
BRIEFING

(797) Pharmaceutical Compounding—Sterile Preparations, USP 41
page 6554 and *PF* 41(6) [Nov.–Dec. 2015].

Based on the number and significance of public comments received in response to the revision proposal published in *PF* 41(6), the USP Compounding Expert Committee is proposing to revise this chapter. The current proposed chapter in *PF* 44(5) [Sept.–Oct. 2018] is posted online at <http://www.uspnf.com/notices/general-chapter-797-proposed-revisions> with line numbers. Submit comments using the form available at https://usp.az1.qualtrics.com/jfe/form/SV_3dDhnN2ZVCYh5yJ.

The Expert Committee seeks stakeholder feedback on the proposed revisions to the chapter, including the following major changes:

1. Reorganization of the chapter to include section and subsection numbers. Placement of procedural information in boxes.
2. Definition of the scope of the chapter to include sterile compounding activities and exclude administration of medication (e.g., withdrawing doses for administration).
3. Simplified compounded sterile preparation (CSP) microbial risk levels from three (low, medium, and high) to two—Category 1 CSPs and Category 2 CSPs. Category 1 and 2 CSPs are distinguished primarily by the facility in which they are made and the time period within which they must be used, i.e., the beyond-use date (BUD).
 - Category 1 CSPs have a shorter BUD and may be prepared in an unclassified segregated compounding area (SCA).
 - Category 2 CSPs have a longer BUD and must be prepared in a cleanroom suite (buffer room with ante-room).
4. Addition of guidance on use and storage of opened or needle-punctured conventionally manufactured products and CSPs.
5. Addition of information on notification and recall of CSPs that have out-of-specification results.
6. Clarification of requirements for compounding allergenic extract prescription sets.
7. Removal of information related to handling of hazardous drugs and addition of references to [Hazardous Drugs—Handling in Healthcare Settings \(800\)](#).
8. Removal of the section on radiopharmaceuticals as CSPs and addition of a reference to [Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging \(825\)](#). General chapter [\(825\)](#) is also proposed for public comment in *PF* 44(5).

Additionally, the Expert Committee is considering the development of new resource(s) to assist compounders in extending BUDs for Category 2 CSPs to 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 testing results.

Minor editorial changes have been made to update the chapter to current *USP* style.

(CMP: J. Sun.)

Correspondence Number—C204411

⟨797⟩ PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS

Add the following:

■ TABLE OF CONTENTS

1. INTRODUCTION AND SCOPE

1.1 Scope

1.2 Factors Affecting the Risks Associated with CSPs

1.3 CSP Categories

2. PERSONNEL QUALIFICATIONS—TRAINING, EVALUATION, AND REQUALIFICATION

2.1 Demonstrating Proficiency in Core Competencies

2.2 Demonstrating Competency in Garbing and Hand Hygiene

2.3 Competency Testing in Aseptic Manipulation

2.4 Reevaluation, Retraining, and Requalification

3. PERSONAL HYGIENE AND GARBING

3.1 Personnel Preparation

3.2 Hand Hygiene

3.3 Garbing Requirements

4. FACILITIES AND ENGINEERING CONTROLS

- 4.1 Protection from Airborne Contaminants
- 4.2 Facility Design and Environmental Controls
- 4.3 Creating Areas to Achieve Easily Cleanable Conditions
- 4.4 Water Sources
- 4.5 Placement and Movement of Materials
- 4.6 Certification and Recertification

5. MICROBIOLOGICAL AIR AND SURFACE MONITORING

- 5.1 General Monitoring Requirements
- 5.2 Monitoring Air Quality for Viable Airborne Particles
- 5.3 Monitoring Surfaces for Viable Particles

6. CLEANING AND DISINFECTING COMPOUNDING AREAS

- 6.1 Cleaning, Disinfecting, and Sporicidal Agents
- 6.2 Cleaning Supplies
- 6.3 Cleaning and Disinfecting the PEC
- 6.4 Cleaning and Disinfecting Compounding Supplies for the Classified Areas and SCAs
- 6.5 Disinfecting Critical Sites within the PEC

7. EQUIPMENT, SUPPLIES, AND COMPONENTS

- 7.1 Equipment
- 7.2 Supplies
- 7.3 Components

8. STERILIZATION AND DEPYROGENATION

- 8.1 Depyrogenation
- 8.2 Sterilization by Filtration
- 8.3 Sterilization by Steam Heat
- 8.4 Sterilization by Dry Heat

9. SOPs AND MASTER FORMULATION AND COMPOUNDING RECORDS

- 9.1 Creating and Following SOPs
- 9.2 Creating Master Formulation Records
- 9.3 Creating Compounding Records

10. RELEASE TESTING

- 10.1 Visual Inspection
- 10.2 Sterility Testing
- 10.3 Bacterial Endotoxins Testing

11. LABELING

12. ESTABLISHING BEYOND-USE DATES

12.1 Terminology

12.2 Parameters to Consider in Establishing a BUD

12.3 Establishing a BUD for a CSP

12.4 Multiple-Dose CSPs

13. USE OF CONVENTIONALLY MANUFACTURED PRODUCTS

13.1 Use of Conventionally Manufactured Single-Dose Containers

13.2 Use of Conventionally Manufactured Multiple-Dose Containers

13.3 Use of a Conventionally Manufactured Pharmacy Bulk Package

14. USE OF CSPs AS COMPONENTS

14.1 Use of Compounded Single-Dose Containers

14.2 Use of Compounded Stock Solutions

14.3 Use of Compounded Multiple-Dose Containers

15. QUALITY ASSURANCE AND QUALITY CONTROL

15.1 Notification About and Recall of Out-of-Specification Dispensed CSPs

15.2 Complaint Handling

15.3 Adverse Event Reporting

16. CSP STORAGE, HANDLING, PACKAGING, SHIPPING, AND TRANSPORT

16.1 Handling and Storing CSPs

16.2 Packaging of CSPs

16.3 Shipping and Transporting CSPs

17. DOCUMENTATION

18. COMPOUNDING ALLERGENIC EXTRACTS

GLOSSARY

APPENDICES

Appendix 1: Acronyms

Appendix 2: Example Designs for Sterile Non-Hazardous Compounding Areas

■ 2S(USP42)

