with various source containers, suppliers, and aseptic technique they may use.

**Response:** Comment not incorporated. Media-fill tests must simulate the most difficult and challenging compounding procedure and processing conditions encountered by the person to help ensure competency in their compounding tasks. Facilities must determine and implement the most appropriate compounding scenarios to simulate during media-fill tests.

**Commentary Summary #136:** Commenter noted that the section should emphasize that gloved fingertip testing must additionally be performed after media-fill testing.

**Response:** Comment incorporated.

**Commentary Summary #137:** Commenter noted that growth promotion tests must be performed on all commercial sterile microbial growth media. Commenter noted that failures in the supply chain may alter the media. Further, the commenter noted that a COA is not sufficient to ensure that the media are growth promoting.

**Response:** Comment not incorporated. Many compounders noted that performing growth promotion tests in a compounding facility risks bringing in microbial contamination. The chapter allows facilities to verify growth promotion through a COA. The chapter is intended to provide a minimum standard. Facilities may choose to verify growth promotion through additional testing.

**Commentary Summary #138:** Multiple commenters noted that media-fill tests must be initiated before the expiration date of the media.

**Response:** Comment incorporated.

**Commentary Summary #139:** Several commenters noted that requiring growth promotion tests to be performed for sterile microbial growth media prepared in-house precludes use of dry media powder to simulate compounding with nonsterile active pharmaceutical ingredients (APIs).

**Response:** Comment incorporated. Clarification was added to the section to state that growth promotion tests are required for sterile microbial growth media prepared in-house for sterile-to-sterile media-fill testing. Further clarification was added to *Box 2-2* for media-fill testing simulating nonsterile-to-sterile compounding.

**Commentary Summary #140:** Commenter suggested that growth promotion testing must be required even for commercial growth media.

**Response:** Comment not incorporated. If preparing a sterile microbial growth medium in-house, the growth promotion capability of the medium must be demonstrated for each batch and documented. The chapter is intended to be a minimum standard; facilities may choose to conduct growth promotion for all media.

**Commentary Summary #141:** Multiple commenters requested the addition of a statement that requires staff who evaluate media-fill test results to receive training in how to properly identify signs of microbial growth in liquid media which is based on written SOPs.

**Response:** Comment not incorporated. The chapter specifies that failure is indicated by visible turbidity and other visual manifestations of growth. Further, *17. SOPs* specifies that personnel must demonstrate competency in performing every procedure that relates to their job function.

**Commentary Summary #142:** Several commenters requested additional examples of other visual manifestations of growth in a media-fill test (e.g., precipitate, gas bubbles, flocculence, and floating debris).

**Response:** Comment not incorporated. Visual manifestations may depend on the media-fill test procedure and media. Facilities may specify examples of other visual manifestations of growth in media-fill tests in their SOPs

**Commentary Summary #143:** Commenter suggested that there are no visual manifestations of growth in media-fill test other than turbidity. The commenter noted that presence of visible particles is not reliably diagnostic of growth.

**Response:** Comment not incorporated. There could potentially be other visual manifestations of growth of media-fill tests (e.g., color changes, bubbles).

**Commentary Summary #144:** Commenter requested deletion of the sentence requiring investigation of media-fill failures to determine possible causes. The commenter noted that media-fill tests are pass or fail and that there is nothing that can be retrospectively investigated. Further, the commenter noted that the only option after failed media-fill tests is education, training, and observation.

**Response:** Comment incorporated.

**Commentary Summary #145:** Commenter noted that there could be other causes of media-test failures such as inadvertent contamination during sampling or microbiological laboratory processing that should be evaluated.

**Response:** Comment not incorporated. The requirement for investigation media-fill failures to determine possible causes was deleted.

**Commentary Summary #146:** Commenter noted that documentation of training must be maintained for 4 years after employee departure, though certain local, state, and federal regulations may require longer maintenance.

**Response:** Comment not incorporated. Facilities must comply with the laws and regulations of the applicable jurisdiction. Further requirements for documentation are described in *20. Documentation*.

**Commentary Summary #147:** Commenter suggested that “evaluation results” should be changed to “evaluation of results” when referring to media-fill tests.

**Response:** Comment partially incorporated. The statement was revised to state that results of the evaluation and corrective actions, in the event of failure, must be documented.

**Commentary Summary #148:** Commenter noted manual aseptic processing is an inherently risky activity and if unacceptable contamination rates are seen in media-fill testing or in products, it is most likely due to inadequacy of the process. The commenter noted that reliance on aseptic technique requires improvement.

**Response:** Comment not incorporated. Compounding provides individualized tailored therapies that are not otherwise available. Media-fill testing is one part of competency assessments that must be performed in addition to the other requirements in the chapter to ensure quality CSPs.

**Commentary Summary #149:** Several commenters noted that electronic documentation should be allowed for maintaining personnel records.

**Response:** Comment incorporated. Documentation may be maintained in written or electronic form as described in *20. Documentation*.

**Commentary Summary #150:** Commenter noted that documentation of media-fill tests must include the following: 1) lot number, 2) procedure used to conduct the media fill, 3) temperature and dates of incubation, 4) test results, 5) any investigations conducted if there is failure, and 6) signatures of the person evaluated and the observer.

**Response:** Comment partially incorporated. The procedures used to conduct the media-fill test should be documented in the facility's SOPs. Other documentation requirements include the name of the person evaluated; evaluation date/time; media and components used, including manufacturer, expiration date, and lot number; starting temperature for each interval of incubation; dates of incubation; test results; and identification of the observer and the person who reads and documents the results.

**Commentary Summary #151:** Commenter noted that the requirement for a signature is unclear on whether this can be an electronic signature.

**Response:** Comment incorporated. The documentation requirements for media-fill testing were changed to identification of the observer and person who reads and documents the results.

**Commentary Summary #152:** Commenter noted that the chapter should prescribe the media-fill testing procedures to be performed.

**Response:** Comment not incorporated. The media-fill test must simulate the most difficult and challenging compounding procedures and processing conditions encountered by the person. The actual testing procedures would be specific to the procedures and processing conditions of the person and facility.

**Commentary Summary #153:** Multiple commenters noted that the incubation conditions for gloved fingertip and thumb sampling, media-fill testing, active air sampling, and surface sampling 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 not incorporated. Environmental air and surface samples are incubated at a high temperature and then a low temperature. Incubation at a lower temperature first may compromise recovery of Gram-positive cocci which are often associated with humans. The incubation conditions are consistent with <1116>. Gloved fingertip and thumb samples must be incubated at a high temperature and then a low temperature to allow for readability and to facilitate growth of micrococcus and staphylococcus. Media-fill test samples are incubated at a low temperature and then a high temperature to detect a broad spectrum of microorganisms. The incubation time

and temperatures for media-fill test samples are consistent with [FDA Guidance for Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practices](#).

**Commentary Summary #154:** Multiple commenters suggested that media-fill test samples should only be required to be incubated at one temperature. One commenter specifically noted that incubation should be at 20°–35° to be consistent with the [FDA Guidance for Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing](#). Other commenters suggested that incubation should be at 30°– 35° for 14 days.

**Response:** Comment not incorporated. The incubation conditions for media-fill testing are consistent with the FDA guidance. The FDA guidance additionally states that if two temperatures are used for incubation, the media-fill test samples should be incubated for 7 days at the lower temperature and then 7 days at the higher temperature.

**Commentary Summary #155:** Several commenters noted that the incubation temperatures and times specified by the manufacturer should be permitted in addition to those described in *Box 2-2*.

**Response:** Comment not incorporated. The incubation temperatures and times may vary depending on the type of sample. The incubation conditions must be sufficient to detect a broad range of microorganisms.

**Commentary Summary #156:** Commenter noted that *Box 2-2* should emphasize that the media-fill test must simulate nonsterile-to-sterile compounding activities at the facility.

**Response:** Comment not incorporated. Subsequent text specifies that media-fill testing must simulate the most difficult and challenging compounding procedures and processing conditions encountered by the person.

**Commentary Summary #157:** Commenter noted that media-fill testing procedures should not be performed using nonsterile media. The commenter noted that media-fill testing can only assess aseptic assembly of materials that have been physically sterilized or sterilized by filtration.

**Response:** Comment not incorporated. The media-fill test procedures are intended to simulate the most difficult and challenging compounding procedures and processing conditions encountered by the person. If the person prepares nonsterile-to-sterile compounding, the media-fill test must start with nonsterile media to simulate the compounding procedures.

**Commentary Summary #158:** Commenter suggested that a negative media control be incubated to ensure that the media used is sterile. Commenter additionally suggested that growth promotion testing be performed on the media prior to use.

**Response:** Comment not incorporated. Many compounders noted that performing growth promotion tests in a compounding facility risks bringing in microbial contamination. The chapter allows facilities to verify growth promotion through a COA when using commercial sterile microbial growth media. However, *Box 2-2* was revised to contain at least one container as a positive control to demonstrate growth promotion for simulating nonsterile-to-sterile compounding.

**Commentary Summary #159:** Commenter noted that media used for simulating nonsterile-to-sterile compounding should be exempted from growth promotion tests

**Response:** Comment incorporated.

**Commentary Summary #160:** Commenter suggested that other methods should be permitted for simulating nonsterile-to-sterile compounding (e.g., use of nonsterile tap water to reconstitute soybean-casein digest powder).

**Response:** Comment not incorporated. Non-bacteriostatic water should be used to prepare a 3% solution of soybean-casein digest media. Tap water must not be used in sterile compounding and thus should not be used to simulate compounding procedures and processing conditions.

### 3. Personal Hygiene and Garbing

**Expert Committee-Initiated Change #1:** Hand hygiene procedures were reorganized to separate hand-washing procedures from hand-sanitizing procedures. Two separate boxes were created to describe hand-washing procedures (*Box 3-1*) and hand-sanitizing procedures (*Box 3-2*).

**Commentary Summary #1:** Multiple commenters recommended that the chapter specify that individuals that enter the compounding room should minimize the risk of contamination to the environment and/or CSPs to emphasize to the users what the risks are.

**Response:** Comment incorporated.

**Commentary Summary #2:** Multiple commenters recommended that the chapter specify that personnel must shower or bathe daily and wear freshly laundered clothing to work.

**Response:** Comment not incorporated. The designated person(s) should determine the specific criteria for personal hygiene and determine how to enforce the facility's policies.

**Commentary Summary #3:** Multiple commenters requested guidance on how to determine whether individuals are at risk of contaminating the environment and the CSP. Commenter requested parameters for determining when an individual may pose a risk.

**Response:** Comment not incorporated. The designated person(s) is responsible for evaluating whether individuals should be excluded from working in compounding areas based on certain conditions (e.g., rashes, recent tattoos, oozing sores, conjunctivitis, or active respiratory infection) on a case-by-case basis. Individuals should be evaluated for their risk of contaminating the CSP and the environment.

**Commentary Summary #4:** Commenter requested clarification on whether facility determination of whether individuals may be at risk of contaminating the CSP or the environment is required to be documented.

**Response:** Comment not incorporated. Documentation requirements should be based on the facility's SOPs and must be in compliance with the laws and regulations of the applicable jurisdiction.

**Commentary Summary #5:** Multiple commenters noted that "recent tattoos" is ambiguous. Commenters recommended changing to "unhealed tattoos"

**Response:** Comment not incorporated. Recent tattoos are intended to be an example where an individual may have a higher risk of contaminating the CSP and the environment.

**Commentary Summary #6:** Commenter noted that individuals with certain conditions must report the condition to their supervisor. Commenters requested clarification on the difference in roles between the supervisor and designated person(s).

**Response:** Comment incorporated. Individuals must report the condition to the designated person(s).

**Commentary Summary #7:** Multiple commenters recommended adding provisions for personnel to have temporary reassignment due to their conditions and to require documentation of the resolution.

**Response:** Comment not incorporated. The designated person(s) and facility must determine the appropriate course of action for personnel who may be at risk of contaminating the environment or the CSP. Documentation requirements should be based on the facility's SOPs and must be in compliance with the laws and regulations of the applicable jurisdiction.

**Commentary Summary #8:** Commenter suggested that dedicated clothing should be required for entering the compounding area. The commenter noted that clothes worn outside of the facility must be laundered before their next use.

**Response:** Comment not incorporated. Personnel must take appropriate steps to minimize microbial contamination of the environment and the CSP. The chapter does state that individuals must at a minimum remove personal outer garments. The requirement for dedicated clothing may be onerous for some facilities and may be difficult to implement and enforce.

**Commentary Summary #9:** Multiple commenters noted that reference to "compounding area" should be capitalized to "Compounding Area" because the term is defined in the glossary.

**Response:** Comment not incorporated. Glossary terms are not capitalized throughout the chapter.

**Commentary Summary #10:** Multiple commenters requested clarification on what is the compounding area.

**Response:** Comment not incorporated. The compounding area is defined in the glossary as the area where compounding is occurring [i.e., a cleanroom suite, inside the perimeter of the SCA, or an allergenics extracts compounding area (AECA)].

**Commentary Summary #11:** Several commenters requested clarification on what constitutes a personal outer garment. Other commenters requested that examples of outer garments be added to the chapter.

**Response:** Comment incorporated. Examples of personal outer garments were added to the chapter.

**Commentary Summary #12:** Multiple commenters noted that head scarves should be permitted if they are covered by garbing.

**Response:** Comment incorporated. The designated person(s) may permit accommodations as long as the quality of the CSP and the environment will not be affected.

**Commentary Summary #13:** Commenter noted that personal outer garments, including shoes, must be removed.

**Response:** Comment not incorporated. Individuals entering the compounding area must wear shoes. Individuals may have dedicated shoes for the compounding area.

However, low-lint disposable shoe covers are required as described in 3.3 *Garbing Requirements*.

**Commentary Summary #14:** Commenter noted the individuals with personal eyeglasses must be cleaned with an appropriate disinfectant solution suitable for glasses frames and lens materials.

**Response:** Comment incorporated.

**Commentary Summary #15:** Commenter noted that cosmetics should be permitted in the compounding area. The commenter suggested that individuals generate more particles when not wearing cosmetics because nearly all cosmetics have a moisturizer base which keeps the skin less dry in harsh conditions of the cleanroom.

**Response:** Comment not incorporated. Individuals entering the compounding area should minimize the risk of any flakes and particles, particularly from cosmetics.

**Commentary Summary #16:** Multiple commenters suggested that the chapter should only prohibit cosmetics that are applied daily. Cosmetics that are semi-permanent (e.g., eye lash extensions) and can be covered by goggles should be permitted. Other commenters noted that false eyelashes must not be permitted.

**Response:** Comment not incorporated. Cosmetics must not be worn in the compounding area because they shed flakes and particles. The designated person(s) may permit accommodations as long as the quality of the CSP and the environment will not be affected.

**Commentary Summary #17:** Multiple commenters requested that cosmetics be defined in the chapter. Commenters noted that skin care products should be permitted (e.g., facial moisturizer, tinted moisturizer, mascara).

**Response:** Comment not incorporated. Cosmetics are defined in the Federal Food, Drug, and Cosmetic Act as “articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body...for cleansing, beautifying, promoting attractiveness, or altering the appearance.” It would not be feasible to list all the different types of cosmetics. Cosmetics must not be permitted in the compounding area because they may shed flakes and particles. However, the designated person(s) may permit accommodations as long as the quality of the CSP and the environment will not be affected.

**Commentary Summary #18:** Commenter noted that the prohibition of cosmetics is discriminatory toward women. The commenter indicated that research shows that women that wear makeup are seen as more professional and make more money. Further, the commenter noted that makeup protects the skin and individuals that wear makeup shed less skin.

**Response:** Comment not incorporated. Cosmetics must not be worn in the compounding area because they shed flakes and particles. The designated person(s) may permit accommodations as long as the quality of the CSP and the environment will not be affected.

**Commentary Summary #19:** Multiple commenters requested clarification on whether earrings, necklaces, and other above the neck jewelry are permitted in the compounding area. Some commenters noted that head and neck jewelry should be specifically prohibited. Other commenters requested that watches and wristbands be included as examples of jewelry that must be removed.

**Response:** Comment not incorporated. The chapter specifies that all hand, wrist, and other exposed jewelry that could interfere with the effectiveness of garbing must be removed. If jewelry, including earrings, necklaces, watches, and wristbands interfere with the effectiveness of the garbing, they must be removed.

**Commentary Summary #20:** Commenter noted that jewelry that impacts the integrity of the garb must be excluded. For example, diamond rings can potentially rip gloves.

**Response:** Comment not incorporated. The chapter specifies that all hand jewelry that could interfere with the effectiveness of garbing must be removed. Hand jewelry includes rings that could impact the integrity of gloves.

**Commentary Summary #21:** Commenter requested clarification on which jewelry cannot be removed. Other commenters suggested deleting the provision allowing jewelry that cannot be removed to be covered. Commenter noted concern that regulatory bodies and accreditation bodies may interpret the requirement to mean that jewelry (e.g., earrings) can be covered and are not required to be removed.

**Response:** Comment not incorporated. The chapter states that all jewelry that could interfere with the effectiveness of garbing must be removed. If the jewelry does not interfere with the effectiveness of the garbing, it is not required to be removed. Further, jewelry such as transdermal implants or body piercings that cannot be removed must be covered.

**Commentary Summary #22:** Commenter noted that only exposed body jewelry should be removed prior to entering the compounding area. Other types of jewelry should be permitted.

**Response:** Comment not incorporated. The chapter specifies that all “other exposed jewelry” that could interfere with the effectiveness of garbing or otherwise increase the risk of contamination of the CSP be removed. Other exposed jewelry includes both facial and body jewelry.

**Commentary Summary #23:** Commenter requested additional language that specifies that jewelry that does not interfere with garbing should be permitted (e.g., rings on the nose, eyebrow, lip, and tongue).

**Response:** Comment not incorporated. The chapter states that all jewelry that could interfere with the effectiveness of garbing must be removed. If the jewelry does not interfere with the effectiveness of the garbing, it is not required to be removed. Further, exposed jewelry such as transdermal implants or body piercings that cannot be removed must be covered.

**Commentary Summary #24:** Commenter noted that the provisions on jewelry are difficult to enforce. Commenter recommended that all visible jewelry be removed. Another commenter noted that removal of jewelry should not be left to an individual’s discretion and that all jewelry must be removed.

**Response:** Comment not incorporated. The chapter states that all jewelry that could interfere with the effectiveness of garbing or otherwise increase the risk of contamination must be removed. If the jewelry does not interfere with the effectiveness of the garbing or otherwise increase the risk of contamination, it is not required to be removed.

**Commentary Summary #25:** Commenter requested guidance on how to cover 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).

**Commentary Summary #26:** Commenter noted that ear plugs should be permitted for noise reduction.

**Response:** Comment not incorporated. The chapter does not prohibit ear plugs but does require that earbuds and headphones be removed.

**Commentary Summary #27:** Multiple commenters noted that listening devices not recognized by the Americans with Disabilities Act (ADA) should be prohibited from the compounding area.

**Response:** Comment not incorporated. At a minimum, earbuds and headphones must be removed before entering the compounding area. The designated person(s) may prohibit additional items and require personnel to remove other items not essential to compounding.

**Commentary Summary #28:** Commenter noted concern that the language could be misinterpreted to exclude hearing aids from the compounding area.

**Response:** Comment not incorporated. The chapter does not prohibit hearing aids but does require that earbuds and headphones be removed. Further, the designated person(s) may permit accommodations as long as the quality of the CSP and environment will not be affected.

**Commentary Summary #29:** Multiple commenters noted that “cleanroom” phones, intercoms, and cell phones used for communication within the facility should be permitted as long as such devices will not generate or retain excessive particulates and are easily cleaned. Other commenters noted that electronic devices should be permitted if they are contained in a plastic bag and wiped with sterile IPA (e.g., cellphones). Commenters noted that cellphones are needed in case of family emergencies or illnesses of children at school. Additional commenters suggested that certain electronic devices that do not leave the compounding area (e.g., electronic tablets and speakers) should be permitted if they are cleaned and disinfected.

**Response:** Comment not incorporated. The chapter prohibits electronic devices that “are not necessary for compounding or other required tasks into the compounding area.” Electronic devices that are necessary for compounding or for other required tasks may be permitted. However, care must be taken to minimize risk of contamination of the environment and the CSPs. The designated person(s) may permit accommodations as long as the quality of the CSP and the environment will not be affected.

**Commentary Summary #30:** Commenter noted that the description of electronic devices as “not necessary for compounding or other required tasks” is vague, and individuals may argue that cellphones are necessary to complete required tasks. Another commenter noted that electronic devices should be permitted only if they are required for other required *compounding* tasks. Other commenters requested that the statement be deleted and that all electronic devices be prohibited.

**Response:** Comment not incorporated. Electronic devices that are necessary for compounding or for other required tasks should be permitted. Other required tasks may include activities not directly related to compounding (e.g., labeling). For any electronic

device, care must be taken to minimize risk of contamination of the environment and the CSPs. Further, the designated person(s) and the facility SOP should implement policies and guidelines on electronic devices that are permitted and not permitted. Further information on equipment is described in *9.1 Equipment*.

**Commentary Summary #31:** Commenter suggested that electronic devices necessary for compounding be expressly permitted in the compounding area. For example, hardware for verification scanning, inventory, and label printing is necessary and should be permitted in the compounding area. Another commenter noted that permitted electronic devices must be cleaned and disinfected.

**Response:** Comment not incorporated. The chapter does not prohibit devices that are necessary for compounding and other required tasks. Further information on equipment is provided in *9.1 Equipment*.

**Commentary Summary #32:** Several commenters suggested that the chapter clarify that natural nails may be kept at a maximum of ¼ inch to avoid glove puncture. Other commenters noted that the chapter should refer to CDC's guidelines on Hand Hygiene in Healthcare Settings.

**Response:** Comment not incorporated. Specifying the length of nails is too prescriptive. Other commenters previously noted that reference to other guidelines may be too broad and subject to revisions independent of the chapter. Facilities may choose to implement more prescriptive requirements such as maximum nail length and may adopt other guidance such as the CDC guidelines for Hand Hygiene in Healthcare Settings.

**Commentary Summary #33:** Commenter noted that the term "nail products" should be used to provide a broader term that accommodates the evolving nail industry.

**Response:** Comment incorporated.

**Commentary Summary #34:** Multiple commenters noted that nail polish should be permitted because nails with nail polish pose a lower risk of harboring bacteria and tearing gloves. Other commenters alternatively suggested differentiating between nail polish and gel polish. Another commenter noted that nail polish does not affect bacterial growth on fingernails and that fresh nail polish does not begin to shed particulates until it has been worn for several days. The commenter recommended that the nail polish can be worn for not longer than 3 days.

**Response:** Comment not incorporated. Nail products including nail polish must be removed to minimize the risk of contaminating the environment and the CSP because they may shed particles. Nail polish may chip and shed particles regardless of how long ago it was applied. The Expert Committee determined that "nail products" includes all types of nail polish and that no distinction is needed between nail polish and gel polish.

**Commentary Summary #35:** Commenters noted that the examples of nail polish, artificial nails, and extenders should be described with an "or" instead of an "and."

**Response:** Comment not incorporated. The listed nail products are intended to be examples.

**Commentary Summary #36:** Multiple commenters requested examples of additional restrictions on items that may be brought into the compounding area.

**Response:** Comment partially incorporated. The statement on restricting additional items based on the risk of contaminating the environment and the CSP was removed. The chapter is intended to be a minimum standard to ensure quality CSPs. Facilities

and the designated person(s) may implement additional restrictions in the compounding area based on the risk of contaminating the environment and the CSP.

**Commentary Summary #37:** Commenter noted that regulators have observed food and drinks in anterooms, as well as used patient medications being returned to the buffer area. The commenter requested additional language to state that “Food and drink items must not be brought into the cleanroom suite or SCA. Materials exposed in patient care and treatment areas must not be introduced into the cleanroom suite or SCA.”

**Response:** Comment not incorporated. Such practices must not be permitted in the compounding area. These practices may be better addressed as insanitary conditions. The Expert Committee determined that it would not be feasible to provide a comprehensive list of all the items that are not permitted in the compounding area.

**Commentary Summary #38:** Commenter noted that the order of garbing is incorrect. The commenter suggested that compounders must first complete hand washing and then put on gloves before they handle any gowning materials.

**Response:** Comment not incorporated. The order of garbing must be determined by the facility and documented in the facility’s SOP. The order of garbing would depend on the type of garbing used (e.g., sterile gowns) and the placement of the sink (i.e., whether the sink is located inside or outside of the ante-room).

**Commentary Summary #39:** Commenter suggested that hand washing should not be required before putting on nonsterile gloves to compound.

**Response:** Comment not incorporated. Personnel must wash hands and forearms before beginning compounding to minimize the risk of microbial contamination to the environment and the CSP. Further, sterile gloves must be donned.

**Commentary Summary #40:** Commenter recommended that the chapter specify that hand washing must be performed before entering the *sterile* compounding area. Another commenter recommended that “compounding area” be revised to buffer room or SCA.

**Response:** Comment partially incorporated. The text was revised to require hand washing to be performed before initiating compounding activities.

**Commentary Summary #41:** Commenter recommended that rings must be removed before hand washing to adequately clean the hand under the ring. Additionally, the commenter noted that rings must be sanitized with alcohol-based hand sanitizer before gloving.

**Response:** Comment not incorporated. The chapter requires all jewelry that could interfere with the effectiveness of garbing to be removed. Facility procedures may include specific procedures for removing and cleaning rings.

**Commentary Summary #42:** Commenter suggested adding a note to state that the steps listed in *Box 3-1* for hand hygiene procedures are not intended to provide a specific order of activities.

**Response:** Comment partially incorporated. Hand hygiene includes both hand washing and hand sanitizing. Hand washing and hand sanitizing procedures were separated and described in two separate boxes. Further, the text clarifies that the order of hand washing and garbing depends on the placement of the sink and should be determined by the facility and documented in facility SOPs.

**Commentary Summary #43:** Commenter noted that brushes should only be used for fingernails. Other commenters noted that compounders should be permitted to use the

soft side of the brush without causing skin irritation or increased bacterial shedding. Another commenter requested clarification on what constitutes a brush and whether that includes a sterile surgical scrub.

**Response:** Comment not incorporated. Brushes must not be used for hand hygiene because they may cause inadvertent irritation or additional shedding. The chapter does not prohibit the use of sterile disposable surgical scrubs.

**Commentary Summary #44:** Commenter noted that “driers” should be corrected to “dryers.”

**Response:** Comment incorporated.

**Commentary Summary #45:** Commenter requested a specific statement that electronic hand dryers are not permitted.

**Response:** Comment partially incorporated. The chapter states that hand dryers, which include electronic hand dryers, must not be used in the compounding area.

**Commentary Summary #46:** Commenter noted that germs can be transferred more easily to and from wet hands; therefore, hands should be dried after washing. Jet air dryers with high-efficiency particulate air (HEPA) filters or low-lint towels are the most hygienic methods to dry hands. Another commenter noted that dryers designed for controlled areas with HEPA filtration do not alter the environmental characteristics of the room (i.e., turbulence, pressure gradient, particle count).

**Response:** Comment not incorporated. Hand dryers, including jet 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 with HEPA filtration are not as effective in drying hands. The chapter specifies that hands and forearms must be dried with low-lint disposable towels or wipers.

**Commentary Summary #47:** Multiple commenters suggested that the chapter should specify that the list of garbing to be donned after hand hygiene is not intended to provide an order of garbing.

**Response:** Comment partially incorporated. The chapter was revised to emphasize that the order of hand washing and garbing depends on the sink placement, and the order of garbing must be determined by the facility and documented in the facility’s SOP.

**Commentary Summary #48:** Several commenters suggested that the chapter should emphasize that hands and forearm need to be washed and dried before performing hand antisepsis.

**Response:** Comment partially incorporated. The noted text was eliminated, but hands and forearms are specified in both *3.2 Hand Hygiene* and *Box 3-1*.

**Commentary Summary #49:** Commenter noted that there is no remaining garb to be donned after washing hands and forearms.

**Response:** Comment partially incorporated. The noted text was eliminated but the section was reorganized and clarified. The chapter was revised to emphasize that the order of hand washing and garbing depends on the sink placement and the order of garbing must be determined by the facility and documented in the facility’s SOP.

**Commentary Summary #50:** Commenter noted that sterile gloves are not always required to be worn in the cleanroom. For example, if personnel are entering the cleanroom for purposes other than compounding (e.g. moving materials, cleaning), sterile gloves should not be required.

**Response:** Comment not incorporated. Sterile gloves must be donned prior to entering the compounding area to minimize the risk of contamination to the environment and to the CSP. Sterile gloves help to minimize the bioburden in the compounding area. Further, some reports have shown that nonsterile gloves may contain microbial and spore contamination.

**Commentary Summary #51:** Commenter noted that nonsterile gloves should be permitted for sterile compounding provided that an alcohol-based hand rub or sterile 70% IPA is applied to the gloves before compounding.

**Response:** Comment not incorporated. Sterile gloves must be donned prior to entering the compounding area to minimize the risk of contamination to the environment and to the CSP. Sterile gloves help to minimize the bioburden in the compounding area. Further, some reports have shown that nonsterile gloves may contain microbial and spore contamination.

**Commentary Summary #52:** Commenter noted that the statement requiring hand antisepsis immediately before donning sterile gloves is in conflict with their current practice. The commenter indicated that they perform hand antisepsis before donning the first pair of sterile gloves, and then don sterile gloves and an additional pair of sterile gloves. Commenter noted that double gloving is strongly encouraged.

**Response:** Comment partially incorporated. The noted text was eliminated, but the section was reorganized and clarified. The chapter was revised to emphasize that the order of hand washing and garbing depends on the sink placement. The order of garbing must be determined by the facility and documented in the facility's SOP. The chapter is intended to provide a minimum standard. Facilities may implement additional requirements such as double sterile gloves and sterile gowns.

**Commentary Summary #53:** Commenter noted that if sterile gloves are donned prior to entering the buffer room or SCA, it might be helpful to add a reminder that sterile gloves must be sterilized with sterile 70% IPA before compounding.

**Response:** Comment partially incorporated. Text was added to *3.3 Garbing Requirements* to specify that sterile 70% IPA must be applied to gloves regularly throughout the compounding process and whenever nonsterile surfaces are touched.

**Commentary Summary #54:** Commenters recommended removing the requirement for using an alcohol-based hand rub because it is not supported by existing data.

**Response:** Comment not incorporated. Each hand must be sanitized with an alcohol-based hand-rub before donning sterile gloves to further minimize the microbial bioburden in the compounding area. The intent of the hand sanitizing procedures is to minimize the risk of contamination to the environment and the CSP.

**Commentary Summary #55:** Commenter requested that the term persistent antimicrobial activity be defined.

**Response:** Comment partially incorporated. The term persistent antimicrobial activity was deleted.

**Commentary Summary #56:** Commenter suggested that the term "persistent antimicrobial activity" be deleted.

**Response:** Comment incorporated.

**Commentary Summary #57:** Commenter requested clarification on whether sterile gloves must be donned in the anteroom or in 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 ante-room) or the design of the SCA.

**Commentary Summary #58:** Commenter noted that prohibition against "topping off" soap dispensers is unclear.

**Response:** Comment incorporated. The chapter was revised to state that a closed system of soap (i.e., a non-refillable container) must be used to minimize the risk of extrinsic contamination.

**Commentary Summary #59:** Commenter noted that the hand washing procedures should specify that debris must be removed after hands have been lathered with soap and water.

**Response:** Comment not incorporated. The Expert Committee decided that debris can be removed from under the nails under warm running water before washing hands with soap and water.

**Commentary Summary #60:** Commenter requested that *Box 3-1* on hand washing procedures be revised to specify the garbing order.

**Response:** Comment not incorporated. The procedural information in *Box 3-1* is intended to be limited to hand washing procedures. The order of garbing must be determined by the facility and documented in the facility's SOP. The order of garbing would depend on the type of garbing used (e.g., sterile gowns) and the placement of the sink (see *4.4 Water Sources*).

**Commentary Summary #61:** Multiple commenters noted that the hand washing procedures should specify that hands and forearms must be actively lathered for 30 seconds and not just washed.

**Response:** Comment not incorporated. Washing hands and forearms includes lathering with soap and water. Further, the Expert Committee decided that the existing text is aligned with other guidelines (e.g., CDC guidelines for Hand Hygiene in Healthcare Settings).

**Commentary Summary #62:** Commenter noted that use of a nail cleaner multiple times a day can have the potential of causing skin irritation and increased bacterial shedding.

**Response:** Comment incorporated. *Box 3-1* was revised to require cleaning under the fingernails only when there is visible debris.

**Commentary Summary #63:** Commenter requested an example of techniques to remove debris from under the fingertip (e.g., a nail pick or nail brush).

**Response:** Comment not incorporated. Facilities may determine the most appropriate method and tool to remove visible debris under the fingernail.

**Commentary Summary #64:** Commenter suggested that waterless alcohol-based hand rub with persistent antimicrobial activity be required. The commenter noted that waterless alcohol-based hand rubs should be required to decrease the formation of spores.

**Response:** Comment not incorporated. The Expert Committee decided that the term "waterless" could generate confusion among users about the amount of water that may

be permitted in the alcohol-based hand rub. The Expert Committee decided that an alcohol-based hand rub is sufficient for sanitizing hands and the terminology is consistent with the CDC guidelines for Hand Hygiene in Healthcare Settings.

**Commentary Summary #65:** Several commenters requested a standard on the order of garbing. Some commenters noted that the best order of garbing should be head covers, face covers, shoe covers and then to step over the line from dirty to clean.

**Response:** Comment not incorporated. Garbing should be donned in an order that proceeds from those activities considered the dirtiest to those considered the cleanest. The order of garbing must be determined by the facility and documented in the facility's SOP. The order of garbing would depend on the type of garbing used (e.g., sterile gowns) and the placement of the sink (see *4.4 Water Sources*).

**Commentary Summary #66:** Several commenters recommended that garbing should be performed following the principle of dirty-to-clean.

**Response:** Comment partially incorporated. Garb must be donned and doffed in an order that reduces the risk of contamination.

**Commentary Summary #67:** Commenter noted that there must be a suitable garment which is donned in a pre-gowning room that includes a microfiber scrub suit, dedicated cleanroom shoes, a head cover, surgical mask, and gloves. The commenter noted that no street clothes or shoes should ever be worn into the aseptic area. Further, the commenter noted that sterile gowns must be worn only once and then either recycled or discarded. The only environment where full aseptic gowning would not be required is an isolator.

**Response:** Comment not incorporated. The garbing requirements listed in the chapter are intended to provide a practical approach for compounding, which is different from current Good Manufacturing Practices (cGMP) requirements. Further, the chapter describes which garb may be re-used and which must be discarded upon exiting the compounding area.

**Commentary Summary #68:** Commenter requested clarification on the specific minimum PPE and asked that alternatives, such as powered air purifying respirators (PAPR), be allowed. The commenter recommended that an N-95 surgical mask should be used instead of a face mask and noted that a PAPR eliminates the need for head and facial covers.

**Response:** Comment not incorporated. The chapter provides the minimum garbing requirements for non-hazardous CSPs. PPE requirements for handling of HDs are further described in <800>. The chapter is intended to provide the minimum standard. Facilities may have more garbing requirements than those specified in the chapter.

**Commentary Summary #69:** Multiple commenters noted that the minimum garbing requirements for RABS (e.g., CAIs and CACIs) should be determined by the manufacturer. Commenters noted that manufacturers of RABS have demonstrated in studies that full garbing is not required to maintain ISO Class 5 air quality. Other commenters noted that full garb should not be required when using a RABS in an SCA.

**Response:** Comment not incorporated. The Expert Committee determined that the minimum garbing requirements should be consistent, regardless of the type of PEC used. Garbing is intended to minimize the risk of contamination of the environment, the CSP, and personnel.

**Commentary Summary #70:** Multiple commenters noted that shoe covers, hair covers, and face masks should be optional for individuals using a RABS in an SCA.

**Response:** Comment not incorporated. The Expert Committee determined that the minimum garbing requirements should be consistent regardless of the type of PEC used. Garbing is intended to minimize the risk of contamination of the environment, the CSP, and personnel.

**Commentary Summary #71:** Commenter suggested that the minimum garbing listed in the chapter should not be required if using a pharmaceutical isolator when the manufacturer can show documentation that the pharmaceutical isolator can maintain ISO Class 5 conditions under dynamic conditions and successful, viable air sampling can be performed.

**Response:** Comment not incorporated. The Expert Committee determined that the minimum garbing requirements should be consistent regardless of the type of PEC used. Garbing is intended to minimize the risk of contamination of the environment, the CSP, and personnel.

**Commentary Summary #72:** Commenter noted that garbing and gloves should not be required inside of an SCA if the individual is not compounding. The commenter noted that they have a relatively large SCA, and pharmacists verifying CSPs should not be required to don garbing.

**Response:** Comment not incorporated. A visual perimeter must be used to establish an SCA. Any person entering the compounding area (e.g., SCA) must be properly garbed to minimize the risk of contamination of the environment, the CSP, and personnel.

**Commentary Summary #73:** Multiple commenters requested clarification that any person entering the compounding area, including the perimeter of the SCA, must be properly garbed.

**Response:** Comment partially incorporated. The statement was revised to note that any person entering the compounding area must be properly garbed. The compounding area is defined in the *Glossary* as the area where compounding is occurring (i.e., a cleanroom suite, inside the perimeter of the SCA, or the AECA).

**Commentary Summary #74:** Commenter requested details on how to don and doff shoe covers in the cleanroom suite or SCA.

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

**Commentary Summary #75:** Commenter noted that 3.3 *Garbing Requirements* should specify that any person entering the clean side of the ante-room, the buffer room, or inside the perimeter of the SCA must be properly garbed.

**Response:** Comment not incorporated. The statement was revised to indicate that any person entering the compounding area must be properly garbed. The compounding area is defined in the *Glossary* as the area where compounding is occurring (i.e., a cleanroom suite, inside the perimeter of the SCA, or the AECA).

**Commentary Summary #76:** Several commenters requested deletion of the sentence that states "donning and doffing garb must not occur in the ante-room or the SCA at the same time." Commenters noted that this language would be constraining and would

make movement in and out of the compounding areas more cumbersome, to the detriment of timely patient care. Other commenters noted that donning and doffing of garb should be allowed by different individuals at the same time provided that they do not come into contact with each other. Additional commenters noted that dynamic testing must be performed to verify that donning and doffing at the same time does not impact the air quality. A commenter noted that donning and doffing must not occur at the same time to reduce the risk of contaminating compounders donning garb.

**Response:** Comment partially incorporated. The Expert Committee revised the statement to be a “should” recommendation instead of a “must” requirement.

**Commentary Summary #77:** Commenter recommended additional language to require garments and accessories to be inspected visually prior to donning. Garment with visual defects (i.e., holes or gaps in seams) should not be used.

**Response:** Comment not incorporated. Personnel should inspect garbing during the donning process. A prescriptive requirement to visually inspect may be misinterpreted to require manual inspection during receipt of garbing, which may expose garbing to contamination. The chapter is not intended to prescribe all step-by-step processes for the facility.

**Commentary Summary #78:** Commenter requested the addition of a note to indicate that skin should not be exposed inside the ISO Class 5 PEC (e.g., gloves should not be donned inside the ISO Class 5 PEC on bare hands).

**Response:** Comment incorporated.

**Commentary Summary #79:** Commenter recommended adding a statement that doffing is not encouraged in the cleanroom.

**Response:** Comment partially incorporated. The chapter was revised to state that garb must be donned and doffed in an order that reduces the risk of contamination.

**Commentary Summary #80:** Commenter noted that the minimum garbing requirements should apply to any persons entering the compounding area and should not be limited to only persons preparing CSPs.

**Response:** Comment incorporated.

**Commentary Summary #81:** Commenter recommended a separate section for minimum garbing requirements for SCAs that are located in an operating room area.

**Response:** Comment not incorporated. The Expert Committee determined that the minimum garbing requirements should be consistent regardless of where the SCA is located. Garbing is intended to minimize the risk of contamination to the environment and to the PEC.

**Commentary Summary #82:** Commenter suggested that non-cotton, low-lint reusable garments should be permitted. Commenter noted concerns that the chapter could be misinterpreted to mean that only disposable garments are permitted.

**Response:** Comment partially incorporated. Low-lint garment is required. However, a statement was added to allow for gowns to be re-used within the same shift if the gown is maintained in a classified area or inside the perimeter of an SCA.

**Commentary Summary #83:** Several commenters noted that sterile garments should be required. Another commenter noted that sterile garments and sterile sleeves should be required because this is an additional microbial contamination risk-reduction measure.

**Response:** Comment not incorporated. The chapter is intended to provide the minimum standard to ensure quality CSPs. Facilities may choose to implement additional requirements such as sterile gowns.

**Commentary Summary #84:** Commenter noted that the list of minimum garbing should be reorganized to reflect the order of garbing.

**Response:** Comment not incorporated. Garbing should be donned in an order that proceeds from those activities considered the dirtiest to those considered the cleanest. The order of garbing must be determined by the facility and documented in the facility's SOP. The order of garbing would depend on the type of garbing used (e.g., sterile gowns) and the placement of the sink (see *4.4 Water Sources*).

**Commentary Summary #85:** Several commenters noted that use of cleanroom shoes should be encouraged to minimize the risk of particulate and microbial contamination.

**Response:** Comment not incorporated. The chapter is intended to provide the minimum standard to ensure quality CSPs. Low-lint disposable shoe covers are required to be placed over shoes. However, facilities may additionally require individuals to have dedicated shoes for the compounding area.

**Commentary Summary #86:** Commenters noted that compounders should be permitted to use disposable covers for shoes or dedicated cleanroom shoes.

**Response:** Comment not incorporated. The chapter is intended to provide the minimum standard to ensure quality CSPs. Low-lint disposable shoe covers are required to be placed over shoes. However, facilities may additionally require individuals to have dedicated shoes for the compounding area.

**Commentary Summary #87:** Multiple commenters noted that the minimum garbing requirements should all be sterile.

**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.

**Commentary Summary #88:** Commenter noted that the term "gown" is overly broad and leads to the use of many inappropriate garments. The commenter noted that "frock" is the correct terminology to be used. Commenter referenced the definition of frock provided by the Institute of Environmental Sciences and Technology (IEST).

**Response:** Comment not incorporated. The term frock may be misinterpreted by users. However, gowns and coveralls are provided as examples of garments that may be used.

**Commentary Summary #89:** Multiple commenters noted that the term "non-cotton, low-lint garment" causes confusion among compounders. Commenters suggested using the term "reusable or disposable garbs and gowns."

**Response:** Comment partially incorporated. The chapter was revised to state that at a minimum, low-lint garment must be worn. The section was further clarified to state that gowns may be re-used within the same shift if the gown is maintained in a classified area or inside the perimeter of the SCA.

**Commentary Summary #90:** Commenter noted that gowns may have cuffs and ties that are cotton. Other commenters suggested that gowns may be cotton.

**Response:** Comment incorporated.

**Commentary Summary #91:** Commenter noted that gloves should not be required to be worn over gloves on the pharmaceutical isolator because it is unnecessary and in some cases impractical.

**Response:** Comment not incorporated. The minimum garbing requirements in the chapter includes sterile powder-free gloves. This may require sterile gloves to be donned over the gloves attached to the pharmaceutical isolator. Sterile gloves help assure that the ISO Class 5 air quality is maintained, especially in the event of any unintentional or inadvertent breach.[NOTE – Response updated to correct an error on 2019-06-28]

**Commentary Summary #92:** Commenter noted that a statement should be added to require reusable garbing to be properly cleaned and sanitized.

**Response:** Comment not incorporated. The chapter states that garb, except for gowns, cannot be reused and must be discarded.

**Commentary Summary #93:** Multiple commenters noted that covers for the head may be reusable or disposable. The commenter added that reusable or disposable covers should be permitted.

**Response:** Comment not incorporated. Garb must not be reused and must be discarded to minimize the risk of particulate and microbial contamination.

**Commentary Summary #94:** Commenter noted that covers for the head should not be required to cover the forehead because goggles cover the eyebrows and eyes.

**Response:** Comment incorporated. Removed the requirement for head covers to cover the forehead.

**Commentary Summary #95:** Commenter noted that covers for the head should cover the hair and ears.

**Response:** Comment incorporated.

**Commentary Summary #96:** Commenter noted that face masks may be composed of reusable fabric or can have a disposable, single-use design.

**Response:** Comment not incorporated. Garb must not be reused and must be discarded to minimize the risk of particulate and microbial contamination.

**Commentary Summary #97:** Commenter noted that a low-lint, disposable face mask should be required.

**Response:** Comment not incorporated. Most face masks may not be labeled as low lint.

**Commentary Summary #98:** Several commenters requested clarification on what type of face mask is permitted (e.g., surgical, reusable, N-95).

**Response:** Comment not incorporated. Facilities must determine the type of face mask to use. General Chapter <800> provides additional information about respiratory protection for handling HDs.