Change to read:

INTRODUCTION

The objective of this chapter is to describe conditions and practices to prevent harm, including death, to patients that could result from (1) microbial contamination (nonsterility), (2) excessive bacterial endotoxins, (3) variability in the intended strength of correct ingredients that exceeds either monograph limits for official articles (see *General Notices, 2.20 Official Articles* (CN 1-May-2018)) or 10% for nonofficial articles, (4) unintended chemical and physical contaminants, and (5) ingredients of inappropriate quality in compounded sterile preparations (CSPs). Contaminated CSPs are potentially most hazardous to patients when administered into body cavities, central nervous and vascular systems, eyes, and joints, and when used as baths for live organs and tissues. When CSPs contain excessive bacterial endotoxins (see *Bacterial Endotoxins Test* (85)), they are potentially most hazardous to patients when administered into the central nervous system.

Despite the extensive attention in this chapter to the provision, maintenance, and evaluation of air quality, the avoidance of direct or physical contact contamination is paramount. It is generally acknowledged that direct or physical contact of critical sites of CSPs with contaminants, especially microbial sources, poses the greatest probability of risk to patients. Therefore, compounding personnel must be meticulously conscientious in precluding contact contamination of CSPs both within and outside ISO Class 5 (see *Table 1*) areas.

To achieve the above five conditions and practices, this chapter provides minimum practice and quality standards for CSPs of drugs and nutrients based on current scientific information and best sterile compounding practices. 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. The standards in this chapter do not pertain to the *clinical administration* of CSPs to patients via application, implantation, infusion, inhalation, injection, insertion, instillation, and irrigation, which are the routes of administration. Four specific categories of CSPs are described in this chapter: low-risk level, medium-risk level, and high-risk level, and immediate use. Sterile compounding differs from nonsterile compounding (see *Pharmaceutical Compounding—Nonsterile Preparations* (795)) primarily by requiring the maintenance of sterility when compounding exclusively with sterile ingredients and components (i.e., with immediate-use CSPs, low-risk level CSPs, and medium-risk level CSPs) and the achievement of sterility when compounding with nonsterile ingredients and components (i.e., with high-risk level CSPs). Some differences between standards for sterile compounding in this chapter and those for nonsterile compounding in *Pharmaceutical Compounding—Nonsterile Preparations* (795) include, but are

not limited to, ISO-classified air environments (see *Table 1*); personnel garbing and gloving; personnel training and testing in principles and practices of aseptic manipulations and sterilization; environmental quality specifications and monitoring; and disinfection of gloves and surfaces of ISO Class 5 (see *Table 1*) sources.

Table 1. ISO Classification of Particulate Matter in Room Air (limits are in particles of 0.5 µm and larger per cubic meter [current ISO] and cubic feet [former Federal Standard No. 209E, FS 209E])^a

Class Name		Particle Count	
ISO Class	U.S. FS 209E	ISO, m ³	FS 209E, ft ³
3	Class 1	35.2	1
4	Class 10	352	10
5	Class 100	3,520	100
6	Class 1,000	35,200	1,000
7	Class 10,000	352,000	10,000
8	Class 100,000	3,520,000	100,000

^a Adapted from former Federal Standard No. 209E, General Services Administration, Washington, DC, 20407 (September 11, 1992) and ISO 14644-1:1999, Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness. For example, 3,520 particles of 0.5 µm per m³ or larger (ISO Class 5) is equivalent to 100 particles per ft³ (Class 100) (1 m³ = 35.2 ft³).

The standards in this chapter are intended to apply to all persons who prepare CSPs and all places where CSPs are prepared (e.g., hospitals and other healthcare institutions, patient treatment clinics, pharmacies, physicians' practice facilities, and other locations and facilities in which CSPs are prepared, stored, and transported). Persons who perform sterile compounding include pharmacists, nurses, pharmacy technicians, and physicians. These terms recognize that most sterile compounding is performed by or under the supervision of pharmacists in pharmacies and also that this chapter applies to all healthcare personnel who prepare, store, and transport CSPs. For the purposes of this chapter, CSPs include any of the following:

1. Compounded biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals, including but not limited to the following dosage forms that must be sterile when they are administered to patients: aqueous bronchial and nasal inhalations, baths and soaks for live organs and tissues, injections (e.g., colloidal dispersions,

emulsions, solutions, suspensions), irrigations for wounds and body cavities, ophthalmic drops and ointments, and tissue implants.

2. ~~Manufactured sterile products that are either prepared strictly according to the instructions appearing in manufacturers' approved labeling (product package inserts) or prepared differently than published in such labeling. [NOTE—The FDA states that “Compounding does not include mixing, reconstituting, or similar acts that are performed in accordance with the directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling” [21 USC 321 (k) and (m)]. However, the FDA approved labeling (product package insert) rarely describes environmental quality (e.g., ISO Class air designation, exposure durations to non-ISO classified air, personnel garbing and gloving, and other aseptic precautions by which sterile products are to be prepared for administration). Beyond-use exposure and storage dates or times (see *Labeling (7)* ^(CN 1-May-2018) and *Pharmaceutical Compounding—Nonsterile Preparations (795)*) for sterile products that have been either opened or prepared for administration are not specified in all package inserts for all sterile products. Furthermore, when such durations are specified, they may refer to chemical stability and not necessarily to microbiological purity or safety.~~

~~ORGANIZATION OF THIS CHAPTER~~

~~The sections in this chapter are organized to facilitate the practitioner's understanding of the fundamental accuracy and quality practices for preparing CSPs. They provide a foundation for the development and implementation of essential procedures for the safe preparation of low-risk, medium-risk, and high-risk level CSPs and immediate-use CSPs, which are classified according to the potential for microbial, chemical, and physical contamination. The chapter is divided into the following main sections:~~

- ~~• Responsibility of Compounding Personnel~~
- ~~• CSP Microbial Contamination Risk Levels~~
- ~~• Personnel Training and Evaluation in Aseptic Manipulation Skills~~
- ~~• Immediate-Use CSPs~~
- ~~• Single-Dose and Multiple-Dose Containers~~
- ~~• Hazardous Drugs as CSPs~~
- ~~• Radiopharmaceuticals as CSPs~~
- ~~• Allergen Extracts as CSPs~~
- ~~• Verification of Compounding Accuracy and Sterility~~
- ~~• Environmental Quality and Control~~
- ~~• Suggested Standard Operating Procedures (SOPs)~~

- Elements of Quality Control
- Verification of Automated Compounding Devices (ACDs) for Parenteral Nutrition Compounding
- Finished Preparation Release Checks and Tests
- Storage and Beyond-Use Dating
- Maintaining Sterility, Purity, and Stability of Dispensed and Distributed CSPs
- Patient or Caregiver Training
- Patient Monitoring and Adverse Events Reporting
- Quality Assurance (QA) Program
- Abbreviations and Acronyms
- Glossary
- Appendices I–V

The requirements and recommendations in this chapter are summarized in *Appendix I*. A list of abbreviations and acronyms is included at the end of the main text, before the *Appendices*.

All personnel who prepare CSPs shall be responsible for understanding these fundamental practices and precautions, for developing and implementing appropriate procedures, and for continually evaluating these procedures and the quality of final CSPs to prevent harm.

RESPONSIBILITY OF COMPOUNDING PERSONNEL

Compounding personnel are responsible for ensuring that CSPs are accurately identified, measured, diluted, and mixed and are correctly purified, sterilized, packaged, sealed, labeled, stored, dispensed, and distributed. These performance responsibilities include maintaining appropriate cleanliness conditions and providing labeling and supplementary instructions for the proper clinical administration of CSPs.

Compounding supervisors shall ensure, through either direct measurement or appropriate information sources, that specific CSPs maintain their labeled strength within monograph limits for *USP* articles, or within 10% if not specified, until their BUDs. All CSPs are prepared in a manner that maintains sterility and minimizes the introduction of particulate matter.

A written quality assurance procedure includes the following in-process checks that are applied, as appropriate, to specific CSPs: accuracy and precision of measuring and weighing; the requirement for sterility; methods of sterilization and purification; safe limits and ranges for strength of ingredients, bacterial endotoxins, and particulate matter; pH; labeling accuracy and completeness; BUD assignment; and packaging and storage requirements. The dispenser shall, when appropriate and practicable, obtain and evaluate results of testing for identity, strength, purity, and sterility before a CSP is dispensed. Qualified licensed healthcare professionals who

supervise compounding and dispensing of CSPs shall ensure that the following objectives are achieved:

1. Compounding personnel are adequately skilled, educated, instructed, and trained to correctly perform and document the following activities in their sterile compounding duties:
 - a. perform antiseptic hand cleansing and disinfection of nonsterile compounding surfaces;
 - b. select and appropriately don protective garb;
 - c. maintain or achieve sterility of CSPs in ISO Class 5 (see [Table 1](#)) PEC devices and protect personnel and compounding environments from contamination by radioactive, cytotoxic, and chemotoxic drugs (see *Hazardous Drugs as CSPs* and *Radiopharmaceuticals as CSPs*);
 - d. identify, weigh, and measure ingredients; and
 - e. manipulate sterile products aseptically, sterilize high-risk level CSPs, and label and quality inspect CSPs.
2. Ingredients have their correct identity, quality, and purity.
3. Opened or partially used packages of ingredients for subsequent use in CSPs are properly stored under restricted access conditions in the compounding facility. Such packages cannot be used when visual inspection detects unauthorized breaks in the container, closure, and seal; when the contents do not possess the expected appearance, aroma, and texture; when the contents do not pass identification tests specified by the compounding facility; and when either the BUD or expiration date has been exceeded.
4. Water-containing CSPs that are nonsterile during any phase of the compounding procedure are sterilized within 6 hours after completing the preparation in order to minimize the generation of bacterial endotoxins.
5. Sterilization methods achieve sterility of CSPs while maintaining the labeled strength of active ingredients and the physical integrity of packaging.
6. Measuring, mixing, sterilizing, and purifying devices are clean, appropriately accurate, and effective for their intended use.
7. Potential harm from added substances and differences in rate and extent of bioavailability of active ingredients for other than oral route of administration are carefully evaluated before such CSPs are dispensed and administered.
8. Packaging selected for CSPs is appropriate to preserve the sterility and strength until the BUD.
9. While being used, the compounding environment maintains the sterility or the presterilization purity, whichever is appropriate, of the CSP.

10. Labels on CSPs list the names and amounts or concentrations of active ingredients, and the labels or labeling of injections ~~•••~~ (GN 1, May 2018) list the names and amounts or concentrations of all ingredients (see *Labeling (7)*). Before being dispensed or administered, the clarity of solutions is visually confirmed; also, the identity and amounts of ingredients, procedures to prepare and sterilize CSPs, and specific release criteria are reviewed to ensure their accuracy and completeness.
11. BUDs are assigned on the basis of direct testing or extrapolation from reliable literature sources and other documentation (see *Stability Criteria and Beyond-Use Dating under Pharmaceutical Compounding—Nonsterile Preparations (795)*).
12. Procedures for measuring, mixing, dilution, purification, sterilization, packaging, and labeling conform to the correct sequence and quality established for the specified CSP.
13. Deficiencies in compounding, labeling, packaging, and quality testing and inspection can be rapidly identified and corrected.
14. When time and personnel availability so permit, compounding manipulations and procedures are separated from postcompounding quality inspection and review before CSPs are dispensed.

This chapter emphasizes the need to maintain high standards for the quality and control of processes, components, and environments and for the skill and knowledge of personnel who prepare CSPs. The rigor of in-process quality-control checks and of postcompounding quality inspection and testing increases with the potential hazard of the route of administration. For example, nonsterility, excessive bacterial endotoxin contamination, large errors in strength of correct ingredients, and incorrect ingredients in CSPs are potentially more dangerous to patients when the CSPs are administered into the vascular and central nervous systems than when administered by most other routes.