**Commentary Summary #99:** Several commenters noted that powder-free sterile gloves should be required.

**Response:** Comment incorporated.

**Commentary Summary #100:** Commenter noted that gloves must be changed every 60 to 90 minutes as they develop leaks and small tears which may not be visible to the unaided eye.

**Response:** Comment not incorporated. The chapter requires gloves to be inspected for holes, punctures, and tears, and they must be replaced immediately if such defects are detected. Facilities may require gloves to be changed frequently based on several

factors including their work practices, types of CSPs prepared, types of manipulations, and the personnel.

**Commentary Summary #101:** Commenter noted that sterile gloves should not be required to be worn over gloves attached to RABS sleeves.

**Response:** Comment not incorporated. Sterile gloves must be worn over gloves attached to RABS sleeves. Sterile gloves help assure that the ISO Class 5 air quality is maintained, especially in the event of any unintentional or inadvertent breach.

**Commentary Summary #102:** Multiple commenters noted that disposable gloves should not be required to be worn inside of gloves attached to the RABS sleeves. Commenter noted that work practices should prohibit multiple compounders from using the same RABS in one day. Alternatively, the commenters recommend that gloves inside of gloves attached to the RABS sleeves should be recommended but not required.

**Response:** Comment incorporated. Gloves inside of gloves attached to the RABS sleeves are recommended but not required.

**Commentary Summary #103:** Several commenters noted that the requirement for triple gloves will significantly reduce dexterity, possibly leading to increased contamination or injury to the compounder due to inadvertent needle sticks.

**Response:** Comment partially incorporated. Gloves inside of gloves attached to the RABS sleeve are recommended but not required. However, sterile gloves must be worn over the gloves attached to the RABS sleeve to help ensure that the ISO Class 5 environment is maintained, especially in the event of any unintentional or inadvertent breach.

**Commentary Summary #104:** Commenter requested clarification on how many times disposable gloves may be used.

**Response:** Comment not incorporated. Disposable gloves must not be reused, as this can increase the risk of microbial contamination, and the reused gloves may develop holes, punctures, or tears.

**Commentary Summary #105:** Commenter noted that sterile gloves must be worn inside of gloves attached to the RABS sleeve.

**Response:** Comment not incorporated. Gloves (sterile or nonsterile) are recommended to be worn inside of the gloves attached to the RABS sleeve. However, sterile gloves must be worn over the gloves attached to the RABS sleeve to help ensure that the ISO Class 5 environment is maintained, especially in the event of any unintentional or inadvertent breach. Gloves inside of the gloves attached to the RABS sleeve are not required to be sterile because they are not in direct contact with the CSP. Facilities may choose to adopt more stringent requirements and require sterile sleeves to be worn under the gloves attached to gauntlet gloves.

**Commentary Summary #106:** Commenter noted that gloves worn inside of the gloves attached to the RABS sleeve should be low lint.

**Response:** Comment not incorporated. Facilities may choose the type of gloves to be worn inside of the gloves attached to the RABS sleeve (e.g., cotton, nonsterile, or sterile). Gloves may not often be labeled as low lint.

**Commentary Summary #107:** Commenter noted that the RABS sleeve should be disposable.

**Response:** Comment not incorporated. RABS sleeves are designed to be used multiple times. A statement was added to the chapter to state that RABS sleeves and gloves should be changed per the manufacturer's recommendations and as defined in the facility's SOP.

**Commentary Summary #108:** Commenter recommended listing the examples of disposable gloves as cotton, nonsterile, or sterile. The commenter noted that the previous text may be misinterpreted so that only cotton gloves are incorporated.

**Response:** Comment incorporated.

**Commentary Summary #109:** Commenter noted a grammatical error in the statement that sterile gloves must *be* worn over gloves attached to the RABS sleeve.

**Response:** Comment incorporated.

**Commentary Summary #110:** Several commenters recommended allowing gowns to be re-used during an entire shift if they remain in a classified area or inside the perimeter of an SCA.

**Response:** Comment incorporated.

**Commentary Summary #111:** Commenter noted that goggles may be re-used.

**Response:** Comment not incorporated. Eye protection is not listed as part of the minimum garbing requirements. However, if used, the facility should address how to clean and disinfect eye protection if they are re-used.

**Commentary Summary #112:** Commenter requested clarification on how far away gowns and other garb should be stored away from sinks to avoid splashing (e.g., 1 meter or 2 meters).

**Response:** Comment not incorporated. The chapter requires gowns and other garb to be stored in a manner that minimizes contamination. Storage away from the sink to avoid splashing is intended to be an example. Facilities must determine an appropriate place for storage (e.g., in a bin or in a specific location) to minimize the risk of contamination.

**Commentary Summary #113:** Commenter noted that gowns and other garb that are not individually wrapped should be covered to avoid exposure to room contaminants.

**Response:** Comment not incorporated. The chapter requires gowns and other garb to be stored in a manner that minimizes contamination. Facilities must determine an appropriate place for storage within their own facility designs to minimize the risk of contamination.

**Commentary Summary #114:** Commenter recommended addition of a statement saying that disposable garb must be discarded and reusable garb must be sent to be laundered.

**Response:** Comment not incorporated. Garb, other than gowns, must not be reused and must be discarded to minimize the risk of particulate and microbial contamination. Gowns may be re-used within the same shift if the gown is maintained in a classified area or inside the perimeter of an SCA.

**Commentary Summary #115:** Commenter requested allowing non-disposable gowns to be re-processed.

**Response:** Comment not incorporated. Gowns must be disposable to minimize the risk of particulate and microbial contamination. Gowns may be re-used within the same shift if the gown is maintained in a classified area or inside the perimeter of an SCA.

**Commentary Summary #116:** Multiple commenters requested specificity on what it means to exit the compounding area. The commenter suggested that the chapter should delineate the act of exiting the compounding area or exiting the compounding area before doffing.

**Response:** Comment not incorporated. Facilities must determine the order of garbing and the location of donning and doffing activities. The intent of the statement is to require garb, except for gowns, to be discarded after use and to not be re-used. Gowns may be re-used within the same shift if it is maintained in a classified area or inside the perimeter of the SCA.

**Commentary Summary #117:** Commenter requested a revision to the chapter to require that when personnel exit the clean side of the anteroom or the SCA, all garb must be doffed and discarded and cannot be reused.

**Response:** Comment not incorporated. Facilities must determine the order of garbing and the location of donning and doffing activities. The intent of the statement is to require garb, except for gowns, to be discarded after use and to not be re-used. Gowns may be re-used within the same shift if it is maintained in a classified area or inside the perimeter of the SCA.

**Commentary Summary #118:** Commenter requested deletion of the reference to <800> for PPE. PPE is described in <800>.

**Response:** Comment not incorporated. The reference to <800> is intended to clarify that *garbing* is required for non-hazardous compounding and *PPE* is required for handling of HDs as described in <797>.

**Commentary Summary #119:** Multiple commenters noted that if gloved hands leave the ISO Class 5 PEC, they must be sprayed with sterile 70% IPA again.

**Response:** Comment not incorporated. The chapter specifies that sterile 70% IPA must be applied to gloves regularly during compounding and whenever nonsterile surfaces are touched. The Expert Committee determined that it may not be feasible to describe step-by-step processes for each facility.

**Commentary Summary #120:** Multiple commenters noted that applying sterile 70% IPA to gloves throughout the compounding process may imply a continuous process. Commenter recommended stating that sterile 70% IPA must be applied *regularly*.

**Response:** Comment incorporated.

**Commentary Summary #121:** Commenter noted that applying sterile 70% IPA to gloves whenever nonsterile surfaces (e.g., vials) are touched would require constant application of sterile 70% IPA. Another commenter requested that vials be removed as an example of a nonsterile surface.

**Response:** Comment not incorporated. Items brought into the PEC must be wiped with sterile 70% IPA (see 8.2 *Introducing Items into the PEC*). Additionally, sterile 70% IPA must be applied to gloves whenever nonsterile surfaces are touched. After all items have been wiped prior to introduction into the PEC, gloves are not required to be continuously wiped after touching each vial. However, the chapter does state that the sterile 70% IPA should be applied regularly.

**Commentary Summary #122:** Commenter requested a frequency for how often compounders must apply sterile 70% IPA to their gloves (e.g., after a specific number of minutes or a specific number of times per shift).

**Response:** Comment not incorporated. The frequency should be specific to the facility and personnel. The intent is to minimize the risk of contamination to the PEC and to the CSP.

**Commentary Summary #123:** Commenter requested clarification on whether the requirements in the subsection *Gloves* apply to RABS and pharmaceutical isolators.

**Response:** Comment not incorporated. The minimum garbing requirements apply regardless of the type of PEC used.

**Commentary Summary #124:** Commenter noted that sterile 70% IPA should be applied immediately before gloved hands enter the PEC.

**Response:** Comment not incorporated. Garbing procedures must be performed as appropriate, and sterile gloves must be donned. Before entering the PEC and performing any manipulations, gloves should be sterile without applying sterile 70% IPA. The Expert Committee noted that it may not be feasible to describe step-by-step processes for each facility. The chapter is intended to provide a minimum standard to ensure a quality CSP. Facilities may require additional steps, including more specific and frequent application of sterile 70% IPA.

**Commentary Summary #125:** Multiple commenters noted that sterile 70% IPA must be applied to gloves immediately prior to entering a critical site.

**Response:** Comment not incorporated. The additional wording may be confusing to users and may be misconstrued to require pauses during compounding procedures in order to wipe gloves with sterile 70% IPA. Further, the section is intended to be specific for garbing requirements.

**Commentary Summary #126:** Commenter noted that rubbing sterile 70% IPA on gloves is a sanitization process and not a disinfection process. The commenter noted that there is no Environmental Protection Agency (EPA)-registered disinfectant approved for use on gloves.

**Response:** Comment incorporated.

**Commentary Summary #127:** Commenter recommended that alcohol-based hand rubs should be prohibited from being applied to gloves because they may negatively impact the integrity of the glove.

**Response:** Comment not incorporated. The chapter states that sterile 70% IPA must be applied to gloves regularly during compounding and whenever nonsterile surfaces are touched. The Expert Committee determined that it would not be feasible to list the prohibited agents or incompatible agents in the chapter.

**Commentary Summary #128:** Commenter noted that the statement that contaminated, gloved hands can be disinfected by rubbing with sterile 70% IPA is not definitive about the need to ensure that the entire glove is sterile. Commenter noted that compounders could alternatively change to new gloves if they become contaminated.

**Response:** Comment partially incorporated. Sentence was duplicative of a statement earlier in the section which states that sterile 70% IPA must be applied to gloves regularly throughout compounding and whenever nonsterile surfaces are touched. Sentence was eliminated. The Expert Committee determined that allowing for replacement of gloves could potentially lead to personnel removing gloves in the PEC, exposing skin to the ISO Class 5 air.

**Commentary Summary #129:** Multiple commenters noted that sterile 70% IPA must be applied to gloves *before proceeding*.

**Response:** Comment not incorporated. The additional language may cause confusion as to what may be proceeding after sterile 70% IPA is applied. The additional language does not add clarity to the chapter and may be subject to misinterpretation.

**Commentary Summary #130:** Commenter recommended including language in the chapter that prohibits compounders from shaking their gloved hands dry in the PEC after applying sterile 70% IPA.

**Response:** Comment not incorporated. The Expect Committee determined that it would not be feasible to provide a comprehensive list of all prohibited actions (e.g., shaking of hands) in the PEC. The facility should train personnel on which practices are unacceptable and should observe personnel for such practices.

**Commentary Summary #131:** Commenter noted that the requirement to *routinely* inspect gloves is ambiguous, and the frequency should be determined by facility SOPs.

**Response:** Comment incorporated. Eliminated “routinely.”

**Commentary Summary #132:** Multiple commenters noted that consistent terminology should be used to refer to gloves attached to RABS sleeves and gauntlet gloves on pharmaceutical isolators.

**Response:** Comment incorporated.

**Commentary Summary #133:** Commenter noted that the RABS sleeve and gauntlet gloves on the pharmaceutical isolators should be changed per the manufacturer’s recommendation and as defined by the facility’s SOPs.

**Response:** Comment incorporated.

**Commentary Summary #134:** Commenter recommended that if defects are found on gloves, an investigation should be conducted and documented.

**Response:** Comment not incorporated. It may not be practical for facilities to investigate defects on gloves. For example, tears on gloves may occur during typical compounding procedures. Requiring the compounder to stop compounding, perform an investigation, and document the investigation may be impractical for typical compounding operations.

**Commentary Summary #135:** Multiple commenters noted that if sleeves on RABS and gauntlet gloves on pharmaceutical isolators are found to have holes, punctures, or tears, surface sampling must be performed on sleeves and CSPs must be sterility tested. The commenters noted that holes and punctures in sleeves on RABS and gauntlet gloves on pharmaceutical isolators are critical failures that can put the function of the unit at risk.

**Response:** Comment not incorporated. The sleeves on RABS and gauntlet gloves on pharmaceutical isolators must be inspected as described in the chapter. Requiring sterility testing and surface sampling may be onerous and impractical for many facilities. For example, if surface sampling is performed, the results may not be known for another 14 days. Facilities should implement appropriate investigative and corrective action in the event of such breaches.

**Commentary Summary #136:** Commenter requested specificity on how often to replace gloves placed over and under gloves attached to RABS sleeves or gauntlet gloves on a pharmaceutical isolator.

**Response:** Comment not incorporated. New sterile gloves should be worn whenever personnel perform hand hygiene and garbing procedures. Facilities may require more frequent replacement of gloves.

#### 4. Facilities and Engineering Controls

**Commentary Summary #1:** Commenter noted that the expected levels of environmental control throughout the chapter are inadequate to assure the sterility of the CSPs. The commenter noted that the levels of background control, personnel gowning, environmental assessment, and other areas have weaknesses in both the performance criteria and the frequency of assessment.

**Response:** Comment not incorporated. The chapter is intended to provide standards for quality CSPs. CSPs are prepared for patient-specific needs and thus are prepared on a much smaller scale compared with large-scale production by manufacturers, who are subject to cGMPs.

**Commentary Summary #2:** Commenter recommended adding figures illustrating conceptual representations of the direct compounding area (DCA) and the ISO classifications.

**Response:** Comment not incorporated. The conceptual representations and example designs are frequently misinterpreted by users, and cannot describe all the facility design and engineering control requirements. However, a summary of the minimum requirements for placement of the PEC is provided in the chapter.

**Commentary Summary #3:** Commenter noted that the PEC and SEC must be maintained 24 hours a day, 7 days a week, and 365 days a year.

**Response:** Comment not incorporated. Facilities must determine appropriate operating conditions for their PEC and SEC. Requiring continuous operation of the PEC and SEC may not be feasible for facilities that do not have uninterrupted power sources.

**Commentary Summary #4:** Commenter recommended specifying that the ante-room and buffer room must be appropriately controlled to achieve and maintain the required air quality. The commenter noted that the SCA should be excluded because it is unclassified.

**Response:** Comment incorporated.

**Commentary Summary #5:** Commenter requested that “separated” be defined when stating that the ante-room, buffer room, and SCA must be separated from areas not related to compounding.

**Response:** Comment not incorporated. Buffer rooms and ante-rooms are separated by fixed walls and doors (see *4.2 Facility Design and Environmental Controls*). SCAs are separated from areas not related to compounding by a visible perimeter (see *4.2 Facility Design and Environmental Controls*).

**Commentary Summary #6:** Commenter noted that the statement that facilities should take into account certain factors in facilitating the maintenance of air quality should be a “must” requirement and not a “should” recommendation.

**Response:** Comment not incorporated. The statement is intended to provide examples of factors that facilities should consider in order to maintain the required air quality in the SEC and PEC. A must requirement may imply that such considerations are the only factors and these must be documented.

**Commentary Summary #7:** Commenter suggested that equal distribution of HEPA filters throughout the room is a critical consideration for maintaining control of environmental conditions in the facility.

**Response:** Comment not incorporated. The statement is intended to provide examples of critical considerations for maintaining control of the air quality in the facility. Requiring equal distribution of HEPA filters may raise questions about the definition of equal distribution and may be a requirement that is too prescriptive.

**Commentary Summary #8:** Commenter noted that the table of ISO Classification of Particulate Matter in Room Air should be deleted, and instead the chapter should refer to ISO 14644. Additional commenters noted that ISO Class 3 and ISO Class 4 environments would never be used in aseptic processing, and ISO Class 8 would not be used in most cases.

**Response:** Comment not incorporated. The table containing the ISO classifications is provided for the convenience of users. The table was adopted from ISO 14644-1. Facilities must have an ISO Class 5 or better PEC. Addition of ISO Class 3 and 4 provides a complete picture for users.

**Commentary Summary #9:** Commenter suggested that the data in the table of ISO Classification of Particulate Matter in Room Air should be expressed as cubic feet, not cubic meters. The commenter noted that the change would align the revision with the US metric system.

**Response:** Comment not incorporated. The particle count is expressed in particle count per cubic meter. This is the industry standard and was adopted from ISO 14644.

**Commentary Summary #10:** Commenter suggested that HEPA-filtered pass-throughs should be added to the design requirements to maintain air quality.

**Response:** Comment not incorporated. Many facilities may not have pass-throughs, and in those facilities that do have pass-throughs, the pass-throughs are not HEPA-filtered. The chapter does require that if a pass-through is used, both doors must never be opened at the same time, and doors should be interlocking.

**Commentary Summary #11:** Multiple commenters noted that the ante-room should be at least ISO Class 7 or better in order to align with <800>.

**Response:** Comment not incorporated. Positive-pressure cleanrooms for non-HD compounding must have an ISO Class 8 or better ante-room. Cleanrooms for HD compounding must have an ISO Class 7 or better ante-room, because it is negative pressure.

**Commentary Summary #12:** Commenter noted that the negative-pressure requirement of 0.01 to 0.03 inches of water column should be a recommendation and not a requirement. The commenter noted that the pressure range in <800> creates a design challenge where negative-pressure rooms serve as a common corridor and may drift to 0.04 inches of water column.

**Response:** Comment not incorporated. Standards for hazardous compounding are specified in <800>. Addition of language specific for HD compounding in <797> may lead to conflicts between the chapters. Further, 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.

**Commentary Summary #13:** Multiple commenters noted that Category 1 should not be permitted to be compounded in unclassified SCAs.

**Response:** Comment not incorporated. Some facilities require the flexibility to be able to compound CSPs with a shorter BUD in an unclassified SCA.

**Commentary Summary #14:** Commenter noted that all CSPs must be prepared in a PEC surrounded by a controlled environment that is ISO Class 7 or better.

**Response:** Comment not incorporated. Some facilities require the flexibility to be able to compound Category 1 CSPs with shorter BUDs in an unclassified SCA.

**Commentary Summary #15:** Multiple commenters noted that when referring to ante-rooms providing access to negative-pressure rooms, the chapter should specify that these rooms typically contain HDs. The commenters noted that the change would assist those who are unfamiliar with <800>, who might otherwise confuse the concepts of negative-pressure and positive-pressure requirements.

**Response:** Comment not incorporated. The chapter provides a cross-reference and hyperlink to <800> when describing negative-pressure requirements. If facilities are handling HDs, they must refer to <800>.

**Commentary Summary #16:** Commenter recommended that the chapter mandate that the entire cleanroom suite have a backup generator to ensure that the temperature, humidity, and HEPA system work at all times to avoid contamination. Commenter additionally noted that if there was a power outage, there would be a vast amount of CSP waste due to the shorter BUD required, depending on how long the facility would be without power.

**Response:** Comment not incorporated. The Expert Committee determined that it would be impractical to require every facility to have a backup generator. Facilities may choose to install a backup generator to provide power in the event of power failure. However, if the PEC or SEC is not operational (e.g., during a power outage), CSPs must not be prepared, even with a short BUD.

**Commentary Summary #17:** Several commenters noted that a temperature of 20° or cooler is an uncomfortable temperature for many personnel. The commenters noted that at cooler temperatures, compounders may wear more layers of clothing, which increases the risk of particle shedding. The commenters recommended that the cleanroom suite should be maintained at controlled room temperature as defined in <659> *Packaging and Storage Requirements*. Other commenters noted that the temperature should be increased to 21°.

**Response:** Comment not incorporated. The chapter recommends that the temperature in the cleanroom suite be maintained at 20° or cooler to help provide comfortable conditions for the compounding personnel wearing the required garb. Facilities may choose to have temperatures higher than those recommended by the chapter.

**Commentary Summary #18:** Commenter noted that since humidity below 60% is a recommendation, humidity monitoring should be a recommendation, not a requirement.

**Response:** Comment not incorporated. Although the recommendation for humidity is below 60%, facilities must still monitor humidity in the cleanroom suite. Humidity may contribute to microbial proliferation and may be important for personnel comfort. Monitoring of humidity in the cleanroom suite helps identify potential causes of failure during other microbial air and surface sampling.

**Commentary Summary #19:** Commenter noted that the cleanroom suite must be maintained at a relative humidity that does not exceed 60%. Commenter indicated that humidity deviations increase the risk of microbial growth.

**Response:** Comment not incorporated. Many commenters noted that it is difficult to maintain humidity below 60% in many locations, especially during the summer. The chapter recommends humidity below 60%.

**Commentary Summary #20:** Commenter noted that the compounding area should be maintained at 20° to 24° with a relative humidity between 20% and 60% to be consistent with operating room guidelines.

**Response:** Comment not incorporated. The chapter recommends a temperature of 20° or lower and a relative humidity below 60%. Many commenters noted discomfort at certain temperatures and difficulties in maintaining relative humidity, especially during the warmer months. Facilities must determine the appropriate temperature and relative humidity for the compounding area, which can be verified through microbial air and surface sampling.

**Commentary Summary #21:** Several commenters noted concerns that the cleanroom suite temperature, at 20° and below, is out of the range of storage temperatures for most medications. Commenters noted that a separate storage area would be required for sterile medications outside of 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. Further, facilities may adjust the cleanroom temperature to allow for storage of medications.

**Commentary Summary #22:** Multiple commenters requested guidance on corrective action or an action plan if the temperature or relative humidity in the cleanroom suite exceeds 20° or 60%, respectively. A commenter noted that the action plan must evaluate the impact of the excursion on drug product integrity.

**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. Further, corrective action must be facility-specific, taking into consideration the cause of the excursions and whether any CSPs may be impacted.

**Commentary Summary #23:** Multiple commenters noted that the temperature and relative humidity recommendations in the chapter should be a “must” requirement. Further, a commenter noted that the temperature and relative humidity requirement should also apply to the SCA, because garbing is required in the SCA.

**Response:** Comment not incorporated. The chapter recommends a temperature of 20° or lower and a relative humidity below 60%. Many commenters noted discomfort at certain temperatures and difficulties in maintaining relative humidity, especially during the warmer months. Many commenters additionally 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, which can be verified through microbial air and surface sampling.

**Commentary Summary #24:** Multiple commenters requested an upper limit for temperature and humidity requirements in the cleanroom suite. Some commenters noted that the relative humidity should be below 50% or below 70%.

**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.

**Commentary Summary #25:** Commenter recommended separating the temperature and humidity recommendations, monitoring requirements, and documentation requirements to improve clarity.

**Response:** Comment incorporated.

**Commentary Summary #26:** Commenter noted that temperature and relative humidity monitoring can be performed by a continuous recording device, which does not require daily documentation.

**Response:** Comment incorporated.

**Commentary Summary #27:** Commenter noted that temperature and humidity recordings must be reviewed by *a designated person* instead of *the designated person*.

**Response:** Comment not incorporated. Review of temperature and humidity recordings may be performed as described by facility SOPs. The facility SOP may delegate the review to a person other than the designated person.

**Commentary Summary #28:** Commenter noted that the results of the temperature and humidity readings must be documented at least once daily. The commenter indicated that otherwise, the review will not occur.

**Response:** Comment incorporated.

**Commentary Summary #29:** Multiple commenters noted that the temperature and humidity monitoring devices must be verified for accuracy at least every 12 months or as required by the manufacturer.

**Response:** Comment incorporated.

**Commentary Summary #30:** Commenter noted that use of the term “efficient” to describe the HVAC system is vague. The commenter noted that the term can be misinterpreted, which can cause older but fully functioning systems to be replaced because they are not deemed efficient.

**Response:** Comment incorporated. Eliminated the term “efficient.”

**Commentary Summary #31:** Commenter suggested that the prohibition of free-standing humidifiers/dehumidifiers and air conditioners should be a recommendation, not a requirement.

**Response:** Comment not incorporated. Free-standing humidifiers/dehumidifiers and air conditioners must not be used because of the risk of contamination, as they may serve as a water source.

**Commentary Summary #32:** Multiple commenters noted that free-standing humidifiers/dehumidifiers and air conditioners must not be permitted within the perimeter of the SCA.

**Response:** Comment incorporated.

**Commentary Summary #33:** Commenter noted that free-standing heaters must be prohibited from the classified areas.

**Response:** Comment not incorporated. Heaters are typically not used in compounding areas since the temperature recommendations are 20° or cooler.

**Commentary Summary #34:** Commenter noted that temperature and humidity monitoring devices must be National Institute of Standards and Technology (NIST)-traceable and calibrated annually.

**Response:** Comment not incorporated. The chapter requires that the temperature and humidity monitoring devices must be verified for accuracy. Calibration requires more extensive testing of the device and may not need to be performed every 12 months. Users should refer to the device manufacturer for information on the frequency of calibration.

**Commentary Summary #35:** Multiple commenters noted that manufacturers of temperature monitoring devices have different verification procedures that should be followed. The chapter should not provide information on verification.

**Response:** Comment not incorporated. The chapter requires verification of the temperature monitoring device at least every 12 months, or as required by the manufacturer. The manufacturer's recommended verification procedures should be followed.

**Commentary Summary #36:** Commenter noted that requiring temperature monitoring devices to be verified requires purchase of additional instruments or purchase of new equipment. Commenter recommended deleting the requirement to verify temperature monitoring devices.

**Response:** Comment not incorporated. Temperature monitoring devices must be verified at least every 12 months or as recommended by the manufacturer to ensure that the device continues to operate accurately and as expected.

**Commentary Summary #37:** Multiple commenters noted that the humidity monitoring device should be verified at least every 12 months or as recommended by the manufacturer.

**Response:** Comment incorporated.

**Commentary Summary #38:** Commenter noted that "a person must be designated" to be responsible for ensuring that each area related to CSP preparation meets the classified air quality for the activities to be conducted in that area.

**Response:** Comment not incorporated. The facility may have one or more designated person(s).

**Commentary Summary #39:** Commenter noted that it should be an assigned person, rather than a designated person, that should be responsible for ensuring that each area related to CSP preparation meets the classified air quality for the activities to be conducted in that area.

**Response:** Comment not incorporated. The role of the designated person is described in the chapter and defined in the glossary.

**Commentary Summary #40:** Commenter recommended that the subsection title should state SECs (with a lowercase s) instead of SECS.

**Response:** Comment not incorporated. The USP Style Guide places all subheads at this level in all caps.

**Commentary Summary #41:** Several commenters noted that buffer rooms and ante-rooms do not have to be separated by fixed walls and doors. Commenters recommended that the chapter permit the principle of displacement airflow, which requires an air velocity of 40 feet per minute or more from the buffer area across the line of demarcation in the ante-area.

**Response:** Comment not incorporated. The Expert Committee decided that with facility design using the principle of displacement airflow, it is difficult to achieve optimal air quality control. Fixed walls and doors are necessary to maintain air quality control in the

cleanroom suite and to help ensure the quality of the CSP, especially Category 2 CSPs with longer BUDs than permitted in the previous chapter.

**Commentary Summary #42:** Multiple commenters noted that the facility design for cleanroom suites should specify whether the ante-room and buffer room must be separated by fixed walls and doors.

**Response:** Comment incorporated.

**Commentary Summary #43:** Multiple commenters noted that HEPA filters should be located at the ceiling and not in the ceiling. The commenter noted that there are many locations that do not have sufficient ceiling space to allow for HEPA filters and proper duct work above the ceiling.

**Response:** Comment not incorporated. HEPA filters should be located in the ceiling. Requiring HEPA filters at the ceiling may be ambiguous and subject to misinterpretation. For example, at the ceiling may be misconstrued to mean in the wall touching the ceiling, or a certain distance from the ceiling, or a duct above the ceiling. HEPA filters located in the ceiling requires ceiling-mounted HEPA filters resulting in the HEPA filter being mounted horizontally so that the air flows down into the room. Otherwise, HEPA filters in the wall close to the ceiling would result in air flow across the ceiling instead of down into the room.

**Commentary Summary #44:** Commenter noted that HEPA filters do not have to be located in the ceiling.

**Response:** Comment not incorporated. HEPA filters must be mounted in the ceiling so that air flows down into the room. If HEPA filters are not placed in the ceiling, air would flow across the ceiling instead of into the room.

**Commentary Summary #45:** Commenter noted that emerging clean air technology does not require HEPA filters to be located in the ceiling (e.g., multi-faced air cleaning technology for infection-controlled patient rooms). Another commenter noted that air may be supplied through inline HEPA filters.

**Response:** Comment not incorporated. HEPA filters must be located in the ceiling. In-line ceiling filters may be susceptible to contamination, especially in the event of water leakage and damage.

**Commentary Summary #46:** Commenter noted that HEPA filters should be permitted to be installed in the interstitial space rather than in the ceiling. The commenter noted that introducing air through ceiling-mounted HEPA filters causes multiple issues and that a HEPA filter within the ventilation duct is easier to seal, easier to replace, and easier to perform in situ testing.

**Response:** Comment not incorporated. HEPA filter placement in the ventilation duct is difficult to leak test and susceptible to contamination, especially in the event of water leakage or other breaches. Additionally, the Expert Committee decided that certification every 6 months would not be sufficient to promptly discover potential breaches.

**Commentary Summary #47:** Commenter noted that HEPA filters can be located outside of the cleanroom suite and continue to meet air quality requirements. Another commenter noted that the HEPA filters may be located at the supply outlet or in the supply duct immediately outside of the cleanroom suite dedicated to the cleanroom suite.

**Response:** Comment not incorporated. HEPA filter placement in the ventilation duct is difficult to leak test and susceptible to contamination especially in the event of water

leakage or other breaches. Additionally, the Expert Committee decided that certification every 6 months would not be sufficient to promptly discover potential breaches.

**Commentary Summary #48:** Commenter suggested deleting “dilution of particles” when describing visual smoke studies. The commenter noted that dilution of particles is not a reliable measure because the particle size range generated is not visible to the human eye.

**Response:** Comment incorporated. The chapter states that a visual smoke study demonstrating an absence of stagnant airflow must be performed if air returns are not located low on the wall.

**Commentary Summary #49:** Multiple commenters recommended that the chapter should provide a detailed description of a visual smoke study. The commenter noted that a detailed description is important for certifiers to perform their function and for regulators to inspect.

**Response:** Comment not incorporated. Visual smoke studies demonstrating an absence of stagnant airflow must be performed if air returns are not located low on the wall. A definition for visual smoke study was added to the glossary to further elaborate on visual smoke studies. The Expert Committee will consider development of future resources and tools to assist facilities in performing visual smoke studies and certification procedures.

**Commentary Summary #50:** Commenter requested clarification on whether air returns in both the ante-room and buffer room must be located low on the wall.

**Response:** Comment not incorporated. The chapter states that air returns in the cleanroom suite, which includes both the ante-room and buffer room) must be located low on the wall unless a visual smoke study demonstrates an absence of stagnant airflow where particulate will accumulate.

**Commentary Summary #51:** Commenter noted that the location of the air return must additionally take into consideration the workflow of the cleanroom suite. For example, the commenter noted that there may be equipment or personnel that consistently block the airflow.

**Response:** Comment not incorporated. The chapter does not prescribe the location of all air returns because it would not be feasible to address all different types of designs. The facility must take care to design the cleanroom suite in order to meet all of the facility requirements in the chapter. The facility must additionally successfully complete certification and microbial air and surface monitoring.

**Commentary Summary #52:** Commenter noted that facilities will have to undergo significant construction in order to place air returns low on the wall. The commenter noted that it is not necessary to create a unidirectional airflow in an ante-room or buffer room, and the functionality of the room is adequately addressed through certification performed every 6 months.

**Response:** Comment not incorporated. For facilities that do not have air returns low on the wall, a visual smoke study may be performed to demonstrate an absence of stagnant airflow where particulate will accumulate. The intent is not to create unidirectional air in the ante-room and buffer room but to dilute and sweep particles out of the room. Additionally, the Compounding Expert Committee noted that returns should be mounted low on the wall to create a general top-down dilution of area air with HEPA-filtered make-up air.

**Commentary Summary #53:** Commenter noted that low wall returns are essential in aseptic processing, and smoke studies are inadequate to prove suitability for a deficient design.

**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.

**Commentary Summary #54:** Commenter noted that returns must be low on the wall. The commenter suggested that a note can be added to accommodate existing facilities where returns are not low on the wall.

**Response:** Comment not incorporated. New and existing facilities must follow the same standard. Returns must be located low on the wall unless a visual smoke study demonstrates an absence of stagnant airflow where particulate will accumulate. This standard applies regardless of whether it is a new facility or an existing facility.

**Commentary Summary #55:** Commenter noted that “visual smoke study” should be changed to “smoke pattern test.”

**Response:** Comment not incorporated. A visual smoke study is used to verify the absence of stagnant airflow in ante-rooms and buffer rooms. A dynamic airflow smoke pattern test is used to observe air patterns within a PEC.

**Commentary Summary #56:** Commenter noted that the visual smoke study in the cleanroom suite must be repeated whenever there is a change in the placement of the PEC within the room or any other alteration is performed within the cleanroom suite that affects the quality of the air (e.g., HVAC alterations, change of HEPA filter units).

**Response:** Comment incorporated.

**Commentary Summary #57:** Commenter noted that the visual smoke study in the cleanroom suite must be repeated whenever there is a change or movement within the room with respect to the PEC, cabinetry, or large equipment.

**Response:** Comment partially incorporated. The chapter requires that the visual smoke study be repeated whenever there is a change in the placement of equipment or any other alteration that affects the quality of the air. The Expert Committee determined that “large equipment” may be subject to different interpretations. The term *any other alteration* is intended to be broad to encompass other movement or change that may impact the quality of air.

**Commentary Summary #58:** Multiple commenters recommended changing “the PEC” to “a PEC” to address facilities that may have more than one PEC.

**Response:** Comment partially incorporated. The chapter was revised to refer to equipment more broadly, which would include one or more than one PEC.

**Commentary Summary #59:** Commenter recommended changing “classified rooms” to “cleanroom suite” when specifying that the rooms are required to be equipped with a pressure-differential monitoring system.

**Response:** Comment not incorporated. All classified rooms, which include both ante-rooms and buffer rooms in a cleanroom suite, must be equipped with a pressure-differential monitoring system.

**Commentary Summary #60:** Commenter noted that requiring a line of demarcation to separate the ante-room into a clean side and a dirty side is unreasonable, burdensome, and difficult to achieve in small pharmacies.

**Response:** Comment not incorporated. The method of drawing the line of demarcation may be determined by the facility (e.g., tape on the floor). The line of demarcation provides guidance for personnel when garbing and moving materials to and from the buffer room.

**Commentary Summary #61:** Multiple commenters requested guidance on how to establish the line of demarcation (e.g., paint or tape on the floor). The commenter also wanted to know if there are acceptable tapes that may be used.

**Response:** Comment not incorporated. The method of drawing the line of demarcation may be determined by the facility. The Expert Committee determined that it would be too prescriptive to require a specific method for establishing the line of demarcation.

**Commentary Summary #62:** Multiple commenters noted that the line of demarcation may not be applicable for every facility type. For example, the commenter noted that their cleanroom suite is composed of two ante-rooms, where one ante-room is for garbing activities and the other ante-room is closest to the buffer room.

**Response:** Comment incorporated. The chapter was revised to discuss facilities that have two separate ante-rooms.

**Commentary Summary #63:** Commenter requested guidance on required garb and how to don garb while moving across the line of demarcation. For example, the commenter noted that shoe covers should be donned as the individual steps over the line of demarcation. Another commenter noted that gowns should be donned on the clean side of the line of demarcation.

**Response:** Comment not incorporated. The order of garbing and location where garbing is donned must be determined by the facility and documented in the facility's SOP. The order of garbing 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 ante-room).

**Commentary Summary #64:** Commenter recommended specifying that the required garb must be donned prior to entering the clean side/room of the ante-room based on the facility's SOP.

**Response:** Comment partially incorporated. The chapter states that required garb must be donned prior to entering the clean side/room of the ante-room. Additionally, 3. *Personal Hygiene and Garbing* specifies that the order of garbing should be documented in the facility's SOP.

**Commentary Summary #65:** Commenter requested guidance on what garb is required to be worn on the clean side of the line of demarcation. The commenter recommended hospital-laundered scrubs and covers for shoes.

**Response:** Comment not incorporated. The minimum garbing requirements are described in 3. *Personal Hygiene and Garbing*. The order of garbing and location where garbing is donned must be determined by the facility and documented in the facility's SOP. The order of garbing 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 outside of the ante-room or inside of the ante-room).

**Commentary Summary #66:** Commenter noted that all personnel must comply with garbing and hand hygiene requirements regardless of the purpose of entering the compounding area. The commenter noted that it is possible for personnel to work only in the ante-room (e.g., staging components and supplies) without needing to enter the

buffer room. These personnel must don hospital-laundered scrubs and covers for shoes.

**Response:** Comment not incorporated. The chapter does not address the purpose of entry into the compounding area. The minimum garbing requirements are described in 3. *Personal Hygiene and Garbing*, and these are applicable regardless of the purpose of entry into the compounding area. Facilities may implement requirements (e.g., scrubs, dedicated shoes) that are in addition to the minimum garbing requirements described in the chapter.

**Commentary Summary #67:** Commenter noted that the description of cleanroom suite should include the requirement for pressure monitoring.

**Response:** Comment incorporated.

**Commentary Summary #68:** Multiple commenters noted that tacky surfaces should be changed to tacky mats.

**Response:** Comment incorporated.

**Commentary Summary #69:** Commenter suggested that tacky mats should be permitted on the dirty side of the ante-room. Another commenter noted that tacky mats can reduce the amount of dust particles carried into 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.

**Commentary Summary #70:** Commenter noted that floor mats should not be used in ISO-classified areas. The commenter noted that fatigue mats can be autoclaved, but if not allowed to dry adequately could be a source of microbial proliferation.

**Response:** Comment not incorporated. Fatigue mats may be permitted. The facility SOPs should address how fatigue mats, if used, are cleaned.

**Commentary Summary #71:** Commenter noted that Category 1 CSPs should not be permitted to be compounded in an unclassified SCA. Only immediate-use CSPs should be permitted to be compounded in an unclassified SCA. Another commenter noted that CSPs must not be prepared in an unclassified room because it is inadequate to assure patient safety.

**Response:** Comment not incorporated. The SCA provides a flexible approach for facilities that do not have a cleanroom suite to provide needed medications patients. The risk associated with using an unclassified SCA is mitigated by facility design requirements described in the chapter and the shorter BUDs.

**Commentary Summary #72:** Multiple commenters recommended the size of operations (e.g., number of Category 1 CSPs per day or 6-hour BUD) that may use the SCA design.

**Response:** Comment not incorporated. Only Category 1 CSPs with a BUD of 12 hours or less at controlled room temperature or 24 hours in a refrigerator may be prepared in an SCA. The number of CSPs that may be prepared depends on such factors as facility design (e.g., number of PECs) and number of personnel.

**Commentary Summary #73:** Commenter requested guidance on the minimum and maximum dimensions for the SCA.

**Response:** Comment not incorporated. The Expert Committee determined that including specific dimensions for the SCA is too prescriptive. Certification and

recertification, as well as microbial air and surface sampling, will help facilities verify their facility design.

**Commentary Summary #74:** Commenter recommended that the SCA must be a separate room.

**Response:** Comment not incorporated. The SCA is not required to be a separate room. The SCA design is intended to provide flexibility to facilities preparing Category 1 CSPs with shorter BUDs. A visible perimeter must establish the boundaries of the SCA. The visible perimeter may include a line on the floor or fixed walls and doors.

**Commentary Summary #75:** Commenter recommended a tiered approach to assigning BUDs based on the type of PEC located in an SCA. For example, the commenter noted that Category 1 CSPs prepared in a laminar airflow system (LAFS) would have a shorter BUD than those prepared in a RABS or a pharmaceutical isolator. The commenter further suggested that the BUD may be tiered based on whether the starting ingredient(s) are sterile or nonsterile.

**Response:** Comment not incorporated. Only Category 1 CSPs with a BUD of 12 hours or less at controlled room temperature or 24 hours or less refrigerated may be prepared in an unclassified SCA. CSPs with longer BUDs must not be prepared in an unclassified SCA and must be prepared in the cleanroom suite as a Category 2 CSP. 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.

**Commentary Summary #76:** Commenter suggested that it is inappropriate to allow PECs to be located in an unclassified environment since it cannot be guaranteed to be sterile.

**Response:** Comment not incorporated. Environmental monitoring, such as air and surface sampling, is routinely utilized to ensure a sterile compounding environment.

**Commentary Summary #77:** Commenter recommended that the SCA not be located adjacent to areas under construction because this can be a source of significant contamination.

**Response:** Comment not incorporated. The chapter has examples of environmental control challenges that may be permanent affixtures (e.g., restrooms, warehouses, or food preparation areas). An example of construction may be misinterpreted to preclude renovations of the compounding area.

**Commentary Summary #78:** Commenter noted that the SCA must be located away from heavily traveled and high-volume hallways. The commenter noted that heavily traveled and high-volume hallways are dirtiest and will cause airflow issues for the SCA.

**Response:** Comment not incorporated. The chapter states that the SCA must be located away from traffic flow. Heavily traveled and high-volume hallways are ambiguous terms and may be subject to varying interpretations.

**Commentary Summary #79:** Commenter noted that particle-generating activity (e.g., nonsterile compounding) adjacent to the SCA must not be performed when sterile compounding is in process.

**Response:** Comment not incorporated. The chapter more broadly states that the impact of activities that will be conducted around or adjacent to the SCA must be considered carefully when designing such an area. These considerations include those mentioned by the commenter (e.g., nonsterile compounding).

**Commentary Summary #80:** Commenter noted that the term “adjacent” is ambiguous and suggested using the term “cannot be contiguous” when describing activities that should not be conducted around the SCA.

**Response:** Comment not incorporated. Adjacent is intended to mean next to or adjoining something else. The Expert Committee determined that “adjacent” is a more easily understood term.

**Commentary Summary #81:** Commenter suggested removing the statement that a visible perimeter must establish the boundaries of the SCA, because SCA is defined in the glossary.

**Response:** Comment not incorporated. The concept of the SCA, including the requirement for a visible perimeter to establish the boundaries, is first described in the chapter and later defined again in the glossary.

**Commentary Summary #82:** Multiple commenters requested clarification on whether the visible perimeter establishing the boundaries of the SCA requires fixed walls or doors or a line of demarcation.

**Response:** Comment not incorporated. The visible perimeter establishing the boundaries of the SCA may be fixed walls and doors or a tape on the floor to designate the boundaries. The facility must select the method of establishing the visible perimeter. Further, the glossary definition of SCA states that the SCA may be an area or a room with a defined perimeter.

**Commentary Summary #83:** Multiple commenters recommended reorganizing the subsection *Types of SECs and Design* to more clearly separate the requirements for the cleanroom suite and the SCA.

**Response:** Comment incorporated.

**Commentary Summary #84:** Multiple commenters noted that the chapter implies that the SCA must be classified based on the organization of the subsection *Types of SECs and Design*.

**Response:** Comment incorporated. Reorganized the subsection *Types of SECs and Design* to separate the requirements for the cleanroom suite and the SCA.

**Commentary Summary #85:** Commenter recommended adding a statement that HEPA filters placed directly above the compounder could disrupt unidirectional airflow of an open-faced PEC.

**Response:** Comment not incorporated. The chapter more broadly states that the PEC must be located in a manner to minimize the risk of microbial contamination. A statement that HEPA filters may not be placed directly above compounders may imply that a compounder may never walk to locations where there is a HEPA filter in the ceiling.

**Commentary Summary #86:** Multiple commenters noted that there should be a visitor policy. For example, SOPs must state that authorized non-staff individuals must be accompanied by cleanroom staff and must comply with all hand hygiene and garbing requirements.

**Response:** Comment not incorporated. The chapter requires any person, whether preparing a CSP or not, entering a sterile compounding area to meet the requirements in 3. *Personal Hygiene and Garbing*. Further, the chapter specifies that access to the SEC must be restricted to authorized personnel and required materials. Facilities may additionally have policies restricting entry to the compounding area.

**Commentary Summary #87:** Commenter noted that the restriction on access to the SEC to authorized personnel may imply a requirement for a security system.

**Response:** Comment not incorporated. The provision is not intended to require a security system but to restrict access to the SEC to authorized personnel and required materials to minimize the risk of microbial contamination.