~~GSP MICROBIAL CONTAMINATION RISK LEVELS~~

The three contamination categories for CSPs described in this section are assigned primarily according to the potential for microbial contamination during the compounding of low-risk level CSPs and medium-risk level CSPs or the potential for not sterilizing high-risk level CSPs, any of which would subject patients to risk of harm, including death. High-risk level CSPs must be sterilized before being administered to patients. The appropriate risk level—low, medium, or high—is assigned according to the corresponding probability of contaminating a CSP with (1) microbial contamination (e.g., microbial organisms, spores, endotoxins) and (2) chemical and physical contamination (e.g., foreign chemicals, physical matter). Potential sources of contamination include, but are not limited to, solid and liquid matter from

~~compounding personnel and objects; nonsterile components employed and incorporated before terminal sterilization; inappropriate conditions within the restricted compounding environment; prolonged presterilization procedures with aqueous preparations; and nonsterile dosage forms used to compound CSPs.~~

~~The characteristics described below for low-, medium-, and high-risk level CSPs are intended as a guide to the breadth and depth of care necessary in compounding, but they are neither exhaustive nor prescriptive. The licensed healthcare professionals who supervise compounding are responsible for determining the procedural and environmental quality practices and attributes that are necessary for the risk level they assign to specific CSPs.~~

~~These risk levels apply to the quality of CSPs immediately after the final aseptic mixing or filling or immediately after the final sterilization, unless precluded by the specific characteristics of the preparation. Upon subsequent storage and shipping of freshly finished CSPs, an increase in the risks of chemical degradation of ingredients, contamination from physical damage to packaging, and permeability of plastic and elastomeric packaging is expected. In such cases, compounding personnel are responsible for considering the potential additional risks to the integrity of CSPs when assigning BUDs. The pre-administration storage duration and temperature limits specified in the following subsections apply in the absence of direct sterility testing results that justify different limits for specific CSPs.~~

~~Low-Risk Level CSPs~~

~~CSPs compounded under all the following conditions are at a low risk of contamination.~~

~~Low-Risk Conditions—~~

- ~~1. The CSPs are compounded with aseptic manipulations entirely within ISO Class 5 (see [Table 1](#)) or better air quality using only sterile ingredients, products, components, and devices.~~
- ~~2. The compounding involves only transfer, measuring, and mixing manipulations using not more than three commercially manufactured packages of sterile products and not more than two entries into any one sterile container or package (e.g., bag, vial) of sterile product or administration container/device to prepare the CSP.~~
- ~~3. Manipulations are limited to aseptically opening ampuls, penetrating disinfected stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile administration devices, package containers of other sterile products, and containers for storage and dispensing.~~
- ~~4. For a low-risk level preparation, in the absence of passing a sterility test (see *Sterility Tests* (71)), the storage periods cannot exceed the following time periods: before administration, the CSPs are properly~~

~~stored and are exposed for not more than 48 hours at controlled room temperature (see *•Packaging and Storage Requirements (659)*), ^(CN-1-May-2018) for not more than 14 days at a cold temperature (see *•Packaging and Storage Requirements (659)*), ^(CN-1-May-2018) and for 45 days in solid frozen state between -25° and -10° .~~

~~Examples of Low-Risk Compounding—~~

- ~~1. Single-volume transfers of sterile dosage forms from ampuls, bottles, bags, and vials using sterile syringes with sterile needles, other administration devices, and other sterile containers. The solution content of ampuls should be passed through a sterile filter to remove any particles.~~
- ~~2. Simple aseptic measuring and transferring with not more than three packages of manufactured sterile products, including an infusion or diluent solution to compound drug admixtures and nutritional solutions.~~

~~**Low-Risk Level CSPs with 12-Hour or Less BUD—** If the PEC is a CAI or CACI that does not meet the requirements described in *Placement of Primary Engineering Controls* or is a laminar airflow workbench (LAFW) or a biological safety cabinet (BSC) that cannot be located within an ISO Class 7 (see [Table 1](#)) buffer area, then only low-risk level nonhazardous and radiopharmaceutical CSPs pursuant to a physician's order for a specific patient may be prepared, and administration of such CSPs shall commence within 12 hours of preparation or as recommended in the manufacturers' package insert, whichever is less. Low-risk level CSPs with a 12-hour or less BUD shall meet all of the following four criteria:~~

- ~~1. PECs (LAFWs, BSCs, CAIs, CACIs,) shall be certified and maintain ISO Class 5 (see [Table 1](#)) as described in *Facility Design and Environmental Controls* for exposure of critical sites and shall be in a segregated compounding area restricted to sterile compounding activities that minimize the risk of CSP contamination.~~
- ~~2. The segregated compounding area shall not be in a location that has unsealed windows or doors that connect to the outdoors or high traffic flow, or that is adjacent to construction sites, warehouses, or food preparation. Note that this list is not intended to be all inclusive.~~
- ~~3. Personnel shall follow the procedures described in *Personnel Cleansing and Garbing* and *Additional Personnel Requirements* prior to compounding. Sinks should not be located adjacent to the ISO Class 5 (see [Table 1](#)) PEC. Sinks should be separated from the immediate area of the ISO Class 5 (see [Table 1](#)) PEC device.~~
- ~~4. The specifications in *Cleaning and Disinfecting the Sterile Compounding Areas, Personnel Training and Competency Evaluation*~~

of Garbing, Aseptic Work Practices and Cleaning/Disinfection Procedures, and Viable and Nonviable Environmental Sampling (ES) Testing shall be followed as described in the chapter.

~~Compounding personnel must recognize that the absence of an ISO Class 7 (see [Table 1](#)) buffer area environment in a general uncontrolled environment increases the potential of microbial contamination, and administration durations of microbially contaminated CSPs exceeding a few hours increase the potential for clinically significant microbial colonization, and thus for patient harm, especially in critically ill or immunocompromised patients.~~

Quality Assurance—~~Quality assurance practices include, but are not limited to the following:~~

- ~~1. Routine disinfection and air quality testing of the direct compounding environment to minimize microbial surface contamination and maintain ISO Class 5 (see [Table 1](#)) air quality.~~
- ~~2. Visual confirmation that compounding personnel are properly donning and wearing appropriate items and types of protective garments, including eye protection and face masks.~~
- ~~3. Review of all orders and packages of ingredients to ensure that the correct identity and amounts of ingredients were compounded.~~
- ~~4. Visual inspection of CSPs to ensure the absence of particulate matter in solutions, the absence of leakage from vials and bags, and the accuracy and thoroughness of labeling.~~

Media-Fill Test Procedure—~~This test or an equivalent test is performed at least annually by each person authorized to compound in a low-risk level environment under conditions that closely simulate the most challenging or stressful conditions encountered during compounding of low-risk level CSPs. Once begun, this test is completed without interruption. *Example of test procedure:* within an ISO Class 5 (see [Table 1](#)) air quality environment, three sets of four 5-mL aliquots of sterile Soybean-Casein Digest Medium (also known as trypticase soy broth or trypticase soy agar [TSA]) are transferred with the same sterile 10-mL syringe and vented needle combination into separate sealed, empty, sterile 30-mL clear vials (i.e., four 5-mL aliquots into each of three 30-mL vials). Sterile adhesive seals are aseptically affixed to the rubber closures on the three filled vials, then the vials are incubated at 20° to 25° or at 30° to 35° for a minimum of 14 days. If two temperatures are used for incubation of media-filled samples, then these filled containers should be incubated for at least 7 days at each temperature (see *Microbiological Control and Monitoring of Aseptic Processing Environments* (1116)). Inspect for microbial growth over 14 days as described in *Personnel Training and Competency Evaluation of Garbing, Aseptic Work Practices and Cleaning/Disinfection Procedures.*~~

Medium-Risk Level CSPs

When CSPs are compounded aseptically under *Low-Risk Conditions* and one or more of the following conditions exists, such CSPs are at a medium risk of contamination:

Medium-Risk Conditions

1. Multiple individual or small doses of sterile products are combined or pooled to prepare a CSP that will be administered either to multiple patients or to one patient on multiple occasions.
2. The compounding process includes complex aseptic manipulations other than the single-volume transfer.
3. The compounding process requires unusually long duration, such as that required to complete dissolution or homogeneous mixing.
4. For a medium-risk preparation, in the absence of passing a sterility test (see *Sterility Tests (71)*), the storage periods cannot exceed the following time periods: before administration, the CSPs are properly stored and are exposed for not more than 30 hours at controlled room temperature (see *Packaging and Storage Requirements (659)*), (CN 1-May-2018) for not more than 9 days at a cold temperature (see *Packaging and Storage Requirements (659)*), (CN 1-May-2018) and for 45 days in solid frozen state between -25° and -10° .

Examples of Medium-Risk Compounding

1. Compounding of total parenteral nutrition fluids using manual or automated devices during which there are multiple injections, detachments, and attachments of nutrient source products to the device or machine to deliver all nutritional components to a final sterile container.
2. Filling of reservoirs of injection and infusion devices with more than three sterile drug products and evacuation of air from those reservoirs before the filled device is dispensed.
3. Transfer of volumes from multiple ampuls or vials into one or more final sterile containers.

Quality Assurance—Quality assurance procedures for medium-risk level CSPs include all those for low-risk level CSPs, as well as a more challenging media fill test passed annually or more frequently.

Media-Fill Test Procedure—This test or an equivalent test is performed at least annually under conditions that closely simulate the most challenging or stressful conditions encountered during compounding. Once begun, this test is completed without interruption. *Example of test procedure:* within an ISO Class 5 (see [Table 1](#)) air quality environment, six 100-mL aliquots of sterile

~~Soybean–Casein Digest Medium are aseptically transferred by gravity through separate tubing sets into separate evacuated sterile containers. The six containers are then arranged as three pairs, and a sterile 10-mL syringe and 18-gauge needle combination is used to exchange two 5-mL aliquots of medium from one container to the other container in the pair. For example, after a 5-mL aliquot from the first container is added to the second container in the pair, the second container is agitated for 10 seconds, then a 5-mL aliquot is removed and returned to the first container in the pair. The first container is then agitated for 10 seconds, and the next 5-mL aliquot is transferred from it back to the second container in the pair. Following the two 5-mL aliquot exchanges in each pair of containers, a 5-mL aliquot of medium from each container is aseptically injected into a sealed, empty, sterile 10-mL clear vial, using a sterile 10-mL syringe and vented needle. Sterile adhesive seals are aseptically affixed to the rubber closures on the three filled vials, then the vials are incubated at 20° to 25° or at 30° to 35° for a minimum of 14 days. If two temperatures are used for incubation of media-filled samples, then these filled containers should be incubated for at least 7 days at each temperature (see *Microbiological Control and Monitoring of Aseptic Processing Environments* (1116)). Inspect for microbial growth over 14 days as described in *Personnel Training and Competency Evaluation of Garbing, Aseptic Work Practices and Cleaning/Disinfection Procedures*.~~

High-Risk-Level CSPs

~~CSPs compounded under any of the following conditions are either contaminated or at a high risk to become contaminated.~~

High-Risk Conditions—

- ~~1. Nonsterile ingredients, including manufactured products not intended for sterile routes of administration (e.g., oral), are incorporated or a nonsterile device is employed before terminal sterilization.~~
- ~~2. Any of the following are exposed to air quality worse than ISO Class 5 (see [Table 1](#)) for more than 1 hour (see *Immediate-Use CSPs*):~~
 - ~~• sterile contents of commercially manufactured products,~~
 - ~~• CSPs that lack effective antimicrobial preservatives, and~~
 - ~~• sterile surfaces of devices and containers for the preparation, transfer, sterilization, and packaging of CSPs.~~
- ~~3. Compounding personnel are improperly garbed and gloved (see *Personnel Cleansing and Use of Barrier Protective Equipment*).~~
- ~~4. Nonsterile water-containing preparations are stored for more than 6 hours before being sterilized.~~
- ~~5. It is assumed, and not verified by examination of labeling and documentation from suppliers or by direct determination, that the chemical purity and content strength of ingredients meet their original or compendial specifications in unopened or in opened~~

~~packages of bulk ingredients (see *Ingredient Selection* under *Pharmaceutical Compounding—Nonsterile Preparations* (795)).~~