**Commentary Summary #88:** Commenter suggested that restriction of access to the SEC should include the SCA.

**Response:** Comment not incorporated. An SEC is defined as the area where the PEC is placed and can be either a cleanroom suite or an SCA. The SEC includes both the cleanroom suite and the SCA.

**Commentary Summary #89:** Multiple commenters noted that airlocks and interlocking doors are an unnecessary expense if proper relationships between the rooms and areas are maintained. Further, the commenter noted that airlocks decrease available space.

**Response:** Comment not incorporated. The chapter does not require airlocks or interlocking doors. The chapter simply notes that airlocks and interlocking doors may be used to facilitate better control of air balance between areas.

**Commentary Summary #90:** Commenter noted that the provisions for airlocks and interlocking doors should only apply to pass-throughs connecting the buffer room to unclassified areas. The commenter noted that it is unnecessary and burdensome to require that pass-throughs between buffer rooms and ante-rooms have airlocks or interlocking doors.

**Response:** Comment not incorporated. The chapter does not require airlocks or interlocking doors. The chapter simply notes that airlocks and interlocking doors may be used to facilitate better control of air balance between areas. Further, the chapter states that if pass-throughs are used, both doors must never be opened at the same time and doors should be interlocking. Interlocking doors is a recommendation and not a requirement.

**Commentary Summary #91:** Commenter recommended that the chapter define pressure and flow requirements for airlocks.

**Response:** Comment not incorporated. The chapter simply notes that airlocks and interlocking doors may be used to facilitate better control of air balance between areas. Airlocks are not required. The pressure and air exchange requirements for the cleanroom suite are further described in *4. Facilities and Engineering Controls*.

**Commentary Summary #92:** Commenter requested language that clarifies whether pass-throughs with interlocking doors may be used between classified and unclassified spaces.

**Response:** Comment not incorporated. The chapter does not prescribe where pass-throughs may be placed but does state that if they are used, both doors must never be opened at the same time. The Expert Committee determined that the chapter should not prescribe where pass-throughs may be placed. The placement of pass-throughs, if used, must be facility-specific, and the impact of their use must be verified through certification and microbial air and surface monitoring at the facility.

**Commentary Summary #93:** Multiple commenters noted that pass-through doors must be interlocking.

**Response:** Comment not incorporated. Other commenters have noted the expense and burden of replacing existing pass-throughs. The chapter recommends that pass-

throughs have interlocking doors. However, if pass-through doors are not interlocking, the chapter states that both doors must never be opened at the same time.

**Commentary Summary #94:** Commenter noted that it should not be acceptable to have dead air or exhaust enter the pass-through from an unclassified space to the buffer area. The commenter suggested that airflow from the pass-through should be HEPA-filtered and the interlock should be positive pressure to the unclassified space but negative to the classified buffer.

**Response:** Comment not incorporated. The chapter does not prescribe the type and location of pass-throughs but does state that if they are used, both doors must never be opened at the same time. The Expert Committee determined that the chapter should not prescribe where pass-throughs may be placed. The placement of pass-throughs, if used, must be facility-specific, and the impact of their use must be verified through certification and microbial air and surface monitoring at the facility.

**Commentary Summary #95:** Commenter recommended that there should be no pass-throughs permitted between the unclassified space and the buffer area unless the pass-through is HEPA filtered.

**Response:** Comment not incorporated. Requiring HEPA-filtered pass-throughs may be too burdensome. The chapter does not prescribe the type and location of pass-throughs but does state that if they are used, both doors must never be opened at the same time. The Expert Committee determined that the chapter should not prescribe where pass-throughs may be placed. The placement of pass-throughs, if used, must be facility-specific and the impact of their use must be verified through certification and microbial air and surface monitoring at the facility.

**Commentary Summary #96:** Multiple commenters requested addition of a list of places where pass-throughs may be located, similar to the information in <825>.

**Response:** Comment not incorporated. General Chapter <797> is a separate chapter. The Expert Committee determined that the chapter should not prescribe where pass-throughs may be placed. The placement of pass-throughs, if used, must be facility-specific, and the impact of their use must be verified through certification and microbial air and surface monitoring at the facility.

**Commentary Summary #97:** Commenter noted that “when designing doors” is a misstatement and recommended changing to “when locating doors.”

**Response:** Comment partially incorporated. The statement was revised to state that the location of door closures, the door surfaces, and the movement of the doors should be taken into consideration.

**Commentary Summary #98:** Multiple commenters noted that door seals and sweeps should be permitted between the buffer room and ante-room to maintain pressure and temperature and to articulate control. Further, the commenter noted that removing seals may be a violation of building codes for fire safety.

**Response:** Comment not incorporated. The chapter recommends not installing seals and sweeps at doors between buffer and ante-rooms to help ensure cleanability, to minimize impact on the airflow in the classified rooms, and to minimize the risk of contamination. Door seals and sweeps are not required to be uninstalled, but the chapter recommends that they not be installed.

**Commentary Summary #99:** Commenter requested that definitions for door seals and sweeps be added.

**Response:** Comment not incorporated. Door seals and sweeps are commonly used terms and are intended to refer to a thin strip of material (e.g., plastic or rubber) that is fitted across the bottom of a door.

**Commentary Summary #100:** Commenter noted that there is no need for air quality classifications better than ISO Class 5.

**Response:** Comment not incorporated. The chapter states that the PEC must be certified to meet ISO Class 5 or better conditions. The chapter does not imply that the PEC must be better than ISO Class 5, and the chapter is intended to provide the minimum standard.

**Commentary Summary #101:** Multiple commenters recommended changing “ISO Class 5 or better conditions” to “ISO Class 5 or better standards.”

**Response:** Comment not incorporated. The chapter refers to ISO Class 5 or better conditions to describe the air quality within the PEC. The term standards may create confusion about which standards must be followed.

**Commentary Summary #102:** Commenter noted that unidirectional airflow must be verified by a smoke study.

**Response:** Comment not incorporated. Subsequent sections of the chapter describe dynamic airflow smoke pattern tests that must be performed in each type of PEC. Dynamic airflow smoke pattern tests are additionally described in *5. Certification and Recertification*.

**Commentary Summary #103:** Commenter recommended that all PECs must be equipped with an electronic HEPA-filter monitor to alert users to HEPA-filter blockage and necessary replacement.

**Response:** Comment not incorporated. The Expert Committee determined that the requirement may be too restrictive and may prevent many existing PEC units from being used. However, facilities may choose to install such PECs if all other requirements of the chapter are met.

**Commentary Summary #104:** Commenter recommended changing “HEPA-filtered air must be supplied to the PEC” to “HEPA-filtered air must be supplied from the PEC” to improve clarity.

**Response:** Comment partially incorporated. The text was revised to state “HEPA-filtered air must be supplied by the PEC.”

**Commentary Summary #105:** Commenter recommended describing the different types of PECs and where they should not be utilized. For example, the commenter wanted to know what types of PECs are suitable for institutions, pharmacies, satellites, operating rooms, or intensive care units.

**Response:** Comment not incorporated. The chapter describes the different types of PECs and requirements for placement of these PECs. Facility-specific designs must be determined by the facility.

**Commentary Summary #106:** Multiple commenters noted that the placement of the PEC must allow for cleaning of adjacent walls, and that flashing may be used to bond the PEC to the wall. Another commenter noted that there must be at least 6 inches between the PEC and the SEC walls to allow for cleaning.

**Response:** Comment not incorporated. Facilities must determine the appropriate method for cleaning areas adjacent to the PEC (see also *7. Cleaning, Disinfecting, and Applying Sporicidal Agents in Compounding Areas*).

**Commentary Summary #107:** Commenter requested alternatives to cleaning the areas adjacent to the PEC if the PEC is not moveable.

**Response:** Comment not incorporated. Facilities must determine the appropriate method for cleaning areas adjacent to the PEC (see also 7. *Cleaning, Disinfecting, and Applying Sporocidal Agents in Compounding Areas*).

**Commentary Summary #108:** Commenter noted that vertical flow units are more appropriate for facilities that place parenteral nutrition machines, systolic pumps, or similarly large items in horizontal clean benches, which creates back streaming into the DCA.

**Response:** Comment not incorporated. The chapter describes the minimum requirements for PECs and their placement. Facilities must determine the appropriate PEC to use based on facility-specific factors (e.g., type of compounding activities, type of CSPs prepared, and personnel).

**Commentary Summary #109:** Commenter noted that LAFS should be changed to “unidirectional airflow system.” The commenter noted that there is no such thing as LAFS and that laminarity requires each molecule in an airstream to be moving at effectively the same velocity.

**Response:** Comment not incorporated. LAFS is intended to refer to a PEC that has unidirectional HEPA-filtered airflow [e.g., integrated vertical laminar flow zones (IVLFZs) and biological safety cabinets (BSCs)]. The term is frequently used and understood in the compounding industry.

**Commentary Summary #110:** Multiple commenters noted that the typographical error in the acronym LAWF should be corrected to laminar airflow workbenches (LAFW).

**Response:** Comment incorporated.

**Commentary Summary #111:** Commenter recommended prohibiting open-faced PECs from being allowed for HD and non-HD compounding. The commenter noted that advanced aseptic compounding reduces the risk for contamination and exposure to personnel.

**Response:** Comment not incorporated. The chapter describes the use of different types of PECs and placement of those PECs for compounding Category 1 and Category 2 CSPs. General Chapter <800> describes the use of containment primary engineering controls (C-PECs) for HD compounding. Open-faced PECs such as LAFW are not permitted to be used for HD compounding. The C-PECs described in <800> are designed for use in HD compounding.

**Commentary Summary #112:** Commenter noted that the chapter should prohibit the use of LAFS for HDs and for high-alert medications (e.g., parenteral nutrition).

**Response:** Comment not incorporated. LAFS must not be used for certain HDs because it does not protect the personnel or environment from exposure. High-alert medications are those that bear a heightened risk of causing significant patient harm when they are used in error. Whether the drug is a high-alert medication may not impact the type of PEC used for compounding. The purpose of the standard is to ensure quality CSPs, there should be other mechanisms in place at the facility to handle high-alert medications.

**Commentary Summary #113:** Commenter noted that BSCs are designed and built to provide safety in the handling of biohazardous material and are not well suited for aseptic processing of any kind.

**Response:** Comment not incorporated. The Expert Committee determined that a Class II BSC providing inward and downward unidirectional HEPA-filtered airflow and HEPA-filtered exhaust, providing an ISO Class 5 or better environment, is suitable for preparing CSPs.

**Commentary Summary #114:** Commenter recommending spelling out all of the acronyms related to LAFS to improve readability and understandability.

**Response:** Comment not incorporated. Based on the USP Style Guide, acronyms are spelled out the first time they are used in the chapter. The acronym is used for all subsequent times that the chapter refers to the term.

**Commentary Summary #115:** Commenter noted that a BSC must not be used for preparation of antineoplastics and/or any API HDs.

**Response:** Comment not incorporated. A BSC may be used for preparation of antineoplastics and/or any API HD if the exhaust air is externally vented (see C-PEC requirements in <800>).

**Commentary Summary #116:** Commenter noted that the IVLFZ must have continuous returns underneath the stainless steel work tables.

**Response:** Comment partially incorporated. The chapter was revised to state that strategic location of air returns in addition to full coverage of HEPA filters above the work surface are required in an IVLFZ.

**Commentary Summary #117:** Multiple commenters noted that IVLFZ must have 100% HEPA filter coverage in the ceiling. Another commenter recommended requiring continuous HEPA-filter coverage in the ISO Class 5 area of the IVLFZ.

**Response:** Comment partially incorporated. The chapter was revised to require full coverage by HEPA filters above the workspace in the IVLFZ.

**Commentary Summary #118:** Commenter recommended striking “stainless steel” for describing work tables in the IVLFZ because there are other materials available that are impervious to cleaning products that may be used as the work surface.

**Response:** Comment incorporated.

**Commentary Summary #119:** Multiple commenters recommended elimination of the IVLFZ because the design can lead to compromises in the sterile compounding process. The commenter noted that the IVLFZ is not comparable to other types of PECs placed in an ISO Class 7 buffer area.

**Response:** Comment not incorporated. An IVLFZ may be able to provide an appropriate compounding environment as long as the requirements of the chapter are met. However, the chapter does state that dynamic airflow smoke pattern tests have shown that it is difficult to achieve this type of design and also achieve and maintain unidirectional airflow under dynamic operating conditions.

**Commentary Summary #120:** Commenter recommended deletion of the note that states that dynamic airflow smoke pattern tests have shown that it is difficult to achieve this type of design and also achieve and maintain unidirectional airflow under dynamic operating conditions because it is a subjective statement.

**Response:** Comment not incorporated. IVLFZ designs are difficult to achieve, as demonstrated by dynamic airflow smoke pattern tests. The statement is not subjective but instead is supported by experience in performing dynamic airflow smoke pattern tests.

**Commentary Summary #121:** Commenter noted that a physical barrier should not be required where results of dynamic smoke studies and air and surface sampling are below the action levels.

**Response:** Comment not incorporated. The Expert Committee determined that a physical barrier is required to direct the airflow downward and over the work area to separate the DCA from potential sources of contamination.

**Commentary Summary #122:** Commenter recommended eliminating BSCs because BSCs have an increased probability of contaminating the CSP and exposing personnel. The commenter noted that advanced aseptic processing greatly reduces the risk and that BSCs do not have unidirectional airflow.

**Response:** Comment not incorporated. The Expert Committee determined that a Class II BSC providing inward and downward unidirectional HEPA-filtered airflow and HEPA-filtered exhaust, providing an ISO Class 5 or better environment, is suitable for preparing CSPs.

**Commentary Summary #123:** Commenter suggested that the chapter should address the size of an acceptable PEC. For example, there may be PECs that are too small and difficult to compound in, which may put the quality of the CSP at risk.

**Response:** Comment not incorporated. The size of the PEC must be facility-specific based on factors such as the number of CSPs, the facility type, and the personnel. The Expert Committee determined that it would be too prescriptive to specify the required dimensions of the PEC.

**Commentary Summary #124:** Commenter noted that BSCs should be addressed in a section separate from LAFS.

**Response:** Comment not incorporated. LAFS includes both LAWFs and BSCs.

**Commentary Summary #125:** Commenter recommended performing a dynamic smoke pattern test if the PEC is moved, if any equipment inside the PEC is moved, or if the cleanroom airflow dynamics have changed. The commenter recommended a more targeted retesting approach rather than relying on an arbitrary time-based requirement.

**Response:** Comment not incorporated. A dynamic airflow smoke pattern test must be performed initially and every 6 months. 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*).

**Commentary Summary #126:** Commenter suggested that a PEC can be located within the dirty side of the ante-room if only Category 1 CSPs are prepared.

**Response:** Comment not incorporated. PECs can be located in an unclassified SCA (or better environment) if used only to prepare Category 1 CSPs. All the requirements of the SCA must be met.

**Commentary Summary #127:** Commenter suggested revising the description of LAFS to refer to airflow patterns in the DCA instead of in the PEC. The commenter noted that the DCA is the most critical area.

**Response:** Comment not incorporated. Airflow patterns must be maintained in the PEC. The DCA is described in other areas of the chapter.

**Commentary Summary #128:** Commenter recommended clarifying that if a LAFS is used to prepare Category 2 CSPs, the LAFS must be located within a cleanroom suite with an ISO Class 7 or better buffer room and an ISO Class 8 or better ante-room.

**Response:** Comment incorporated.

**Commentary Summary #129:** Commenter noted that a dynamic airflow smoke pattern test does not ensure that compounders understand how to utilize the unidirectional airflow to maintain first air in the DCA. The commenter noted that staff should be educated about how to utilize the unidirectional airflow to maintain first air in the DCA. The dynamic smoke pattern test should not be used as a teaching tool while it is being performed.

**Response:** Comment not incorporated. The dynamic smoke pattern study can help compounders understand how to utilize the unidirectional airflow in the DCA. However, compounders must undergo training and evaluation as described in *2. Personnel Training and Evaluation*.

**Commentary Summary #130:** Commenter requested clarification on whether the dynamic smoke pattern test should be repeated for every single compounder initially and every 6 months.

**Response:** Comment not incorporated. The dynamic smoke pattern test is only required to be performed in the PEC initially and at least every 6 months. The dynamic smoke pattern study may be a tool to help compounders understand how to utilize the unidirectional airflow in the DCA but is not required to be repeated for each compounder.

**Commentary Summary #131:** Commenter suggested that smoke pattern testing should not be required every 6 months if there is no movement of the PEC or any other changes within the air patterns inside of the PEC. Other commenters noted that performing smoke pattern testing every 6 months is too frequent.

**Response:** A dynamic airflow smoke pattern test must be performed initially and every 6 months. Performing a dynamic smoke pattern test only if the PEC is moved or if there are any changes 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*).

**Commentary Summary #132:** Multiple commenters requested clarification that the dynamic smoke pattern test is performed inside of the PEC.

**Response:** Comment incorporated.

**Commentary Summary #133:** Commenter suggested revising “smoke studies” to “smoke pattern tests.”

**Response:** Comment incorporated.

**Commentary Summary #134:** Commenter requested allowing a particular manufacturer of PECs to be used for preparing CSPs.

**Response:** Comment not incorporated. Based on USP’s Code of Ethics, USP cannot endorse a particular organization’s products or services. The chapter provides the minimum facility requirement (e.g., PECs and SECs) to help ensure quality CSPs.

**Commentary Summary #135:** Commenter recommended describing two types of RABS: open RABS and closed RABS. The commenter noted that closed RABS must never be opened and does not include CAIs and CACIs.

**Response:** Comment not incorporated. The Expert Committee determined that it is not necessary to differentiate between open and closed RABS. Examples of RABS include CAI and CACIs. RABS must be opened for transfer of components and supplies.

**Commentary Summary #136:** Commenter recommended deleting the statement that all transport ports on the RABS must be closed during compounding.

**Response:** Comment incorporated.

**Commentary Summary #137:** Commenter recommended specifying that RABS are designed and validated to preclude transfer of environmental air contamination.

**Response:** Comment incorporated.

**Commentary Summary #138:** Commenter noted that the chapter should specify that all types of PECs must be located out of traffic patterns and not just LAFS.

**Response:** Comment not incorporated. LAFS typically have open fronts which makes it critical to locate LAFS out of traffic patterns. The subsection *Types of SECs and Design* more broadly specifies the requirement that the PEC be located in a manner that minimizes conditions that could increase the risk of microbial contamination (e.g., strong air currents and personnel traffic).

**Commentary Summary #139:** Commenter noted that air exchange into the RABS during transfer of materials must not allow the RABS air quality to exceed ISO Class 5 air quality.

**Response:** Comment not incorporated. The chapter states that air exchange into the CAI from the surrounding environment must not occur unless the air has first passed through a HEPA filter. Additionally, RABS are designed and validated to preclude the transfer of contamination. The suggested text may imply the need to perform nonviable particle testing during materials transfer.

**Commentary Summary #140:** Multiple commenters recommended deleting the sentence that requires that air exchange of the CACI with the surrounding environment must not occur unless it is first passed through a HEPA filter capable of containing airborne concentrations of the physical size and state of the drug compounded. Other commenters noted that this may imply that the CACI may not be placed in an SCA.

**Response:** Comment incorporated.

**Commentary Summary #141:** Commenter recommended performing dynamic airflow smoke pattern tests whenever there are quality-related events (e.g., environmental failure, certification failure, or repair) or a controlled change.

**Response:** Comment not incorporated. Smoke pattern tests must be performed at least every 6 months. Facilities must have appropriate QA and QC procedures to detect failures and to perform additional testing if required for remediation and corrective action.

**Commentary Summary #142:** Several commenters requested an allowance for the CAI or CACI to be placed in an unclassified area, provided that certain conditions are met, to be used for preparing Category 2 CSPs.

**Response:** Comment not incorporated. For preparing Category 2 CSPs, the PEC must be located in a controlled environment to minimize the risk of contamination. Movement of materials in and out of the CAI/CACI in unclassified air carries a higher risk of contamination. Placement of the CAI/CACI in a classified area mitigates the risk for CSPs with Category 2 BUDs.

**Commentary Summary #143:** Commenter noted that preparations compounded in CAI/CACI located in an unclassified area should be allowed a BUD longer than 12 hours at controlled room temperature and 24 hours when refrigerated.

**Response:** Comment not incorporated. For preparing CSPs with longer BUDs (e.g., Category 2 CSPs), the PEC must be located in a controlled environment to minimize the risk of contamination. Movement of materials in and out of the CAI/CACI in unclassified air carries a higher risk of contamination. Placement of the CAI/CACI in a classified area mitigates the risk for CSPs with longer BUDs.

**Commentary Summary #144:** Several commenters noted that it would be burdensome to locate a CAI/CACI in a classified area in order to apply the BUDs for Category 2 CSPs. Commenters noted that CAI/CACI provides adequate microbial protection to assign the longer BUDs.

**Response:** Comment not incorporated. For preparing Category 2 CSPs, the PEC must be located in a controlled environment to minimize the risk of contamination. Movement of materials in and out of the CAI/CACI in unclassified air carries a higher risk of contamination. Placement of the CAI/CACI in a classified area mitigates the risk for CSPs with Category 2 BUDs. Further, a CAI/CACI is not pharmaceutical isolator, which is comprised of a controlled workspace, transfer device, access device, and integral decontamination system.

**Commentary Summary #145:** Commenter recommended revising the placement of RABS to allow RABS to be located within a cleanroom suite with an ISO Class 7 or buffer room with an ISO Class 8 ante-room. Another commenter recommended clarifying the placement of RABS so that users would not misinterpret the chapter and place RABS in the ante-room instead of the buffer room.

**Response:** Comment incorporated.

**Commentary Summary #146:** Multiple commenters recommended deleting the concepts of CAI and CACI because they are not pharmaceutical isolators.

**Response:** Comment not incorporated. The chapter distinguishes between RABS (e.g., CAI and CACI) and pharmaceutical isolators, and further notes that RABS are not pharmaceutical isolators.

**Commentary Summary #147:** Commenter noted that the use of RABS for handling cytotoxic or high-pharmaceutical-activity compounds is not adequately covered in the chapter.

**Response:** Comment not incorporated. Information on handling of HDs is addressed in <800>.

**Commentary Summary #148:** Multiple commenters requested guidance on how to determine the recovery time after opening the transfer chamber of RABS.

**Response:** Comment incorporated. The manufacturer was added as a potential example of where to obtain the recovery information specific for a RABS.

**Commentary Summary #149:** Commenter noted that there are two types of airflow smoke tests, actual smoke pattern tests and airflow visualization studies. The commenter recommended that the chapter refer to airflow visualization study and specify the frequency of performing such test.

**Response:** Comment not incorporated. The term was changed to dynamic airflow smoke pattern test, which is defined in the glossary as a PEC test in which a visible source of smoke, which is neutrally buoyant, is used to observe air patterns within the unidirectional space (i.e., the DCA) under dynamic operating conditions. Further, the chapter states that the dynamic airflow smoke pattern test must be performed initially and at least every 6 months.

**Commentary Summary #150:** Commenter requested specific manufacturers, makes, and models of RABS and isolators.

**Response:** Comment not incorporated. Based on USP's Code of Ethics, USP cannot endorse a particular organization's products or services. The chapter provides the minimum facility requirement (e.g., PECs and SECs) to help ensure quality CSPs.

**Commentary Summary #151:** Multiple commenters noted that the description of the pharmaceutical isolator is incorrect. For example, the commenter noted that there are no simple doors in the pharmaceutical isolator; there is a hatch-type door that would be used in a transfer airlock.

**Response:** Comment partially incorporated. The description of pharmaceutical isolators was revised and simplified to contain four major elements: controlled workspace, transfer device(s), access devices(s), and integral decontamination system.

**Commentary Summary #152:** Commenter requested clarification on whether a compounding robot would be classified as an isolator. Another commenter recommended describing placement of robotic enclosures.

**Response:** Comment not incorporated. A robotic device would have to meet all of the requirements of the type of PEC described in the chapter in order to be used as a PEC. Further, the chapter states that if a robotic enclosure is used as the PEC, a dynamic airflow smoke visualization pattern test must be performed initially and every 6 months.

**Commentary Summary #153:** Commenter noted that a pharmaceutical isolator should be permitted to be located in an SCA.

**Response:** Comment not incorporated. A pharmaceutical isolator may be located in an unclassified SCA if used only to prepare Category 1 CSPs. A pharmaceutical isolator must be placed in an ISO Class 8 positive-pressure room if used to prepare Category 2 CSPs. An ante-room is not required when using a pharmaceutical isolator. A controlled area helps minimize the risk of microbial contamination, especially with the BUDs in *Table 11* for Category 2 CSPs.

**Commentary Summary #154:** Commenter requested clarification on the difference between a RABS and a pharmaceutical isolator.

**Response:** Comment not incorporated. The chapter describes a RABS as a CAI or CACI, while an isolator contains four major elements: controlled workspace, transfer device(s), access devices(s), and integral decontamination system.

**Commentary Summary #155:** Commenter recommended deleting the reference to ISO 14644-7 standard when describing the pharmaceutical isolator.

**Response:** Comment incorporated.

**Commentary Summary #156:** Commenter noted that a decontamination system should not be required in a pharmaceutical isolator since materials can be adequately decontaminated in the buffer room and then passed into the isolator. Another commenter requested clarification on the decontamination agent and method of delivery (e.g., mist, gas, or spray bottle).

**Response:** Comment not incorporated. One of the elements of a pharmaceutical isolator is an integral decontamination system. The decontamination system is integrated within the isolator and uses a generator to distribute the sporicidal agent throughout the chamber.

**Commentary Summary #157:** Multiple commenters noted that a RABS comprised of a closed system automated device which provides separate and internal protection of the

ISO Class 5 environment should be permitted to be placed in an ISO Class 8 or better environment for preparing Category 2 CSPs.

**Response:** Comment not incorporated. A closed system automated device is not well defined and may be subject to misinterpretation. For preparing Category 2 CSPs, the PEC must be located in a controlled environment to minimize the risk of contamination. Movement of materials in and out of the RABS in unclassified air carries a higher risk of contamination. Placement of the CAI/CACI in a classified area mitigates the risk for CSPs with Category 2 BUDs. The Expert Committee will discuss robotics and automation in compounding at the next compounding workshop.

**Commentary Summary #158:** Commenter requested testing requirements for an isolator and to allow for a BUD of 48 to 72 hours.

**Response:** Comment not incorporated. Pharmaceutical isolators are described in the chapter. A dynamic airflow smoke pattern test must be performed initially and at least every 6 months. Additionally, certification and recertification are required. If the pharmaceutical isolator is placed in an unclassified SCA, the BUDs in *Table 10* apply. If the pharmaceutical isolator is placed in an ISO Class 8 or better room, the BUDs in *Table 11* (which are longer than 48 to 72 hours) apply.

**Commentary Summary #159:** Multiple commenters noted that the pharmaceutical isolator should be placed in an ISO Class 8 or better room and not a buffer room. The term buffer room should not be used for placement of the pharmaceutical isolator because the glossary defines the buffer room as having an ante-room.

**Response:** Comment incorporated.

**Commentary Summary #160:** Commenter noted that dynamic airflow smoke pattern tests every 6 months is too frequent.

**Response:** Comment not incorporated. A dynamic smoke pattern test must be performed at least every 6 months to ensure that the PEC is properly integrated into the facility and that compounders understand how to utilize the unidirectional airflow to maintain first air in the DCA.

**Commentary Summary #161:** Commenter requested clarification on whether the dynamic smoke pattern test must be performed in the PEC or the entire cleanroom.

**Response:** Comment incorporated. The dynamic airflow smoke pattern test must be performed in the PEC.

**Commentary Summary #162:** Multiple commenters noted that <800> does not reference the use of isolators.

**Response:** Comment not incorporated. Isolators may be used to prepare non-hazardous CSPs. The Expert Committee will consider future revisions to <800> to include isolators.

**Commentary Summary #163:** Commenter recommended deleting CAI and CACI because they are not isolators.

**Response:** Comment not incorporated. CAI and CACI are types of RABS that are used in preparing CSPs. RABS are used in many facilities for preparing Category 1 and Category 2 CSPs.

**Commentary Summary #164:** Commenter recommended avoiding the term CACI and CAI and instead referring to them as negative or positive pressure gloveboxes because of the confusion of these with the term isolators.

**Response:** Comment not incorporated. CACI and CAI are terms that have been used in <797>, and RABS is further defined in <1116> *Microbiological Control and Monitoring of Aseptic Processing Environments*. Gloveboxes are not well defined. However, isolators were changed to pharmaceutical isolators in order to better differentiate between CAI/CACI and isolators.

**Commentary Summary #165:** Multiple commenters requested deletion of the statement that an ante-room is not required when using an isolator. The commenter noted that in order to be used, isolators must demonstrate that unfiltered air from the environment cannot enter the isolator during decontamination or compounding procedures.

**Response:** Comments partially incorporated. The text was revised to remove buffer room to minimize the confusion about placement of the pharmaceutical isolators. Pharmaceutical isolators must still undergo dynamic airflow smoke pattern testing and certification.

**Commentary Summary #166:** Commenter recommended changing smoke visualization test to smoke pattern test when describing robotic enclosures.

**Response:** Comment incorporated.

**Commentary Summary #167:** Commenter noted that if the robotic enclosures meet ISO Class 5 or better conditions, placement in an ISO Class 7 room is required.

**Response:** Comment not incorporated. A robotic device would have to meet all of the requirements of the type of PEC described in the chapter in order to be used as a PEC. The placement of the robotic device would be the same as for the PEC (see *Table 3. Summary of Minimum Requirements for Placement of PEC for Compounding Non-HD*).

**Commentary Summary #168:** Commenter recommended moving the statement on placement of CACIs for antineoplastic and/or API HDs to the first paragraph under placement of RABS for better organization.

**Response:** Comment incorporated.

**Commentary Summary #169:** Commenter recommended adding testing time frames to the table of summary requirements for placement of the PEC.

**Response:** Comment not incorporated. Certification and microbial air and surface monitoring are described in subsequent sections.

**Commentary Summary #170:** Commenter recommended adding guidance on the SEC for presterilization procedures to the table of summary requirements for the placement of the PEC.

**Response:** Comment not incorporated. The table is intended to include summary requirements for the placement of the PEC. Information on presterilization activities can be found in the subsection *Facilities Preparing CSPs from Nonsterile Starting Ingredient(s) or Component(s)*.

**Commentary Summary #171:** Multiple commenters noted that the table of summary requirements for placement of the PEC should provide an option for negative-pressure HEPA-filtered air in the ante-room. The commenters also noted that sterile compounding should be permitted in restricted areas that have negative pressure for preparation of adjunct medications in nuclear pharmacy.

**Response:** Comments not incorporated. Category 2 non-hazardous CSPs are required to be compounded in a positive pressure room to minimize the risk of microbial contamination to the environment and to the CSP, especially with the BUDs in *Table 11*

for Category 2 CSPs. Additionally, radiopharmaceutical compounding is described in <825>.

**Commentary Summary #172:** Commenter noted that RABS may be placed in an ISO Class 8 positive-pressure cleanroom if a disinfection system is used (spraying a sporicidal agent through the chamber and on all materials entering and exiting the RABS).

**Response:** Comment not incorporated. For preparing Category 2 CSPs, RABS are required to be placed in an ISO Class 7 positive-pressure buffer room with an ISO Class 8 positive-pressure ante-room. If the PEC meets all the requirements of an isolator, it may be placed in an ISO Class 8 positive-pressure room for preparing Category 2 CSPs.

**Commentary Summary #173:** Commenter recommended that the table of summary requirements for placement of the PEC should specify that facilities may exceed the air quality requirements in the table. Another commenter noted that RABS should be permitted to be placed in an ISO Class 7 positive-pressure buffer room with an ISO Class 7 positive-pressure ante-room.

**Response:** Comment not incorporated. The table is intended to provide minimum requirements for placement of the PEC for compounding non-HDs. Facilities may place the PEC in a higher-quality environment than that described in the chapter.

**Commentary Summary #174:** Commenter noted that isolators should be required to be placed in an ISO Class 7 positive-pressure buffer room with an ISO Class 8 positive-pressure ante-room.

**Response:** Comment not incorporated. Isolators are designed to ensure a higher level of air quality during compounding and can be expected to maintain such a workplace if placed in an ISO Class 8 or better environment.

**Commentary Summary #175:** Commenter noted that the table of minimum requirements for placement of the PEC should describe negative-pressure buffer rooms.

**Response:** Comment not incorporated. The table is intended to describe requirements for the PEC for compounding non-HDs. Placement of C-PECs for HD compounding is described in General Chapter <800>.

**Commentary Summary #176:** Commenter noted that all devices must be placed in at least ISO Class 7 for preparing Category 1 CSPs.

**Response:** Comment not incorporated. Category 1 CSPs may be prepared in an unclassified SCA. An unclassified SCA provides a flexible approach for facilities that do not have a cleanroom suite in order to provide needed medications for patients. The risk of an unclassified SCA is mitigated by facility design requirements described in the chapter and the shorter BUDs.

**Commentary Summary #177:** Commenter noted that the table of summary requirements for placement of the PEC should address placement of robots.

**Response:** Comment not incorporated. A robotic device would have to meet all of the requirements of the type of PEC described in the chapter in order to be used as a PEC. The placement requirements of the PEC would apply to the robotic device if it meets all of the requirements of the PEC.

**Commentary Summary #178:** Commenter noted that the different air changes per hour (ACPH) should not be required if other requirements are met (e.g., ISO

classification). Another commenter noted that professional judgement must be incorporated with regard to exposure and containment level.

**Response:** Comment not incorporated. ACPH helps maintain ISO classification and microbial state of control. ACPH is consistent with the current version of <797> as well as industry guidelines (e.g., [FDA Guidance: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice](#)) and <1116>. Further, ACPH provides an objective measurement to monitor the quality of the classified compounding areas.

**Commentary Summary #179:** Commenter noted that typical ISO Class 7 environments have more than 60 ACPH, and operators should be wearing aseptic bunny suits.

**Response:** Comment not incorporated. The chapter states that the ISO Class 7 area must have  $\geq 30$  ACPH. The ACPH requirement may need to be higher based on several factors as described in the chapter.

**Commentary Summary #180:** Commenter requested clarification on how many personnel are permitted in the classified areas.

**Response:** Comment not incorporated. The list of factors is intended to provide examples of situations where higher ACPH requirements may be necessary, but the number of personnel that can be permitted in the classified area may depend on the facility design.

**Commentary Summary #181:** Commenter requested a reference to the ACPH requirements in the chapter.

**Response:** Comment not incorporated. The ACPH requirements in the chapter are based on the previous version of the chapter and industry guidelines (e.g., [FDA Guidance: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice](#)).

**Commentary Summary #182:** Commenter recommended adding the definition of dynamic operating condition.

**Response:** Comment incorporated.

**Commentary Summary #183:** Commenter noted that air from the RABS unit is not HEPA filtered and thus cannot be part of the ACPH.

**Response:** Comment not incorporated. A RABS is required to provide HEPA-filtered ISO Class 5 unidirectional air.

**Commentary Summary #184:** Multiple commenters recommended revising the language to state that ACPH from the HVAC system must be documented, and if the PEC is used to meet the ACPH requirement, that must also be documented. The commenter noted that the PEC may not be used to meet the minimum total ACPH requirement.

**Response:** Comment not incorporated. The chapter states that the ACPH from HVAC and PEC, as well as total ACPH, must be documented. If the ACPH from the PEC is zero, then zero may be the number that is documented.

**Commentary Summary #185:** Commenter noted that for the ISO Class 8 room, at least half of the ACPH can come from the PEC.

**Response:** Comment partially incorporated. A bullet was added to state that at least 15 ACPH of the total air change rate in a room must come from the HVAC through HEPA filters located in the ceiling.

**Commentary Summary #186:** Commenter noted that the ACPH should be documented on the certification report to prove a state of control. The commenter noted that exceeding 20 ACPH in a room designed for 50 ACPH may cause confusion for inspectors.

**Response:** Comment not incorporated. The chapter states that the ACPH requirements are the minimum requirements in the ISO Class 7 and ISO Class 8 rooms. Higher ACPH may be required based on the factors listed in the chapter. Additionally, the Expert Committee determined that ACPH is not the only consideration for determining whether there is a state of control.

**Commentary Summary #187:** Commenter recommended using criteria other than ACPH for validating cleanrooms.

**Response:** Comment not incorporated. A cleanroom must meet the facility requirements in the chapter, including but not limited to ACPH, positive-pressure differential, and ISO classification to help ensure quality CSPs.

**Commentary Summary #188:** Commenter noted that the continuous pressure-gradient monitoring between each classified room requires infrastructure changes, and monitoring will be an ongoing expense. Commenter recommended that continuous pressure-gradient monitoring not be required.

**Response:** Comment not incorporated. When pressure differentials are required, a pressure-monitoring device must be used to continuously monitor the pressure differential. Pressure differentials are important to ensure that air is flowing from higher-quality air to lower-quality air. There are numerous options for pressure-monitoring devices, and the chapter requires that the quantitative results of pressure monitoring be reviewed and documented at least daily on days when compounding is occurring.

**Commentary Summary #189:** Commenter recommended that the pressure-differential monitoring system should have a digital display and must be capable of a resolution of at least 0.001. Several commenters additionally noted that pressure monitoring must be quantitative.

**Response:** Comment not incorporated. The Expert Committee decided that it would be too prescriptive to specify the type and specification of the pressure-differential monitoring device. The chapter does further specify that the quantitative results from the pressure-monitoring system must be reviewed and documented at least daily on the days when compounding is occurring.

**Commentary Summary #190:** Commenter noted that pressure-monitoring systems that have electronic or audible alerts should not be required to be monitored daily.

**Response:** Comment not incorporated. The Expert Committee determined that there should still be daily review of the pressure in the classified rooms to ensure that the pressure is maintained at the appropriate level during compounding activities.

**Commentary Summary #191:** Commenter requested clarification on whether there was a maximum positive-pressure recommendation.

**Response:** Comment not incorporated. There is no maximum positive-pressure recommendation. The chapter requires that the positive pressure not be less than 0.02 inches of water column.

**Commentary Summary #192:** Commenter requested guidance on remediation and action plans for situations where the positive-pressure differential is outside of the required range.

**Response:** Comment not incorporated. Facilities must determine the appropriate remediation and corrective action in the event that the positive-pressure differential is outside of the required range. This may depend on facility-specific factors such as the circumstances causing the loss of required pressure, as well as consideration of whether any CSPs are impacted.

**Commentary Summary #193:** Commenter noted that the pressure differential should be expressed to the thousandth place, for example 0.020, to assist with rounding.

**Response:** Comment incorporated.

**Commentary Summary #194:** Commenter requested that deviations be allowed for instances where the positive-pressure differential may be less than 0.02 inches of water column. Further, the commenter requested guidance on how long the pressure may be out of the specified range. Another commenter requested that fluctuations from 0.02 inches of water column be allowed.

**Response:** Comment not incorporated. The chapter requires that the positive-pressure differential be at least 0.020 inches of water column at all times. Facilities must determine the appropriate remediation and corrective action in the event that the positive-pressure differential is outside of the required range.

**Commentary Summary #195:** Multiple commenters requested specifying that the SCA be unclassified.

**Response:** Comment not incorporated. The SCA is by definition unclassified.

**Commentary Summary #196:** Multiple commenters requested clarification on how to test the pressure-monitoring device for accuracy. Other commenters noted that manufacturers have different verification procedures that should be followed. Other commenters noted that this should be performed every 12 months or be performed by the certifier.

**Response:** Comment partially incorporated. The accuracy testing was removed. Users should refer to the manufacturer of the pressure-monitoring device for calibration and verification of accuracy.

**Commentary Summary #197:** Commenter recommended adding a statement that an action plan must be put in place for excursions, including evaluation of excursion effects on drug product integrity.

**Response:** Comment not incorporated. Facilities must determine the appropriate remediation and corrective action in the event that the positive-pressure differential is outside of the required range. This may depend on facility-specific factors such as the circumstance causing the loss of required pressure and consideration of whether any CSPs are impacted. Previous commenters have noted difficulty in evaluating whether CSPs have been impacted. The assessment must be facility-specific and determined by the designated person.

**Commentary Summary #198:** Commenter noted that a dynamic smoke pattern test must be performed initially and every 6 months thereafter to ensure proper movement of room air and to show that the pressure differential is consistent across the openings.

**Response:** Comment not incorporated. A dynamic smoke pattern test performed in a PEC is different from a visual smoke study, which is performed in an ISO Class 7 and ISO Class 8 room. Certification is further described in 5. *Certification and Recertification*.

**Commentary Summary #199:** Several commenters requested clarification on whether the presterilization procedures can be performed in the buffer room, ante-room, or PEC.

**Response:** Comment incorporated. The chapter states that presterilization procedures must be performed in no worse than an ISO Class 8 environment.

**Commentary Summary #200:** Commenter recommended allowing nonsterile components to be weighed in unclassified areas.

**Response:** Comment not incorporated. If preparing Category 2 CSPs, presterilization procedures, including weighing and measuring, must be performed in an ISO Class 8 or better environment to minimize the microbial bioburden in the materials handled.

**Commentary Summary #201:** Multiple commenters noted that presterilization procedures should be performed in an ISO Class 8 room that is not part of the cleanroom suite to minimize the risk of adversely affecting the air quality in the SEC. The commenter noted that the ISO Class 8 room for presterilization procedures should not be required to meet the ACPH and positive-pressure differential.

**Response:** Comment not incorporated. Presterilization procedures must be performed in at least an ISO Class 8 environment to reduce the risk of contamination to the CSP. Many facilities do not have a separate ISO Class 8 room that is separate from the ante-room to perform presterilization activities. However, if facilities do have a separate room, the room should still meet the ACPH and positive-pressure requirements to minimize the microbial bioburden during the presterilization procedures.

**Commentary Summary #202:** Commenter recommended changing the “must” requirement that presterilization procedures be done in at least an ISO Class 8 environment to a “should” recommendation.

**Response:** Comment not incorporated. If preparing Category 2 CSPs from nonsterile component(s), presterilization procedures are required to be performed in an ISO Class 8 or better environment to minimize the microbial bioburden.

**Commentary Summary #203:** Commenter noted that presterilization procedures should be permitted in the ISO Class 5 PEC provided the PEC has been cleaned and disinfected.

**Response:** Comment incorporated. The chapter states that presterilization procedures may be performed in a single-use containment glove bag, containment ventilated enclosure (CVE), BSC, or CACI to minimize the risk of airborne contamination.

**Commentary Summary #204:** Multiple commenters recommended deleting the requirement for presterilization procedures to be performed in a CVE, BSC, or CACI, or specifying how to perform presterilization procedures in <800>.

**Response:** Comment not incorporated. The standard for presterilization procedures is intended to minimize the risk of airborne contamination. Standards specific for handling HDs are in <800>. The Expert Committee will consider future revisions to <800> in order to provide more specific guidance on presterilization procedures.

**Commentary Summary #205:** Multiple commenters noted that BSCs and CACIs are designed to provide ISO Class 5 air quality and would not be necessary for presterilization activities. Further, the commenter noted that CVEs are not defined in the chapter and are specified only in <800>.

**Response:** Comment partially incorporated. The chapter states that presterilization procedures may be performed in a single-use containment glove bag, CVE, BSC, or

CACI to minimize the risk of airborne contamination. CVEs are also described in the revision of <795> for particle-generating activities.

**Commentary Summary #206:** Multiple commenters noted that the requirement to perform presterilization procedures in a CVE, BSC, or CACI would require the purchase of additional equipment. The commenter suggested changing this to a “should” recommendation.

**Response:** Comment not incorporated. The Expert Committee decided that it is important to minimize the risk of airborne contamination during presterilization procedures. The chapter was revised to permit the use of single-use containment glove bags for particle containment during presterilization activities.

**Commentary Summary #207:** Commenter recommended that the CVE, BSC, and CACI used for presterilization procedures must be certified at least every 6 months.

**Response:** Comment incorporated.

**Commentary Summary #208:** Commenter recommended deleting the reference to 3. *Personal Hygiene and Garbing* for presterilization procedures because sterile gloves should not be required for handling nonsterile components. Another commenter noted that only gloves, gowns, and masks should be required.

**Response:** Comments not incorporated. Personnel must perform proper hand hygiene and don appropriate garbing when entering the ISO Class 8 during presterilization procedures. Sterile gloves are required to minimize the microbial bioburden when handling components during presterilization procedures.

**Commentary Summary #209:** Several commenters requested that the acronym “CVE” be removed because it may appear as an endorsement of a particular brand of enclosure manufacturer.

**Response:** Comment not incorporated. CVE is intended to be a generic term to refer to a type of device. The term was first used and described in <800> and additionally was used in <795>.