~~For a sterilized high-risk level preparation, in the absence of passing a sterility test, the storage periods cannot exceed the following time periods: before administration, the CSPs are properly stored and are exposed for not more than 24 hours at controlled room temperature (see *Packaging and Storage Requirements* (659)), ^(CN 1, May 2018) for not more than 3 days at a cold temperature (see *Packaging and Storage Requirements* (659)), ^(CN 1, May 2018) and for 45 days in solid frozen state between -25° and -10° . [NOTE—Sterility tests for autoclaved CSPs are not required unless they are prepared in batches of more than 25 units.]~~

~~All nonsterile measuring, mixing, and purifying devices are rinsed thoroughly with sterile, pyrogen-free water, and then thoroughly drained or dried immediately before use for high-risk compounding. All high-risk level CSP solutions subjected to terminal sterilization are prefiltered by passing through a filter with a nominal pore size not larger than $1.2\ \mu\text{m}$ preceding or during filling into their final containers to remove particulate matter. Sterilization of high-risk level CSPs by filtration shall be performed with a sterile $0.2\text{-}\mu\text{m}$ or $0.22\text{-}\mu\text{m}$ nominal pore size filter entirely within an ISO Class 5 (see [Table 1](#)) or superior air quality environment.~~

~~Examples of High-Risk Conditions—~~

- ~~1. Dissolving nonsterile bulk drug and nutrient powders to make solutions that will be terminally sterilized.~~
- ~~2. Exposing the sterile ingredients and components used to prepare and package CSPs to room air quality worse than ISO Class 5 (see [Table 1](#)) for more than 1 hour (see *Immediate-Use CSPs*).~~
- ~~3. Measuring and mixing sterile ingredients in nonsterile devices before sterilization is performed.~~
- ~~4. Assuming, without appropriate evidence or direct determination, that packages of bulk ingredients contain at least 95% by weight of their active chemical moiety and have not been contaminated or adulterated between uses.~~

~~**Quality Assurance—**Quality assurance procedures for high-risk level CSPs include all those for low-risk level CSPs. In addition, a media-fill test that represents high-risk level compounding is performed semiannually by each person authorized to compound high-risk level CSPs.~~

~~**Media-Fill Test Procedure for CSPs Sterilized by Filtration—**This test or an equivalent test is performed under conditions that closely simulate the most challenging or stressful conditions encountered when compounding~~

high-risk level CSPs. Once begun, this test is completed without interruption. *Example of test procedure (in the following sequence):-*

1. Dissolve 3 g of nonsterile commercially available Soybean-Casein Digest Medium in 100 mL of nonbacteriostatic water to make a 3% nonsterile solution.
2. Draw 25 mL of the medium into each of three 30-mL sterile syringes. Transfer 5 mL from each syringe into separate sterile 10-mL vials. These vials are the positive controls to generate exponential microbial growth, which is indicated by visible turbidity upon incubation.
3. Under aseptic conditions and using aseptic techniques, affix a sterile 0.2- μ m or 0.22- μ m nominal pore size filter unit and a 20-gauge needle to each syringe. Inject the next 10 mL from each syringe into three separate 10-mL sterile vials. Repeat the process for three more vials. Label all vials, affix sterile adhesive seals to the closure of the nine vials, and incubate them at 20° to 25° or at 30° to 35° for a minimum of 14 days. If two temperatures are used for incubation of media-filled samples, then these filled containers should be incubated for at least 7 days at each temperature (see *Microbiological Control and Monitoring of Aseptic Processing Environments* (1116)). Inspect for microbial growth over 14 days as described in *Personnel Training and Competency Evaluation of Garbing, Aseptic Work Practices and Cleaning/Disinfection Procedures*.

PERSONNEL TRAINING AND EVALUATION IN ASEPTIC MANIPULATION SKILLS

Personnel who prepare CSPs shall be trained conscientiously and skillfully by expert personnel and through audio-video instructional sources and professional publications in the theoretical principles and practical skills of aseptic manipulations and in achieving and maintaining ISO Class 5 (see [Table 1](#)) environmental conditions before they begin to prepare CSPs. Compounding personnel shall perform didactic review and pass written and media-fill testing of aseptic manipulative skills initially, at least annually thereafter for low- and medium-risk level compounding, and semiannually for high-risk level compounding. Compounding personnel who fail written tests or whose media-fill test vials result in gross microbial colonization shall be immediately re-instructed and re-evaluated by expert compounding personnel to ensure correction of all aseptic practice deficiencies.

Media-Fill Challenge Testing—The skill of personnel to aseptically prepare CSPs may be evaluated using sterile fluid bacterial culture media-fill verification^a (i.e., sterile bacterial culture medium transfer via a sterile syringe and needle). Media-fill testing is used to assess the quality of the aseptic skill of compounding personnel. Media-fill tests represent the most

~~challenging or stressful conditions actually encountered by the personnel being evaluated when they prepare particular risk level CSPs and when sterilizing high-risk level CSPs. Media-fill challenge tests that simulate high-risk level compounding are also used to verify the capability of the compounding environment and process to produce a sterile preparation.~~

~~Commercially available sterile fluid culture media, such as Soybean-Casein Digest Medium (see *Sterility Tests* (71)), shall be able to promote exponential colonization of bacteria that are most likely to be transmitted to CSPs from the compounding personnel and environment. Media-filled vials are generally incubated at 20° to 25° or at 30° to 35° for a minimum of 14 days. If two temperatures are used for incubation of media-filled samples, then these filled containers should be incubated for at least 7 days at each temperature (see *Microbiological Control and Monitoring of Aseptic Processing Environments* (1116)). Failure is indicated by visible turbidity in the medium on or before 14 days.~~

~~IMMEDIATE-USE CSPS~~

~~The immediate-use provision is intended only for those situations where there is a need for emergency or immediate patient administration of a CSP. Such situations may include cardiopulmonary resuscitation, emergency room treatment, preparation of diagnostic agents, or critical therapy where the preparation of the CSP under conditions described for *Low-Risk Level CSPs* subjects the patient to additional risk due to delays in therapy. Immediate-use CSPs are not intended for storage for anticipated needs or batch compounding. Preparations that are medium-risk level and high-risk level CSPs shall not be prepared as immediate-use CSPs.~~