**Commentary Summary #210:** Commenter requested that the chapter address laminate wood.

**Response:** Comment not incorporated. The chapter states that surfaces must be smooth, impervious, free from cracks and crevices, and non-shedding. The facility must evaluate and select the specific materials to be used.

**Commentary Summary #211:** Commenter recommended prohibiting shelving and cabinets and instead requiring movable rack shelving because shelving and cabinetry do not allow for proper air circulation in the cleanroom.

**Response:** Comment not incorporated. Facilities have the flexibility to use shelving, cabinets, and movable rack shelving. Air circulation and other environmental conditions should be verified through certification and microbial air and surface monitoring as described in the chapter.

**Commentary Summary #212:** Commenter recommended stating that all surfaces in the classified areas must be smooth, instead of listing the types of surfaces (e.g., surfaces of ceilings, walls, floors, doors, door frames, fixtures, shelving, work surfaces, counters, and cabinets)

**Response:** Comment not incorporated. The Expert Committee decided that it was important to list the surfaces in the classified areas to help ensure that facilities consider all of these surfaces.

**Commentary Summary #213:** Commenter recommended adding a statement that where room and furniture installations are difficult to clean, effective mitigating work practices must be developed, followed, and documented in SOPs.

**Response:** Comment not incorporated. This addition could cause confusion about the definition of difficult to clean, and users might seek guidance on mitigating work practices. Facilities must follow SOPs for cleaning and disinfecting (see 7. *Cleaning, Disinfecting, and Applying Sporicidal Agents in Compounding Areas*).

**Commentary Summary #214:** Multiple commenters noted that surfaces must be resistant to damage by cleaning agents, disinfectants, and tools used to clean. Commenter noted that this should be a requirement and not a recommendation.

**Response:** Comment not incorporated. Comments on previous revisions to the chapter noted that it is impossible to show and prove that all surfaces are resistant to cleaning agents, disinfectants, and tools used to clean. For example, micro-abrasions to surfaces that are not visible to the naked eye are difficult for facilities to detect.

**Commentary Summary #215:** Multiple commenters recommended deleting the statement that ceiling panels may otherwise be sealed and secure.

**Response:** Comment incorporated.

**Commentary Summary #216:** Commenter recommended that the term scrubbable either be defined or removed from the chapter.

**Response:** Comment incorporated. Deleted the term scrubbable.

**Commentary Summary #217:** Commenter recommended removing the term soil-resistant from the chapter because it may be subject to various interpretations by regulatory bodies.

**Response:** Comment incorporated.

**Commentary Summary #218:** Commenter recommended deleting the phrase “designed for use in a cleanroom” because it may imply a type of qualification.

**Response:** Comment incorporated.

**Commentary Summary #219:** Multiple commenters noted that floors may be coved to the sidewalls but this should not be a requirement. The commenter noted that it is sufficient for the juncture between the floor and wall panel to be sealed. Other commenters noted that modular cleanrooms have silicon sealant around the bottom of the walls to the floor and will not be coved to the sidewalls.

**Response:** Comment incorporated.

**Commentary Summary #220:** Commenter recommended removing the statement that floors must be smooth, sealed, and impervious because it is previously stated in the chapter.

**Response:** Comment incorporated.

**Commentary Summary #221:** Commenter recommended requiring the SCA to be placed inside a pharmacy or requiring the SCA to be a separate room inside the pharmacy.

**Response:** Comment not incorporated. The SCA design is intended to allow facilities the flexibility to prepare Category 1 CSPs with shorter BUDs. The facility designed requirements for an SCA are described in the chapter. The Expert Committee decided that it would be too restrictive to require the SCA be placed in a particular location. Further, the definition of a SCA states that the SCA may be a space, area, or room with a defined perimeter.

**Commentary Summary #222:** Commenter noted that the ceiling of the SCA must be clean, uncluttered, and dedicated to compounding.

**Response:** Comment partially incorporated. Previous commenters have noted that ceilings are not cluttered and it may not be practical for some facilities to change the ceiling type in an unclassified SCA. However, *Table 8* does specify that ceilings of the SCA are required to be cleaned, disinfected, and wiped with a sporicidal agent when visibly soiled and when surface contamination is known or suspected.

**Commentary Summary #223:** Commenter recommended that the chapter should emphasize that only sterile preparations may be prepared in an SCA.

**Response:** Comment not incorporated. The SCA is described in the context of sterile compounding. Further, the glossary definition of SCA states that only Category 1 CSPs may be prepared in a PEC located in an SCA.

**Commentary Summary #224:** Commenter noted that the examples of surfaces in the SCA (e.g., walls, floors, counters, and equipment) imply that the SCA must be a separate room.

**Response:** Comment not incorporated. The SCA is defined as an unclassified space, area, or room with a defined perimeter that contains a PEC and is suitable for preparation of Category 1 CSPs only.

**Commentary Summary #225:** Multiple commenters noted that surfaces in the SCA must be smooth, impervious, free from cracks and crevices, and non-shedding. Commenters noted that this should be a requirement and not a recommendation.

**Response:** Comment not incorporated. Previous commenters noted that it is difficult to require such surfaces for the unclassified SCA. The SCA design is intended to allow facilities the flexibility to prepare Category 1 CSPs with shorter BUDs. The specifications for the surfaces are recommendations and not requirements.

**Commentary Summary #226:** Commenter recommended clarification of whether ceilings are included in the surfaces of the SCA that should be smooth, impervious, free from cracks and crevices, and non-shedding.

**Response:** Comment not incorporated. The recommendations for the surfaces in the SCA apply to all surfaces including the ceiling.

**Commentary Summary #227:** Commenter recommended reorganizing the section to separate the requirements for the cleanroom and the SCA.

**Response:** Comment incorporated.

**Commentary Summary #228:** Commenter recommended deleting the statement that the sink must not be located within the perimeter of the SCA because otherwise the garbing sequence would increase the risk of contamination and negate the benefits of hand washing.

**Response:** Comment not incorporated. In SCA design, the sink must be located at least 1 meter away from the PEC, and the sink must be placed outside the perimeter of the SCA to help minimize the risk of contamination, especially from water sources. Facilities should determine the appropriate garbing order based on the location of the sink. The garbing order must be documented in the facility's SOP.

**Commentary Summary #229:** Commenter requested clarification on garbing order if the sink is placed outside of the ante-room.

**Response:** Comment not incorporated. The order of hand washing and garbing should be determined by the facility and should depend on the placement of the sink.

**Commentary Summary #230:** Multiple commenters noted that <800> requires the sink to be placed in the ante-room at least 1 meter away from the entrance of the buffer room. Commenters requested that the requirements for <797> and <800> be aligned.

**Response:** Comment not incorporated. The requirements for sink placement in <797>, either inside or outside of the ante-room, do not conflict with the requirements in <800>. However, the Expert Committee will consider future revisions to <800> to align the standards for placement of the sink.

**Commentary Summary #231:** Multiple commenters recommended that the sink must be required to be located inside the ante-room. The sink is required for hand hygiene, and allowing the sink to be outside of the ante-room would require either garbing outside the ante-room or garbing and exiting the ante-room to perform hand hygiene.

**Response:** Comment not incorporated. The order of hand washing and garbing should be determined by the facility and should depend on the placement of the sink. For example, in facilities where the sink is placed outside the ante-room, personnel may perform hand hygiene before entering the ante-room to garb.

**Commentary Summary #232:** Commenter requested clarification on where the sink should be placed if it is located inside of the ante-room.

**Response:** Comment incorporated.

**Commentary Summary #233:** Commenter requested guidance on how far away the sink should be placed outside of the ante-room.

**Response:** Comment not incorporated. The distance of the sink to the ante-room should be determined by the facility to help facilitate appropriate hand hygiene and garbing procedures.

**Commentary Summary #234:** Commenter recommended specifying that sink placement inside of the ante-room is recommended.

**Response:** Comment not incorporated. Facilities should have the flexibility to determine the location of their sink. If the sink is placed outside of the ante-room, it must be located in a clean space to minimize the risk of bringing in contaminants.

**Commentary Summary #235:** Multiple commenters requested clarification on whether the sink may be placed on the clean or dirty side of the ante-room.

**Response:** Comments incorporated.

**Commentary Summary #236:** Commenter noted that the sink must be placed on the clean side of the ante-room.

**Response:** Comment not incorporated. The chapter provides flexibility to facilities to locate the sink either on the clean or the dirty side of the ante-room. The order of hand washing and garbing should be determined by the facility and should depend on the placement of the sink.

**Commentary Summary #237:** Commenter recommended prohibiting plumbed water sources instead of just water sources.

**Response:** Comment incorporated.

**Commentary Summary #238:** Commenter recommended making the list of water sources examples instead of an all-inclusive list.

**Response:** Comment incorporated.

**Commentary Summary #239:** Commenter recommended adding a detailed description for sinks and eye wash fixtures. For example, the commenter recommended specifying that the handwashing sink must provide running hot and cold or tempered potable

water; allowing the use of wrist-blade type faucets; and describing self-closing or metering faucets. The commenter added that any emergency fixture (i.e., eyewash) must be piped independently of the faucet and must deliver tepid water within the American National Standards Institute (ANSI) temperature range.

**Response:** Comment not incorporated. The Expert Committee decided that the additional descriptions are too prescriptive. Requirements such as these may also conflict with laws and regulations of the applicable jurisdiction.

**Commentary Summary #240:** Commenter recommended rewording the chapter to state that sprinkler systems should be recessed and covered and the covers should be cleanable.

**Response:** Comment incorporated.

**Commentary Summary #241:** Commenter noted that recessed and covered sprinkler systems must be included in the facility's surface sampling plan.

**Response:** Comment partially incorporated. Requiring surface sampling of sprinkler covers may be too burdensome. The chapter does require that each classified area be sampled, and sampling sites must be determined by the facility and described in the facility's SOPs, which can include sprinkler systems (see *6.3 Monitoring Surfaces for Viable Particles*).

**Commentary Summary #242:** Commenter noted that the placement of the sink with respect to the SCA is irrelevant because of the short BUD and because the PEC is required to pass certification and microbial air and surface sampling.

**Response:** Comment not incorporated. Sinks are a water source and may be a potential source of microbial contamination. Placement of the sink away from the PEC additionally helps minimize the risk of splashing.

**Commentary Summary #243:** Commenter recommended removing the requirement for hands-free doors and faucets.

**Response:** Comment not incorporated. Hands-free doors and faucets are recommended and not required.

**Commentary Summary #244:** Commenter noted that it is important for all the furniture, equipment, and materials used during compounding to be present during certification. Commenter recommended adding that all furniture, equipment, and other materials must be cleaned and disinfected and present in the cleanroom suite and ISO Class 5 PEC during certification.

**Response:** Comment not incorporated. The subsection is intended to describe the placement and movement of materials. The subsection additionally specifies that proper placement of the PEC must be initially verified by a dynamic airflow smoke pattern test. Certification is described in *6. Certification and Recertification*, and cleaning and disinfecting are described in *7. Cleaning, Disinfecting, and Applying Sporidical Agents in Compounding Areas*.

**Commentary Summary #245:** Multiple commenters noted that shipping cartons and other corrugated and uncoated cardboard should not be permitted in the ante-room at all and not just prohibited from the clean side of the ante-room.

**Response:** Comment incorporated.

**Commentary Summary #246:** Commenter suggested changing "certain items" to "certain materials" to refer to the prohibition of shipping cartons and other corrugated and uncoated cardboard.

**Response:** Comment partially incorporated. Revised statement to prohibit shipping cartons and other corrugated and uncoated cardboard from classified areas or the SCA.

**Commentary Summary #247:** Commenter noted that shipping cartons and other corrugated and uncoated cardboard should not be permitted in the SCA.

**Response:** Comment incorporated.

**Commentary Summary #248:** Commenter requested clarification on whether the prohibition of paper towels applies to low-lint paper towels used to dry hands.

**Response:** Comment incorporated. Eliminated examples of paper towels and tissues.

**Commentary Summary #249:** Commenter recommended reorganizing the subsection to separate information related to placement and movement of materials from information related to materials that are required to be wiped with an appropriate disinfectant.

**Response:** Comment incorporated. Information on wiping items with sterile 70% IPA was moved to 8. *Introducing Items into the SEC and PEC.*

**Commentary Summary #250:** Commenter recommended reorganizing the information related to carts to streamline the information.

**Response:** Comment incorporated.

**Commentary Summary #251:** Commenter requested more specific criteria for the type of carts permitted (e.g., wired stainless steel).

**Response:** Comment not incorporated. Carts are required to be constructed from nonporous materials, which may include stainless steel. The facility must determine the appropriate equipment to use. The equipment should be low-shedding and easily cleaned and disinfected.

**Commentary Summary #252:** Commenter recommended adding rationale for why non-essential items are not permitted in the clean side of the ante-room. For example, the commenter noted that non-essential items are likely to generate an excessive amount of particulate.

**Response:** Comment not incorporated. The intent of the chapter is to provide minimum standards to help ensure quality CSPs. Certain materials, such as shipping cartons and corrugated or uncoated cardboard, may have particulate matter and increase the risk of microbial contamination. There may be additional considerations as to why certain materials should not be permitted in the classified areas.

**Commentary Summary #253:** Commenter noted that material should be transferred through an airlock into the ISO Class 7 classified area and should be disinfected on the way in. The commenter further noted that the material should have a defined residence time in the airlock after disinfection. The commenter also noted that carts used in the unclassified areas of the facility must never enter the classified areas.

**Response:** Comment not incorporated. Airlocks and interlocking doors are not required in the chapter. Further, the chapter does not require the use of pass-throughs for material transfers. If used, the chapter requires that both doors must never be opened at the same time.

**Commentary Summary #254:** Commenter recommended deleting the statement that carts must not be moved from the dirty side to the clean side of the ante-room unless the entire cart, including casters, is cleaned and disinfected. The commenter noted that if the cart does not leave the ante-room, it should not be required to be cleaned and disinfected.

**Response:** Comment not incorporated. Carts should not move from the dirty side to the clean side of the ante-room to minimize the risk of transferring microbial contamination. If moved, the cart must be cleaned and disinfected to reduce the particulates and microbial bioburden potentially on the cart.

**Commentary Summary #255:** Commenter noted that the statement that only equipment necessary for performing compounding can be in the PEC is too restrictive and prohibits necessary equipment such as computer hardware from being placed in the PEC.

**Response:** Comment not incorporated. Only equipment necessary for compounding is permitted in the PEC to help minimize the risk of microbial contamination to the environment and to the PEC. If computer hardware or other equipment (e.g., pumps) is required for compounding, it is permitted in the PEC.

**Commentary Summary #256:** Multiple commenters recommended changing smoke visualization study to dynamic airflow smoke pattern test.

**Response:** Comment incorporated.

**Commentary Summary #257:** Multiple commenters noted that the dynamic airflow smoke pattern test is additionally used to identify any resulting change to the location and size of the DCA and verify that the DCA is sufficient for compounding.

**Response:** Comments not incorporated. The Expert Committee decided that the additional test was too prescriptive. The intent of the dynamic airflow smoke pattern test is to verify that the placement of material demonstrates minimal disruption. The suggested text may imply that there is a requirement to measure the size of the DCA and map the location of the DCA within the PEC.

**Commentary Summary #258:** Commenter noted that dynamic smoke pattern tests should only be required for initial entry of equipment into the PEC.

**Response:** Comment incorporated.

**Commentary Summary #259:** Commenter recommended adding a cross-reference to *5. Certification and Recertification* when describing the dynamic smoke pattern tests.

**Response:** Comment not incorporated. A dynamic smoke pattern test may need to be performed outside of certification and recertification (e.g., initial placement of a new device).

**Commentary Summary #260:** Commenter requested clarification on whether the dynamic airflow smoke pattern test needs to be repeated if equipment inside the PEC is moved.

**Response:** Comment incorporated.

**Commentary Summary #261:** Commenter recommended requiring new equipment (e.g., PECs, carts, refrigerators, etc.) to be wiped with a cleaning agent until the wipers come away visually clean, after which all surfaces of the item must be cleaned with an EPA-registered, sporicidal one-step disinfectant cleaner.

**Response:** Comment not incorporated. The Expert Committee decided that the added language may be too prescriptive and subject to misinterpretation. Further, cleaning, disinfecting, and applying a sporicidal agent are described in *7. Cleaning, Disinfecting, and Applying Sporicidal Agents in Compounding Areas*.

## 5. Certification and Recertification

**Expert Committee-initiated Change #1:** The section on certification and recertification was moved to a separate section to improve the organization and flow of the chapter. Subsequent sections were renumbered accordingly.

**Commentary Summary #1:** Commenter noted that the chapter should require certification to be performed by an independent and qualified individual.

**Response:** Comment not incorporated. Facilities must select the certifier or vendor to use for certification and recertification. Previous commenters requested clarification on who is deemed qualified and how to verify such qualification. Further, some qualification programs may not be available at all locations or countries where the standard is applied.

**Commentary Summary #2:** Commenter recommended expanding certification to include cleaning validation.

**Response:** Comment not incorporated. Surface sampling is useful for evaluating cleaning and disinfecting procedures (see *6.3 Monitoring Surfaces for Viable Particles*).

**Commentary Summary #3:** Commenter noted that the Controlled Environment Testing Association (CETA) certification guide allows for RABs to be placed outside of the cleanroom suite to prepare Category 2 CSPs and thus should allow Category 2 CSPs to be prepared in these types of facility designs.

**Response:** Comment not incorporated. RABs must be placed in a cleanroom suite to prepare Category 2 CSPs; otherwise, they would qualify for Category 1 BUDs.

**Commentary Summary #4:** Commenter requested deletion of the reference to the CETA certification guide.

**Response:** Comment not incorporated. Previous commenters have requested guidance on which certification to use. The chapter states that the CETA certification guide or an equivalent guideline may be used.

**Commentary Summary #5:** Several commenters noted that there is no equivalent guide for certification and recommended deleting the option for an equivalent guide.

**Response:** Comment not incorporated. The Expert Committee wanted to allow flexibility in case there are other equivalent certification guides, especially in other countries where the standard may be used.

**Commentary Summary #6:** Commenter requested clarification on whether the SCA must be certified.

**Response:** Comment not incorporated. The chapter specifies that classified areas are required to be certified. Unclassified SCAs do not need to be certified. However, PECs are required to be certified.

**Commentary Summary #7:** Commenter recommended adding the number of personnel present in each PEC and SEC to the documentation during certification.

**Response:** Comment incorporated.

**Commentary Summary #8:** Multiple commenters noted that certification should be required only initially and when there are changes to the facility. Another commenter recommended allowing latitude on the frequency of recertification for facilities that perform routine total particulate count testing. Commenter additionally noted that there is no need to require smoke testing on an annual or more frequent schedule unless physical changes have been made to the facility. Another commenter noted that routine

or continuous environmental monitoring during dynamic conditions will sufficiently assess HEPA issues. The commenter noted that certification does not provide value because it only assesses filter integrity and functionality of the PEC.

**Response:** Comments not incorporated. Certification is required at least every 6 months to help ensure that the classified rooms continue to meet the air quality requirements. 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.

**Commentary Summary #9:** Commenter recommended deleting state-of-the-art when describing electronic equipment for total particle count testing. Another commenter recommended changing to “calibrated.”

**Response:** Comments incorporated.

**Commentary Summary #10:** Commenter recommended changing smoke pattern test to airflow visualization studies. Commenter recommended expanded airflow visualization to include fluid dynamics airflow studies, thermodynamic airflow studies, and smoke visualization studies. The commenter noted that the studies should be well documented, and videotape or other recording mechanisms are useful in assessing airflow.

**Response:** Comment not incorporated. The dynamic airflow smoke pattern test is defined as a PEC test in which a visible source of smoke, which is neutrally buoyant, is used to observe air patterns within the unidirectional space (i.e., the DCA) under dynamic operating conditions. Facilities should refer to certification guidelines for more specific and granular information on performing certification and documenting the results.

**Commentary Summary #11:** Commenter requested clarification on who can perform the certification.

**Response:** Comment not incorporated. The facility must select the appropriate person or vendor to perform certification as described in the chapter.

**Commentary Summary #12:** Commenter recommended changing the description of the dynamic airflow smoke pattern test as referring to the critical sites and not the preparation(s).

**Response:** Comment not incorporated. Certification must be performed during dynamic operating conditions. Air must sweep over all items in the PEC, and the compounder must ensure that the air sweeps over and away from the preparation(s).

**Commentary Summary #13:** Commenter noted that recertification should not be required if there are minor repairs. Another commenter requested clarification on whether construction includes removing doors, caulking, drilling, or painting.

**Response:** Comments not incorporated. The chapter states that recertification must be performed when there is construction or other alteration in the configuration of the room that would affect airflow or air quality. If minor repairs do not change the area or alter the configuration of the room in a way that could affect airflow or air quality, recertification may not be required.

**Commentary Summary #14:** Commenter noted that certification and recertification reports should be reviewed by designated person(s) and not a single designated person.

**Response:** Comment incorporated.

**Commentary Summary #15:** Commenter recommended stating that sterile operations must not be resumed before recertification after there has been construction or changes to the HEPA filter because there is no assurance that the classified room can maintain the required ISO classification or unidirectional air.

**Response:** Comment not incorporated. This addition may create confusion as to when compounding may be resumed (e.g., when certification procedures are completed, or when the final certification report is received). Further, other commenters have noted concerns that restricting compounding while awaiting certification results will interfere with providing critical therapies to patients.

**Commentary Summary #16:** Commenter recommended adding a statement that data collected in response to corrective action must be reviewed to confirm that the actions taken have been effective.

**Response:** Comment incorporated.

**Commentary Summary #17:** Commenter recommended adding a statement that a monitoring program for nonviable particles providing the recommended levels of air cleanliness must be included in the ongoing certification and recertification process.

**Response:** Comment not incorporated. The certification requirements include total particle count monitoring.

**Commentary Summary #18:** Commenter noted that the facility must obtain training records for the contractor performing certification.

**Response:** Comment not incorporated. Facilities must determine the appropriate documentation to obtain from certifiers and vendors.

**Commentary Summary #19:** Commenter suggested that it is unclear what approach to take when the environment is out-of-specification, and suggested including whether compounding must stop until corrective actions have taken place. Another commenter suggested that cleaning and disinfection must take place in the event of a power failure.

**Response:** Comments not incorporated. A corrective action plan must be implemented and documented based on the facility in response to any out-of-range results. Cleaning and disinfection procedures after a power failure should be determined by the facility SOPs based on the type of equipment used, monitoring implemented, and length of power outage.

**Commentary Summary #20:** Commenter requested clarification on the monitoring program and whether it implies continuous monitoring.

**Response:** Comment not incorporated. The chapter requires certification, which includes measuring total airborne particles, at least every 6 months. The chapter does not require continuous monitoring.

**Commentary Summary #21:** Commenter recommended requiring nonviable airborne particle sampling more frequently than every 6 months. Another commenter recommended performing the sampling monthly.

**Response:** Comments not incorporated. The chapter is intended to provide the minimum standard for preparing quality CSPs. Facilities may perform nonviable airborne particle sampling more frequently than every 6 months.

**Commentary Summary #22:** Commenter recommended changing nonviable airborne particle sampling to total particle airborne sampling because electronic particle counters do not distinguish between viable and nonviable air contaminants.

**Response:** Comment incorporated.

**Commentary Summary #23:** Commenter recommended referring to the ISO standard for performing nonviable particle sampling.

**Response:** Comment not incorporated. ISO classifications are summarized in *Table 2*, and certification should be performed as described in the certification guidelines.

**Commentary Summary #24:** Commenter noted that the areas of greatest risk in the PEC are not adequately defined in the chapter.

**Response:** Comment not incorporated. The sampling locations must be determined by the facility and should be specific for the PEC.

**Commentary Summary #25:** Commenter recommended allowing certifiers to specify the sampling sites and procedures instead of requiring that they be described in the facility SOPs.

**Response:** Comment not incorporated. Facilities must select the appropriate sampling sites within the PEC and the facility. Facilities may work with certifiers but cannot rely on certifiers' SOPs; the facility must have its own SOPs.

**Commentary Summary #26:** Commenter recommended restructuring the sentence on examples of corrective actions.

**Response:** Comment not incorporated. The chapter provides examples of corrective actions, and the structure of the sentence is similar to others placed where this information is given.

**Commentary Summary #27:** Commenter recommended removing the discussion of evaluation of trends if total airborne particle testing is only performed every 6 months.

**Response:** Comment not incorporated. The chapter is intended to provide the minimum standards for preparing quality CSPs. Facilities may perform the testing more frequently than every 6 months and may evaluate the trends. Further, facilities may also evaluate trends with sampling every 6 months.

**Commentary Summary #28:** Commenter recommended adding a requirement that after corrective action has been taken, total airborne particle sampling should be performed again to ensure that the corrective action was successful.

**Response:** Comment partially incorporated. A statement was added that data collected in response to corrective actions must be reviewed to confirm that the actions taken have been effective.

## **6. Microbiological Air and Surface Monitoring**

**Expert Committee-initiated Change #1:** The section number was revised to align with the re-numbering of other sections.

**Commentary Summary #1:** Commenter noted that the cfu of microorganisms detected during microbiological air and surface monitoring should be identified by a qualified microbiologist in an accredited laboratory.

**Response:** Comment not incorporated. Facilities should determine the qualifications and accreditation requirements when selecting vendors.

**Commentary Summary #2:** Commenter noted that the previous version of the chapter required identification of a cfu, at least to the genus level, during air and surface sampling while the revised chapter only requires identification if the air and surface sample results exceed the action levels in *Table 5* and *Table 6*, respectively.

**Response:** Comment not incorporated. The Expert Committee took note of the public comments that described the burden of identifying microorganisms on samples that do not exceed the action levels in *Table 5* and *Table 6*. Further, the frequency of surface sampling may not allow adequate time for identification, remediation, and continuation of compounding if each cfu has to be identified regardless of whether the action levels were exceeded.

**Commentary Summary #3:** Commenter requested the ability to replace sampling on TSA with sampling on two types of media [e.g., TSA and malt extract agar (MEA) or sabouraud dextrose agar (SDA)] to shorten the incubation time.

**Response:** Comment incorporated.

**Commentary Summary #4:** Commenter recommended adding a statement to require review of corrective actions to confirm that actions taken have been effective.

**Response:** Comment incorporated.

**Commentary Summary #5:** Commenter recommended clarifying that the chapter pertains to viable air and surface monitoring.

**Response:** Comment partially incorporated. Changed to microbiological air and surface monitoring.

**Commentary Summary #6:** Commenter recommended adding text that says to consider a trend of out-of-specification samples rather than basing the evaluation on one out-of-specification sample.

**Response:** Comment not incorporated. The microbiological air and surface monitoring program should evaluate all samples and will provide useful information to assess risks for contamination, potential routes of contamination, and the adequacy of cleaning and disinfection agents and procedures.

**Commentary Summary #7:** Commenter recommended adding examples of practices where microbiological airborne and surface sampling may be helpful in assessing personnel (e.g., hand hygiene and garbing, material handling and conduct in controlled environments).

**Response:** Comment not incorporated. The chapter is intended to provide examples of practices that sampling may help assess personnel. Further, the chapter states that the results of sampling must be reviewed in conjunction with personnel data.

**Commentary Summary #8:** Commenter noted that the adequacy of cleaning and disinfection in some areas must be validated by viable sampling weekly, monthly, every 3 months, or every 6 months.

**Response:** Comment not incorporated. The adequacy of cleaning and disinfecting procedures must be determined by reviewing data from sampling. Results from air and surface sampling must be reviewed in conjunction with personnel data to help assess the state of control and to identify potential causes. Further, facilities may perform sampling more frequently than described in the chapter.

**Commentary Summary #9:** Commenter recommended changing regular review of sampling data to review every 3 months. Another commenter requested clarification on the frequency of review.

**Response:** Comments not incorporated. Facilities must determine how often to perform reviews of the sampling data to detect trends.

**Commentary Summary #10:** Commenter recommended deleting the sentence that requires regular review of sampling data.

**Response:** Comment not incorporated. Sampling data must be reviewed to detect any potential trends.

**Commentary Summary #11:** Commenter suggested revising the chapter to state that data must also be reviewed following corrective actions in accordance with facility SOPs to confirm that the actions taken have been effective in achieving required air and surface quality levels.

**Response:** Comment partially incorporated. Facilities must follow SOPs, which can include reviewing data to determine subsequent actions.

**Commentary Summary #12:** Multiple commenters recommended deleting the “such as” elements that may be detected on review of sampling data (i.e., elevated microbial bioburden, elevated levels of nonviable particulates, or other adverse changes).

**Response:** Comments incorporated.

**Commentary Summary #13:** Commenter requested clarification on what must be trended.

**Response:** Comment not incorporated. Microbial air and surface sampling procedures and action levels are described in subsequent sections. Results from air and surface sampling must be trended.

**Commentary Summary #14:** Commenter noted that the review of sampling results should be a recommendation and not a “must” requirement.

**Response:** Comment not incorporated. Microbial air and surface sampling results must be reviewed in conjunction with personnel data to assess the state of control and to identify potential risks of contamination. Such reviews are required to be documented to help ensure that they were performed.

**Commentary Summary #15:** Commenter recommended clarifying that “adverse findings” refers to action levels in *Table 2*, *Table 5*, and *Table 6* for the microbiological air and surface quality levels.

**Response:** Comment incorporated. The body of the paragraph references the respective tables.

**Commentary Summary #16:** Multiple commenters recommended adding a statement that the effectiveness of the corrective action must be verified.

**Response:** Comments incorporated.

**Commentary Summary #17:** Multiple commenters noted that corrective action must be taken in accordance with facility SOPs to confirm that the actions have been effective in achieving the required air and surface quality levels.

**Response:** Comments not incorporated. Facilities must determine the appropriate action levels based on the specific situation. The evaluation may be described in the SOP; however, each type of corrective action may require a case-specific investigation and corrective action that might not be specified in the SOP.

**Commentary Summary #18:** Commenter requested clarification on whether microbiological air and surface monitoring must be performed during dynamic operating conditions.

**Response:** Comment not incorporated. The chapter states that microbiological air and surface monitoring must be performed during dynamic operating conditions.

**Commentary Summary #19:** Commenter recommended changing “minimum frequencies” to “at least according to the minimum frequencies.”

**Response:** Comment not incorporated. The term “minimum frequencies” is generally understood among users, and users may perform sampling more frequently than described in the chapter.

**Commentary Summary #20:** Multiple commenters recommended changing “specific limits” to “specified level” when referring to microbiological air and surface sampling.

**Response:** Comments incorporated.

**Commentary Summary #21:** Commenter noted that air and surface sampling must be conducted during dynamic operating conditions, except within the PEC, because the chapter additionally states that care should be taken to avoid distributing airflow within the PEC.

**Response:** Comment not incorporated. Not disturbing the unidirectional airflow within the PEC refers to total airborne particulate monitoring. Microbiological air and surface sampling must be conducted in all classified areas during dynamic operating conditions.

**Commentary Summary #22:** Commenter requested clarification on how to perform air and surface sampling during dynamic operating conditions. For example, the commenter requested the development of instructions in an FAQ or box with bullet points.

**Response:** Comment not incorporated. Procedures on how to perform active air sampling and surface sampling are described in *Box 6-1* and *Box 6-2*. The procedures to be used during dynamic operating conditions must be facility-specific.

**Commentary Summary #23:** Multiple commenters requested a definition or examples of servicing of facilities or equipment that would require microbiological air and surface sampling.

**Response:** Comments not incorporated. Servicing is intended to refer to construction or other repairs that would require additional sampling.

**Commentary Summary #24:** Commenter recommended adding a statement that sampling must be performed in accordance with the facility’s SOPs.

**Response:** Comment not incorporated. The section states that the air and surface monitoring program must be clearly described in the facility’s SOP.

**Commentary Summary #25:** Commenter recommended adding specific language to state that during the commissioning of new facilities and equipment, sampling of viable air and surfaces must occur in association with certification activities and at least during one additional instance. Commenter also noted that results from both sampling occurrences must not exceed designated action levels.

**Response:** Comment not incorporated. The chapter states that microbiological air and surface monitoring must be performed initially. The use of “commissioning” may be misinterpreted (e.g., new facilities, reconstructions, etc.). Further, the chapter states that the sampling must be performed at the specific frequencies described in the chapter as well as any of the listed circumstances.

**Commentary Summary #26:** Commenter requested specific examples of circumstances where air and surface sampling must be repeated, and requested guidelines for awaiting sampling results. Another commenter requested specifics on how long the power outage can last before sampling must be performed again.

**Response:** Comments not incorporated. The chapter lists circumstances in which microbiological air and surface sampling must be repeated. The facility must develop facility-specific SOPs to include the frequencies, procedures, sampling locations, and

potential remediation and corrective actions. The facility must determine the appropriate remediation and corrective action depending on the circumstances and whether the action levels are exceeded.

**Commentary Summary #27:** Commenter recommended adding language to require trending of samples that are out-of-specification instead of evaluating one out-of-specification result.

**Response:** Comment not incorporated. Microbial air and surface sampling results must be evaluated and should be trended to assess the risk of contamination, potential routes of contamination, and the adequacy of cleaning and disinfecting agents and procedures.

**Commentary Summary #28:** Multiple commenters noted that sampling must be repeated as part of an investigation of an identified excursion in sterility test results, identification of recurring organisms, and repeated failure of personnel testing.

**Response:** Comments not incorporated. The chapter more broadly states that sampling must be repeated in response to identified programs and identified trends. Examples are provided in a bulleted list.

**Commentary Summary #29:** Commenter requested clarification on whether microbiological air and surface sampling must be repeated for the person or for the entire staff.

**Response:** Comment not incorporated. The section refers to microbiological and surface sampling that is performed in the facility, not specifically for each personnel.

**Commentary Summary #30:** Commenter recommended changing the example of changes to the sterile compounding environment to changes to both cleaning and disinfecting agents.

**Response:** Comment not incorporated. Cleaning agents are listed as an example. There may be other examples such as disinfecting agents and sporicidal agents, or facilities may use a one-step disinfecting agent.

**Commentary Summary #31:** Multiple commenters noted that certifiers and vendors may supply the maps and procedures for the microbiological air and surface sampling, and this information should not be required in the facility's SOPs.

**Response:** Comments not incorporated. Facilities must determine their own facility-specific microbiological air and surface sampling program. Vendors and certifiers may assist in developing the SOP, but the facility must have their own SOPs.

**Commentary Summary #32:** Commenter requested examples of SOPs and procedures for collecting air and surface samples, depending on the products used.

**Response:** Comment not incorporated. Procedures for performing viable airborne sampling and surface sampling are described in *Box 6-1* and *Box 6-2*. SOPs must be facility-specific.

**Commentary Summary #33:** Multiple commenters requested guidelines on suggested locations where sampling must be performed (e.g. size of location, number of locations). Other commenters recommended adding a table to display the number of sample locations based on volume or to provide a formula with which this can be calculated.

**Response:** Comments not incorporated. The selection of sampling locations must be facility-specific, based on the size of the facility and the activities performed in the classified areas. The sampling locations must be representative of the conditions throughout the area.

**Commentary Summary #34:** Commenter noted that air and surface sampling should be recommended (rather than required) to be performed during dynamic operating conditions because it would not be possible to obtain samples when compounding is occurring.

**Response:** Comment partially incorporated. Dynamic operating conditions is defined to mean conditions in the compounding area in which operating personnel are present and simulating or performing compounding. Simulated compounding activities may be occurring during sampling.

**Commentary Summary #35:** Commenter recommended adding a statement that air monitoring devices must not disrupt unidirectional airflow and must be sterile when brought into the ISO Class 5 PEC.

**Response:** Comment not incorporated. The section states that the monitoring program must be designed and conducted in a manner that minimizes the chance that sampling will contribute to contamination of the CSP and environment.

**Commentary Summary #36:** Commenter recommended deleting “however” when describing the monitoring program.

**Response:** Comment incorporated.

**Commentary Summary #37:** Commenter recommended defining the training and documentation requirements for proper operation of the air and surface sampling equipment.

**Response:** Comment not incorporated. The training and documentation requirements should be determined by the facility.

**Commentary Summary #38:** Commenter recommended adding “active” when describing air sampling devices.

**Response:** Comment incorporated.

**Commentary Summary #39:** Commenter recommended adding a statement that personnel performing sampling must also have demonstrated competency in hand hygiene and garbing. If they are sampling in the ISO 5 PEC, they must also have successfully completed the hand hygiene and garbing competency as well as three instances of initial gloved fingertip sampling.

**Response:** Comment not incorporated. Personnel and vendors performing air and surface sampling must be trained. The chapter further states that personnel entering the compounding area must perform hand hygiene and don proper garbing. The Expert Committee determined that the additional requirements may be too prescriptive.

**Commentary Summary #40:** Commenter noted that personnel performing air and surface sampling must be properly trained unless the sampling is performed by an outside vendor.

**Response:** Comment not incorporated. Individuals performing air and surface sampling must be properly trained regardless of whether they are staff at the facility or vendors.

**Commentary Summary #41:** Commenter recommended the additional language that use of settling plates for qualitative air sampling may not be able to determine adequately the quality of air in the controlled environment.

**Response:** Comment not incorporated. The chapter requires active airborne sampling.

**Commentary Summary #42:** Commenter noted that the frequency of performing viable air sampling every 6 months is inadequate to assess the state of control in classified areas and does not provide enough data points for trending. Commenter suggested

monitoring at least quarterly, with a more frequent schedule (at least monthly) when performing higher-risk processes such as nonsterile to sterile compounding. Several commenters recommended more frequent monitoring (e.g., daily or weekly).

**Response:** Comment not incorporated. The chapter is intended to provide the minimum standard to help ensure the quality of CSPs. Facilities are required to perform viable air sampling at least monthly. Facilities and regulatory bodies may adopt requirements that are different from and more stringent than those in the chapter.

**Commentary Summary #43:** Multiple commenters recommended increasing the allowable concentration of viable airborne particles and specifying the wait time before sampling.

**Response:** Comments not incorporated. The ISO-classified areas must meet the action levels for viable airborne sampling in *Table 5* to help ensure control over the classified areas. The appropriate wait time and specific sampling program should be facility specific. Vendors and equipment manufacturers may help facilities determine the appropriate waiting time.

**Commentary Summary #44:** Multiple commenters requested clarification that viable airborne sampling is only required in the classified areas.

**Response:** Comments not incorporated. The section states that a monitoring program must be developed and implemented to assess microbiological air quality in all classified areas.

**Commentary Summary #45:** Commenter requested a definition of every 6 months.

**Response:** Comment not incorporated. Every 6 months is commonly understood to require sampling at least once in 6 months (e.g., 180 days).

**Commentary Summary #46:** Commenter recommended increasing the frequency of monitoring to at least quarterly (e.g., every 3 months) to assess the state of control. The commenter noted that semi-annual monitoring does not provide adequate data points to conduct trending analysis of viable microorganisms.

**Response:** Comment not incorporated. The Expert Committee supports more frequent monitoring. However, many commenters noted that more frequent monitoring is burdensome and impractical for many facilities.

**Commentary Summary #47:** Commenter recommended requiring repeat viable airborne sampling 1 month after failed results in order to ensure that the corrective actions are appropriate.

**Response:** Comment partially incorporated. An additional statement was added that data collected in response to corrective actions must be reviewed to confirm that the actions taken have been effective.

**Commentary Summary #48:** Commenter recommended changing TSA medium to TSA.

**Response:** Comment incorporated.

**Commentary Summary #49:** Commenter noted that if fungal-selective media are no longer acceptable, a specific statement should be included to state that fungal-selective media may not be used for duplicate plate sampling.

**Response:** Comment not incorporated. The chapter states that general growth media that support growth of bacteria and fungi must be used. Further examples of growth media are specified in *Box 6-1*.

**Commentary Summary #50:** Commenter requested clarification on how long media can be refrigerated before they must be used or discarded.

**Response:** Comment not incorporated. Facilities should refer to information from the manufacturer about the specific media. Further, the chapter states that the facility should verify that the media meet the expected growth promotion, pH, and sterilization requirements as determined from the COA.

**Commentary Summary #51:** Commenter recommended moving the information about the general growth media from the subsection on *Sampling Procedures* to *6.1 General Monitoring*.

**Response:** Comment not incorporated. The information is pertinent to the sampling procedures and should be addressed where other procedural information is provided.

**Commentary Summary #52:** Several commenters recommended removing the requirement for an incubator to be calibrated because manufacturers have indicated that certain thermometers on incubators cannot be calibrated. Another commenter requested clarification on the definition of a calibrated incubator. Multiple commenters noted that the incubator must be calibrated annually to a NIST standard.

**Response:** Comments not incorporated. Incubators should be verified and/or calibrated as specified by the manufacturer.

**Commentary Summary #53:** Commenter noted that the incubator temperature must be monitored daily during incubation.

**Response:** Comment partially incorporated. The section was revised to require the incubator temperature to be monitored as described in the facility's SOPs. Further, other commenters have noted that they are not open daily and may not be able to monitor incubation temperatures daily.

**Commentary Summary #54:** Commenter requested guidance on developing an action plan for temperature excursions in the incubator and for evaluating the impact of the excursion on sample integrity.

**Response:** Comment not incorporated. Facilities must determine the appropriate corrective action plan and evaluate the samples on a case-by-case basis. For example, facilities must evaluate the cause of the temperature excursion, determine how the excursion occurred, and evaluate whether the excursion impacted the samples.

**Commentary Summary #55:** Commenter requested clarification of the term "microbiological incubator."

**Response:** Comment incorporated. Changed to incubator.

**Commentary Summary #56:** Multiple commenters recommended adding that the incubator "must be placed outside of the sterile compounding area and away from areas of drug storage and product labeling/packaging."

**Response:** Comments not incorporated. Facilities must determine the appropriate location for placement of the incubator. Facilities must consider the risk of contamination and the size of the facility. The suggested wording may raise concerns about the proper distances for placement of the incubator.

**Commentary Summary #57:** Commenter requested clarification on the training requirements for air sampling.

**Response:** Comment partially incorporated. Eliminated statement on training for air sampling because it was described in *6.1 General Monitoring Requirements*. Training requirements must be determined by the facility.

**Commentary Summary #58:** Commenter requested guidance on cleaning the air sampling device.

**Response:** Comment not incorporated. Facilities should follow the manufacturer's instructions for operation, maintenance, and cleaning of the air sampling device.

**Commentary Summary #59:** Commenter requested guidance on how to ensure that vendors and certifiers are following the active air sampling procedures described in the chapter.

**Response:** Comment not incorporated. Facilities must work with vendors and certifiers to ensure that the appropriate sampling procedures are implemented.

**Commentary Summary #60:** Commenter requested clarification of whether the active air sampling procedures are "must" requirements or "should" recommendations.

**Response:** Comment not incorporated. *Box 6-1* describes the required procedures for active air sampling. The procedure also allows manufacturer's instructions to be followed to operate the air sampling device.

**Commentary Summary #61:** Multiple commenters recommended changing the alternative incubation method using 2 samples to 30°–35° for 48 hours and then 20°–25° for 5 days.

**Response:** Comments incorporated.

**Commentary Summary #62:** Commenter noted that the air sampling device must be NIST traceable and must be calibrated annually.

**Response:** Comment not incorporated. The chapter states that the device must be serviced and calibrated as recommended by the manufacturer.

**Commentary Summary #63:** Multiple commenters recommended revising *Box 6-1* to specify the procedures, to include opening the sampler, covering it, and retrieving the device.

**Response:** Comments not incorporated. Facilities must follow the manufacturer's instructions for operation of the active air sampling device. The Expert Committee determined that the additional language would be too prescriptive.

**Commentary Summary #64:** Commenter recommended changing the en-dashes between temperature ranges to the word "to" to clarify the temperature range.

**Response:** Comment not incorporated. Temperature ranges are described with an en-dash, which is consistent with the USP Style Guide.

**Commentary Summary #65:** Commenter requested clarification on whether incubation at 20°–25° can be at room temperature if temperature is monitored daily.

**Response:** Comment not incorporated. The chapter states that samples must be incubated in an incubator.

**Commentary Summary #66:** Commenter requested clarification on how to record the results if two samples are collected for active air sampling.

**Response:** Comment incorporated.

**Commentary Summary #67:** Commenter recommended requiring the air sample volume to be 500 L or less to save time, money, and downtime. Another commenter noted that 400 L of air is sufficient for the PEC.

**Response:** Comments not incorporated. Facilities should collect at least 1000 L of air for air sampling. The action levels in *Table 5* are based on 1000 L of air per plate.

**Commentary Summary #68:** Multiple commenters noted that air samples do not need to be incubated for an additional 5 days at 20°–25°.

**Response:** Comments not incorporated. Incubation at two temperatures facilitates the recovery of a broader range of microorganisms.

**Commentary Summary #69:** Commenter noted that the alternative incubation method with two samples should be done according to the manufacturer's instructions and should be aligned with <1116>.

**Response:** Comment partially incorporated. The alternative incubation method was revised to be consistent with <1116>. Manufacturers of air sampling devices may not always provide the incubation conditions. The incubation conditions provided in *Box 6-1* are designed to maximize the recovery of potential microorganisms.

**Commentary Summary #70:** Commenter recommended that two individual plates be used for the alternative incubation method in *Box 6-1*.

**Response:** Comment not incorporated. *Box 6-1* requires two samples to be collected for each sample location and incubated concurrently if the alternative incubation method is used.

**Commentary Summary #71:** Commenter requested the addition of language that specifies that the action plan must be reviewed to confirm that the actions taken have been effective.

**Response:** Comment incorporated.

**Commentary Summary #72:** Commenter noted concerns about the remediation plan, especially if it involves closing the pharmacy, investigating the source and root cause, cleaning, and retesting. Another commenter requested clarification on whether compounding can occur if the action levels are exceeded.

**Response:** Comments not incorporated. The chapter states that the corrective action plan must be dependent on the cfu count and the microorganism recovered. Facilities must investigate and implement the appropriate corrective action on a case-by-case basis. Facilities must make the determination of whether compounding can continue based on the investigation and the corrective action.

**Commentary Summary #73:** Multiple commenters requested clarification on how to count the total number of cfu when the alternative incubation method is used.

**Response:** Comments incorporated.

**Commentary Summary #74:** Commenter recommended adding language on recording the cfu count if a single plate was used for incubation.

**Response:** Comment not incorporated. Active air sampling procedures are described in *Box 6-1*.

**Commentary Summary #75:** Commenter recommended changing "plate" to "media device" in *Box 6-1*.

**Response:** Comment incorporated.

**Commentary Summary #76:** Commenter recommended deleting the incubation conditions in *Box 6-1* and allowing facilities to incubate samples according to the manufacturer's recommendations.

**Response:** Comment not incorporated. The incubation conditions described in *Box 6-1* are intended to provide the minimum standard for viable air samples to help ensure consistent monitoring and recovery of microorganisms.

**Commentary Summary #77:** Commenter noted that identification of microorganisms should be performed with the assistance of a microbiologist from an accredited laboratory.

**Response:** Comment not incorporated. Facilities must select the appropriate microbiologist or vendor to use in identification of microorganisms. There may be different accreditation organizations that may not be accessible by all facilities and countries where the standard is applied.

**Commentary Summary #78:** Commenter recommended adding a reduction in BUD during investigation as a corrective action if air sampling results exceed action levels described in the chapter.

**Response:** Comment not incorporated. The chapter provides examples of corrective actions for air sampling results that exceed the action levels in the chapter. Shortening BUDs is not a corrective action that would remedy the cause of the failure. Facilities must investigate and implement the appropriate corrective action on a case-by-case basis.

**Commentary Summary #79:** Commenter requested a definition of deviation.

**Response:** Comment not incorporated. Deviation is a generic term that in this case refers to any nonconformity in the sampling results (e.g., exceeding the action levels for sampling results).

**Commentary Summary #80:** Commenter recommended requiring identification of the microorganisms to the genus level if the cfu is recovered in the ISO Class 5 PEC.

**Response:** Comment not incorporated. The chapter requires identification of the cfu to the genus level if the air sampling results exceed those in *Table 5*. *Table 5* has an action level of >1; thus, the presence of >1 cfu in the ISO Class 5 PEC will require identification to the genus level.

**Commentary Summary #81:** Multiple commenters noted that all recovered cfu must be identified. The commenter noted that otherwise, pathogenic microorganisms may exist and not be mitigated. Multiple other commenters recommended identification of any pathogenic microorganism regardless of cfu count.

**Response:** Comments 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.

**Commentary Summary #82:** Commenter suggested that microorganisms must be identified to the species level, not the genus level.

**Response:** Comment not incorporated. The microorganisms must be identified to the genus level if the cfu counts exceed the action levels in *Table 5*. Facilities may identify the microorganisms to the species level. However, fungal samples may not have a species for identification.

**Commentary Summary #83:** Multiple commenters noted that identification of the microorganism should be a “should” recommendation instead of a “must” requirement because it is costly and time consuming.

**Response:** Comments not incorporated. The microorganisms must be identified to the genus level if the cfu counts exceed the action levels in *Table 5*. The identification will help facilities investigate the cause and implement the corrective action.

**Commentary Summary #84:** Multiple commenters recommended changing all of the action levels in *Table 5* to greater than or equal to ( $\geq$ ) instead of greater than ( $>$ ) to be consistent with the FDA guidance.

**Response:** Comments not incorporated. The action levels are consistent with the [FDA Guidance for Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practices](#).

**Commentary Summary #85:** Commenter recommended deleting the statement that surface sampling is important because transfer of microbial contamination from improperly disinfected work surfaces is a potential source of contamination. The commenter recommended deleting this statement because there are other potential sources that are not addressed.

**Response:** Comment incorporated.

**Commentary Summary #86:** Commenter recommended deleting the statement that surface sampling is useful for evaluating facility cleaning and material handling procedures, work surface cleaning and disinfecting procedures, and personnel competency in work practices such as cleaning and disinfecting of component and/or vial surfaces.

**Response:** Comment not incorporated. The Expert Committee decided that the statement provides a useful introduction about surface sampling.

**Commentary Summary #87:** Commenter noted that cleaning validation must be done as part of the certification of the PEC and SEC.

**Response:** Comment not incorporated. The chapter states that surface sampling is useful for evaluating facility cleaning. Facilities may perform surface sampling as part of their certification or may implement additional cleaning validation.

**Commentary Summary #88:** Commenter noted that <1116> and <797> are contradictory and <1116> should not be referenced.

**Response:** Comment not incorporated. Reference to <1116> is provided for informational purposes.

**Commentary Summary #89:** Commenter noted that since surface sampling is not required in the unclassified SCA, these facilities will not be able to trend surface sampling results.

**Response:** Comment not incorporated. Previous commenters noted that it was unnecessary to perform surface sampling in unclassified SCAs because cfu will invariably be collected and there may not be value in the results. Surfaces within the PEC located in an SCA are required to be sampled.

**Commentary Summary #90:** Commenter recommended clarifying that surface sampling is not required around the PEC in the SCA.

**Response:** Comment not incorporated. The chapter only requires surface sampling in classified areas. Surface sampling is not required in the unclassified SCA.

**Commentary Summary #91:** Multiple commenters recommended revising the surface sampling areas to include the surface of the DCA and the equipment.

**Response:** Comments not incorporated. The chapter specifies that surface sampling must be performed in the interior of the PEC and the equipment contained in it.

**Commentary Summary #92:** Multiple commenters noted that surface sampling should only be required for classified areas where aseptic processing occurs. Commenter noted that surface sampling should not be required for classified areas where only presterilization procedures are performed.

**Response:** Comments not incorporated. Surface sampling must be performed in all classified areas to help ensure a state of control and to minimize the microbial bioburden in classified areas.

**Commentary Summary #93:** Commenter requested additional clarification on surface sampling in staging or work areas and on frequently touched surfaces. Other commenters requested a definition of frequently touched surfaces or removal of the requirement to sample frequently touched surfaces. Another commenter requested the addition of electronic devices, hand controls, scanners, and bins to the sampling requirements.

**Response:** Comments not incorporated. The intent of the list is to identify general classified areas where surface sampling must be performed. The specific sampling locations must be facility specific and must be documented in the facility's monitoring program.

**Commentary Summary #94:** Commenter recommended that surface sampling must be required in the PEC, and surface sampling should be recommended for other locations such as the staging or work area and frequently touched surfaces.

**Response:** Comment not incorporated. The intent of the list is to identify general classified areas where surface sampling must be performed. Staging or work areas and frequently touched surfaces must be sampled to help ensure a state of control and to monitor for potential contaminants.

**Commentary Summary #95:** Commenter recommended referring to ISO air standards to help ensure that an adequate number of samples are obtained by the certifier.

**Response:** Comment not incorporated. Facilities must implement a microbiological air and surface sampling program that specifies the locations to be sampled, the number of sampling locations, and the frequency of sampling.

**Commentary Summary #96:** Commenter noted that a pass-through may be unclassified and noted that listing it as a classified area that must be surface sampled may imply a requirement that the pass-through be classified.

**Response:** Comment incorporated. Removed pass-through from the list of areas that must be sampled.

**Commentary Summary #97:** Commenter noted that surface sampling should not be required to be performed at the end of the compounding activity or shift. Another commenter noted that sampling at the end of compounding activities will lead to failures and recommended that sampling occur after cleaning. Another commenter requested clarification on frequency of sampling if there are multiple shifts. Another commenter noted that surface sampling should be performed during active operation of compounding.

**Response:** Comments not incorporated. Surface sampling should be performed at the end of the compounding activity or shift. If surfaces are cleaned and disinfected before surface sampling, it provides false-negative results. Facilities must determine the appropriate times to sample (e.g., after which shift to sample; whether to rotate shifts for sampling). Sampling during active compounding may risk contamination of the environment or the CSP.

**Commentary Summary #98:** Commenter suggested that surface sampling of non-work surfaces must be performed at least quarterly.

**Response:** Comment not incorporated. Facilities must implement a monitoring program that describes the location of sampling sites and frequency of sampling. At a minimum, the sites listed in the chapter must be sampled. Surface sampling must occur at least monthly to help ensure continued microbial monitoring between recertifications every 6 months.

**Commentary Summary #99:** Commenter recommended adding language to require thorough sanitization after sampling.

**Response:** Comment not incorporated. Sanitization is not described in the chapter. The chapter notes that surfaces must be cleaned and disinfected after sampling.

**Commentary Summary #100:** Commenter requested clarification on the exact type of media that may be used.

**Response:** Comment partially incorporated. *Box 6-2* provides examples of media that may be used. Facilities must determine the appropriate sampling device and media to be used.

**Commentary Summary #101:** Commenter recommended specifying that only contact plates are required to have a raised convex surface.

**Response:** Comment partially incorporated. Changed to a broader term to refer to surface sampling devices. These devices must have a raised convex surface.

**Commentary Summary #102:** Commenter recommended adding surface sampling procedures for using a swab method, including the minimum size of area that must be sampled.

**Response:** Comment not incorporated. Facilities must determine the specific locations to sample. Further, the chapter states that when sampling irregular surfaces and difficult-to-reach locations, sterile swabs wetted with sterile water or a sterile neutralizing buffer may be used. The chapter also references <1116> for additional information on sampling.

**Commentary Summary #103:** Commenter recommended revising the procedures for surface sampling in *Box 6-2* to be similar to the procedures for viable airborne sampling in *Box 6-1*.

**Response:** Comment incorporated.

**Commentary Summary #104:** Commenter recommended revising *Box 6-2* to require sanitization of the sample site. Another commenter recommended more specific requirements to clean and disinfect. Another commenter recommended removing sterile 70% IPA when referring to cleaning the sampled area. Commenter recommended revising the statement to require removal of residue with sterile 70% IPA.

**Response:** Comments partially incorporated. Revised *Box 6-2* to require removing residue with sterile 70% IPA after sampling. Further cleaning and disinfecting procedures must be performed as described in *7. Cleaning, Disinfecting, and Applying Sporicidal Agents in Compounding Areas*.

**Commentary Summary #105:** Commenter recommended removing the requirement for wipers to be sterile.

**Response:** Comment incorporated.

**Commentary Summary #106:** Commenter recommended changing the alternative surface sampling incubation to 30°–35° for no less than 48 hours.

**Response:** Comment incorporated.

**Commentary Summary #107:** Commenter requested clarification on whether incubation at 20°–25° can be done in the general room if the temperature of the room is maintained and documented daily.

**Response:** Comment not incorporated. The chapter requires samples to be incubated in an incubator.

**Commentary Summary #108:** Multiple commenters recommended deleting the requirement to incubate surface samples at 20°–25° for no less than 5 days. Another commenter recommended removing the need to incubate at two temperatures.

**Response:** Comments not incorporated. Incubation at two temperatures facilitates the recovery of a broader range of microorganisms.

**Commentary Summary #109:** Commenter recommended allowing surface samples to be incubated as recommended by the manufacturer.

**Response:** Comment not incorporated. The incubation conditions described in *Box 6-2* are intended to provide the minimum standards to help ensure consistent monitoring and recovery of microorganisms. Some manufacturers of sampling devices may not provide incubation conditions.

**Commentary Summary #110:** Multiple commenters recommended allowing air and surface sampling procedures that are alternatives to those described in *Box 6-1* and *Box 6-2*.

**Response:** Comments not incorporated. The procedures in *Box 6-1* and *Box 6-2* are intended to provide minimum standards for viable air and surface sampling to help ensure consistent monitoring and recovery of microorganisms.

**Commentary Summary #111:** Commenter recommended deleting the procedures on irregular surface sampling.

**Response:** Comment incorporated.

**Commentary Summary #112:** Multiple commenters recommended changing the incubation conditions for the Box on using devices for sampling irregular surfaces. Some commenters requested revisions to the Box including plating the TSA with neutralizers; requiring determination of the swabs sampling method recovery; allowing an alternative to the traditional pour plate processing of swabs; removing the alternative incubation method; and defining the extraction step. Some commenters requested clarifications to the Box on wiping the residue after sampling. Other commenters noted that the use of swabs for surface sampling should be restricted to independent, qualified individuals and should only be performed during certification and recertification.

**Response:** Comment not incorporated. The Box describing procedures for surface sampling of irregular surfaces was removed based on public comments.

**Commentary Summary #113:** Several commenters recommended requiring surface sampling every 3 months, 6 months, or annually. Some noted that surface sampling can only be performed during certification. Another commenter suggested that surface sampling should be a “should” recommendation and not a “must” requirement. Another commenter noted that monthly surface sampling is a major change from the previous version of the chapter, which required periodic surface sampling.

**Response:** Comment not incorporated. Surface sampling every 6 months may be too infrequent to identify potential problems. The Expert Committee determined that monthly sampling provides monitoring to ensure control of the classified area in between the viable air monitoring and the certification requirements every 6 months. In

addition, stakeholders and previous commenters had requested clarification on the definition of periodic.

**Commentary Summary #114:** Commenter recommended delineating surface sampling for Category 1 and Category 2 CSPs. Further, surface sampling for Category 2 CSPs may be further divided into CSPs prepared from nonsterile components and CSPs prepared from only sterile starting components.

**Response:** Comment not incorporated. The Expert Committee decided that monthly sampling provides monitoring to ensure control of the classified area in between the viable air monitoring and certification requirements every 6 months. Ensuring control of the classified area is important regardless of whether only Category 1 or Category 2 CSPs are prepared. Further, surface sampling is required only for classified areas and not required for unclassified areas in the SCA.

**Commentary Summary #115:** Commenter recommended specifying whether compounding can continue if surface sampling action levels are exceeded.

**Response:** Comment not incorporated. The chapter states that the corrective action plan must be dependent on the cfu count and the microorganism(s) recovered. Facilities must investigate and implement the appropriate corrective action on a case-by-case basis. Facilities must make the determination on whether compounding can continue based on the investigation and the corrective action.

**Commentary Summary #116:** Multiple commenters noted that the action level for pathogenic organisms should be  $> 1$  or  $\geq 1$ .

**Response:** Comment not incorporated. The surface sampling action level for ISO Class 5 areas is  $> 3$ . Previous commenters noted concerns that the term highly pathogenic may be interpreted differently by different users. Further, most microorganisms are potentially pathogenic if they contaminate CSPs.

**Commentary Summary #117:** Commenter suggested that the action levels should be applied to “both devices” instead of “each device.”

**Response:** Comment not incorporated. Facilities may perform surface sampling in multiple sites and may have more than two devices.

**Commentary Summary #118:** Commenter recommended clarifying the requirements for recording results if the alternative, two-sample incubation method is used for surface sampling.

**Response:** Comment incorporated. *Box 6-2* was revised to specify procedures for counting and recording the surface sampling results.

**Commentary Summary #119:** Commenter recommended adding a statement that any pathogenic microorganisms, regardless of cfu count, require corrective action, which must be documented. Alternatively, the commenter recommended adding a statement that any microorganism recovered in the ISO Class 5 PEC must be identified with the assistance of a microbiologist.

**Response:** Comment not incorporated. The chapter states that if surface sampling results exceed the levels in *Table 6*, an attempt must be made to identify any microorganisms recovered at least to the genus level. Previous commenters have noted difficulty or concerns with practicality to require identification of every cfu encountered, especially with the frequency of monitoring required.

**Commentary Summary #120:** Commenter recommended changing the action levels of surface sampling to be similar to the action levels for air sampling. Another commenter requested clarification on why the air and surface sampling action levels are different.

**Response:** Comment not incorporated. 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>.

**Commentary Summary #121:** Several commenters recommended lowering the action levels of surface sampling in *Table 6* to ensure an aseptic processing environment.

**Response:** Comment not incorporated. 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.

**Commentary Summary #122:** Commenter recommended combining the action levels for air and surface sampling.

**Response:** Comment not incorporated. Air and surface sampling are described separately and thus their action levels are described in separate subsections and separate tables.

**Commentary Summary #123:** Several commenters recommended identification of any highly pathogenic microorganism regardless of cfu count.

**Response:** Comment not incorporated. The term highly pathogenic may be interpreted differently among users. Further, most microorganisms are potentially pathogenic if they contaminate CSPs.

**Commentary Summary #124:** Commenter noted that the identification of microorganisms if the action level of > 50 is exceeded is cost-prohibitive.

**Response:** Comment not incorporated. Facilities should obtain the assistance of a microbiologist for identifying microorganisms to the species 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.

**Commentary Summary #125:** Commenter recommended adding a statement to require review of data collected in response to corrective action to confirm that the actions taken have been effective.

**Response:** Comment incorporated.

**Commentary Summary #126:** Commenter requested clarification on application of the action level on cfu recovery from two devices collected at a single device.

**Response:** Comment incorporated. The chapter was revised to state that the action levels are applied to each device. Further, *Table 6* states that the action level is presented as cfu/device.

## **7. Cleaning, Disinfecting, and Applying Sporicidal Agents in Compounding Areas**

**Expert Committee-initiated Change #1:** The section number was revised to align with the re-numbering of other sections.

**Commentary Summary #1:** Commenter suggested that this section should undergo substantial revision to modernize the content and eliminate erroneous guidance.

Commenter suggested that one-size-fits-all frequency for cleaning and disinfection is unnecessarily prescriptive given the breadth of practice.

**Response:** Comment not incorporated. Chapter <797> is intended to be a minimum standard; facilities may choose to implement more stringent requirements.

**Commentary Summary #2:** Commenter recommended clarifying all points in which items are to be wiped down.

**Response:** Comment incorporated. The chapter was revised to incorporate sections on introducing items into the classified areas and SCA, and to the PEC.

**Commentary Summary #3:** Commenter suggested adding the reasoning for wearing gloves to stock items on the clean side of the ante-room. Another commenter suggested that gloves do not need to be sterile for wiping supplies. Several commenters requested removing the requirement to wear gloves when stocking items on the clean side of the ante-room.

**Response:** Comments not incorporated. Gloves are necessary to avoid using bare hands which may cause touch contamination in the area. Additionally, gloves are needed if using a sporicidal agent or peroxide to wipe items to protect personnel.

**Commentary Summary #4:** Several commenters recommended the use of sterile IPA to remove residue after using a one-step disinfectant for cleaning.

**Response:** Comment incorporated.

**Commentary Summary #5:** Commenter suggested that it is not always appropriate to clean surfaces prior to disinfection. Cleaning the ceiling, walls, bars, and equipment is required only daily (unless contaminated), but if disinfection of all interior surfaces of the PEC is required at the beginning and end of each shift and cleaning must precede disinfection, then all surfaces must be cleaned and disinfected at the beginning and end of each shift.

**Response:** Comment partially incorporated. *Table 8* was revised to specify cleaning, disinfecting, and applying sporicidal agents at their own frequencies.

**Commentary Summary #6:** Several commenters suggested that one-step agents should be removed since the EPA does not differentiate one-step from multi-step products.

**Response:** Comments not incorporated. "One-step" is an EPA term. Additionally, products that are EPA-registered or equivalent may be used.

**Commentary Summary #7:** Commenter suggested clarifying the statement that cleaning and disinfecting of work surfaces must be completed before initiating compounding, since it alludes to cleaning everything.

**Response:** Comment not incorporated. Cleaning and disinfecting is not limited to the work surface. *Table 8* includes many other surfaces that must be cleaned and disinfected.

**Commentary Summary #8:** Commenter suggested that cleaning and disinfecting must be completed at the end of the compounding day. Twenty-four hour operations must clean and disinfect at least daily at a predetermined time during which compounding cannot occur.

**Response:** Comment not incorporated. Cleaning and disinfecting must be repeated as described in *Table 8*.

**Commentary Summary #9:** Several commenters noted that compounding areas may not be used daily. A commenter requested addition of this information to *Table 8*.

**Response:** Comments partially incorporated. Cleaning and disinfecting surfaces and applying a sporicidal agent must occur at the minimum frequencies specified in *Table 8* or, if compounding is not performed daily, cleaning and disinfecting must be completed before initiating compounding. *Table 8* is intended to be a summary of recommendations, and to be used in conjunction with the text of the chapter, which contains relevant information.

**Commentary Summary #10:** Commenter suggested that the definition of spills should be documented in the facility's SOPs.

**Response:** Comment not incorporated. Spills of any volume have the potential to cause contamination of the compounding area.

**Commentary Summary #11:** Commenter suggested better defining which "surfaces" must be cleaned in the cleanroom suite.

**Response:** Comment partially incorporated. *Table 8* was revised to specify areas needing cleaning and disinfecting, and at what frequency.

**Commentary Summary #12:** Commenter recommended striking use of the manufacturer's directions or published data for contact time. Commenter suggested that the EPA label is the only official source of information.

**Response:** Comment not incorporated. Information on contact times in EPA labels may not apply to non-EPA registered products.

**Commentary Summary #13:** Several commenters suggested that IPA will not have a dwell time and would not be an effective disinfectant.

**Response:** Comment incorporated. The chapter was revised to distinguish IPA from disinfectants.

**Commentary Summary #14:** Commenter suggested that documentation may need to occur after all cleaning and disinfecting activities, such as spills.

**Response:** Comment partially incorporated. The section was revised to specify that documentation must occur according to facility SOPs.

**Commentary Summary #15:** Commenter recommended changing *Table 8* to include sanitizing, cleaning, disinfecting, and use of one-step and/or sporicidal agents.

**Response:** Comment not incorporated. The suggestion is too prescriptive and may lead to confusion. The table was revised in a bulleted format to improve readability.

**Commentary Summary #16:** Commenter suggested that the frequency of cleaning should be further elaborated for cleanrooms operating 24 hours with contiguous shifts in order to avoid redundancy.

**Response:** Comment incorporated. *Table 8* was revised to require cleaning at least daily and when surface contamination is known or suspected.

**Commentary Summary #17:** Commenter suggested that compounding does not always occur on weekends, therefore cleaning should occur daily or when the facility is open.

**Response:** Comment incorporated. The section was revised to state that if compounding is not performed daily, cleaning and disinfecting must be completed before initiating compounding.

**Commentary Summary #18:** Commenter suggested that the sink and surfaces outside of the PEC should not need to be done on days when no compounding is performed.

**Response:** Comment incorporated. If compounding is not performed daily, cleaning and disinfecting must be completed before initiating compounding.

**Commentary Summary #19:** Commenter suggested adding a row to *Table 8* for cleaning and disinfecting non-work surfaces outside of the PEC.

**Response:** Comment incorporated.

**Commentary Summary #20:** Commenter suggested that ceilings, walls, bars, and equipment inside the PEC should match the cleaning frequencies for horizontal work surfaces inside the PEC. Several other comments also requested clarification.

**Response:** Comments incorporated.

**Commentary Summary #21:** Several commenters recommended applying sporicidal agents weekly instead of monthly.

**Response:** Comments not incorporated. The chapter is intended to be a minimum standard; facilities may choose to apply sporicidal agents more frequently.

**Commentary Summary #22:** Several commenters suggested that cleaning and disinfecting small spills or drips from syringe needles is onerous.

**Response:** Comments incorporated. *Table 8* was revised to require cleaning and disinfecting daily and when surface contamination is known or suspected.

**Commentary Summary #23:** Commenter recommended defining “spill”. Other commenters suggested distinguishing between hazardous and non-hazardous spills.

**Response:** Comment not incorporated. All spills have the potential to introduce contamination to the compounding environment, regardless of volume. Distinguishing and addressing HDs is out of scope of the chapter (see <800>).

**Commentary Summary #24:** Commenter suggested that all interior surfaces of the PEC must be disinfected prior to initiating compounding and after compounding, instead of at the beginning and end of shift. Another commenter suggested that disinfection of the PEC should only be at the beginning of the shift, if soiled, after spills, and every 30 minutes.

**Response:** Comments incorporated. *Table 8* was revised to require cleaning and disinfecting daily and when surface contamination is known or suspected.

**Commentary Summary #25:** Commenter suggested that documentation of cleaning and disinfecting may be required every 30 minutes as written.

**Response:** Comment partially incorporated. The section was revised to note that cleaning and disinfecting, as well as application of sporicidal agents, must be documented according to facility SOPs.

**Commentary Summary #26:** Commenter suggested cleaning at the end of a shift, and disinfecting at the beginning and end of a shift.

**Response:** Comment partially incorporated. *Table 8* was revised to require cleaning and disinfecting daily and when surface contamination is known or suspected. This is especially important for facilities that do not compound regularly, where there may be several days before the next compounding session.

**Commentary Summary #27:** Commenter noted confusion in separating cleaning and disinfecting as different activities and requested clarification.

**Response:** Comment not incorporated. Cleaning and disinfecting are separate steps, unless a one-step disinfectant is used. Cleaning removes soil and residues, and disinfection destroys microorganisms. Frequencies for cleaning and disinfecting also differ based on the surface (see *Table 8*). The terms cleaning agent and disinfectant are defined in the *Glossary*.

**Commentary Summary #28:** Multiple commenters suggested that cleaning and disinfecting at the beginning and end of every shift is redundant for 24-hour facilities or those with multiple shifts in a day.

**Response:** Comments partially incorporated. *Table 8* was revised to require cleaning and disinfecting daily and when surface contamination is known or suspected. This is especially important for facilities that do not compound regularly, where there may be several days before the next compounding session.

**Commentary Summary #29:** Commenter suggested that monthly cleaning of walls, floors, doors, and other surfaces will always be with a sporicidal agent.

**Response:** Comment not incorporated. Sporicidal agents are not considered cleaning agents. Walls, doors, door frames, ceiling, and storage shelving/bins must be cleaned, disinfected, and a sporicidal agent monthly. If the sporicidal agent is an EPA-registered (or equivalent) one-step disinfectant sporicidal cleaner, separate cleaning and disinfecting steps are not required.

**Commentary Summary #30:** Commenter requested a method for cleaning pass-throughs.

**Response:** Comment not incorporated. A method for cleaning pass-throughs must be established in written SOPs in accordance with the manufacturer's instructions, and must be followed by all cleaning personnel.

**Commentary Summary #31:** Commenter recommended stating that all items in the SEC and the SCA should be cleaned, including items such as products in bins.

**Response:** Comment not incorporated. *Table 8* describes cleaning of facilities. Items (e.g., components, supplies) must be wiped down before they are brought into the SEC or brought inside the perimeter of the SCA (see *8. Introducing Items into the SEC and PEC*).

**Commentary Summary #32:** Commenter recommended that bins below the cleanroom bench or BSC need to be cleaned weekly.

**Response:** Comment not incorporated. Storage bins must be cleaned at least monthly. The chapter is intended to be a minimum standard; facilities may choose to clean storage bins more frequently. Additionally, surface sampling helps to monitor cleaning processes.

**Commentary Summary #33:** Commenter recommended changing the *Table 8* headers to distinguish IPA from disinfectants.

**Response:** Comment partially incorporated. The chapter was revised to distinguish IPA from disinfectants.

**Commentary Summary #34:** Commenter suggested that the ceiling of the SCA must be cleaned monthly.

**Response:** Comment partially incorporated. The ceiling within the perimeter of the SCA must be cleaned monthly as described in *Table 8*.

**Commentary Summary #35:** Commenter asked if cleaning inside an SCA means cleaning within its perimeter.

**Response:** Comment not incorporated. The *Glossary* defines the SCA to be a designated, unclassified space, area, or room with a defined perimeter. Therefore, cleaning activities occur within the perimeter of the SCA.

**Commentary Summary #36:** Commenter suggested omitting the requirement to disinfect the PEC every 30 minutes.

**Response:** Comment partially incorporated. *Table 8* was revised to clarify that sterile IPA must be applied every 30 minutes.

**Commentary Summary #37:** Commenter suggested that not all disinfectants are required to be sterile. Another commenter recommended that the agent used to disinfect and sanitize the inside of the PEC must be sterile.

**Response:** Comments partially incorporated. Disinfectants are not required to be sterile unless specified. The chapter does not use the term “sanitize,” however sterile IPA is required for the PEC.

**Commentary Summary #38:** Commenter recommended referring to IPA and wipers as “sterilized” or “terminally sterilized”. Commenter suggested that products that are packaged for multiple uses after opening have the issue of how sterility or antisepsis will be maintained after opening the package.

**Response:** Comment not incorporated. IPA and wipers may not be labeled as sterilized or terminally sterilized and such requirements may cause confusion for purchasers.

**Commentary Summary #39:** Commenter recommended defining appropriate agents and cleaning versus disinfecting. Another commenter recommended providing a source or link that users can consult to determine if the agent is compliant.

**Response:** Comments partially incorporated. *Table 7* describes the differences between agents and their purposes. The facility must determine the appropriate agents based on facility design and practices.

**Commentary Summary #40:** Multiple commenters requested clarifying what cleaning and/or disinfecting agents can be used. Multiple commenters requested examples of different agents.

**Response:** Comments not incorporated. *Table 7* describes the differences between agents and their purposes. The facility must determine the appropriate agents based on facility design and practices. One-step agents are an option for consideration. Considerations when selecting and using disinfectants include their antimicrobial activity, inactivation by organic matter, residue, shelf life, preparation requirements of the agent, and suitability for surfaces being disinfected.

**Commentary Summary #41:** Several commenters recommended providing examples of one-step cleaners. A commenter suggested specifying which ones have sporicidal properties.

**Response:** Comments not incorporated. *Table 7* describes the differences between agents and their purposes. The facility must determine the appropriate agents based on facility design and practices. One-step agents are an option for consideration.

**Commentary Summary #42:** Commenter recommended striking the consideration of inappropriate or toxic residues or fumes when selecting agents. Commenter also noted that these characteristics are too vague to help with selection and requested clarification.

**Response:** Comment incorporated. The section was revised to strike the qualifier, and replaced with “user safety”.

**Commentary Summary #43:** Commenter noted a clerical error in the title of chapter <1072>, and suggested to correct it as “(see *Disinfectants and Antiseptics* <1072>)”.

**Response:** Comment incorporated.

**Commentary Summary #44:** Multiple commenters suggested that common sporicidal agents may not be effective against *Bacillus* species, and this is not part of the label.

Several commenters suggested that the dwell time of 10 minutes would not be practical or effective against Bacillus.

**Response:** Comments incorporated. The section was revised to strike the requirement for agents to be effective against Bacillus.

**Commentary Summary #45:** Commenter suggested that a sporicidal agent shown to be effective against Bacillus species is necessary.

**Response:** Comment not incorporated. The statement was removed as multiple commenters have expressed that ensuring effectiveness is not practical and EPA testing is performed against many representative species, not just Bacillus.

**Commentary Summary #46:** Commenter suggested that disinfectants must be allowed to dwell on the surface for a minimum contact time, but the term “cannot be disturbed” could cause confusion.

**Response:** Comment incorporated. The section was revised to strike the statement that the surface cannot be disturbed.

**Commentary Summary #47:** Commenter noted that the definition of “dwell” is not given and suggested incorporating a definition.

**Response:** Comment not incorporated. “Dwell time” or “contact time” is a commonly used term for letting disinfectants stay on a surface for a period of time to ensure effectiveness. The facility should consult manufacturer information for recommendations on how to use the disinfectant.

**Commentary Summary #48:** Commenter noted a clerical error and suggested adding the text “classified area”.

**Response:** Comment incorporated.

**Commentary Summary #49:** Commenter suggested that sporicidal agents may have consequences from an employee-patient perspective.

**Response:** Comment not incorporated. The facility must determine what agents to use. Cleaning and disinfecting agents must be selected and used with careful consideration of compatibilities, effectiveness, and user safety. Considerations when selecting and using disinfectants include their antimicrobial activity, inactivation by organic matter, residue, shelf life, preparation requirements of the agent, and suitability for surfaces being disinfected.

**Commentary Summary #50:** Commenter suggested that disinfectants used in the PEC must be sterile along with all other cleaners, water, wipes, and other items.

**Response:** Comment not incorporated. Cleaning supplies must be low-lint. Wipers, sponges, and mop heads should be disposable. Additionally, other commenters suggested that it is impractical to require that all cleaning supplies be sterile for compounders. The chapter does require sterile disinfectants to be used inside of the PEC.

**Commentary Summary #51:** Commenter suggested that sanitizing agents (e.g., sterile IPA) must be sterile when used in the PEC. Commenter recommended distinguishing between disinfectants and sterile IPA.

**Response:** Comment incorporated.

**Commentary Summary #52:** Several commenters requested clarification of whether one-step disinfectants must be sterile for disinfecting the PEC. Another commenter asked if sporicidal agents for the PEC must be sterile. Several commenters requested clarifying whether disinfectants must be sterile for disinfecting the PEC.

**Response:** Comments incorporated. Disinfectants are not required to be sterile for use in the PEC, whether they are sporicidal disinfecting agents or one-step agents.

**Commentary Summary #53:** Several commenters suggested that IPA for use in the PEC must be sterile. Another commenter suggested that agents used in the PEC do not need to be sterile unless it's the last agent used. Another commenter suggested that one-step agents are not sterile, but should be followed by sterile IPA.

**Response:** Comments incorporated. The section was revised to state that sterile IPA is applied as a last step.

**Commentary Summary #54:** Commenter suggested adding a definition of "sterile," or redirecting to a reference document that defines sterile solutions; otherwise, the commenter suggested eliminating the word sterile.

**Response:** Comment partially incorporated. Unless specified, agents are not required to be sterile. Additionally, the definition of sterility was added to the *Glossary*, which states it is "the absence of viable microorganisms."

**Commentary Summary #55:** Several commenters suggested providing examples and information on specific agents, concentrations, and contact times.

**Response:** Comment not incorporated. Facilities must determine which agents are appropriate for the facility design and practice. Contact times are specified by the manufacturer, and may vary per agent.

**Commentary Summary #56:** Commenter recommended changing the definition of cleaning agent to "an agent used to remove dirt, debris, microbes, and residual drugs or chemicals from surfaces. These agents contain detergents or surfactants. An EPA-registered one-step disinfectant cleaner must be used."

**Response:** Comment partially incorporated. The section was revised to distinguish between disinfectants and sterile IPA. Specifying the characteristics that the agents must have is too restrictive. Facilities may choose to use an EPA-registered or equivalent one-step agent.

**Commentary Summary #57:** Commenter suggested that disinfection can only occur after a surface has been cleaned. Some cleaning agents (EPA-registered one-step disinfectant cleaners) are also disinfectants, however some disinfectant agents (e.g., sterile 70% IPA) only provide disinfection if they are applied immediately after a surface has been cleaned (e.g., use of sterile 70% IPA inside the PEC after daily cleaning).

**Response:** Comment not incorporated. The section already states, "Surfaces must be cleaned prior to being disinfected unless an EPA-registered one-step disinfectant cleaner is used to accomplish both the cleaning and disinfection in one step."

**Commentary Summary #58:** Several commenters recommended including a definition for sanitization.

**Response:** Comments not incorporated. The word "sanitize" has not been used in the chapter.

**Commentary Summary #59:** Commenter suggested that "endospores" is the appropriate term for describing the highly-resistant spore forms from Gram-positive bacteria.

**Response:** Comment not incorporated. The term "spores" is used in many related industries and throughout the chapter.

**Commentary Summary #60:** Commenter suggested that not all one-step agents may be EPA-registered.

**Response:** Comment incorporated. The chapter was revised to allow EPA-registered or equivalent one-step agents.

**Commentary Summary #61:** Multiple commenters suggested that cleaning supplies used inside of the PEC should be sterile.

**Response:** Comment not incorporated. Cleaning supplies must be low-lint. Wipers, sponges, and mop heads should be disposable. Cleaning supplies are not required to be sterile unless otherwise indicated. For example, reusable cleaning tools are not required to be sterile but must be cleaned and disinfected. The chapter is intended to be a minimum standard; however, facilities may choose to implement stricter requirements. Commenters have also suggested that it is impractical to require that all cleaning supplies need to be sterile for compounders.

**Commentary Summary #62:** Commenter suggested that sponges must not be used within the cleanroom suite regardless of whether they are disposable because they can shed and harbor contamination.

**Response:** Comment incorporated. The section was revised to remove sponges from the list of examples.

**Commentary Summary #63:** Commenter recommended that mop heads can be reused if laundered in a validated cleanroom facility. Another commenter asked whether cleaning supplies must be sent to a central area to be sterilized.

**Response:** Comments not incorporated. Current text states that reusable cleaning tools must be cleaned and disinfected before and after each use. The facility may determine the most appropriate way to implement these requirements, such as laundering in a cleanroom facility or being sterilized in a central location.

**Commentary Summary #64:** Commenter suggested that mop head covers are disposable, and not mop heads.

**Response:** Comment not incorporated. Many mop heads are refillable and disposable.

**Commentary Summary #65:** Commenter suggested that laundered mop heads should not increase bioburden.

**Response:** Comment not incorporated. The chapter does not prohibit reusable mop heads.

**Commentary Summary #66:** Commenter suggested that reusable cleaning tools must be made of cleanable materials and must be disinfected before and after each use.

**Response:** Comment incorporated.

**Commentary Summary #67:** Commenter suggested that storing reusable tools in the cleanroom increases clutter and promotes bioburden. Another commenter suggested striking “must not be removed from these areas except for disposal”.

**Response:** Comments not incorporated. Reusable cleaning tools must remain in the classified areas or SCA to limit the contamination introduced during storage.

Alternatively, disposable cleaning tools are preferred.

**Commentary Summary #68:** Commenter suggested that many reusable cleaning tools may last for decades; requiring their disposal is unnecessary. Another commenter suggested that “appropriate amount of time” is ambiguous.

**Response:** Comments partially incorporated. Facilities must determine the appropriate frequency for replacing and discarding reusable cleaning tools based on the condition of the tools and its frequency of use. The section was revised to strike the need to assess the tools based on an appropriate amount of time.

**Commentary Summary #69:** Several commenters suggested that if cleaning tools are put away clean and are kept in the cleanroom, there is no reason to clean them again before use.

**Response:** Comment not incorporated. Cleaning tools must be cleaned and disinfected before and after use to minimize bioburden.

**Commentary Summary #70:** Several commenters suggested defining the correct storage procedures for reusable cleaning tools.

**Response:** Comments not incorporated. Reusable cleaning tools must be dedicated for use in the classified areas or SCA and must not be removed from these areas except for disposal. Additional storage precautions may be incorporated based on the facility.

**Commentary Summary #71:** Commenter suggested that cleaning tools do not have to be dedicated for use and may be removed from the compounding area if they are wiped down.

**Response:** Comment not incorporated. Cleaning tools must be dedicated to a specific area and stored in that specific area to reduce contamination from other areas.

**Commentary Summary #72:** Commenter proposed that reusable cleaning tools must be dedicated for use in the classified areas or SCA and must not be removed from these areas except for disposal, and must be discarded.

**Response:** Comment not incorporated. Proposal is redundant and can cause confusion.

**Commentary Summary #73:** Commenter suggested that wipes should be non-shedding instead of low-lint.

**Response:** Comment not incorporated. Low-lint wipes can also be non-shedding. Low-lint is consistent with the rest of the chapter.

**Commentary Summary #74:** Commenter suggested that the order of cleaning and the method should be included (e.g., back of PEC from top to bottom, then bar/hook, then sides from top to bottom, etc.) Another commenter suggested clarifying if the cleaning process is different for the different airflow patterns of the hood type.

**Response:** Comments not incorporated. Methods of cleaning may depend on the facility and type of PEC. The facility should establish cleaning protocols in the SOPs based on the type of PEC and manufacturer recommendations.

**Commentary Summary #75:** Commenter recommended that the work tray under the PEC should be cleaned at the same frequency as other internal surfaces. Another commenter suggested that work trays are not sealed, therefore any liquid can drip underneath. Commenter recommended that the work tray must be cleaned and disinfected at the beginning and end of each shift, after spills, and when surface contamination is known or suspected.

**Response:** Comments not incorporated. The removable work tray must be cleaned daily. All surfaces and the area underneath the work tray must be cleaned monthly. The chapter is intended to be a minimum standard; facilities may choose to clean the work tray more frequently.

**Commentary Summary #76:** Commenter recommended that the work tray must be cleaned and disinfected and must have a sporicidal agent applied at least monthly.

**Response:** Comment incorporated.

**Commentary Summary #77:** Several commenters suggested that sterile water should not be used to remove particles, debris, and residue.

**Response:** Comments not incorporated. Sterile water is an example solution, but facilities may use another appropriate solution.

**Commentary Summary #78:** Commenter suggested clarifying proper terminology for each step of cleaning and disinfecting the PEC, and noted that one-step agents may be used. Commenter suggested that it is ambiguous to wipe with a sporicidal agent since it is actually a disinfectant.

**Response:** Comment incorporated.

**Commentary Summary #79:** Commenter suggested that the cleaning and disinfecting procedures for the PEC are recommendations.

**Response:** Comment not incorporated. *Box 7-1* describes required minimum procedures for cleaning and disinfecting the PEC.

**Commentary Summary #80:** Multiple commenters suggested that sterile wipers are required to be used in the PEC.

**Response:** Comments incorporated.

**Commentary Summary #81:** Several commenters suggested that the contact time must be achieved when disinfecting the PEC.

**Response:** Comments incorporated.

**Commentary Summary #82:** Several commenters suggested that the cleaning agent must be sterile when used for the PEC. Another commenter suggested that sterile sporicidal agents must be used for the PEC.

**Response:** Comments not incorporated. The cleaning and disinfecting agents are not required to be sterile, but the facility may choose to use a sterile cleaning agent.

**Commentary Summary #83:** Commenter suggested that a sporicidal agent must be used inside and outside of the PEC at least monthly, and this should be included in the procedures box.

**Response:** Comment not incorporated. *Table 8* requires that sporicidal agent be applied to the PEC monthly.

**Commentary Summary #84:** Commenter suggested that wipers used for the PEC are not required to be sterile.

**Response:** Comment not incorporated. A sterile wiper must be used for cleaning the PEC.

**Commentary Summary #85:** Commenter recommended including the work tray in the procedures box for cleaning and disinfecting the PEC.

**Response:** Comment partially incorporated. *Box 7-1* was revised to include all interior surfaces in the PEC. *Table 8* further specifies work tray cleaning and disinfecting frequencies.

**Commentary Summary #86:** Commenter suggested that sterile wipers must be used for the PEC.

**Response:** Comment incorporated.

**Commentary Summary #87:** Commenter suggested that the description of cleaning agent in *Table 7* conflicts with PEC cleaning and disinfecting procedures.

**Response:** Comment not incorporated. *Table 7* does not conflict with cleaning requirements because the facility must determine the appropriate solution to remove particles, debris, and/or residues, which may also be a cleaning agent.

**Commentary Summary #88:** Commenter suggested that there should be distinct clarification of the use of an EPA-registered one-step disinfectant cleaner for surfaces

other than a PEC since it acts as both a cleaner and disinfectant, so sterile water or sterile IPA would not be needed.

**Response:** Comment incorporated. *Box 7-1* was revised to distinguish one-step agents as an alternative. Additionally, the first bullet was revised to specify removing “visible” particles, debris, or residue with an appropriate solution which can be the one-step agent.

**Commentary Summary #89:** Multiple commenters suggested that wipes cannot remain sterile once opened and exposed to nonsterile air. Multiple commenters suggested that multi-packs of sterile wipers will be affected. Several commenters suggested that the wipers do not have to be sterile; however they must be packaged with intention to be sterile. A commenter requested clarifying whether wipes must be sterile.

**Response:** Comments not incorporated. Wipers used for the PEC must be sterile to minimize bioburden in the PEC.

**Commentary Summary #90:** Commenter recommended using EPA-registered sporicidal agents.

**Response:** Comment not incorporated. Sporicidal agents are not required to be EPA-registered.

## 8. Introducing Items into the SEC and PEC

**Expert Committee-initiated Change #1:** Standards for Introducing Items into the SEC and PEC were moved to a separate section to improve the organization and flow of the chapter. Subsequent sections were renumbered accordingly.

**Commentary Summary #1:** Multiple commenters recommended addressing supplies with paper packaging.

**Response:** Comments not incorporated. Facilities may incorporate procedures specific to paper packaging. Packages must be wiped before entering the cleanroom suite and/or SCAs.