~~Immediate-use CSPs are exempt from the requirements described for *Low-Risk Level CSPs* only when all of the following criteria are met:~~

- ~~1. The compounding process involves simple transfer of not more than three commercially manufactured packages of sterile nonhazardous products or diagnostic radiopharmaceutical products from the manufacturers' original containers and not more than two entries into any one container or package (e.g., bag, vial) of sterile infusion solution or administration container/device. For example, anti-neoplastics shall not be prepared as immediate-use CSPs because they are hazardous drugs.~~
- ~~2. Unless required for the preparation, the compounding procedure is a continuous process not to exceed 1 hour.~~
- ~~3. During preparation, aseptic technique is followed and, if not immediately administered, the finished CSP is under continuous supervision to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, mix-ups with other CSPs, and direct contact of outside surfaces.~~

- ~~4. Administration begins not later than 1 hour following the start of the preparation of the CSP.~~
- ~~5. Unless immediately and completely administered by the person who prepared it or immediate and complete administration is witnessed by the preparer, the CSP shall bear a label listing patient identification information, the names and amounts of all ingredients, the name or initials of the person who prepared the CSP, and the exact 1-hour BUD and time.~~
- ~~6. If administration has not begun within 1 hour following the start of preparing the CSP, the CSP shall be promptly, properly, and safely discarded.~~

~~Compounding in worse than ISO Class 5 (see [Table 1](#)) conditions increases the likelihood of microbial contamination, and administration durations of microbially contaminated CSPs exceeding a few hours increase the potential for clinically significant microbial colonization and thus for patient harm, especially in critically ill or immunocompromised patients.~~

~~**SINGLE-DOSE AND MULTIPLE-DOSE CONTAINERS**~~

~~Opened or needle-punctured single-dose containers, such as bags, bottles, syringes, and vials of sterile products and CSPs shall be used within 1 hour if opened in worse than ISO Class 5 (see [Table 1](#)) air quality (see *Immediate-Use CSPs*), and any remaining contents must be discarded. Single-dose vials exposed to ISO Class 5 (see [Table 1](#)) or cleaner air may be used up to 6 hours after initial needle puncture. Opened single-dose ampuls shall not be stored for any time period. Multiple-dose containers (e.g., vials) are formulated for removal of portions on multiple occasions because they usually contain antimicrobial preservatives. The BUD after initially entering or opening (e.g., needle-punctured) multiple-dose containers is 28 days (see *Antimicrobial Effectiveness Testing* (51)) unless otherwise specified by the manufacturer.~~

~~**HAZARDOUS DRUGS AS CSPS**~~

~~Although the potential therapeutic benefits of compounded sterile hazardous drug preparations generally outweigh the risks of their adverse effects in ill patients, exposed healthcare workers risk similar adverse effects with no therapeutic benefit. Occupational exposure to hazardous drugs can result in (1) acute effects, such as skin rashes; (2) chronic effects, including adverse reproductive events; and (3) possibly cancer (see Appendix A of NIOSH Publication no. 2004-165).~~

~~Hazardous drugs shall be prepared for administration only under conditions that protect the healthcare workers and other personnel in the preparation and storage areas. Hazardous drugs shall be stored separately from other~~

inventory in a manner to prevent contamination and personnel exposure. Many hazardous drugs have sufficient vapor pressures that allow volatilization at room temperature; thus storage is preferably within a containment area such as a negative pressure room. The storage area should have sufficient general exhaust ventilation, at least 12 air changes per hour (ACPH)² to dilute and remove any airborne contaminants.

Hazardous drugs shall be handled with caution at all times using appropriate chemotherapy gloves during receiving, distribution, stocking, inventorying, preparation for administration, and disposal. Hazardous drugs shall be prepared in an ISO Class 5 (see [Table 1](#)) environment with protective engineering controls in place and following aseptic practices specified for the appropriate contamination risk levels defined in this chapter. Access shall be limited to areas where drugs are stored and prepared to protect persons not involved in drug preparation.

All hazardous drugs shall be prepared in a BSC² or a CACI that meets or exceeds the standards for CACI in this chapter. The ISO Class 5 (see [Table 1](#)) BSC or CACI shall be placed in an ISO Class 7 (see [Table 1](#)) area that is physically separated (i.e., a different area from other preparation areas) and optimally has not less than 0.01-inch water column negative pressure to adjacent positive pressure ISO Class 7 (see [Table 1](#)) or better ante-areas, thus providing inward airflow to contain any airborne drug. A pressure indicator shall be installed that can be readily monitored for correct room pressurization. The BSC and CACI optimally should be 100% vented to the outside air through HEPA filtration.

If a CACI that meets the requirements of this chapter is used outside of a buffer area, the compounding area shall maintain a minimum negative pressure of 0.01-inch water column and have a minimum of 12 ACPHs.

When closed system vial transfer devices (CSTDs) (i.e., vial transfer systems that allow no venting or exposure of hazardous substance to the environment) are used, they shall be used within the ISO Class 5 (see [Table 1](#)) environment of a BSC or CACI. The use of a CSTD is preferred because of their inherent closed system process. In facilities that prepare a low volume of hazardous drugs, the use of two tiers of containment (e.g., CSTD within a BSC or CACI that is located in a non-negative pressure room) is acceptable.

Appropriate personnel protective equipment (PPE) shall be worn when compounding in a BSC or CACI and when using CSTD devices. PPE should include gowns, face masks, eye protection, hair covers, shoe covers or dedicated shoes, double gloving with sterile chemo-type gloves, and compliance with manufacturers' recommendations when using a CACI.

All personnel who compound hazardous drugs shall be fully trained in the storage, handling, and disposal of these drugs. This training shall occur prior to preparing or handling hazardous CSPs, and its effectiveness shall be verified by testing specific hazardous drugs preparation techniques. Such verification shall be documented for each person at least annually. This

training shall include didactic overview of hazardous drugs, including mutagenic, teratogenic, and carcinogenic properties, and it shall include ongoing training for each new hazardous drug that enters the marketplace. Compounding personnel of reproductive capability shall confirm in writing that they understand the risks of handling hazardous drugs. The training shall include at least the following: (1) safe aseptic manipulation practices; (2) negative pressure techniques when utilizing a BSC or CACI; (3) correct use of CSTD devices; (4) containment, cleanup, and disposal procedures for breakages and spills; and (5) treatment of personnel contact and inhalation exposure.