**Commentary Summary #2:** Commenter recommended that uncorrugated cardboard cannot be brought into the cleanroom suite. Another commenter suggested that uncoated cardboard should be allowed into the classified area or SCA since coating can be one-sided. Another commenter suggested that unboxing of supplies would need to be performed in patient care areas if cardboard is not allowed in the SCA.

**Response:** Comments not incorporated. *4.5 Placement and Movement of Materials* does not prohibit uncorrugated cardboard, but uncoated cardboard is not allowed in a classified area or SCA. Unboxing can occur outside of the perimeter of an SCA. Additionally, before introducing compounding supplies into the SCA, they must be wiped with a sporicidal agent, disinfectant, or sterile IPA.

**Commentary Summary #3:** Commenter recommended that drug vials and ampules must also be wiped before introducing them into classified areas.

**Response:** Comment incorporated.

**Commentary Summary #4:** Commenter recommended disinfecting at each transition from areas of lower classification to higher classification.

**Response:** Comment partially incorporated. The section was revised to clarify that supplies are wiped before being introduced into a classified area through a pass-through from an unclassified area, clean side of the ante-room, or SCA.

**Commentary Summary #5:** Commenter suggested that a sporicidal agent and sterile disinfectant must be used to wipe down compounding supplies.

**Response:** Comment not incorporated. Compounding supplies may be wiped with a sporicidal agent, disinfectant, or sterile IPA. The chapter does not require supplies to be wiped with multiple agents. The chapter is intended to be a minimum standard; regulatory bodies may choose to enforce more stringent requirements. USP has no role in enforcement.

**Commentary Summary #6:** Commenter asked if cleaning and disinfecting compounding supplies (e.g., corrugated cardboard) for the SCA only includes the perimeter of the SCA, or being brought into the entire room.

**Response:** Comment not incorporated. The *Glossary* defines the SCA to be a designated, unclassified space, area, or room with a defined perimeter. Therefore, corrugated cardboard cannot enter the perimeter of the SCA.

**Commentary Summary #7:** Commenter requested clarification on whether supplies need to be wiped before entering the perimeter of the SCA.

**Response:** Comment incorporated. The section was revised to indicate items must be wiped before being introduced into the perimeter of the SCA.

**Commentary Summary #8:** Commenter suggested wiping of equipment, supplies and components must take place at each change in ISO classification (e.g., transferring from the ante-room to the buffer room, and from the buffer room to the PEC). Introducing items within the ISO Class 5 area without first wiping them down is an insanitary condition.

**Response:** Comment not incorporated. This would not be applicable in HD compounding areas when moving to ISO 7 classified areas.

**Commentary Summary #9:** Commenter suggested clarifying how many wipes are required.

**Response:** Comment not incorporated. The number of wipes required depends on the product and risk of contamination. It is too prescriptive to suggest a number of wipes. Additionally, the Expert Committee determined the term “wipers” is more appropriate than “wipes” since it may imply pre-saturated sheets.

**Commentary Summary #10:** Several commenters recommended using the term “wipes” instead of “wipers”.

**Response:** Comments not incorporated. The Expert Committee determined that the term “wipers” is more appropriate than “wipes” since it may imply pre-saturated sheets.

**Commentary Summary #11:** Commenter suggested that a sterile disinfectant should be used to wipe supplies.

**Response:** Comment not incorporated. Facilities may choose to wipe with nonsterile disinfectants. Environmental monitoring will help assess the effectiveness of the agents used and the corrective actions that may be taken.

**Commentary Summary #12:** Commenter recommended that compounding supplies may be disinfected with a sporicidal agent. Commenter suggested that sterile IPA is not a disinfectant. Commenter also suggested that sterile low-lint wipers are necessary.

**Response:** Comment partially incorporated. Compounding supplies may be wiped with a sporicidal agent, disinfectant, or sterile IPA. The chapter was revised to distinguish disinfectants from sterile IPA. Wipers are not required to be sterile for wiping compounding supplies.

**Commentary Summary #13:** Commenter suggested specifying what items must be cleaned and disinfected prior to crossing the line of demarcation in the ante-room.

**Response:** Comment partially incorporated. The section was revised to state that all items must be wiped prior to being introduced into the clean side of the ante-room.

**Commentary Summary #14:** Commenter suggested that before compounding supplies are introduced into a compounding area, they must be wiped with a sporicidal agent or sterile disinfectant using low-lint wipes.

**Response:** Comment partially incorporated. The section was revised to state that supplies must be wiped prior to being introduced to the clean side of the ante-room. Wipers do not need to be sterile.

**Commentary Summary #15:** Commenter noted that sterile IPA does not have a surfactant that would clean supplies.

**Response:** Comment not incorporated. Facilities may choose to wipe with sporicidal agents, disinfectants, or sterile IPA.

**Commentary Summary #16:** Commenter suggested replacing “a classified area” with “clean side of the ante-room”.

**Response:** Comment partially incorporated. The section was revised to address introducing any item into the classified area or SCA, and the PEC. This applies regardless of the method of entry.

**Commentary Summary #17:** Commenter suggested that one-step disinfectant cleaners may be used to wipe supplies.

**Response:** Comment partially incorporated. An EPA-registered disinfectant may be used, which may include a one-step disinfectant.

**Commentary Summary #18:** Commenter suggested clarifying whether sterile alcohol is needed for wiping compounding supplies before introducing them into classified areas.

**Response:** Comment incorporated. The section was revised to allow wiping with a sporicidal agent, EPA-registered disinfectant, or sterile IPA using low-lint wipers.

**Commentary Summary #19:** Several commenters suggested that the disinfectant does not need to be sterile when wiping down supplies to be introduced into the cleanroom suite and SCAs.

**Response:** Comments incorporated.

**Commentary Summary #20:** Commenter suggested that disinfectants must be allowed to dwell on the surface of items to be introduced into the cleanroom suite and SCAs for a minimum contact time, but the term “cannot be disturbed” could cause confusion.

**Response:** Comment incorporated. The section was revised to strike the statement that the surface cannot be disturbed.

**Commentary Summary #21:** Commenter recommended adding a dwell time for sterile IPA.

**Response:** Comment not incorporated. Dwell times are provided by the manufacturer.

**Commentary Summary #22:** Commenter suggested removing the reference to a dwell time.

**Response:** Comment partially incorporated. The section was revised to strike the dwell time requirement for sterile IPA.

**Commentary Summary #23:** Commenter recommended noting that the dwell time is specified by the manufacturer.

**Response:** Comment incorporated.

**Commentary Summary #24:** Multiple commenters suggested that it is not possible to wipe packaging without altering the product label.

**Response:** Comments partially incorporated. The section was revised to ensure that wiping does not render the label unreadable.

**Commentary Summary #25:** Commenter recommended changing “any item” to “items”.

**Response:** Comment not incorporated. Current verbiage highlights that all items transferred into the PEC must be wiped.

**Commentary Summary #26:** Commenter suggested that any items to be transferred into the PEC must be wiped down with an EPA-registered disinfectant using low-lint wipers in order to address endospores.

**Response:** Comment partially incorporated. The section was revised to allow use of sporicidal agents when items are transferred into the cleanroom suite and SCAs, and then items must be wiped again with sterile IPA before introducing them into the PEC. Supplies are generally introduced temporarily into the PEC and are not intended to remain there beyond the compounding activity. Additionally, environmental monitoring is used routinely to verify the effectiveness of cleaning practices.

**Commentary Summary #27:** Commenter emphasized that sterile IPA is not a disinfectant.

**Response:** Comment incorporated. The chapter was revised to distinguish IPA from disinfectants.

**Commentary Summary #28:** Several commenters supported sterile IPA for wiping items to be introduced to the PEC.

**Response:** Comments incorporated.

**Commentary Summary #29:** Commenter suggested that the section does not require sporicidal agents to be sterile. Another commenter suggested that sporicidal agents may leave a residue. Another commenter suggested that items to be introduced into the PEC must be wiped with both a sporicidal agent and a sterile disinfectant.

**Response:** Comments partially incorporated. The section was revised to strike sporicidal agents as an option when introducing items to the PEC.

**Commentary Summary #30:** Commenter suggested that requiring items to be wiped “immediately” before introduction into the PEC requires that the cleaning and disinfection process to occur when the item enters the compounding area and when it enters the PEC.

**Response:** Comment partially incorporated. The section was revised to clarify that the item must be wiped just before introduction into the PEC.

**Commentary Summary #31:** Several commenters suggested that the dwell time of the sporicidal agent must be determined by the manufacturer.

**Response:** Comments partially incorporated. The section was revised to require wiping items to be introduced into the PEC with sterile IPA, which must be allowed to dry.

**Commentary Summary #32:** Commenter recommended that the wiping procedure must not render the product label unreadable.

**Response:** Comment incorporated.

**Commentary Summary #33:** Commenter asked where the dwell time should occur, and if it can occur in the PEC.

**Response:** Comment not incorporated. Location of where dwell time may occur should be included in work practices. Adding the location of dwell time is too prescriptive for the purposes of the chapter.

**Commentary Summary #34:** Multiple commenters suggested that it is not possible to wipe packaging without altering the product label.

**Response:** Comment partially incorporated. The section was revised to ensure that wiping does not render the label unreadable.

**Commentary Summary #35:** Commenter suggested that paper packages do not need to be individually wiped if they are loaded into the side of the PEC, opened to the side of the DCA, and compounder's gloved hands are sanitized after the packages are opened.

**Response:** Comment not incorporated. Adding the proposed text would be too prescriptive for the purposes of the chapter. Regardless of the packaging type, the item must be wiped in order to reduce contamination into the PEC. Not opening within the DCA is also controversial, as critical sites may not access first air. The term "sanitize" has not been introduced into <797>.

**Commentary Summary #36:** Commenter suggested that sterile wipers are not necessary for wiping items to be introduced into the PEC.

**Response:** Comment incorporated.

**Commentary Summary #37:** Commenter requested clarification that alcohol could either be sterile IPA for wiping critical sites or individually wrapped alcohol swabs, which are routinely used in current operations.

**Response:** Comment not incorporated. Critical sites must be wiped with sterile IPA. The chapter does not prescribe the way of disinfecting (e.g., sterile 70% IPA on a wipe versus alcohol swab).

**Commentary Summary #38:** Commenter requested clarification on whether vial septums are required to be wiped with sterile IPA frequently when dispensing several doses from a vial or between every needle puncture.

**Response:** Comment not incorporated. The chapter cannot address each scenario and type of CSPs. Facilities should determine and implement appropriate SOPs and work practices dependent on their equipment, types of PECs, and facility designs.

**Commentary Summary #39:** Commenter suggested adding information on how many surfaces can be wiped by a single alcohol wipe. Another commenter asked whether a single swab can be used for multiple septums.

**Response:** Comment not incorporated. Specifying the number of surfaces that a wipe can be used on is too prescriptive and would depend on processes and procedures of the practice. The Expert Committee will consider creating additional resources for aseptic technique in the future.

**Commentary Summary #40:** Commenter suggested that bottles of sterile IPA can be used instead of single-dose alcohol swabs.

**Response:** Comment not incorporated. Facilities may determine whether to use a single-dose swab or a bottle of sterile IPA.

**Commentary Summary #41:** Commenter suggested that critical sites must be disinfected by wiping with sterile IPA in a single direction in the PEC. Commenter suggested that IPA must be allowed to dry before entering or puncturing critical sites. Commenter also suggested that multiple vials may be wiped with the same wiper.

**Response:** Comment not incorporated. The Expert Committee determined that the level of detail is too prescriptive and refers to aseptic technique. The Expert Committee will consider creating additional resources for aseptic technique in the future.

**Commentary Summary #42:** Commenter suggested that critical sites must be wiped with low-lint sterile wipers with sterile IPA in the PEC.

**Response:** Comment partially incorporated. Critical sites must be wiped with sterile IPA in the PEC. Sterile alcohol swabs may be used instead of wipers.

## 9. Equipment, Supplies, and Components

**Expert Committee-initiated Change #1:** The section number was revised to align with the re-numbering of other sections.

**Commentary Summary #1:** Commenter suggested that equipment must be of suitable composition such that surfaces are not reactive or sorptive. Another commenter suggested that ACDs, repeater pumps, and other similar equipment should be of suitable composition such that the surfaces that contact components are not reactive or sorptive. The external surfaces of the equipment must be able to withstand application of sporicidal, germicidal, and disinfecting agents.

**Response:** Comments not incorporated. Commenters have suggested that it is not possible to determine sorption and reactivity to each component.

**Commentary Summary #2:** Commenter suggested that all product contact equipment downstream of sterilizing grade filtration must be proven to be sterile and pyrogen free. Commenter suggested that sterility of all product contact materials would not be required but they must be cleaned or filtered to remove particulates, the bioburden must be controlled and microbial proliferation prevented, and the materials must be pyrogen free.

**Response:** Comment not incorporated. Other commenters have suggested that it is not possible for equipment to be sterile and pyrogen-free.

**Commentary Summary #3:** Several commenters suggested that equipment brought into classified areas must be wiped with a sporicidal or sterile disinfectant using low-lint wipers. Another commenter suggested that disinfectants and wipers do not need to be sterile.

**Response:** Comment incorporated. The section was revised to include wiping with a sporicidal agent, EPA-registered disinfectant, or sterile IPA using low-lint wipers. Although the disinfectant and wipers are not required to be sterile, facilities may choose to use sterile disinfectants and wipers.

**Commentary Summary #4:** Commenter recommended that equipment must be wiped with an EPA-registered, one-step sporicidal disinfectant cleaner.

**Response:** Comment partially incorporated. Equipment that must be brought into classified areas must be wiped with a sporicidal agent, EPA-registered disinfectant, or sterile 70% IPA using low-lint wipers. Manufacturers may also have guidance on how to clean equipment.

**Commentary Summary #5:** Commenter recommended that agents for wiping equipment must be sterile.

**Response:** Comment partially incorporated. Equipment that must be brought into classified areas must be wiped with a sporicidal agent, EPA-registered disinfectant, or sterile 70% IPA using low-lint wipers. Sporicidal agents and EPA-registered disinfectants do not need to be sterile; however facilities may choose to use sterile agents.

**Commentary Summary #6:** Commenter suggested that performing an accuracy assessment for manual equipment would be impractical. Multiple commenters were unclear on the difference between calibration and accuracy assessment. Several commenters requested accuracy requirements for specific equipment.

**Response:** Comments not incorporated. Accuracy measurements must be performed on days that equipment is used based on manufacturer guidance, which varies depending on the piece of equipment. Calibration is performed to ensure delivery of specific volumes, and other similar functions.

**Commentary Summary #7:** Several commenters suggested that equipment must operate within the required performance parameters, and the manufacturer's specifications. Compounding personnel must follow established SOPs.

**Response:** Comments incorporated. The section was revised for compounding personnel to follow established SOPs, but not establish them.

**Commentary Summary #8:** Commenter noted that there is no guidance regarding how accurate the delivery of a component must be. The commenter suggested that a 5% deviation is reasonable.

**Response:** Comment not incorporated. Calibration must occur as described by the manufacturer and facility SOPs. Requirements, including degree of deviation in each piece of equipment, may vary.

**Commentary Summary #9:** Multiple commenters indicated that "repeater pumps" is a proprietary name.

**Response:** Comments incorporated. The section was revised to strike the example of "repeater pumps".

**Commentary Summary #10:** Commenter suggested better defining the use of ACDs as those that can deliver specific volumes of solutions automatically under computerized control.

**Response:** Comment not incorporated. ACD is listed as an example of equipment. The specific requirements of each equipment must be determined by the facility based on their needs and the CSPs prepared.

**Commentary Summary #11:** Commenter suggested that corrective actions must be implemented if accuracy measurements are out-of-specification.

**Response:** Comment not incorporated. This information is often found per manufacturer, and is not always facility specific.

**Commentary Summary #12:** Commenter recommended striking the need for corrective action when accuracy measurements are outside of the manufacturer's specifications.

**Response:** Comment not incorporated. Corrective action must be performed when accuracy measurements are outside of the manufacturer's specification. The manufacturer instructions may have troubleshooting guidance for common problems.

**Commentary Summary #13:** Commenter suggested that supplies must be of suitable composition such that surfaces are not reactive or sorptive.

**Response:** Comment not incorporated. Compounders commented that it is not possible to determine sorption and reactivity to each component.

**Commentary Summary #14:** Commenter suggested specifying whether paper-backed supplies should be disinfected and sanitized.

**Response:** Comment not incorporated. Supplies must be wiped down as described in *8. Introducing Items into the SEC and PEC*. Not wiping down certain areas would be a contamination risk. Although the term "sanitize" has not been introduced into the chapter, supplies may be wiped with sterile IPA.

**Commentary Summary #15:** Several commenters recommended that supplies in direct contact with the CSP that have not been sterilized must be clean and dedicated to the sterile compounding area. The commenters suggested that it is not necessary for supplies to be sterile and depyrogenated.

**Response:** Comment not incorporated. Sterilized and depyrogenated supplies minimize the microbial burden in the CSP, and nonsterile supplies should not be brought into the PEC.

**Commentary Summary #16:** Commenter suggested adding that the surface of the PEC is not sterile; therefore, opening sterile supplies should only be done when they are ready for use.

**Response:** Comment partially incorporated. *8.3 Use of Sterile 70% IPA on Critical Sites within the PEC* was revised to specify that just before any item is introduced into the PEC, it must be wiped with sterile 70% IPA using low-lint wipers and allowed to dry before use. When sterile items are received in sealed containers designed to keep them sterile until opening, the sterile items may be removed from the covering containers 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.

**Commentary Summary #17:** Commenter recommended to strike allowing sterile supplies received in sealed pouches to be exempt from wiping. Commenter suggested that supplies may sit for an indeterminate period of time.

**Response:** Comment not incorporated. Packages of components must be wiped down before introducing into classified areas, however when removing items from the pouch, wiping down is not necessary since the product is already sterile.

**Commentary Summary #18:** Commenter suggested that supplies may be received in double bags, and the sterile supplies may be removed from the outermost bag as it is introduced into the PEC without the need to disinfect the items. Another commenter noted that exterior surfaces of supplies are not considered sterile by the manufacturers. Another commenter recommended that sterile pouches must be wiped with a sterile disinfectant before being introduced into the ISO Class 5 PEC.

**Response:** Comment incorporated. Disinfection is not required if items are introduced in the PEC by removing the covering so that the covering is not brought into the PEC. Additionally, all items must be wiped when they are transferred into the classified area or SCA. When sterile items are received in sealed containers designed to keep them sterile until opening, the sterile items may be removed from the sealed containers 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.

**Commentary Summary #19:** Several commenters asked if covering pouches can be removed inside the buffer room or PEC. Another commenter asked if packages of sterile components can be wiped in an area adjacent to the DCA.

**Response:** Comments not incorporated. Packages of components must be wiped down before introduction into classified areas or the SCA, however when removing from the sterile pouch for introduction into the PEC, it is not necessary to wipe the item down since the product is already sterile. Sterile items may be removed from the covering as the supplies are introduced into the ISO Class 5 PEC.

**Commentary Summary #20:** Commenter recommended that syringes must be opened in an ISO Class 5 environment and filled there, and they cannot be opened and stored outside of this environment.

**Response:** Comment not incorporated. The current chapter does not make this statement and it is too prescriptive for the purposes of the chapter. Facilities are responsible for ensuring the sterility of supplies, such as when supplies are received in sealed pouches to keep them sterile until opening and are removed when introduced into the PEC.

**Commentary Summary #21:** Commenter requested clarifying the documentation requirements and providing examples for documenting components (e.g., invoices).

**Response:** Comment not incorporated. Documentation is described in 20.

*Documentation.* Documentation requirements must be outlined in facility SOPs.

**Commentary Summary #22:** Commenter stated that components obtained from regulatory agency-approved API suppliers may contain unacceptable levels of contaminants and/or degradants. Commenter suggested that APIs should be sourced only from reputable suppliers and should undergo chemical and microbiological analysis using standardized analytical methods.

**Response:** Comment not incorporated. In the United States, APIs used in compounding must be obtained from an FDA-registered facility and must comply with the criteria in a *USP-NF* monograph, if one exists. This is aligned with current statutory requirements.

**Commentary Summary #23:** Commenter suggested that conventionally manufactured sterile products must be used when available and appropriate for the intended CSP. Another commenter wanted to ensure that this is a recommendation. Another commenter requested clarifying whether the statement applies to nonsterile components.

**Response:** Comments not incorporated. All sterile conventionally manufactured products may be subject to availability and appropriateness for the CSP. The word “should” denotes a recommendation.

**Commentary Summary #24:** Commenter noted that COAs are not always supplied by the vendor and can be electronic.

**Response:** Comment incorporated. The section was revised to state that APIs must have a COA, instead of being accompanied by a COA. This can be electronic.

**Commentary Summary #25:** Commenter noted that investigational items do not always have a COA.

**Response:** Comment not incorporated. All APIs must have a COA that includes the specifications and test results and show that the API meets the specifications. All 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 specification. Compounding of investigational drugs are additionally addressed in General Chapter <1168> *Compounding for Phase I Investigational Studies*.

**Commentary Summary #26:** Commenter requested noting that APIs are intended to mean bulk APIs.

**Response:** Comment partially incorporated. The term active pharmaceutical ingredient was added to the *Glossary*.

**Commentary Summary #27:** Commenter noted that there is no statement indicating that the excipients or APIs used should be of pharmaceutical grade.

**Response:** Comment partially incorporated. There is no clear definition of "pharmaceutical grade," which could be problematic for veterinary injections, some of which are monographed and are labeled with prohibitions against use in humans due to toxicity. The section was revised to state that APIs and other components must be evaluated for suitability. Components labeled with "not for pharmaceutical use", "not for injectable use", "not for human use" or an equivalent statement must not be used to compound for these purposes.

**Commentary Summary #28:** Commenter suggested that APIs used in compounding must be obtained from a facility registered with government agencies responsible for drug manufacturing, such as the FDA, European Medicines Agency (EMA), or other national or international agencies.

**Response:** Comment not incorporated. Although <797> is U.S.-centric, it is also used internationally, and compounders must follow other applicable regulatory requirements. In the U.S., APIs used in compounding must be obtained from an FDA-registered facility and must comply with the criteria in the *USP-NF* monograph, if one exists. This is aligned with current statutory requirements.

**Commentary Summary #29:** Several commenters noted that it is unclear how to validate and operationalize COAs for containers. Another commenter suggested that it is not always necessary for containers and container-closure systems to show sterility conformance.

**Response:** Comment not incorporated. A COA is an example of documentation to verify sterility and depyrogenation specifications, but other documentation is also acceptable. The chapter refers to <1229> *Sterilization of Compendial Articles* for additional information on sterilization of compendial articles.

**Commentary Summary #30:** Commenter suggested striking the requirement to document the quality of CSP components.

**Response:** Comment not incorporated. Compounders must verify the quality of CSP components.

**Commentary Summary #31:** Commenter indicated that components may not be used for a few months, by which point a 1-year assigned expiration becomes restrictive. Multiple commenters expressed that changing the assigned expiration of components from 3 years to 1 year will increase waste, turnover, and cost.

**Response:** Comment not incorporated. If a component lacks a vendor expiration date, a conservative 1-year expiration date must be assigned to minimize bioburden that accumulates over time for components used in sterile compounding.

**Commentary Summary #32:** Commenter recommended striking the need to document the date of receipt if the component will be marked with a 1-year expiry.

**Response:** Comment not incorporated. The date of receipt must be marked on containers that lack an expiration date.

**Commentary Summary #33:** Commenter indicated that the terms “inactive ingredient” and “excipient” are used inconsistently.

**Response:** Comment partially incorporated. A definition of Added Substances was added to the *Glossary*, to be synonymous with inactive ingredients and excipients.

**Commentary Summary #34:** Commenter recommended allowing the pharmacy to contact a vendor if the date is not listed on the container.

**Response:** Comment not incorporated. Vendors may not have information on expiration dating, especially if it is not on the label, but the chapter does not prohibit or deny this. Facilities may still contact vendors for information on the stability and expiration date.

**Commentary Summary #35:** Commenter suggested it is important that the temperature and humidity of the storage area be monitored and documented.

**Response:** Comment incorporated. The section was revised to add a provision for monitoring.

## 10. Sterilization and Depyrogenation

**Expert Committee-initiated Change #1:** The section number was revised to align with the re-numbering of other sections.

**Commentary Summary #1:** Commenter noted that terminal and parts sterilization are described in a single section, whereas these two topics are separated in <1229>. Commenter suggested that in <797>, sterilization procedures should be separated and outlined similarly to <1229>.

**Response:** Comment not incorporated. Sterilization procedures are outlined in *10. Sterilization and Depyrogenation* and are tailored to meet the needs of compounders. However, several references were made to the <1229> family of chapters to provide users with additional information.

**Commentary Summary #2:** Commenter suggested that terminal sterilization is only as good as the validation, and recommended ensuring that chemical stability is maintained during sterilization.

**Response:** Comment not incorporated. For sterilization, the chapter refers to <1229>. The sterilization method used must not degrade the CSP.

**Commentary Summary #3:** Commenter recommended clarifying whether media-fill testing can be avoided if a terminal sterilization method is used.

**Response:** Comment not incorporated. Media-fill testing is an objective way to demonstrate aseptic practices. This must be performed to assess personnel proficiency in compounding.

**Commentary Summary #4:** Commenter recommended striking the statement limiting the use of non-terminal sterilization.

**Response:** Comment not incorporated. Terminal sterilization cannot be performed when the container-closure system cannot tolerate the treatment.

**Commentary Summary #5:** Several commenters requested adding pellets to the list of items that can be steam sterilized.

**Response:** Comments partially incorporated. Examples of CSPs not suitable for steam sterilization include solid CSPs, which implies pellets. The section was revised to strike the examples.

**Commentary Summary #6:** Commenter suggested adding the phrase “unless the lot passes General Chapter <71> *Sterility Tests*” to allow steam sterilization. Commenter suggested that using the process of sterilization by pasteurization, even solid CSPs in sealed containers can be safely sterilized.

**Response:** Comment partially incorporated. The section was revised to strike the examples.

**Commentary Summary #7:** Commenter suggested that CSPs that are terminally sterilized in their sealed final container must undergo a process (e.g., dry heat, steam, irradiation, or terminally filtered sterilization) intended to achieve a sterility assurance level (SAL) of  $10^{-6}$  or better. Commenter suggested that the term “terminally filtered sterilization” can be used to describe a system and process that sterilizes the final product by filtration through a pharmaceutical-grade sterilizing filter. This filter is an integral part of a closed-system final container. This system validates the integrity of the filter via a test that does not compromise the integrity of the closed-system final container; provides final labeling only after the integrity is validated; and allows isolation of the filter from the final container after compounding to prevent contamination by filter infiltration. Conditions and a calculation of the SAL would be intended to achieve the above, when following manufacturer recommendations including aseptic technique, in an ISO Class 5 PEC within an ISO Class 7 SEC and using only sterile manufactured starting ingredients.

**Response:** Comment not incorporated. Sterilization by filtration is not terminal sterilization. The chapter cannot promote or endorse a particular vendor.

**Commentary Summary #8:** Commenter recommended changing SAL to probability of a nonsterile unit (PNSU).

**Response:** Comment incorporated.

**Commentary Summary #9:** Commenter suggested that the dry heat depyrogenation cycle must be verified using endotoxin challenge vials (ECVs). This verification must be documented. The information regarding ECVs must be included in the SOPs.

**Response:** Comment incorporated.

**Commentary Summary #10:** Commenter noted that the current method of sterilization has not produced any reported safety issues and has delivered years of successful therapy to the population of patients that have implanted pumps. Each admixture is compounded in a “patient specific” manner, never batched, and prepared only pursuant to a prescription order by a provider for that patient. Stock solutions that would grow

bacteria over time are not used as part of the compounding process. Commenter stated that there has never been a reported catheter infection secondary to the compounding or administration of the medications that fill these implanted pumps. This record is due directly to the refill procedure, the use of patient-specific admixtures, and the current filter sterilization process that has consistently been in use for these admixtures. Commenter cited cost and accessibility implications.

**Response:** Comment not incorporated. If one or more of the starting components being used to compound is not sterile, the sterility of the compounded preparation must be achieved through a sterilization process. The effectiveness of the sterilization step is critical to achieving a sterile preparation. Although autoclaving is preferred, the facility may determine the best sterilization procedure for the particular CSP. Additionally, the chapter does not specify certain dosage forms or formulations.

**Commentary Summary #11:** Commenter recommended adding a section for sterilization by irradiation. Another commenter noted that there is not an existing paragraph for irradiation parameters.

**Response:** Comments not incorporated. The Expert Committee will consider future revisions to <797> to include additional sterilization procedures.

**Commentary Summary #12:** Commenter suggested that allergenic extracts that are terminally sterilized and have undergone sterility tests should receive longer BUDs, especially if formulation-specific testing has been conducted. Without formulation-specific testing, 90 days should be the BUD for a CSP at room temperature. With formulation-specific evidence, the BUD can be extended as far as the testing results allow.

**Response:** Comment not incorporated. Allergenic extracts have special characteristics that differentiate them from other CSPs (e.g., preservative systems and risk of anaphylaxis). Additionally, there is FDA guidance for mixing biologics. The BUDs of CSPs should consider several factors including sterility, stability, environmental monitoring, and personnel monitoring.

**Commentary Summary #13:** Commenter suggested inserting a reference or depyrogenation chart for clarity.

**Response:** Comment partially incorporated. The chapter references <1228.1> *Dry Heat Depyrogenation* and <51> *Antimicrobial Effectiveness Testing*.

**Commentary Summary #14:** Commenter noted that pyrogen-free indicates zero pyrogen count and this should be clarified.

**Response:** Comment not incorporated. Containers and components must be pyrogen free following dry heat depyrogenation.

**Commentary Summary #15:** Commenter suggested that if changes are made to the depyrogenation cycle, the effectiveness of the dry heat cycle must be re-established.

**Response:** Comment partially incorporated. A new oven must be verified initially and addressed as described in the section. The section was revised to add examples of changes in load conditions.

**Commentary Summary #16:** Commenter suggested that pyrogen-free water does not exist. The monographs for *Sterile Water for Injection* and *Sterile Water for Irrigation* also have endotoxin limits.

**Response:** Comment incorporated. The statement was revised to “non-pyrogenic water”.

**Commentary Summary #17:** Commenter suggested that multiple rinse cycles are necessary to depyrogenate material.

**Response:** Comment not incorporated. It is difficult to determine the number of cycles or the appropriate methods necessary.

**Commentary Summary #18:** Commenter suggested addition of examples for depyrogenating nonsterile APIs that are not thermostable.

**Response:** Comment not incorporated. The section refers to depyrogenation of containers and components. The chapter does not require depyrogenation of nonsterile APIs.

**Commentary Summary #19:** Commenter suggested that the manufacturer must meet American Society for Testing and Materials (ASTM) F838, Standard Test Method for Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration.

**Response:** Comment not incorporated. ASTM is incorporated into <1229.4> *Sterilizing Filtration of Liquids*.

**Commentary Summary #20:** Commenter suggested that sterilizing filters must remove  $10^7$  microorganisms.

**Response:** Comment not incorporated. Sterilization by filtration is not terminal sterilization.

**Commentary Summary #21:** Commenter recommended striking direct challenge (e.g., filtering the CSP) because this concept has not been described in this chapter. The example provided, filtering the CSP, does not provide sufficient information such as any assurances about the chemical and physical compatibility of the filters with the ingredients in the CSP or the filter capacity when sterilizing the CSP without any final product testing (e.g., potency).

**Response:** Comment not incorporated. Filters may not specify all compatibility information. The bubble point test will provide information if the filter fails.

**Commentary Summary #22:** Several commenters suggested removing the statement requiring filters to have capacity to filter required volumes.

**Response:** Comments not incorporated. Capacity information is available from the manufacturer. Additionally, the bubble point test provides assurance.

**Commentary Summary #23:** Commenter recommended that changing the filter during the processing of the batch can pose a risk of contamination. Commenter suggested it is important that the sterilization process be completed without the need to replace the filter during the process. Another commenter suggested that the filter used must have sufficient ability to complete the process without the need to switch to another filter.

**Response:** Comment not incorporated. Although it is ideal to use only one filter, there are situations where more than one is required (e.g., large batches). If multiple filters are used, each one must be filter-integrity tested.

**Commentary Summary #24:** Commenter suggested that if the batch is being tested by an analytical laboratory for sterility and endotoxins, bubble testing is not necessary or practical. Commenter suggested that the bubble point test should be recommended if a Category 2 CSP is being made for an individual patient and administered before testing results are known.

**Response:** Comment not incorporated. Sterility testing does not provide 100% assurance of sterility. Post-filter integrity testing is another measure to ensure the sterility of the CSP.

**Commentary Summary #25:** Commenter suggested that the filter used must have sufficient ability to complete the process without the need to switch to another filter.

**Response:** Comment not incorporated. Some components or volumes of components require multiple filters.

**Commentary Summary #26:** Commenter suggested that a bubble point test should be clearly defined for pass or fail per a facility's SOPs, accounting for the fact that a filter's pound per square inch (PSI) rating is typically an average, but not the minimum PSI rating to pass.

**Response:** Comment not incorporated. The bubble point test is an example of filter integrity testing, however the facility may choose to use other testing per the manufacturer's recommendations.

**Commentary Summary #27:** Commenter suggested that the filtration process is not required to be validated, so there is no assurance that multiple filtration processes will not affect the intended amount of active ingredient(s) or excipients in the CSP. If a filter fails, there should be an investigation to determine the cause and whether resterilization using the same type of filter or a new type of filter is appropriate.

**Response:** Comment partially incorporated. The section was revised to add that after investigating the cause of the failure and selecting an appropriate filter, CSPs that were prepared using a filter that failed integrity tests must be discarded or refiltered for sterilization no more than one additional time.

**Commentary Summary #28:** Commenter noted that some CSPs cannot be filtered and suggested adding exceptions.

**Response:** Comment not incorporated. The facility must determine the most appropriate method of sterilization for the CSP. A list of exceptions may be interpreted to be all-inclusive.

**Commentary Summary #29:** Commenter recommended separating sterilization from terminal sterilization to align with <1229>.

**Response:** Comment not incorporated. Sterilization by steam heat is most suitable under the sterilization section for the purposes of the chapter.

**Commentary Summary #30:** Commenter recommended providing clarification for what items must be placed in an autoclave bag. Another commenter noted that there is not always a need to wrap a container.

**Response:** Comments incorporated. The section was revised to address the need to wrap certain items for autoclaving.

**Commentary Summary #31:** Commenter recommended striking the statement indicating that the steam supplied must be free of contaminants and generated using water per the manufacturer's recommendation.

**Response:** Comment not incorporated. The chapter is intended to be the minimum standard. Facilities may use the water recommended by the manufacturer of the steam sterilizer or higher-quality water as determined by the facility.

**Commentary Summary #32:** Commenter suggested that sterilization by steam heat processes must be monitored by a designated person and documented. Commenter suggested that chemical integrators and biological indicators be used in each load in addition to sterility testing. The commenter noted that charts and graphs are not necessary.

**Response:** Comment not incorporated. The date, run, and load of the steam sterilization cycle must be documented in the compounding record. Further, the chapter requires that the effectiveness of steam sterilization be verified and documented with each sterilization run or load by using an appropriate biological indicator. Charts and/or graphs are not required.

**Commentary Summary #33:** Commenter suggested that the section on dry heat sterilization is restrictive.

**Response:** Comment not incorporated. The language is not restrictive and is intended to provide information. Additionally, <1229> is referenced for more information.

**Commentary Summary #34:** Several commenters suggested striking “validated” for dry heat sterilization effectiveness since it is historically associated with drug manufacturing.

**Response:** Comment incorporated.

## 11. Master Formulation and Compounding Records

**Expert Committee-initiated Change #1:** The section number was revised to align with the re-numbering of other sections.

**Expert Committee-initiated Change #2:** The content on SOPs was moved to its own section.

**Commentary Summary #1:** Multiple commenters expressed concern that the term “batch” requires creating a Master Formulation Record any time a CSP is prepared for more than one patient, which would be burdensome. Another commenter suggested that if a batch is prepared and given a BUD within the scope of a Category 2 item, a Master Formulation Record should not be required with the exception of nonsterile to sterile processes. Another commenter suggested that patient-specific preparations should not require a Master Formulation Record. Several other commenters suggested that a Master Formulation Record should only be required for nonsterile compounding activities. Multiple commenters suggested that Master Formulation Records should not be required for patient-specific preparations.

**Response:** Comments partially incorporated. The section was revised to state that a Master Formulation Record must be created for CSPs prepared for more than one patient and for CSPs prepared from nonsterile ingredients. It is not required if the preparation was only made for only one specific patient. The qualifier “in a batch” was struck. Additionally, nonsterile compounding is addressed in <795>.

**Commentary Summary #2:** Commenter requested clarifying whether proprietary docking systems require a Master Formulation Record.

**Response:** Comment partially incorporated. Vial bag systems prepared for future use are considered compounding and must therefore follow the chapter. If prepared for more than one patient, it must have a Master Formulation Record.

**Commentary Summary #3:** Commenter suggested adding additional conditions that would require a Master Formulation Record. Specifically, (a) high-risk level CSPs; (b) CSPs with extended BUDs; (c) CSPs compounded in anticipation of a patient-specific prescription or order; (d) allergen extracts as CSPs; and (e) CSPs prepared by a sterile compounding robot.

**Response:** Comment not incorporated. The suggestions are too prescriptive and could lead to confusion. Additionally, concepts of CSP risk levels no longer apply and have been incorporated into Category 1 and 2 CSPs.

**Commentary Summary #4:** Commenter suggested including centralization of Master Formulation Records. Multiple commenters recommended that the ability to change Master Formulation Records can be assigned to more than one person.

**Response:** Comments incorporated. The section was revised to defer to facility SOPs for changes to the Master Formulation Record.

**Commentary Summary #5:** Commenter recommended deleting the need to make a Master Formulation Record for CSPs prepared from nonsterile ingredients. Another commenter recommended that Master Formulation Records be required for all CSPs.

**Response:** Comment not incorporated. A Compounding Record is required for all CSPs. The purpose of a Master Formulation Record is for recordkeeping to describe how the CSP is prepared. A Master Formulation Record is required for CSPs prepared for more than 1 patient and for CSPs prepared from nonsterile ingredient(s).

**Commentary Summary #6:** Commenter suggested that Master Formulation Records need to show a trail of who, what, when, and why a change was made.

**Response:** Comment partially incorporated. The chapter was revised to state that any changes or alterations to the Master Formulation Record must be approved and documented according to the facility's SOP. The facility's SOP must describe how the Master Formulation Record may be changed and the documentation required for each change.

**Commentary Summary #7:** Commenter recommended that the date and time of when a change was made to the Master Formulation Record should not be required to be documented.

**Response:** Comment incorporated.

**Commentary Summary #8:** Commenter asked whether electronic systems can be used for Master Formulation Records.

**Response:** Comment incorporated. The chapter does not prohibit electronic Master Formulation Records.

**Commentary Summary #9:** Commenter recommended changing the headings of the Boxes.

**Response:** Comment not incorporated. The Boxes are titled according to the USP Style Guide.

**Commentary Summary #10:** Commenter recommended requiring the details of lot number and expiration date for each component only when batches of three or more CSPs are prepared. Commenter noted that current requirements are very burdensome.

**Response:** Comment not incorporated. Technology in most practices will allow ease of documentation.

**Commentary Summary #11:** Commenter recommended adding release testing to Master Formulation Records.

**Response:** Comment incorporated. Release testing would be considered QC procedures, which is in *Box 11-1 Master Formulation Records*.

**Commentary Summary #12:** Several commenters suggested striking the type and size of container-closure systems from the Master Formulation Records. The size of the container is determined by the size the compounder is dispensing. To require the size of

container to be listed on the Master Formulation Record is burdensome and might lead to inconsistent information.

**Response:** Comment not incorporated. For different amounts or sizes of CSP, different Master Formulation Records may be made. Container-closure systems must be specific to the Master Formulation Record.

**Commentary Summary #13:** Commenter recommended adding the date and time of compounding and the checker's information into the Master Formulation Record.

**Response:** Comment not incorporated. The commenter is referring to information that is present in the Compounding Record.

**Commentary Summary #14:** Commenter recommended that a physical description is not always applicable for clear liquids.

**Response:** Comment not incorporated. A clear liquid may be used as the physical description.

**Commentary Summary #15:** Multiple commenters suggested that the Compounding Record requirements are cumbersome and require copious paperwork. Commenter suggested that an extra label would need to be printed and kept for every CSP made, which is burdensome. Another commenter asked if Compounding Records are only applicable for outsourcing facilities. Several commenters noted that the requirement of a compounding record would prevent facilities from batching CSPs. Multiple commenters noted that it is not achievable to meet the requirement of creating a Compounding Record for all CSPs. Another commenter suggested that a Compounding Record is only required for CSPs not administered within the facility. Several commenters suggested that Compounding Records are only required for non-patient-specific CSPs. Several commenters requested that Compounding Records are only required for CSPs made from nonsterile ingredients. Commenter suggested that if information is being recorded upon receipt, it is unnecessary to be recorded again for each CSP. Another commenter suggested that Compounding Records are only required for batching.

**Response:** Comments not incorporated. A Compounding Record is required for all CSPs. CSP labels and other prescription records may be used to maintain a Compounding Record to prevent it from being cumbersome or burdensome. Labels or other documentation generated from the normal workflow/dispensing process may be used, including electronic labels. The section does not prohibit batching. Record keeping is necessary to track the quality and history of preparing CSPs, and this is not limited to outsourcing facilities.

**Commentary Summary #16:** Several compounders were unsure what is meant by "compounding".

**Response:** Comments incorporated. Compounding is described under *1. Introduction and Scope*.

**Commentary Summary #17:** Several commenters suggested striking "by the compounder preparing the CSP" since it implies that the individual performing compounding must create or print the Compounding Record.

**Response:** Comments incorporated.

**Commentary Summary #18:** Commenter recommended that a Compounding Record may be stored electronically and must be in a searchable record system to be retrieved in a timely manner.

**Response:** Comment partially incorporated. Compounding Records may be stored electronically but the chapter does not indicate a temporal restriction to when it must be retrieved. “Timely” is ambiguous.

**Commentary Summary #19:** Several commenters recommended striking the section *11.2 Creating Compounding Records*.

**Response:** Comment not incorporated. A Compounding Record is required for all CSPs to document the compounding or repackaging process.

**Commentary Summary #20:** Commenter recommended striking the examples of what may serve as the Compounding Record since they do not usually contain all the information required.

**Response:** Comment not incorporated. Facilities may choose to add additional information to the aforementioned sources, while using them as a foundation (e.g., additional notations).

**Commentary Summary #21:** Several commenters recommended removing “repeater pump” from *11.2 Creating Compounding Records*.

**Response:** Comments incorporated.

**Commentary Summary #22:** Commenter suggested that release testing must be documented in the Compounding Record.

**Response:** Comment incorporated. Release testing is a part of QC procedures.

**Commentary Summary #23:** Commenter recommended that Compounding Records must contain the lot number and expiration date for each component. Another commenter recommended striking the need for manufacturer name, lot number, and expiration date for inpatient settings.

**Response:** Comments partially incorporated. The section was revised to include vendor, lot number, and expiration date for each component for CSPs prepared for more than one patient and for CSPs prepared from nonsterile ingredient(s). The chapter does not stratify requirements for inpatient settings.

**Commentary Summary #24:** Commenter recommended that Compounding Records are only required for anticipatory batching.

**Response:** Comment not incorporated. The chapter does not stratify requirements for anticipatory batching. Additionally, anticipatory batching may be difficult to define.

**Commentary Summary #25:** Commenter suggested clarifying what steps need to be delineated when identifying associated individuals. Another commenter noted that current electronic health records (EHRs) do not support the documenting of all individuals involved in each step of the compounding process.

**Response:** Comments incorporated. The section was revised to require a method to identify the individuals involved in the compounding process and verifying the final CSP.

**Commentary Summary #26:** Commenter suggested clarifying whether components in the Compounding Record include inactive ingredients as well.

**Response:** Comment incorporated. All components include both APIs and added substances, which are defined in the *Glossary*.

**Commentary Summary #27:** Commenter recommended adding a stability reference to the Compounding Record.

**Response:** Comment not incorporated. Facilities may choose to input a stability reference, but it is not required as it may be a burdensome process.

**Commentary Summary #28:** Commenter recommended adding a reference to <1160>.

**Response:** Comment not incorporated. The chapter may not include all calculations that a facility utilizes.

**Commentary Summary #29:** Commenter recommended striking all but the name of the CSP, vendor or manufacturer, lot number, and expiration date for each ingredient.

**Response:** Comment not incorporated. The chapter is intended to be a minimum standard; *Box 11-2* describes the minimum recordkeeping requirements for a Compounding Record.

## 12. Release Inspections and Testing

**Expert Committee-initiated Change #1:** The section number was revised to align with the re-numbering of other sections.

**Commentary Summary #1:** Commenter noted concerns that regulatory bodies may require sterility testing more often than described in the chapter.

**Response:** Comment not incorporated. USP has no role in enforcement of compounding chapters. Pursuant to *General Notices, 2.30 Legal Recognition*, assuring compliance with USP standards is the responsibility of regulatory bodies. Regulatory bodies may impose different or more stringent requirements than those in the chapter.

**Commentary Summary #2:** Commenter requested the addition of language that all high-risk level CSPs that have been assigned an extended BUD in single-dose containers be sterility tested before they are dispensed or administered.

**Response:** Comment not incorporated. The contamination risk levels (low, medium, and high) were removed from the chapter. The BUDs in *Table 11* for Category 2 CSPs are based on the compounding method, starting components, sterility testing, and storage conditions.

**Commentary Summary #3:** Commenter suggested adding clarification regarding if and when a facility must carry out retesting of a CSP if it fails initial testing, since it is not clear in the chapter whether this is a requirement or can be determined based on the facility's QA and QC programs. There is no guidance provided for QA and QC programs regarding the timeframe for investigation and corrective action.

**Response:** Comment partially incorporated. Organizations are required to investigate any out-of-specification results, and a corrective action plan must be implemented and documented as part of the QA and QC program. Retesting may be a corrective action and should be described in the facility's QA and QC program. More details have been added to *18. Quality Assurance and Quality Control*.

**Commentary Summary #4:** Commenter suggested adding a requirement for visual inspection of all CSPs before sending them to a patient, regardless of the need for additional testing.

**Response:** Comment incorporated. All CSPs must be visually inspected before being dispensed.

**Commentary Summary #5:** Several commenters suggested adding a requirement for all visual inspections to be documented because this should be part of the pharmacist's competency in working in a pharmacy. Some commenters suggested using a checklist to document the process of visual inspection.

**Response:** Comment partially incorporated. Documentation must be determined by the facility. Facilities may choose to use a checklist to accomplish documentation.

**Commentary Summary #6:** Commenter suggested specifying who has to do the visual inspection since there are facilities that have only one compounder working at a time. If the compounder has to wait for another party to do the visual inspection, patients may lose timely access to medications and facilities may experience drug waste.

**Response:** Comment not incorporated. The chapter does not prohibit nor deny a sole compounder to also perform visual inspection.

**Commentary Summary #7:** Several commenters suggested adding more clarification and recommendations on the best practices for visual inspection. Some commenters suggested adding a requirement that the visual inspection must be done against a lighted white or dark box because defining this requirement will limit misinterpretation of the results between compounders and by inspectors.

**Response:** Comment not incorporated. Facilities can determine their own SOP for visual inspection (including use of white lights) to best fit their setting while minimizing errors and subjective interpretations.

**Commentary Summary #8:** Commenter recommended adding a definition for dispensing to make it clearer to readers when a CSP needs to be visually inspected. The commenter noted that although it is important for a CSP to be inspected prior to final labeling for patient use, this requirement is not conducive to the health-system setting where products may be compounded, verified, and labeled long before they are dispensed and released from the pharmacy.

**Response:** Comment not incorporated. Dispensing refers to distribution of the CSP. This occurs, minimally, at the completion of compounding, before release. Facilities may choose to inspect the product each time it is dispensed.

**Commentary Summary #9:** Commenter suggested clarifying the expression 'promptly dispensed' when referring to how soon a CSP should be visually inspected after compounding because 'promptly' is open to interpretation.

**Response:** Comment incorporated. Clarified that promptly refers to dispensing on the day of preparation.

**Commentary Summary #10:** Commenter suggested omitting the requirement for visual inspections of CSPs that are not dispensed immediately upon admixing because this will be problematic for drugs that require special packaging such as protection from light.

**Response:** Comment not incorporated. Regardless of packaging, the CSP must be inspected visually for particulates or other observed defects.

**Commentary Summary #11:** Commenter suggested omitting the section because it is potentially confusing and references <71>, which already provides sufficient details on sterility testing.

**Response:** Comment not incorporated. The chapter specifies numbers of units for testing if less than 40 units are made to prevent the scenario where four CSPs are required to test the sterility of one CSP. The chapter refers to <71> for testing and for

CSPs exceeding 40 units in a single batch. Additional clarification was provided for compounding less than 40 CSPs.

**Commentary Summary #12:** Commenter recommended determining the need for sterility testing based on the number of items compounded in a batch and exposure of CSPs to storage in a refrigerator for more than 12 hours or at room temperature for more than 6 hours before sterilization. The commenter noted that this is consistent with current standards and has served the compounding community well.

**Response:** Comment not incorporated. The concepts of risk-level categorization have been incorporated into Category 1 and Category 2 CSPs.

**Commentary Summary #13:** Commenter suggested the addition of more clarification on the need for sterility testing to state that this is only needed if a compounder assigns a BUD outside the defaults stated in *Table 11*.

**Response:** Comment not incorporated. *Table 11* describes BUDs for Category 2 CSPs based on several factors including on whether sterility testing is performed.

**Commentary Summary #14:** Commenter suggested adding that validated alternative methods include tests like RapidScan or the alternatives that the analytical laboratories may be using.

**Response:** Comment not incorporated. The chapter cannot specify a vendor-specific or proprietary testing system. An alternative sterility testing method may be used if it has been validated as described in <1223>.

**Commentary Summary #15:** Commenter suggested clarifying that the sterility testing must be done on the CSP in the final container in which it will be administered.

**Response:** Comment not incorporated. Category 2 CSPs assigned a BUD requiring sterility testing must be tested in its final container. The final container may be subsequently used (e.g. administered or used as a component).

**Commentary Summary #16:** Commenter suggested adding a requirement for prompt investigation of possible causes of sterility testing failures, including that the investigation should identify microorganisms to the species level. The commenter added that the investigation should allow compounders to benefit from recent advances in technologies and development of new sterility test methods, based on the direct detection of viable contaminating microorganisms. These methods will provide clear flexibility and very rapid time to result.

**Response:** Comment not incorporated. Facilities should work with vendors and testing laboratories to validate methods. Corrective actions should be addressed by the facility's SOPs.

**Commentary Summary #17:** Commenter suggested adding further clarification on what is meant by recovery of microorganisms during sterility testing because it was not clear whether this meant identification of microorganisms to the genus level or removability of the microorganisms.

**Response:** Comment not incorporated. Readers are referred to <71> for further requirements for sterility testing.

**Commentary Summary #18:** Commenter suggested removing direct inoculation of the culture medium as an alternative-method suitability test when testing sterility of CSPs according to <71>, because direct inoculation is promoted by laboratories but is not necessarily the best alternative.

**Response:** Comment not incorporated. Direct inoculation is the preferred method and is consistent with <71>.

**Commentary Summary #19:** Commenter suggested eliminating the description of bacterial endotoxin testing for CSPs because there is sufficient information in <85> *Bacterial Endotoxins Test* and any description in <797> could cause confusion.

**Response:** Comment not incorporated. The chapter refers to <85> for endotoxin testing, however it is important to recognize that <85> was not written explicitly for CSPs. Additional verbiage is therefore necessary.

**Commentary Summary #20:** Commenter suggested adding a minimum batch size for when endotoxin testing is required so that small batches are not required to undergo endotoxin testing. The commenter added that requiring this testing for small batches is an unnecessary burden and will negatively impact patient ability to afford many CSPs.

**Response:** Comment not incorporated. Sterility testing is not aimed at detecting pyrogens, therefore both tests are necessary.

**Commentary Summary #21:** Commenter suggested adopting the same language used in <825> to have the same requirements for endotoxin testing because this would lead to uniform standards across compounding settings.

**Response:** Comment not incorporated. Radiopharmaceuticals are outside of the scope of <797>, therefore each chapter may have different requirements.

**Commentary Summary #22:** Commenter suggested adding a clear statement that Category 2 CSPs that are prepared only from sterile starting components do not need to be tested for endotoxins because starting components that are sterile from the manufacturer are usually labeled "non-pyrogenic or pyrogen-free". Testing in this instance would be redundant and unnecessary.

**Response:** Comment not incorporated. Endotoxin testing is required specifically when nonsterile ingredients are used.

**Commentary Summary #23:** Commenter noted that products intended for the epidural space should have the same endotoxin levels as those intended for intrathecal administration. The commenter therefore, suggested adding that intrathecally administered CSPs prepared from any nonsterile ingredient regardless of category must be tested to ensure that they do not exceed the endotoxin limit for intrathecal administration.

**Response:** Comment partially incorporated. Category 2 injectable CSPs made from one or more nonsterile components and assigned a BUD not requiring sterility testing should be tested for bacterial endotoxins for humans, otherwise the limits can be calculated in non-human species.

**Commentary Summary #24:** Commenter noted that there is no specific description of the process to be followed when compounders are handling blood and blood products, and yet proper cleaning and disinfection must be completed prior to manipulation of non-blood-related activities. The commenter cautioned against requiring a dedicated room solely for the use of radiolabeled blood components because this will hinder the efficient use of laboratories that do minimal blood studies over a given period. The commenter therefore suggested adding that proper cleaning and sanitation of the room after radiolabeling and manipulation of blood materials and products can be done in a safe and effective manner without the risk of cross-contamination.

**Response:** Comment incorporated. A statement was added to clarify that when compounding activities require the manipulation of a patient's blood-derived or other biological material (e.g., autologous serum), the manipulations must be clearly separated from routine material-handling procedures and equipment used in CSP preparation activities, and they shall be controlled by specific SOPs in order to avoid any cross-contamination.

### 13. Labeling

**Expert Committee-initiated Change #1:** The section number was revised to align with the re-numbering of other sections.

**Commentary Summary #1:** Commenter suggested adding a requirement that the label on the immediate container of the CSP must display prominently whether it is a single-dose or multiple-dose CSP, as is required in the currently official chapter, because without an appropriate label, users may inappropriately use a single-dose CSP for multiple patients or use it over an extended period of time, increasing the risk of infection.

**Response:** Comment incorporated. Added language that a CSP must be labeled as a single dose when space permits. This is aligned with FDA guidance on labeling and General Chapter <7>.

**Commentary Summary #2:** Commenter suggested that route of administration be added to the list of items required to be added to the label on the immediate container of the CSP because it enhances patient safety.

**Response:** Comment incorporated. Route of administration was added to the list of items required on the label of the CSP.

**Commentary Summary #3:** Several commenters noted that the high number of requirements for items to be added on the label of the immediate container of the CSP would distract the reader and reduce readability of the label without adding to safety. Too much information on a label can cause label fatigue, and users may miss pertinent information such as dose, concentration, and route of administration. Some commenters pointed out that having multiple different dates such as BUD and date of preparation on the label might be confusing. Some commenters suggested that the date when the CSP was prepared, the name of the active ingredient, route of administration, and an indication that the product is compounded should be removed from the list of items to be displayed prominently on the label, because they do not add to the safety of the CSP.

**Response:** Comments partially incorporated. The chapter is intended to provide only the minimum labeling requirements for CSPs. The date prepared was removed from the list of items to be added to the label.

**Commentary Summary #4:** Several commenters noted that some of the labeling requirements in the chapter are in conflict with the labeling requirements in their states and suggested various changes for alignment. Some commenters noted that some states require inactive ingredients to be included on the label.

**Response:** Comments not incorporated. The chapter labeling requirements are a minimum standard. In addition, all labels must also comply with laws and regulations of the applicable regulatory jurisdiction.

**Commentary Summary #5:** A commenter suggested differentiating between items that must be included on the label of the immediate container of the CSP and the labeling of the CSP.

**Response:** Comment incorporated. Storage information and route of administration must be on the label attached to the immediate container of the CSP. Contact information if the facility is sending the CSP to another facility and a statement that a CSP is compounded may be included in the labeling. The labeling of the CSP must also provide any applicable special handling instructions or warning statements.

**Commentary Summary #6:** A commenter recommended adding that if using the prescription or order number as the assigned internal identification number it must be recorded on the compounding record because requiring only a prescription number is not sufficient to determine the medication was made for that prescription.

**Response:** Comment not incorporated. The facility may determine the source of the internal identification number and how it relates to other aspects of the workflow specific to the setting of their compounding practice.

**Commentary Summary #7:** Commenter suggested matching the requirements for CSPs in single-dose containers with those for <659>, which require that single-dose containers be labeled to indicate that they are single-dose containers.

**Response:** Comment incorporated. A statement to indicate single-dose container was added to the list of items required on the label.

**Commentary Summary #8:** Commenter suggested removing route of administration from the list of items required on the label attached to the immediate container of the CSP.

**Response:** Comment not incorporated. Route of administration is required to be on the label on the immediate container of the CSP to help ensure the correct and safe use of the CSP.

## 14. Establishing Beyond-Use Dates

**Expert Committee-initiated Change #1:** The section number was revised to align with the re-numbering of other sections.

**Expert Committee-initiated Change #2:** The section was reorganized to streamline information on the parameters to consider when establishing a BUD. Each of the parameters is described in the context of BUDs in *Tables 10 and 11* for Category 1 and Category 2 CSPs.

**Commentary Summary #1:** Several commenters requested adding the ability to extend the BUD of CSPs beyond those in *Table 11* if potency-over-time studies and <51> antimicrobial effectiveness studies are performed.

**Response:** Comments not incorporated. Potency-over-time studies are not stability indicating. Strength (potency) over time testing determines the amount of active ingredient in a CSP; however, it may not be able to separate the active ingredient from its degradation products and impurities for quantitation depending on the analytical methods used for the test. A stability-indicating method will be able to quantitate the active ingredient and its degradation products or related impurities in the preparation by separating the active ingredient from its degradation products and impurities, and showing a change in the concentration of the active ingredient with increasing storage

time. (See article, "[Strength and Stability Testing for Compounded Preparations.](#)") Further, for CSPs, compounders must additionally take into consideration testing for sterility, endotoxins, container-closure integrity, and particulate matter. The Expert Committee is considering the development of new resource(s) to assist compounders in extending BUDs for Category 2 CSPs.

**Commentary Summary #2:** Several commenters noted that the description of BUD is potentially confusing since it seems to indicate two dates. A commenter noted that it is unclear in the definition when both hour and date are required to be labeled on the CSP and suggested that both must be added to the label.

**Response:** Comments not incorporated. The BUD indicates the date by which the CSP must be discarded. Facilities may develop SOPs describing their own formats for indicating the BUD on CSP labels.

**Commentary Summary #3:** A commenter suggested removing any reference to administration from the definition of BUD because administration is out of the scope of the chapter.

**Response:** Comment incorporated. Mention of the time before which administration must begin was removed from the definition of BUD.

**Commentary Summary #4:** A commenter suggested adding a requirement for the inclusion of both BUD and expiration dates on the labels of CSPs.

**Response:** Comment not incorporated. Expiration dates do not apply to CSPs. CSPs are labeled with only BUDs.

**Commentary Summary #5:** Several commenters suggested including infusion time in the definition of BUD. Some commenters suggested describing the infusion time as administration time and including a definition in the chapter.

**Response:** Comments not incorporated. Administration time, including infusion times, is out of the scope of the chapter. The BUD does not include infusion times as this can vary per CSP due to several factors such as stability. Infusion must not begin after the BUD.

**Commentary Summary #6:** Commenter suggested defining BUD from the time when the CSP is entered to the beginning of administration.

**Response:** Comment not incorporated. The BUD is determined from the time when the compounding of the CSP is initiated.

**Commentary Summary #7:** Commenter suggested removing the definition for expiry dates from the chapter because it does not provide any value or practice standards for compounding CSPs. The commenter added that the distinction between expiry dates and BUDs for CSPs is not necessary.

**Response:** Comment not incorporated. Provision is added to clarify a common misconception that BUD and expiration dates are the same.

**Commentary Summary #8:** Several commenters suggested defining BUD as the date after which a CSP must be discarded because this would reduce opportunities for confusion among compounders. Some commenters proposed removing the reference stating "after which it should not be used" because this gives the false impression that sterility is impacted and infusion should be stopped once BUD time passes.

**Response:** Comments incorporated. Adjusted verbiage to clarify that BUD is when the CSP must not be used and must be discarded.

**Commentary Summary #9:** Commenter suggested removing the reference to the date by which a CSP must be discarded from the BUD definition because it is not possible to enforce when a person receiving medicine discards it.

**Response:** Comment not incorporated.

**Commentary Summary #10:** Commenter suggested adding the effect of water evaporation from flexible plastic containers, also known as WVTR (water vapor transmission rate), to the list of factors to be considered when establishing a BUD for the CSPs because there may be stability issues arising from evaporation from over-potent drugs in small bags after 30 days.

**Response:** Comment not incorporated. Addition of WVTR may lead to confusion on whether facilities have to measure WVTR. Furthermore, WVTR may be related to compatibility of the formulation with the container-closure system, which is already listed as one of the factors to consider when establishing BUDs for CSPs.

**Commentary Summary #11:** Several commenters suggested removing whether or not sterility testing is performed from the list of factors to be considered when establishing BUDs because assurance of sterility of CSPs is not achieved through sterility testing but through the use of verified container-closure systems, preservatives, and controlled storage.

**Response:** Comments not incorporated. Sterility testing offers additional rigorous and scientifically justified assurance that a CSP is sterile.

**Commentary Summary #12:** Several commenters suggested extending the default BUD for aseptically prepared CSPs using sterile ingredients (such as some parenteral nutrition products) from 9 days to 17 days because the 9 day limit is based on empiric evidence and not on sterility or stability data. Some commenters also added that the 9 day BUD is costly and impractical given the time required for sterility testing. Other commenters noted that a longer BUD would enable continuity of care for patients in remote locations or during times of inclement weather. Others noted that longer BUDs would be more convenient for patients and improve the operational efficiency of pharmacies.

**Response:** Comments not incorporated. The BUDs in *Table 11* are based on several considerations such as stability data, sterility data, and compounding environment.

**Commentary Summary #13:** Commenter suggested changing the BUD for aseptically prepared CSPs that had no sterility testing performed and were stored in a refrigerator to greater than 9 days (e.g., between 10 and 14 days) because this would allow for once weekly compounding for those items that are shipped to homes in rural areas.

**Response:** Comment incorporated. The BUD was changed to 10 days.

**Commentary Summary #14:** Several commenters suggested allowing compounders to use stability studies published in peer-reviewed journals and performed according to ICH guidelines to extend BUDs. Some commenters noted that allowing compounders to extend BUDs using stability studies would encourage investment in studies to generate the scientific evidence required to extend BUDs for CSPs. Other commenters suggested adding a list of criteria that compounders could follow if they wish to extend the BUD for CSPs beyond the defaults in *Table 11*.

**Response:** Comments not incorporated. Extending BUDs requires consideration of several factors including additional personnel and environmental monitoring, sterility

considerations, container-closure integrity, antimicrobial preservative effectiveness testing, and stability testing using a validated stability indicating assay.

**Commentary Summary #15:** Several commenters suggested allowing compounders to extend BUDs and storage for CSPs using USP Compounded Preparation Monographs (CPMs) if the CSP meets specifications from the testing in that monograph.

**Response:** Comments incorporated. CPMs for CSPs may be used provided all the conditions are met. *General Notices 3.10 Applicability of Standards* states that monograph specifications (e.g., BUDs) supersede those of chapters.

**Commentary Summary #16:** Commenter suggested limiting the BUD for aseptically prepared CSPs that are not undergoing sterility testing, only using sterile products, and stored at controlled room temperature to 24 or 30 hours as previously required instead of 4 days as proposed. The commenter noted that the increase in BUD could result in patient harm.

**Response:** Comment not incorporated. The BUD was increased to 4 days due to the need to balance patient access to CSPs as well as the more robust environmental monitoring procedures required in the revised chapter.

**Commentary Summary #17:** Several commenters suggested adding detailed description of the references that can be used to determine the chemical and physical stability of a compounded preparation. Some commenters suggested adding more guidance for assessing the true stability of CSPs because there are various interpretations of stability data and the compounding profession would benefit from standardized guidelines for assessing chemical, physical, and microbiological stability.

**Response:** Comments not incorporated. Appeared too granular. Additional resources may be developed in the future.

**Commentary Summary #18:** Commenter suggested excluding the expiry date of acids and bases used to adjust the pH of CSPs from factors that need to be considered when establishing the BUD of CSPs.

**Response:** Comment not incorporated. The BUD of a CSP must not exceed the expiration date of any of the components including acids and bases.

**Commentary Summary #19:** Commenter suggested removing the ability of category 1 CSPs from being prepared in cleanroom suites because only category 2 CSPs should be prepared in a cleanroom suite unless the cleanroom has lost its state of control.

**Response:** Comment not incorporated. The facility is responsible for determining corrective actions in the event of an excursion in the cleanroom suite, and the change of Category of CSP is one of many potential solutions.

**Commentary Summary #20:** Several commenters suggested increasing the BUD for category 1 CSPs to 48 hours at controlled room temperature and 4 days if refrigerated because there is no scientific evidence for shorter BUDs. Some commenters suggested that if they use a compounding aseptic isolator (CAI) they should be allowed to label category 1 CSPs with the same BUDs used for category 2 CSPs. Other commenters suggested allowing compounders to use longer BUDs if they use RABS. Other commenters noted that the shorter BUDs would result in more immediate-use compounding at the bedside and less compounding in the pharmacy.

**Response:** Comments not incorporated. The BUDs in *Table 10* are for CSPs prepared in a SCA. The BUD of 12 hours at room temperature is consistent with the BUDs in the existing chapter for low-risk level CSPs prepared in a SCA. The revised BUDs are

intended to balance the amount of environmental monitoring required in SCAs and cleanroom suites.

**Commentary Summary #21:** Commenter suggested adding water activity as one of the factors to be considered when establishing BUDs for CSPs because CSPs with low water activity are less likely to support microbial growth.

**Response:** Comment not incorporated. Not every CSP may require water activity considerations. This is not addressed in current default BUDs and there is no existing evidence of water activity to support proposed BUDs. Water activity is not globally considered in BUDs for all CSPs.

**Commentary Summary #22:** A commenter noted that there is potential for the language in *Table 11* to be misinterpreted as requiring all CSPs to be filtered during compounding, as part of the process of aseptic processing. The commenter noted that not all CSPs prepared from sterile ingredients need to be filtered. The commenter suggested adding a statement to indicate that CSPs prepared from sterile ingredients only need to be filtered if required.

**Response:** Comment not incorporated. The text in *Table 11* as well as accompanying text in *14.3 Establishing a BUD for a CSP* describes how both aseptic preparation and terminal sterilization should be used when assigning BUDs.

**Commentary Summary #23:** Commenter suggested removing irradiation as a means of achieving terminal sterilization of CSPs because the chapter does not provide sufficient details on how it is performed.

**Response:** Comment incorporated. Reference to irradiation as a means of terminal sterilization was removed. Readers are referred to <1229> for details.

**Commentary Summary #24:** Commenter suggested specifying in *Table 11* that all CSPs to be labeled with BUDs that require stability testing must be shown to have passed a sterility test.

**Response:** Comment not incorporated. Adding such verbiage will be confusing to compounders since it is not clear what passing a sterility test entails. Passing a sterility test does not guarantee that all units of a batch of CSPs are sterile because contamination may not be uniformly distributed throughout the batch.

**Commentary Summary #25:** Commenter suggested adding guidance on how often sterility testing is required for different batches of the same formulation because the current chapter does not specify and this is likely to be open to interpretation by regulators.

**Response:** Comment not incorporated. Sterility testing must be performed on each batch of Category 2 CSPs if a BUD requiring sterility testing is used. Further information on sterility testing frequency is also described in 10.2.

**Commentary Summary #26:** Commenter suggested adding instructions for what BUDs compounders should use if they transfer a CSP from controlled room temperature storage conditions to refrigeration.

**Response:** Comment not incorporated. Storage conditions vary per CSP and can affect stability. Compounders should refer to chemical stability information which is unique for each CSP.

**Commentary Summary #27:** Commenter suggested adding more examples of real life scenarios to illustrate that the BUDs for a CSP cannot accumulate from changing storage to different conditions. The commenter noted that without more examples this

section could be misinterpreted as permitting the extension of BUDs beyond those required in Table 11.

**Response:** Comment not incorporated. *14.3 Establishing a BUD for a CSP* already specifies that the BUD is not cumulative and is per the BUD assigned when the CSP is compounded.

**Commentary Summary #28:** Several commenters suggested that terminally sterilized CSPs be given the same BUDs as aseptically prepared CSPs that have successfully undergone sterility testing because there is no justification for treating terminally sterilized CSPs differently. Several commenters added that there is no scientific rationale for why an aseptically prepared CSP that passes sterility testing would be more likely to become contaminated between day 30 and day 45 (when stored at room temperature) compared to a terminally sterilized CSP that also passes sterility testing. Some commenters suggested that terminally sterilized CSPs that have passed a sterility test should be allowed a minimum 90-day BUD at room temperature.

**Response:** Comments not incorporated. BUDs are markedly extended from current Chapter BUD requirements for low-, medium-, and high-risk CSPs. Terminally sterilized CSPs contain one or more nonsterile ingredients that need to be sterilized.

**Commentary Summary #29:** A commenter noted that requiring CSPs to be stored at controlled room temperature is very restrictive because most pharmacies/clinical sites will have a difficult time complying with this temperature range. The commenter suggested redefining room temperature as 15–25° because this is more reasonable.

**Response:** Comment not incorporated. Temperature ranges for the storage of medicines are defined in <659>. Storage conditions must be controlled in order to ensure the quality of the CSP.

**Commentary Summary #30:** Several commenters suggested that terminally sterilized CSPs that have passed a sterility test should be allowed a minimum 90-day BUD at room temperature because these CSPs are already nearing day 30 by the time sterility testing is completed which does not give ample time for the CSP to be dispensed and utilized by patients before expiring. Other commenters added that if a CSP has passed a sterility testing and there is documentation on the integrity of the container/closure system, the CSP will be sterile until it is opened. In these instances, the BUD should be based on the stability of the CSP and not the sterility.

**Response:** Comments not incorporated. Most sterility tests can be completed within 14-20 days which allows the CSPs to continue to be used for 45 days at controlled room temperature, 60 days refrigerated, and 90 days frozen. Furthermore, CSPs may be dispensed before sterility results are known provided recall procedures are available.

**Commentary Summary #31:** Commenter suggested adding that CSPs sterilized by irradiation should not require sterility testing on every batch. They should receive BUDs based on product-specific evidence which is consistent with the FDA requirement for conventionally manufactured products sterilized by irradiation.

**Response:** Comment not incorporated. Sterilization by irradiation is currently not a method that is described in <1229>. The EC may consider adding sterilization by other methods.

**Commentary Summary #32:** Commenter suggested adding a section describing the requirements for BUDs for anhydrous CSPs because anhydrous formulations are inherently less prone to microbial growth than water containing ones and should have

their own section similar to <795>. The commenter proposed longer BUDs for anhydrous CSPs.

**Response:** Comment not incorporated. There are risks with sterility and stability with aqueous and nonaqueous CSPs. Not every CSP may require water activity considerations. There is no existing evidence of water activity to support proposed BUDs.

**Commentary Summary #33:** Several commenters suggested including route of administration and the addition of preservatives as factors to be considered when establishing BUDs for multiple-dose CSPs because they have evidence from method suitability testing that preserved CSPs are sterile for at least 42 days. Some commenters added that CSPs with an effective antimicrobial preservative system should be labeled with a BUD of at least 1 year in a freezer, 150 days if stored in a refrigerator, and 90 days if stored at room temperature. Other commenters suggested that all CSPs with an effective preservative system should have a BUD of at least 1 year, such as is permitted for allergenic compounded extracts.

**Response:** Comments not incorporated. Regardless of route of administration or presence of a preservative system, CSPs are required to be sterile and the BUD assignment is based on sterility and stability considerations. Preservatives should not be used as a substitute for good aseptic practices. Antimicrobial effectiveness testing based on <51> is also required to ensure that the preservative system is effective. Allergenic extracts have special characteristics that differentiate them from other CSPs.

**Commentary Summary #34:** A commenter suggested changing the name of *Table 11* to “BUDs for Single Dose, Category 2 CSPs.”

**Response:** Comment not incorporated. The BUDs apply to multiple dose CSPs as well.

**Commentary Summary #35:** Commenter suggested adding that aseptically prepared CSPs include those sterilized by filtration, either made from one or more nonsterile starting components or from only sterile starting components.

**Response:** Comment incorporated. A statement was added in 12.3 to describe aseptic preparation to include both preparations from sterile starting ingredients and sterilization by filtration.

**Commentary Summary #36:** Commenter suggested adding a footnote to *Table 11* to remind compounders that sterilization by filtration is not a form of terminal sterilization because the table could be misinterpreted leading to labeling of longer BUDs than permitted.

**Response:** Comment incorporated. Text was added in the main section to remind compounders that sterilization by filtration is not a form of terminal sterilization.

**Commentary Summary #37:** Several commenters suggested maintaining the BUDs for CSPs according to the currently official chapter based on low-, medium-, and high-risk CSPs because changing to Category 1 and Category 2 is unrealistic since there are very few 503A facilities that do a significant amount of terminal sterilization. Other commenters added that the limitation on BUD for aseptic compounding with sterility testing seems unreasonable when a 503B facility can do aseptic compounding and assign much longer BUDs with the same sterility testing.

**Response:** Comments not incorporated. Category 1 and Category 2 CSPs have replaced the concept of risk categories, and depend on the compounding environment.

The BUDs in Table 11 are based on a conservative approach considering factors of environmental and personnel monitoring, risk of contamination, and stability.

**Commentary Summary #38:** Several commenters suggested adding a description of how to assign BUD for CSPs compounded following the instructions in the labeling information (e.g. package inserts) for conventionally manufactured medicines. Some commenters suggested adding that the BUD for CSPs compounded following instructions in approved labeling of conventionally manufactured products should not exceed the BUD in the product labeling.

**Response:** Comments not incorporated. Compounding following the instructions in approved labeling provided by the product manufacturer is out of the scope of this chapter, as described in 1.4.

**Commentary Summary #39:** Several commenters suggested adding special BUDs for aseptically prepared topical Ophthalmic CSPs because many of them are prepared in containers that cannot withstand the high temperature and pressure required for terminal sterilization.

**Response:** Comments not incorporated. The standard cannot stratify requirements for specific ophthalmic products. <1228> describes methods for sterilization of products that are sensitive to heat and pressure.

**Commentary Summary #40:** Several commenters suggested removing the reference to preservatives as substances that inhibit microbial growth because this contradicts the definition in the glossary.

**Response:** Comments incorporated. Reference was changed to preservatives as substances which are intended to inhibit microbial growth.

**Commentary Summary #41:** Several commenters suggested specifying which multiple-dose CSPs are required to contain preservatives and specifying that only multiple-dose CSPs containing preservatives must pass antimicrobial effectiveness testing. Other commenters added that there are several multiple-dose CSPs that are assigned very short BUDs (3-4 days), or multiple-dose CSPs assigned conservative BUDs, that will not support rapid microbial proliferation (such as a petroleum-based ophthalmic ointment with a 10-day BUD) and may not need preservatives, particularly in situations where patients have a sensitivity to preservatives.

**Response:** Comments not incorporated. All CSPs containing antimicrobial preservatives must undergo <51> testing. The compounder determines when and which preservatives are appropriate.

**Commentary Summary #42:** Commenter recommended adding that each multiple-dose CSP formula of identical ingredients must additionally pass antimicrobial effectiveness testing in accordance with <51>. Another commenter suggested adding that bracketing may be utilized to establish preservative effectiveness across various strengths of the same formula because the demands in healthcare often require compounders to prepare the same formula in various strengths. The cost for <51> testing would unnecessarily limit the availability of these formulas.

**Response:** Comments incorporated. Statements to allow bracketing were added.

**Commentary Summary #43:** Commenter suggested adding that if a CSP does not pass antimicrobial effectiveness testing it can still be used as a compounded single dose CSP or stock solution and get the shorter dating of 6 hours.

**Response:** Comment incorporated. CSPs must pass <51> testing in order to be used as a multiple dose container. Stock solutions and single-dose containers are addressed in Section 15.

**Commentary Summary #44:** Several commenters suggested clarifying whether conventionally manufactured multiple-dose vials are permitted to be used to prepare CSPs according to the requirements in the chapter.

**Response:** Comments not incorporated. The section is intended to describe compounding of multiple-dose CSPs. This section does not apply to use of conventionally manufactured multiple-dose containers, which are further described in section 13.2. Conventionally manufactured multiple-dose containers are also tested and designed to be entered outside of an ISO Class 5 PEC.

**Commentary Summary #45:** Commenter suggested reducing the requirement for bactericidal and bacteriostatic CSPs to be tested for antimicrobial effectiveness to be used as a multiple-dose container because there is no scientific rationale for requiring the additional testing unless the compounder wishes to use BUDs beyond those given in *Table 11*.

**Response:** Comment not incorporated. Bactericidal and bacteriostatic CSPs must be tested for antimicrobial effectiveness to be able to be used as a multiple-dose container.

**Commentary Summary #46:** Commenter suggested clarifying whether studies performed by reputable third parties can be used to confirm that multiple dose CSPs have passed antimicrobial effectiveness because such organizations are capable of producing high quality studies that stand up to scrutiny and such studies result in improved patient care and convenience.

**Response:** Comment incorporated. Added allowance for antimicrobial effectiveness testing results provided by FDA registered facilities.

**Commentary Summary #47:** Commenter suggested removing the requirement for multiple-dose CSPs to be used before their BUD or within 28 days if supported by <51> testing because retail pharmacies are unable to control what happens to CSPs once they are dispensed.

**Response:** Comment not incorporated. The chapter describes the responsibilities for compounders and not for patients.

**Commentary Summary #48:** Commenter suggested removing the requirement for container closure integrity testing if the compounder uses pre-assembled and sterilized containers from an FDA recognized source because there is no justification for such testing in these conditions.

**Response:** Comment not incorporated. Container closure integrity testing is needed if the container is meant to be punctured multiple times. FDA does not approve and evaluate the sterilized containers with use of the particular CSP.

**Commentary Summary #49:** Commenter suggested adding that the container-closure integrity test needs to be conducted only once on each formulation following a worst case scenario because more frequent testing for the container-closure integrity for each fill volume is excessive. Validating a worst-case scenario would suffice, since most compounding is done using commercial empty sterile containers.

**Response:** Comment not incorporated. It is difficult to determine which fill volume is the worst-case scenario because each CSP is formulation specific. Fill volumes for CSPs

are not always identical. If there is a change in the container closure system, the testing needs to be repeated for the new container closure system.

## 15. Use of Conventionally Manufactured Products as Components

**Expert Committee-initiated Change #1:** The section number was revised to align with the re-numbering of other sections.

**Commentary Summary #1:** Commenter suggested adding language to require labeling sterile components when they are entered or punctured with when the product has been entered, by whom, and when it must be discarded.

**Response:** Comment not incorporated. Facilities must determine a method to determine the time within which the product must be used.

**Commentary Summary #2:** Commenter requested clarifying if use of conventionally manufactured products requires media-fill testing.

**Response:** Comment not incorporated. Media-fill testing is required for assessing aseptic technique. It is not targeted towards manipulating specific components.

**Commentary Summary #3:** Commenter suggested that preservatives should not take the place of good compounding practices.

**Response:** Comment not incorporated. Preservatives are not a substitution for good compounding practices. Additionally, the preservative cannot be arbitrary and the effectiveness is tested per <51>. The chapter requires that the preservative must be appropriate considering the patient (e.g., neonates) and route of administration (e.g., intrathecal).

**Commentary Summary #4:** Commenter proposed that if a single dose vial is punctured or entered in worse than ISO Class 5 air, it must be prepared and injected or infused according to the FDA-approved label or must be used within 1 hour, and any remaining contents discarded. Commenter suggested that single-dose vials may be used according to package inserts which would be out of scope of the chapter. Additionally, the intent of “by the end of the case” is unclear.

**Response:** Comment partially incorporated. The section was revised to remove “end of the case”. The section *1.4 Preparation per Approved Labeling* was added to clarify the role of approved manufacturer directions.

**Commentary Summary #5:** Commenter suggested striking *Use of Conventionally Manufactured Single-Dose Containers* since it applies to conventional manufacturing, but not compounding.

**Response:** Comment not incorporated. This provision clarifies the length of time a component may be used once punctured, not manufactured. This clarification has been requested in numerous public comments.

**Commentary Summary #6:** Commenter suggested specifying the BUD for conventionally manufactured products prepared according to the manufacturer’s directions, and when it is punctured in an ISO 5 PEC.

**Response:** Comment not incorporated. Section *14. Establishing Beyond-Use Dates* describes the BUDs of CSPs. The single-dose vial may be used up to 12 hours after initial entry or puncture, and can only be punctured in ISO Class 5 or cleaner air.

**Commentary Summary #7:** Commenter recommended confirming how the 6-hour BUD applies to lyophilized vials or doses already prepared to administer to the patient.

**Response:** Comment partially incorporated. The 12-hour time frame applies when a single-dose vial is entered or punctured in an ISO Class 5 or cleaner air, after initial entry or puncture regardless of storage requirements. The section refers to use of these single-dose containers “as components”.

**Commentary Summary #8:** Commenter suggested removing the qualifying verbiage “designed for use with a single patient as a single injection/infusion” in the provision introduction to avoid misinterpretation by regulators and accreditors.

**Response:** Comment incorporated.

**Commentary Summary #9:** Commenter suggested removing the introduction of the provision indicating that single-dose containers are not required to meet antimicrobial effectiveness testing requirements since it does not affect the discard time.

**Response:** Comment not incorporated. The sentence is intended to clarify which components apply to this provision. The sentence does not conflict with the 12-hour time frame that follows.

**Commentary Summary #10:** Commenter recommended specifying where single-dose containers may be stored after initial entry or puncture.

**Response:** Comment incorporated. The section was revised to state that the storage requirements during the 12-hour use period must be maintained.

**Commentary Summary #11:** Commenter requested clarifying whether a single-dose container is considered a CSP.

**Response:** Comment partially incorporated. Revised the title to clarify that the provision refers to when conventionally manufactured products are used as components. Another section, *16. Use of CSPs as Components*, describes the use of CSPs.

**Commentary Summary #12:** Commenter suggested clarifying the time frame for when a vial entered or punctured in worse than ISO Class 5 air must be discarded.

**Response:** Comment partially incorporated. A single-dose vial is entered or punctured only in an ISO Class 5 or cleaner air. If punctured in lesser environments, the product is simple single-dose.

**Commentary Summary #13:** Commenter requested BUD guidance for nursing and procedural area for spiking fluid bags to be used for the entire day at the start of a shift.

**Response:** Comment not incorporated. Spiking fluids is not considered compounding and would be out of scope of the chapter.

**Commentary Summary #14:** Several commenters suggested that it is confusing that single-dose vials must be given within an hour or by the “end of a case”.

**Response:** Comments partially incorporated. The section was revised to remove “end of the case” and a provision for administration has been incorporated into *1.2 Administration*.

**Commentary Summary #15:** Multiple commenters suggested that conventionally manufactured single-dose containers can be used up to 6 hours regardless of storage outside of an ISO Class 5 area.

**Response:** Comments partially incorporated. The section was revised to state 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 hours after initial entry or puncture as long as the storage requirements during that 12-hour period are maintained.

**Commentary Summary #16:** Multiple commenters suggested that if a single-dose vial is entered or punctured using a closed system transfer device (CSTD), the BUD may be extended.

**Response:** Comments not incorporated. Drug vial optimization, such as CSTDs, have not been approved nor cleared for use in extending BUDs. The Expert Committee does not feel that there are adequate performance testing protocols and evaluation tools to allow CSTDs to extend BUDs.

**Commentary Summary #17:** Commenter requested clarifying whether single-dose vials may be used for a single patient or multiple patients. Commenter also stated that single-dose vials can be removed from the ISO Class 5 air for checking purposes.

**Response:** Comment partially incorporated. The section was revised to strike the statement that single-dose containers are designed to be used for a single dose in a single patient. 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 hours after initial entry or puncture as long as the storage requirements during that 12-hour period are maintained.

**Commentary Summary #18:** Commenter suggested that a single-dose vial may be used for the duration of time specified in the manufacturer approved labeling as long as storage requirements are met.

**Response:** Comment not incorporated. 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 hours after initial entry or puncture as long as the storage requirements during that 12-hour period are maintained.

**Commentary Summary #19:** Commenter suggested that conventionally manufactured single-dose vials may be used for up to 12 hours after puncturing in an ISO Class 5 environment.

**Response:** Comment incorporated.

**Commentary Summary #20:** Several commenters suggested that conventionally manufactured single-dose vials may be used for up to 24 hours after puncturing in an ISO Class 5 environment.

**Response:** Comments partially incorporated. The section was revised to allow 12 hours after initial entry or puncture in an ISO Class 5 or cleaner air.

**Commentary Summary #21:** Multiple commenters suggested that it is unclear whether conventionally manufactured single-dose vials may be stored outside of the ISO Class 5 environment to maintain its 6 hour use window.

**Response:** Comments partially incorporated. The storage period or use window applies even when stored outside of an ISO Class 5 area. 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 hours after initial entry or puncture as long as the storage requirements during that 12-hour period are maintained.

**Commentary Summary #22:** Commenter stated that single-dose ampules cannot be stored for any time period, and requested clarification.

**Response:** Comment not incorporated. Single-dose ampules open in such a manner where reclosing the container is not possible, leading to greater risk of contamination. Additionally, single-dose vials usually do not contain preservatives.

**Commentary Summary #23:** Commenter recommended changing the name to “single-use containers”.

**Response:** Comment not incorporated. The term “use” has been strongly discouraged by other commenters throughout the comment period due to ambiguity.

**Commentary Summary #24:** Commenter suggested that the 6-hour BUD contradicts the package insert of 4 hours.

**Response:** Comment not incorporated. A use time frame of 12-hours was added in response to overwhelming public comments concerned with waste. The chapter is intended to be a minimum standard; the manufacturer or facility may require shorter times of use.

**Commentary Summary #25:** Commenter suggested that conventionally manufactured single-dose containers may contain preservatives which allow for longer use times.

**Response:** Comment partially incorporated. The section was revised to allow 12 hours after initial entry or puncture in an ISO Class 5 or cleaner air.

**Commentary Summary #26:** Multiple commenters suggested that it is unclear whether conventionally manufactured multiple-dose vials may be stored outside of the ISO Class 5 environment.

**Response:** Comments not incorporated. Multiple-dose containers are not required to be stored in an ISO Class 5 environment.

**Commentary Summary #27:** Commenter suggested specifying the BUD of the dose withdrawn from a multiple-dose vial.

**Response:** Comment not incorporated. CSPs made from multiple-dose vials are subject to BUDs in *14. Establishing Beyond-Use Dates*.

**Commentary Summary #28:** Commenter suggested that in the absence of a package insert, the expiration date for a multiple-dose container is 28 days.

**Response:** Comment not incorporated. Expiration dates are a part of the product labeling.

**Commentary Summary #29:** Multiple commenters suggested that ophthalmic products may be repackaged into multiple-dose containers.

**Response:** Comments not incorporated. Chapter <797> does not prohibit packaging drugs into multiple-dose containers.

**Commentary Summary #30:** Commenter suggested that pharmacy bulk package BUDs require additional clarification.

**Response:** Comment not incorporated. BUDs refer to CSPs and are based on a multitude of factors (see *14. Establishing Beyond-Use Dates*). Pharmacy bulk packages are subject to expiration dates described per manufacturer.

**Commentary Summary #31:** Multiple commenters suggested that bulk packages may be stored outside of an ISO Class 5 PEC.

**Response:** Comments not incorporated. The pharmacy bulk package must be entered or punctured only in an ISO Class 5 PEC, but is not required to be stored there.

## 16. Use of CSPs as Components

**Expert Committee-initiated Change #1:** The section number was revised to align with the re-numbering of other sections.

**Commentary Summary #1:** Commenter suggested that CSPs just for preparing compounded solutions are not the same as conventionally manufactured products.

**Response:** Comment partially incorporated. The title has been revised to *15. Use of Conventionally Manufactured Products as Components* as opposed to *16. Use of CSPs as Components*.

**Commentary Summary #2:** Several commenters requested reinstatement of in-use times. A commenter noted that it would align with FDA guidance.

**Response:** Comments not incorporated. Numerous comments received stated that in-use times are too confusing.

**Commentary Summary #3:** Several commenters noted that compounded multiple-dose CSPs are similar to compounded stock solutions. Commenters suggested differentiating the terms.

**Response:** Comments incorporated. The section was revised to add a cross-reference to *14.4 Multiple-Dose CSPs* to distinguish the requirements for a compounded multiple-dose container.

**Commentary Summary #4:** Commenter suggested that the BUD of the final CSP should not be defaulted to 6 hours (the component).

**Response:** Comment partially incorporated. The section was revised to allow the component CSP to be used for up to 12 hours or its assigned BUD, whichever is shorter. 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 (see *14. Establishing Beyond-Use Dates*).

**Commentary Summary #5:** Commenter suggested that a compounded single-dose container intended for one-time administration for a single patient must be used within one hour or by the end of case, if punctured outside of an ISO 5 environment.

**Response:** Comment partially incorporated. Compounded single-dose containers must be manipulated in an ISO Class 5 PEC if used as a component. Otherwise, the provisions for immediate use apply.

**Commentary Summary #6:** Commenter suggested defining compounded single-dose containers by preservatives, one-time administration, and by differentiation from multiple-dose or stock solutions.

**Response:** Comment partially incorporated. The section was revised to include subsections for *16.1 Use of Compounded Multiple-Dose CSPs* and *16.2 Use of Compounded Single-Dose CSPs and CSP Stock Solutions*. A definition for compounded stock solution was added to the *Glossary*.

**Commentary Summary #7:** Commenter suggested that a compounded single-dose container may be used for up to 6 hours after initial entry or puncture, or its stated BUD, whichever is sooner and use of a compounded CSP as a component cannot exceed its original BUD.

**Response:** Comment incorporated. The section was revised to indicate 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 (see *14. Establishing Beyond-Use Dates*). The component CSP may be used for sterile compounding for up to 12 hours or its assigned BUD, whichever is shorter, and any remainder must be discarded.

**Commentary Summary #8:** Multiple commenters recommended extending the use of compounded single-dose containers to 8 hours, 24 hours, or 48 hours.

**Response:** Comments partially incorporated. The section was revised to indicate the component CSP may be used for sterile compounding for up to 12 hours or its assigned BUD, whichever is shorter, and any remainder must be discarded.

**Commentary Summary #9:** Multiple commenters were unclear on whether punctured compounded single-dose containers must be stored in a specific manner, and how storage affects the time it can continue to be used.

**Response:** Comments partially incorporated. The section was revised to indicate that component CSPs must be stored under the conditions upon which its BUD is based (e.g., refrigerator, controlled room temperature). The component CSP may be used for sterile compounding for up to 12 hours or its assigned BUD, whichever is shorter, and any remainder must be discarded.

**Commentary Summary #10:** Commenter suggested a 4-day BUD for all subsequent doses pulled from a compounded stock solution.

**Response:** Comment partially incorporated. The section was revised to allow stock solutions to be used up to 12 hours. The resulting CSP would be assigned a BUD as described in *14. Establishing Beyond-Use Dates*.

**Commentary Summary #11:** Commenter suggested providing additional detail on compounded stock solutions.

**Response:** Comment incorporated.

**Commentary Summary #12:** Multiple commenters suggested that compounded stock solutions may be used for up to 24 hours after initial entry or puncture.

**Response:** Comments partially incorporated. The section was revised to indicate the component CSP may be used for sterile compounding for up to 12 hours or its assigned BUD, whichever is shorter, and any remainder must be discarded.

**Commentary Summary #13:** Several commenters suggested clarifying the BUD of the compounded stock solution.

**Response:** Comments partially incorporated. The section was revised to clarify the compounded 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, controlled room temperature). The component CSP may be used for sterile compounding for up to 12 hours or its assigned BUD, whichever is shorter, and any remainder must be discarded.

**Commentary Summary #14:** Commenter suggested that premixed sterile containers may be used as stock solutions.

**Response:** Comment not incorporated. Premixed components are not considered compounded CSPs used as components, therefore *15. Use of Conventionally Manufactured Products as Components* applies.

**Commentary Summary #15:** Commenter suggested addressing nonsterile compounded stock solutions.

**Response:** Comment not incorporated. Stock solutions must be sterilized as described in *16.2 Use of Compounded Single-Dose CSPs and CSP Stock Solutions*.

**Commentary Summary #16:** Commenter requested examples of compounded stock solutions.

**Response:** Comment partially incorporated. The *Glossary* was revised to include a definition for compounded stock solutions. The EC will consider other resources or educational opportunities in the future to further clarify compounded stock solutions.

**Commentary Summary #17:** Commenter suggested that compounded stock solutions are considered compounded multiple-dose containers.

**Response:** Comment partially incorporated. The section was revised to include the subsection *16.1 Use of Compounded Multiple-Dose CSPs*, which differ from compounded stock solutions.

**Commentary Summary #18:** Multiple commenters requested clarifying whether compounded stock solutions are subject to Category 2 BUDs.

**Response:** Comments incorporated. The section was revised to clarify 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 (see *14. Establishing Beyond-Use Dates*).

**Commentary Summary #19:** Several commenters asked whether compounded stock solutions that have been entered or punctured must be stored in the refrigerator.

**Response:** Comments partially incorporated. The section was revised to state 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, controlled room temperature).

**Commentary Summary #20:** Commenter recommended specifying that the remaining BUD cannot exceed its original BUD after puncture.

**Response:** Comment incorporated. The section was revised to indicate that component CSP may be used for sterile compounding for up to 12 hours or its assigned BUD, whichever is shorter, and any remainder must be discarded. 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 (see *14. Establishing Beyond-Use Dates*).

**Commentary Summary #21:** Commenter suggested striking the section for compounded stock solutions and applying Category 2 requirements.

**Response:** Comment partially incorporated. The section was revised to indicate that component CSP may be used for sterile compounding for up to 12 hours or its assigned BUD, whichever is shorter, and any remainder must be discarded. 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 (see *14. Establishing Beyond-Use Dates*).

**Commentary Summary #22:** Commenter suggested that compounded stock solutions may be used for 7 days to be consistent with medium-risk.

**Response:** Comment partially incorporated. The section was revised to state the component CSP may be used for sterile compounding for up to 12 hours or its assigned BUD, whichever is shorter, and any remainder must be discarded. While stored, 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 (see *14. Establishing Beyond-Use Dates*). The Expert Committee suggested that a single contaminated stock solution has the potential to affect multiple patients, therefore 7 days is too long to use once punctured.

**Commentary Summary #23:** Several commenters requested to reinstate in-use times.

**Response:** Comment not incorporated.

## 17. SOPs

**Expert Committee-initiated Change #1:** Standards related to SOP was moved to its own section.

**Commentary Summary #1:** Commenter requested that a list of recommended SOPs be included In the chapter.

**Response:** Comment not incorporated. SOPs should be facility specific. Sections within the chapter describes aspects that must be addressed in SOPs.

**Commentary Summary #2:** Multiple commenters recommended the SOPs be reviewed between every 24 to 36 months.

**Response:** Comments not incorporated. SOPs must be reviewed every 12 months for appropriateness and accuracy. Twelve months is also in alignment with <800>.

**Commentary Summary #3:** Commenter requested clarifying whether the designated person that revises SOPs must be the same designated person for other responsibilities. Commenter suggested the designated person must approve any SOP revisions prior to implementation.

**Response:** Comment incorporated. Any changes or alterations to an SOP must be made only by a designated person and must be documented. A designated person must conduct a review of SOPs every 12 months. The facility must determine who the designated person(s) must be, which can be one or more persons and may have other responsibilities.

## 18. Quality Assurance and Quality Control

**Expert Committee-initiated Change #1:** The section number was revised to align with the re-numbering of other sections.

**Commentary Summary #1:** Commenter suggested clarifying if QA and QC are only for large compounding facilities that batch and transport CSPs to other pharmacies.

**Response:** Comment not incorporated. The chapter applies wherever sterile compounding is performed and does not stratify requirements by facility type.

**Commentary Summary #2:** Commenter recommended introducing QA and QC as acronyms.

**Response:** Comment incorporated. The *Glossary* and *Appendix* were revised to include the acronyms.

**Commentary Summary #3:** Several commenters suggested incorporating elements of the WHO Pharmaceutical Quality System ICH Q10.

**Response:** Comments not incorporated. The chapter is intended to be a minimum standard. Facilities may choose to incorporate additional or more elaborate requirements in their institution.

**Commentary Summary #4:** Commenter recommended striking the requirement to follow applicable jurisdictional laws and regulations.

**Response:** Comment not incorporated. In addition to this chapter, there may be other regulations or laws to which the facility must adhere. The chapter is considered a minimum standard and USP has no role in enforcement.

**Commentary Summary #5:** Commenter recommended adding verbiage regarding compounded stock solutions.

**Response:** Comment not incorporated. Compounded stock solutions are described in *16. Use of CSPs as Components*.

**Commentary Summary #6:** Multiple commenters requested providing example SOPs and QA/QC programs.

**Response:** Comments not incorporated. SOPs and QA/QC programs are determined based on specific facility practice. An example may be misunderstood to be the sole expectation.

**Commentary Summary #7:** Commenter suggested there was a clerical error where the SOPs must describe the roles, duties, and training of the personnel responsible for each aspect of the QA program. Commenter suggested that the QC program is missing from this sentence. Another commenter added that it should be QA and QC programs (plural).

**Response:** Comment not incorporated. The statement was intentionally written to specify the QA program, which is a system of procedures, activities, and oversight that ensures that the compounding process consistently meets quality standards. QA and QC may be a singular program.

**Commentary Summary #8:** Commenter recommended that in the event of a recall, a requirement that facilities notify the prescriber must be completed if a CSP is being dispensed before the results of release testing are known and if the CSP prepared from nonsterile components, was not terminally sterilized, and sterility testing was not performed.

**Response:** Comment not incorporated. Most CSPs are dispensed without sterility testing. Only Category 2 CSPs assigned certain BUDs require sterility testing. Adding a requirement to notify the prescriber whether sterility testing is performed and whether nonsterile starting components are used can mislead prescribers.

**Commentary Summary #9:** Commenter recommended changing the nomenclature from “facilities” to “pharmacies” for recall requirements.

**Response:** Comment not incorporated. Sterile compounding is not limited to pharmacies.

**Commentary Summary #10:** Commenter recommended addressing recalls for CSPs which were compounded in PECs that have had positive growth, especially pathogenic growth.

**Response:** Comment not incorporated. Environmental monitoring excursions require corrective actions. The facility may determine that corrective actions include recalling CSPs.

**Commentary Summary #11:** Several commenters suggested that a recall must be performed any time the CSP’s quality is in question.

**Response:** Comments not incorporated. It is difficult to define when quality is considered to be in question and could be open to interpretation. QA and QC must include other quality problems and investigatory and corrective actions.

**Commentary Summary #12:** Commenter suggested a grammatical change: “an SOP”

**Response:** Comment incorporated.

**Commentary Summary #13:** Commenter suggested that CSP specifications are facility-specific.

**Response:** Comment partially incorporated. The section was revised to include parenthetical examples of specifications. Facilities must determine their own testing procedures in their policies and procedures.

**Commentary Summary #14:** Commenter recommended adding a note stipulating if a Category 2 CSP is dispensed before the results of release testing are known, the BUDs for sterility testing performed and passed cannot be used.

**Response:** Comment not incorporated. The chapter provides BUD assignments for when sterility testing has not passed. The addition of the proposed note may cause confusion since it may be interpreted as optional.

**Commentary Summary #15:** Commenter suggested that patients must also be notified of recalls.

**Response:** Comment not incorporated. Procedures to identify patients who have received the CSP must be within the SOP. Additionally, patient notification requirements may be mandated by laws and regulations of the applicable regulatory jurisdiction. Prescribers must be informed and the prescriber may also inform patients, if appropriate.

**Commentary Summary #16:** Commenter noted that state regulations that require reporting recalls to the Board of Pharmacy within 48 hours of confirmed product contamination should also include suspected product contamination.

**Response:** Comment not incorporated. Boards of Pharmacy should specify reporting requirements.

**Commentary Summary #17:** Commenter asked whether hospitals are required to have a formal complaint system and whether nursing would be the ones filing the complaint. Commenter also requested examples of relevant complaints. Another commenter asked whether complaint reports only apply to facilities that conduct release testing. Another commenter asked whether only outsourcing facilities must adhere to complaint handling requirements.

**Response:** Comments not incorporated. The section applies to all compounding facilities and does not stratify requirements based on the facility type. The facility must have an SOP for handling complaints, and may incorporate examples of relevant complaints and responsible parties. Institutions, regulatory bodies, and accreditation organizations may have additional requirements for a formal complaint system. Outsourcing facilities must comply with FDA requirements.

**Commentary Summary #18:** Commenter suggested striking *18.2 Complaint Handling* as the additional clarification statements are duplicative of the introductory statements.

**Response:** Comment not incorporated. Multiple commenters have requested clarification of complaint handling requirements to reduce misinterpretation.

## **19. CSP Handling, Storage, Packaging, Shipping, and Transport**

**Expert Committee-initiated Change #1:** The section number was revised to align with the re-numbering of other sections.

**Commentary Summary #1:** Commenter suggested removing “shipping” from the title as the section does not describe shipping.

**Response:** Comment not incorporated. Shipping is described in *19.3 Shipping and Transporting CSPs*.

**Commentary Summary #2:** Multiple commenters recommended clarifying acceptable time frame for temperature excursions (e.g., refrigerator door left ajar temporarily).

**Response:** Comments not incorporated. The facility must determine appropriate corrective actions, which is situation-specific. Addition of a time frame for excursions cannot adequately address all situations.

**Commentary Summary #3:** Commenter requested specifying how a pharmacy detects temperature excursions.

**Response:** Comment incorporated. The section was revised to add temperature monitoring requirements.

**Commentary Summary #4:** Commenter recommended striking the requirement for personnel to ensure the effectiveness and reliability of packaging materials since there is no defined way to make this assessment.

**Response:** Comment incorporated.

**Commentary Summary #5:** Commenter suggested 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.

**Commentary Summary #6:** Commenter recommended including periodic testing of the ability to ship preparations with acceptable temperature range.

**Response:** Comment not incorporated. Compounding personnel must select modes of transport that are expected to deliver properly packed CSPs in undamaged, sterile, and stable conditions. The chapter is intended to be a minimum standard; facilities may choose to conduct periodic testing to confirm effectiveness of methods. Additionally, some facilities may not have control over the shipping and transporting process.

## 20. Documentation

**Expert Committee-initiated Change #1:** The section number was revised to align with the re-numbering of other sections.

**Commentary Summary #1:** Commenter suggested that gloved fingertip and thumb testing must be documented.

**Response:** Comment incorporated. Competency assessment and qualification records include glove fingertip and thumb testing monitoring results.

**Commentary Summary #2:** Commenter suggested that not all pharmacies conduct sterility testing or its subsequent investigations and corrective actions. Commenter recommended adding that documentation only applies, if applicable.

**Response:** Comment not incorporated. The list in *20. Documentation* is intended to be a minimum documentation to include. Results of investigations and corrective actions are not limited to sterility testing.

**Commentary Summary #3:** Commenter recommended that the "retrievable" period be modified to two years after preparation unless required by jurisdictional laws and regulations in which that specified period would apply. Commenter noted that some regulatory bodies require a different length of time and this would mean the pharmacy maintains two sets of records.

**Response:** Comment not incorporated. The chapter is intended to be a minimum standard. Records must be readily retrievable for at least 3 years or as required by laws and regulations of the regulatory jurisdiction, whichever is longer. Enforcement agencies, such as regulatory bodies or accreditation agencies may choose to enforce other requirements. USP has no role in enforcement. Therefore it is not necessary to keep two sets of records to satisfy the requirement.

**Commentary Summary #4:** Commenter requested clarifying how long Compounding Records must be kept.

**Response:** Comment not incorporated. The chapter is intended to be a minimum standard. Records must be readily retrievable for at least 3 years or as required by laws and regulations of the regulatory jurisdiction, whichever is longer. Compounding Records must also be kept with these requirements; labels and other electronic records can assist in this process.

## 21. Compounding Allergenic Extracts

**Expert Committee-initiated Change #1:** The section number was revised to align with the re-numbering of other sections.

**Commentary Summary #1:** Commenter requested that the section be moved to a new chapter as it applies to a very small percentage of compounders.

**Response:** Comment not incorporated. Allergenic extracts are described as a subset of compounding described in a separate section.

**Commentary Summary #2:** Commenter requested that the section on allergenic extracts be eliminated because there is no justification for allowing these preparations to have lesser requirements than other 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 the requirements in the chapter that are applicable to other sterile CSPs. Further, patients must be maintained on a maintenance dose of prepared allergenic extracts for a period of time longer than the BUDs specified for Category 1 and Category 2, thus longer BUDs are required for prescription sets to achieve effective therapy.

**Commentary Summary #3:** Commenter noted that the requirements for compounding allergenic extracts would make it very difficult for allergists. The commenter noted that the bacteriostatic and bactericidal agents in the allergenic extract vials require that compounding be “clean” and not “sterile.”

**Response:** Comment not incorporated. Personnel must continue to demonstrate good compounding practices and aseptic technique to help ensure the quality of the compounded allergenic extract prescription set.

**Commentary Summary #4:** Commenter noted the allergen serums in multiple dose formats with extended expiration dates should be allowed to be prepared in a controlled environment by a provider.

**Response:** Comment partially incorporated. Allergenic extracts prescription sets prepared for an individual patient must meet the standards described in 21. *Compounding Allergenic Extracts*. If the conditions specified in the chapter are met,

allergenic extract prescription sets are not required to meet the standards in the chapter for Category 1 or Category 2.

**Commentary Summary #5:** Commenter noted that allergen immunotherapy would not be possible without a BUD that allows for an extended treatment schedule. Changing source materials to prepare the prescription set would expose patients to a higher risk of an anaphylactic reaction. Allergenic extracts include preservatives that reduce the risk of any infectious events from contamination. There has been no evidence of infectious adverse events attributable to compounding procedures.

**Response:** Comment not incorporated. The chapter allows the BUD for the prescription to 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. This BUD is aligned with the FDA Guidance on [Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application](#).

**Commentary Summary #6:** Commenter noted that allergen extracts should not be exempt from the requirements of the chapter because they need longer BUDs. The commenter noted that allergen extracts prepared as Category 2 CSPs are subject to shorter BUDs and allergenic extracts prepared in an allergenic extracts compounding area (AECA) would have a BUD of up to a year. Another commenter noted that allergenic extracts should not be subject to a lesser standard.

**Response:** Comments not incorporated. Because of certain characteristics of allergenic extracts and allergy practice, preparation of allergenic extract prescription sets is not subject to the requirements in the chapter that are applicable to other sterile CSPs. Patients must be maintained on a maintenance dose of prepared allergenic extracts for a period of time longer than the BUDs specified for Category 1 and Category 2, thus longer BUDs are required for prescription sets to achieve effective therapy. Commenters have noted the risk of anaphylactic reactions and that allergenic extracts include preservatives that reduces the risk of microbial proliferation. Further, facilities that have a cleanroom suite and meet all of the requirements in *21. Compounding Allergenic Extracts* may apply the BUDs described in that section.

**Commentary Summary #7:** Commenter recommended that the chapter should specify that allergenic extracts are for routine patient testing and therapy. Commenter additionally noted that patients are maintained on dilutions of concentrated extracts.

**Response:** Comment not incorporated. The chapter is intended to provide standards to ensure quality preparations. The Expert Committee felt that the chapter should not address the intended use of certain preparations since it is the practice of medicine.

**Commentary Summary #8:** Commenter recommended deletion of all personnel qualifications for those preparing allergenic extracts. The commenter noted that since allergenic extracts involve simple transfers, there should not be extensive qualifications.

**Response:** Comment not incorporated. Personnel must be trained, competent, and successfully past competencies (e.g., gloved fingertip and thumb sampling and media-fill testing) to help ensure that they prepare quality allergenic extracts and minimize the risk of inadvertent contamination.

**Commentary Summary #9:** Commenter noted that allergenic extracts should be considered a HD and the standards for HD compounding should apply.

**Response:** Comment not incorporated. Allergenic extracts are not classified as hazardous by CDC National Institute for Occupational Safety and Health (NIOSH).

**Commentary Summary #10:** Commenter requested clarification on whether there are mandatory sterile compounding certificates for allergenic extracts.

**Response:** Comment not incorporated. The chapter does not require allergenic extract specific certification. However, USP has no role in enforcement of compounding chapters. Regulatory bodies may adopt the chapter and/or require other types of certification.

**Commentary Summary #11:** Commenter noted that gloved fingertip and thumb sampling should not be required for compounding allergenic extracts. The commenter noted that allergenic extracts are clean and not sterile.

**Response:** Comment not incorporated. Allergenic extracts are required to be sterile because they are injected into patients. Personnel preparing allergenic extracts must perform gloved fingertip and thumb initially and every 12 months to help ensure proper hand hygiene and garbing procedures.

**Commentary Summary #12:** Commenter noted that media-fill testing should not be required for compounding allergenic extracts. The commenter noted that preparation of allergenic extracts only involves simple aseptic transfers in a nonsterile environment and that there is no need to confirm aseptic technique.

**Response:** Comment not incorporated. Allergenic extracts are required to be sterile because they are injected into patients. Personnel preparing allergenic extracts must perform media-fill testing at least every 12 months to ensure proper aseptic technique to minimize the risk of inadvertent contamination.

**Commentary Summary #13:** Commenter noted that the reference to *Box 2-2* for media-fill testing should specify that it is a sample procedure. The commenter noted that alternative valid media-fill tests exist and should be permitted.

**Response:** Comment not incorporated. *Box 2-2* provides broad procedures on performing media-fill testing. *Box 2-2* specifies that the media-fill testing procedures must simulate compounding activities. The media-fill testing procedures should be facility-specific based on the compounding activities performed by personnel.

**Commentary Summary #14:** Multiple commenters noted that each subsection within *21. Compounding Allergenic Extracts* should be numbered (e.g. 21.1, 21.2, and 21.3).

**Response:** Comments not incorporated. The requirements for allergenic extract are intended to be provided as a list of minimum requirements.

**Commentary Summary #15:** Commenter noted that the order of garbing for allergenic extracts should be from dirty to clean (e.g., head covers, face mask, hand hygiene, garment, sanitizer, and sterile gloves).

**Response:** Comment not incorporated. The order of garbing must be determined by the facility and documented in the facility's SOP. The chapter was revised to clarify that the list is intended to provide the minimum garb requirements, which does not imply an order for garbing.

**Commentary Summary #16:** Commenter noted that sterile gloves should not be required for compounding allergenic extracts because allergenic extracts are clean but not sterile.

**Response:** Comment not incorporated. Allergenic extracts are required to be sterile because they are injected into patients. Sterile gloves help reduce bioburden and help to minimize the risk of inadvertent contamination.

**Commentary Summary #17:** Multiple commenters recommended deleting “non-cotton” when referring to gowns because gowns may have cuffs and ties that are cotton.

**Response:** Comments incorporated.

**Commentary Summary #18:** Commenter noted that sterile 70% IPA must be applied to gloves periodically throughout the compounding process.

**Response:** Comment not incorporated. Periodic is imprecise and does not give guidance on how often sterile 70% IPA must be applied to gloves.

**Commentary Summary #19:** Commenter noted that applying sterile 70% IPA is not disinfecting the gloves but sanitizing the gloves.

**Response:** Comment incorporated. Removed the term disinfect to state that sterile 70% IPA must be rubbed onto all surfaces of the gloves.

**Commentary Summary #20:** Commenter recommended providing the glove material and type to use for compounding allergenic extracts.

**Response:** Comment not incorporated. The chapter requires sterile powder-free gloves. Facilities must select the appropriate glove material and type to use.

**Commentary Summary #21:** Commenter suggested revising the text to read that the sink may not be located within a 1-meter perimeter of the PEC or AECA. Otherwise, facilities will interpret the standard to require the sink to be placed within 1 meter from the PEC or AECA.

**Response:** Comment not incorporated. The chapter is clear in requiring the PEC or work surfaces of the AECA to be located at least 1 meter *away* from a sink.

**Commentary Summary #22:** Commenter noted that it is impractical to locate the sink 1 meter away from the PEC and AECA. The commenter noted that sinks should be permitted within 1 meter of the PEC and AECA provided that they are not used during compounding and will be cleaned.

**Response:** Comment not incorporated. Sinks must be located at least 1 meter away from the PEC and AECA to minimize the risk of microbial contamination. Water source can be a source of microbial contamination.

**Commentary Summary #23:** Commenter noted that visible perimeter should be removed from the description of the AECA because the AECA is defined in the glossary.

**Response:** Comment not incorporated. The AECA is first described in the text of the chapter and should clarify that a visible perimeter is used to establish the AECA.

**Commentary Summary #24:** Commenter requested guidance on how often surfaces in the PEC or AECA must be cleaned.

**Response:** Comment incorporated.

**Commentary Summary #25:** Commenter recommended that the text describing cleaning and disinfecting procedures and frequency should be similar to those described in *7. Cleaning, Disinfecting, and Applying Sporicidal Agents in Compounding Areas*.

**Response:** Comment incorporated.

**Commentary Summary #26:** Commenter noted that surfaces of walls, floors, fixtures, shelving, counters, and cabinets in the AECA must be cleanable and kept clean daily before and after use.

**Response:** Comment not incorporated. The subsection is intended to describe the facility design requirements for areas where allergenic extracts are compounded. Cleaning and disinfecting procedures and frequency are described in the subsequent subsection.

**Commentary Summary #27:** Commenter noted that frequency of cleaning in the AECA should be added.

**Response:** Comment incorporated.

**Commentary Summary #28:** Commenter noted that surfaces of the AECA must be resistant to damage by disinfectant agents.

**Response:** Comment not incorporate. The chapter requires application of sterile 70% IPA to the horizontal work surface of the PEC and to the work surfaces in the AECA. Other commenters have noted that sterile 70% IPA is not a disinfectant.

**Commentary Summary #29:** Commenter noted that the cleaning and disinfecting procedures for areas where allergenic extracts are prepared should reference *Box 7-1* for cleaning and disinfecting the PEC.

**Response:** Comment not incorporated. Cleaning and disinfecting procedures for PECs where allergenic extracts are compounded are described in *21. Compounding Allergenic Extracts*.

**Commentary Summary #30:** Multiple commenters noted that work surfaces in the PEC and AECA do not need to be cleaned at the end of each shift if they are cleaned at the beginning of the shift. Other commenters noted that work surfaces in the PEC and AECA do not need to be cleaned at the beginning of the shift if they are cleaned at the end of the shift.

**Response:** Comments partially incorporated. The PEC must be cleaned daily and when surface contamination is known or suspected.

**Commentary Summary #31:** Multiple commenters noted the cleaning and disinfection should be done using products as directed on the labels. The commenter noted that application of sterile 70% IPA is not a disinfecting procedure.

**Response:** Comments partially incorporated. The chapter was revised to specify that the PEC and AECA must be cleaned and disinfected. Additionally, the section was revised to state that sterile 70% IPA must be applied to work surfaces.

**Commentary Summary #32:** Commenter noted that the cleaning and disinfecting procedures for allergenic extracts should refer to *7. Cleaning, Disinfecting, and Applying Sporocidal Agents in Compounding Areas* to provide more detailed information.

**Response:** Comment partially incorporated. Additional detailed information was added to the cleaning and disinfecting section for areas where allergenic extracts are compounded.

**Commentary Summary #33:** Commenter noted that vial stoppers should be wiped with sterile 70% IPA and not disinfected.

**Response:** Comment incorporated.

**Commentary Summary #34:** Commenter noted that the BUD for allergenic extracts must not exceed the shortest remaining expiration date or BUD of any of the starting components, regardless of the source. All use of sterile components must follow the

provisions set forth in *15. Use of Conventionally Manufactured Products as Components* and *16. Use of CSPS as Components*.

**Response:** Comment not incorporated. Most allergenic extracts are commercially manufactured multiple-dose containers and thus most of the provisions in *15. Use of Conventionally Manufactured Products* do not apply. Further, *16. Use of CSPS as Components*, does not apply to compounding of allergenic extracts. The chapter does state that the BUD of the prescription set must not exceed the earliest expiration date of any of the allergenic extract or diluent that is part of the prescription set. The BUD provisions for allergenic extracts are also aligned with the [FDA Guidance on Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application](#).

**Commentary Summary #35:** Commenter noted that the BUD provisions for allergenic extracts should be permitted for extending the BUDs for Category 2 CSPs in *Table 11*.

**Response:** Comment not incorporated. Because of certain characteristics of allergenic extracts and allergy practice, preparation of allergenic extract prescription sets is not subject to the requirements in the chapter that are applicable to Category 1 and Category 2 CSPs. Patients must be maintained on a maintenance dose of prepared allergenic extracts for a period of time longer than the BUDs specified for Category 1 and Category 2, thus longer BUDs are required for prescription sets to achieve effective therapy. Commenters have noted the risk of anaphylactic reactions and that allergenic extracts include preservatives that reduces the risk of microbial proliferation.

**Commentary Summary #36:** Commenter noted that the BUD of the prescription set must not exceed the earliest expiration date of the concentrated vial of allergenic extract.

**Response:** Comment not incorporated. The chapter states that the BUD for the prescription set must not be later than the earliest expiration date of allergenic extracts. Allergenic extracts is intended to include containers of concentrated allergenic extracts.

**Commentary Summary #37:** Commenter noted that the label of each multiple-dose container of the allergenic extract must be for a specific patient.

**Response:** Comment not incorporated. The chapter requires that the patient name be prominently and understandably placed on the label of each vial of allergenic extract prescription set. The labeling requirements imply that the prescription set is for a specific patient.

**Commentary Summary #38:** Multiple commenters noted that the BUD for allergenic extracts must not exceed 380 days from the date the prescription set is mixed or diluted instead of 1 year. A commenter noted that data from manufacturers of allergenic extracts suggests that the prescription sets remain sterile and potent for up to 380 days.

**Response:** Comments not incorporated. One year is intended to be 365 days which is easily determined by the facility. Further, 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](#).

**Commentary Summary #39:** Commenter noted that the identity of the physician should also be required to be on the label of the allergenic extract prescription set.

**Response:** Comment not incorporated. Labeling must additionally comply with the laws and regulations of the applicable regulatory jurisdiction. Allergenic extracts prepared,

stored, and administered at a physician's office may not need to be additionally labeled with the name of the physician.

**Commentary Summary #40:** Commenter recommended additional language to state that the BUD for stock solutions of allergenic extracts containing 50% glycerin or greater should be assigned a BUD equivalent to that of the shortest expiration date of the allergenic extracts used in the stock solution, so long as all extracts in the solution are compatible based on manufacturer or clinical literature.

**Response:** Comment not incorporated. Stock solutions of allergenic extracts are not well defined and may be subject to errors in dosing or inadvertent contamination. 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](#).

**Commentary Summary #41:** Commenter noted that compounding logs should not be required since they are not required for facilities preparing Category 1 and Category 2 CSPs.

**Response:** Comment incorporated.

**Commentary Summary #42:** Commenter requested additional guidance of what should be included in the cleaning log for areas where allergenic extracts are compounded.

**Response:** Comment partially incorporated. Deleted the requirement for cleaning logs.

**Commentary Summary #43:** Commenter noted that *Box 21-1* should state component instead of ingredient.

**Response:** Comment incorporated.

**Commentary Summary #44:** Commenter noted that *Box 21-1* should include the storage requirements of the allergenic extract prescription set.

**Response:** Comment incorporated.

## Glossary

**Commentary Summary #1:** Commenter recommended defining the term "should".

**Response:** Comment not incorporated. The term is used consistently across USP Compounding Chapters. "Must: and "shall" denote requirements, whereas "should" denotes a recommendation. This will be clarified in a future FAQ.

**Commentary Summary #2:** Commenter suggested that the *Glossary* should be in the beginning of the chapter.

**Response:** Comment not incorporated. The current order is reflective of USP Style Guide requirements.

**Commentary Summary #3:** Commenter recommended defining "sanitize".

**Response:** Comment not incorporated. Sanitizing is not introduced in the chapter. Adding a definition may cause confusion.

**Commentary Summary #4:** Commenter recommended striking "bee venom" from the definition for allergenic extracts.

**Response:** Comment not incorporated. Bee venom is used as an example and the list is not intended to be all inclusive.

**Commentary Summary #5:** Commenter requested clarifying what conditions are involved in aseptic processing.

**Response:** Comment not incorporated. The conditions were not added into the definition of aseptic processing because conditions refer to a multitude of different factors that are involved in achieving aseptic technique.

**Commentary Summary #6:** Commenter suggested that the definition for aseptic technique needs to be more specific. Another commenter suggested adding that aseptic technique practices must be evaluated.

**Response:** Comments not incorporated. Specifying aseptic technique is too prescriptive for the purposes of the chapter. Additionally, facility-specific aseptic practices can be evaluated as part of the training program. The Expert Committee will consider developing a chapter for aseptic technique in the future.

**Commentary Summary #7:** Multiple commenters requested clarifying the definition for a batch as it pertains to Master Formulation Records and Compounding Records.

**Response:** Comments partially incorporated. The chapter was revised to strike the term from *11. Master Formulation Records and Compounding Records* and the *Glossary*.

**Commentary Summary #8:** Commenter recommended removing the word “use” from the definition for BUD because it would include the administration period.

**Response:** Comment not incorporated. The word “use” encompasses the different methods in which the drug is used. Additionally, section *14. Establishing Beyond-Use Dates* further describes BUDs.

**Commentary Summary #9:** Commenter recommended changing the term BUD to “Storage Beyond-Use Date”.

**Response:** Comment not incorporated. Storage periods and BUDs are different. BUDs take into consideration multiple factors, such as sterility, storage conditions, and stability.

**Commentary Summary #10:** Commenter suggested adding albumin into a definition for blood components. Another commenter suggested including that blood components are not plasma-derived.

**Response:** Comments incorporated.

**Commentary Summary #11:** Commenter requested clarifying why the air quality controlled by air flow (i.e. 40 feet per minute) was removed and solid walls and doors are now required for the buffer room.

**Response:** Comment not incorporated. Fixed walls and doors are necessary to minimize contaminated air from flowing into the cleanroom suite, and preserve overall air quality. A buffer room is defined to be a room, which implies walls and doors. An SCA is not required to have walls and doors.

**Commentary Summary #12:** Commenter suggested defining the ISO 8 room that a pharmaceutical isolator could be in.

**Response:** Comment not incorporated. Further definition of ISO Class 8 rooms may cause confusion.

**Commentary Summary #13:** Commenter suggested that the definition for BSC should be under “B”.

**Response:** Comment incorporated.

**Commentary Summary #14:** Commenter suggested distinguishing that BSCs are not a subset of LAFS in the *Glossary*. Commenter suggested that BSCs are only adequate for HD compounding.

**Response:** Comment not incorporated. BSCs are allowed to be used for non-HD compounding provided that certain conditions are met to minimize the risk of contamination.

**Commentary Summary #15:** Commenter noted a clerical error where a word is missing from “on the ISO standards”.

**Response:** Comment incorporated.

**Commentary Summary #16:** Commenter suggested that without immediate use guidance, the definition of compounding is unclear.

**Response:** Comment incorporated. The chapter was revised to add a provision on immediate use CSPs.

**Commentary Summary #17:** Commenter recommended aligning the definition for administration with the introduction.

**Response:** Comment incorporated.

**Commentary Summary #18:** Commenter recommended giving examples of compounding.

**Response:** Comment not incorporated. The scope of compounding is described in *1. Introduction and Scope* whereas the glossary terms are intended to describe how the terms are used in the chapter.

**Commentary Summary #19:** Several commenters recommended defining preparation.

**Response:** Comments not incorporated. The Expert Committee determined that defining preparation may be confusing. Compounding, and therefore relevant preparations, is further described under *1. Introduction and Scope*.

**Commentary Summary #20:** Commenter suggested capitalizing Compounding Area.

**Response:** Comment not incorporated. Other glossary terms are not capitalized as proposed.

**Commentary Summary #21:** Several commenters recommended that the compounding area includes the buffer room, SCA, and AECA. Commenter suggested that compounding occurs in the buffer room and not the ante-room.

**Response:** Comments partially incorporated. The section was revised to include AECA and cleanroom suite because compounding may occur in the ante-room as well as the buffer room.

**Commentary Summary #22:** Commenter suggested that RABS must be located in classified environments while pharmaceutical isolators are not required to be placed in a classified environment. Another commenter suggested clarifying the BUD for a CSP prepared in a CAI or pharmaceutical isolator placed in an ISO Class 7 or better room.

**Response:** Comments not incorporated. The information is not appropriate for the *Glossary*.

**Commentary Summary #23:** Commenter suggested putting the definition of compounded stock solution in alphabetical order.

**Response:** Comment incorporated.

**Commentary Summary #24:** Commenter suggested striking “the sum of” from the definition of container-closure systems.

**Response:** Comment incorporated.

**Commentary Summary #25:** Commenter suggested changing the word “components” from the container-closure system definition.

**Response:** Comment not incorporated. Terminology is consistent with the chapter and <659>.

**Commentary Summary #26:** Commenter recommended that the designated person is a single individual and should be changed as such.

**Response:** Comment not incorporated. Multiple commenters have expressed concern that the single designated individual for a responsibility is not always practical, especially when they are not on site at all times. An alternate designated person is necessary for time-sensitive matters.

**Commentary Summary #27:** Commenter suggested that the designated person should have more training than other individuals.

**Response:** Comment not incorporated. The facility must determine how to appoint designated persons and what qualifications are necessary.

**Commentary Summary #28:** Commenter suggested being consistent in naming “a” versus “the” designated person.

**Response:** Comment not incorporated. “The” versus “A” does not diminish the requirement that a designated person, which is defined in the *Glossary*, is necessary to carry out a responsibility.

**Commentary Summary #29:** Commenter recommended striking the sentence describing characteristics of detergents.

**Response:** Comment incorporated.

**Commentary Summary #30:** Several commenters recommended delineating the responsibilities of a designated person.

**Response:** Comments not incorporated. The *Glossary* is not the appropriate section to describe responsibilities of a designated person. Additionally, the facility determines how the designated person is appointed and the specific responsibilities given.

**Commentary Summary #31:** Commenter suggested that it is misleading for the definition of the DCA to include first air. First air does not exist in directional air flow devices. Commenter suggests striking the statement.

**Response:** Comment not incorporated. The DCA must have unidirectional air to minimize the risk of contamination to the CSP during compounding activities.

**Commentary Summary #32:** Commenter recommended adding that sporicidal agents also destroy fungal spores, a dangerous environmental contaminant.

**Response:** Comment incorporated.

**Commentary Summary #33:** Commenter recommends specifying that dynamic operating conditions are not the same as “worst case scenario or worst-case operating conditions.” Another commenter suggested that the dynamic operating conditions should include the maximum number of personnel in the room for recertification.

**Response:** Comments not incorporated. Dynamic operating conditions are stimulated compounding operations, and not necessarily worst case scenarios. Indicating a maximum number of personnel and worst case scenarios may be during power outages, construction, or other unusual conditions which would provide inadequate information to assess the effectiveness of the operation. The facility may determine the number of personnel that constitutes a dynamic operating condition in the specific practice.

**Commentary Summary #34:** Commenter recommended removing “actual compounding” from the definition of dynamic operating conditions.

**Response:** Comment incorporated.

**Commentary Summary #35:** Commenter recommended aligning the definition for expiration date to the body of the chapter. Another commenter recommended aligning the definition of expiration date to <825>.

**Response:** Comments not incorporated. The section was revised to strike the definition for expiration date since the body of the text more effectively describes it.

**Commentary Summary #36:** Commenter recommended that garb should include gowns or coveralls.

**Response:** Comment incorporated.

**Commentary Summary #37:** Commenter recommended reordering the definition of germicidal detergent under D instead.

**Response:** Comment not incorporated. The section was revised to strike “germicidal detergent” since detergent is not used in the chapter.

**Commentary Summary #38:** Commenter recommended adding a definition for immediate use.

**Response:** Comment incorporated. A provision for immediate use CSPs was incorporated.

**Commentary Summary #39:** Commenter recommended adding a definition for IVFLZ.

**Response:** Comment incorporated.

**Commentary Summary #40:** Commenter recommended consistently hyphenating “media-fill testing”.

**Response:** Comment incorporated.

**Commentary Summary #41:** Commenter recommended pharmaceutical isolators may also be robotic.

**Response:** Comment not incorporated. Robotics is described under *Types of PECs*. Robotics may be BSCs, CACI, and/or CAI depending on the device.

**Commentary Summary #42:** Commenter recommended referring to RABS in the note indicating that pharmaceutical isolators are not CAI/CACI.

**Response:** Comment not incorporated. Users should refer to *4. Facilities and Engineering Controls* for further information. The text in the chapter will provide additional information on use and placement for RABS.

**Commentary Summary #43:** Commenter suggested pointing out that process stimulation is not a media-fill test.

**Response:** Comment not incorporated. Media-fill testing is further explained in *2.3 Competency Testing in Aseptic Manipulation*.

**Commentary Summary #44:** Commenter recommended incorporating the definitions for single-dose container, multiple-dose container, and pharmacy bulk packages as defined in <659>.

**Response:** Comment incorporated.

**Commentary Summary #45:** Commenter recommended changing “one-step disinfectant” to “disinfectant, one-step”.

**Response:** Comment not incorporated. The current term is aligned with how it is presented in the chapter.

**Commentary Summary #46:** Commenter recommended adding a definition for AECA.

**Response:** Comment incorporated.

**Commentary Summary #47:** Commenter recommended aligning the definition for pass-through with <825>.

**Response:** Comment not incorporated. The requirements for radiopharmaceuticals are out of scope of the chapter.

**Commentary Summary #48:** Commenter recommended defining product.

**Response:** Comment not incorporated. The term product is a generic term.

Additionally, conventionally manufactured products are defined in the *Glossary*.

**Commentary Summary #49:** Commenter recommended providing examples of repackaging.

**Response:** Comment not incorporated. Specific practices, such as repackaging, are described in *1. Introduction and Scope*.

**Commentary Summary #50:** Commenter recommended specifying that the SCA does not need to be classified.

**Response:** Comment incorporated. The term unclassified is in the definition of SCA.

**Commentary Summary #51:** Commenter requested providing examples of two-step disinfectants. Another commenter recommended changing the term to “disinfectant, two-step” in the *Glossary*.

**Response:** Comments partially incorporated. The section was revised to strike the term because it was not used in the chapter.

**Commentary Summary #52:** Commenter recommended clarifying each room of the cleanroom suite.

**Response:** Comment not incorporated. The *Glossary* defines the cleanroom suite as a classified area that consists of both an ante-room and buffer room.

**Commentary Summary #53:** Commenter noted that the definitions of cleanroom suite, compounding area, and ante-room imply there would be the possibility to perform a very broad range of tasks in the ante room. Commenter recommended redefining the three terms.

**Response:** Comment not incorporated. The definition of ante-room does not conflict with terminology for compounding area or cleanroom suite. The definition allows for flexibility in facility designs.

**Commentary Summary #54:** Commenter recommended referring to smoke visualization studies as airflow visualization studies.

**Response:** Comment not incorporated. The Expert Committee determined that for testing PECs, the term “dynamic airflow smoke pattern test” will be used. For testing of the rooms, the term “visual smoke study” will be used.

## Appendix

**Commentary Summary #1:** Commenter noted that PPE is included in the acronym table but not defined in the *Glossary*.

**Response:** Comment not incorporated. PPE is used in the chapter and the acronym is included in the *Appendix*. The term PPE is only used once in the chapter in reference to <800>. Users should refer to the definition of PPE in <800>.

**Commentary Summary #2:** Commenter requested the addition of the acronym “sIPA” to refer to sterile 70% IPA.

**Response:** Comment not incorporated. The acronym sIPA is not used in the chapter.

**Commentary Summary #3:** Commenter recommended removing the example designs for sterile non-hazardous compounding areas from the chapter. The example designs should not be part of a standard.

**Response:** Comment incorporated.

**Commentary Summary #4:** Commenter recommending renaming the example “designs” for sterile non-hazardous compounding areas to “layouts.” Commenter noted that an example of an SCA as an entire room should also be added. Alternatively, the commenter recommended removing the example designs from the chapter.

**Response:** Comment partially incorporated. Example designs were eliminated from the chapter based on public comments.

**Commentary Summary #5:** Commenter requested the addition of a graphic for an AECA in the example designs for sterile non-hazardous compounding areas.

**Response:** Comment not incorporated. Example designs were eliminated from the chapter based on public comments.

**Commentary Summary #6:** Multiple commenters requested that the example designs for sterile non-hazardous compounding areas include sink placement.

**Response:** Comments not incorporated. Example designs were eliminated from the chapter based on public comments. Further, *4.4 Water Sources* specifies where a sink may be located in a cleanroom suite and in a SCA.

**Commentary Summary #7:** Commenter requested that an *Appendix* be added with a summary of required (“must”) and recommended (“should”) statements in the chapter.

**Response:** Comment not incorporated. Users must read and apply the entire chapter.

**Commentary Summary #8:** Commenter requested the addition of sample forms for assessing hand hygiene and garbing, aseptic technique, and cleaning and disinfecting procedures.

**Response:** Comment not incorporated. Forms for assessment should be specific for the facility. The Expert Committee will consider the development of forms and resources to assist users in implementing the chapter in the future.