NOTE—Because standards of assay and unacceptable quantities of contamination of each drug have not been established in the literature, the following paragraph is a recommendation only. Future standards will be adopted as these assay methods are developed and proven.

In order to ensure containment, especially in operations preparing large volumes of hazardous drugs, environmental sampling to detect uncontained hazardous drugs should be performed routinely (e.g., initially as a benchmark and at least every 6 months or more often as needed to verify containment). This sampling should include surface wipe sampling of the working area of BSCs and CACIs; counter tops where finished preparations are placed; areas adjacent to BSCs and CACIs, including the floor directly under the working area; and patient administration areas. Common marker hazardous drugs that can be assayed include cyclophosphamide, ifosfamide, methotrexate, and fluorouracil. If any measurable contamination (cyclophosphamide levels greater than 1.00 ng per cm² have been found to cause human uptake) is found by any of these quality assurance procedures, practitioners shall make the decision to identify, document, and contain the cause of contamination. Such action may include retraining, thorough cleaning (utilizing high-pH soap and water), and improving engineering controls. Examples of improving engineering controls are (1) venting BSCs or CACIs 100% to the outside, (2) implementing a CSTD, or (3) re-assessing types of BSCs or CACIs.

Disposal of all hazardous drug wastes shall comply with all applicable federal and state regulations. All personnel who perform routine custodial waste removal and cleaning activities in storage and preparation areas for hazardous drugs shall be trained in appropriate procedures to protect themselves and prevent contamination.

~~RADIOPHARMACEUTICALS AS CSPS~~

In the case of production of radiopharmaceuticals for positron emission tomography (PET), general test chapter *Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses* (823) supersedes this chapter. Upon release of a PET radiopharmaceutical as a finished drug product from a production facility, the further handling,

manipulation, or use of the product will be considered compounding, and the content of this section and chapter is applicable.

For the purposes of this chapter, radiopharmaceuticals compounded from sterile components in closed sterile containers and with a volume of 100 mL or less for a single-dose injection or not more than 30 mL taken from a multiple-dose container (see *Packaging and Storage Requirements (659)* (CN 1-May-2018)) shall be designated as, and conform to, the standards for *Low-Risk Level CSPs*:

These radiopharmaceuticals shall be compounded using appropriately shielded vials and syringes in a properly functioning and certified ISO Class 5 (see [Table 1](#)) PEC located in an ISO Class 8 (see [Table 1](#)) or cleaner air environment to permit compliance with special handling, shielding, and negative air flow requirements.

Radiopharmaceutical vials designed for multi-use, compounded with technetium-99m, exposed to ISO Class 5 (see [Table 1](#)) environment, and punctured by needles with no direct contact contamination may be used up to the time indicated by manufacturers' recommendations. Storage and transport of properly shielded vials of radiopharmaceutical CSPs may occur in a limited access ambient environment without a specific ISO class designation.

Technetium-99m/molybdenum-99 generator systems shall be stored and eluted (operated) under conditions recommended by manufacturers and applicable state and federal regulations. Such generator systems shall be eluted in an ISO Class 8 (see [Table 1](#)) or cleaner air environment to permit special handling, shielding, and air flow requirements. To limit acute and chronic radiation exposure of inspecting personnel to a level that is as low as reasonably achievable (ALARA), direct visual inspection of radiopharmaceutical CSPs containing high concentrations of doses of radioactivity shall be conducted in accordance with ALARA.

Radiopharmaceuticals prepared as *Low-Risk Level CSPs with 12-Hour or Less BUD* shall be prepared in a segregated compounding area. A line of demarcation defining the segregated compounding area shall be established. Materials and garb exposed in a patient care and treatment area shall not cross a line of demarcation into the segregated compounding area.

ALLERGEN EXTRACTS AS CSPS

Allergen extracts as CSPs are single-dose and multiple-dose *intra*dermal or *subcutaneous injections* that are prepared by specially trained physicians and personnel under their direct supervision. Allergen extracts as CSPs are not subject to the personnel, environmental, and storage requirements for all *CSP Microbial Contamination Risk Levels* in this chapter only when all of the following criteria are met:

1. ~~The compounding process involves simple transfer via sterile needles and syringes of commercial sterile allergen products and appropriate sterile added substances (e.g., glycerin, phenol in sodium chloride injection).~~
2. ~~All allergen extracts as CSPs shall contain appropriate substances in effective concentrations to prevent the growth of microorganisms. Nonpreserved allergen extracts shall comply with the appropriate CSP risk level requirements in the chapter.~~
3. ~~Before beginning compounding activities, personnel perform a thorough hand-cleansing procedure by removing debris from under fingernails using a nail cleaner under running warm water followed by vigorous hand and arm washing to the elbows for at least 30 seconds with either nonantimicrobial or antimicrobial soap and water.~~
4. ~~Compounding personnel don hair covers, facial hair covers, gowns, and face masks.~~
5. ~~Compounding personnel perform antiseptic hand cleansing with an alcohol-based surgical hand scrub with persistent activity.~~
6. ~~Compounding personnel don powder-free sterile gloves that are compatible with sterile 70% isopropyl alcohol (IPA) before beginning compounding manipulations.~~
7. ~~Compounding personnel disinfect their gloves intermittently with sterile 70% IPA when preparing multiple allergen extracts as CSPs.~~
8. ~~Ampul necks and vial stoppers on packages of manufactured sterile ingredients are disinfected by careful wiping with sterile 70% IPA swabs to ensure that the critical sites are wet for at least 10 seconds and allowed to dry before they are used to compound allergen extracts as CSPs.~~
9. ~~The aseptic compounding manipulations minimize direct contact contamination (e.g., from glove fingertips, blood, nasal and oral secretions, shed skin and cosmetics, other nonsterile materials) of critical sites (e.g., needles, opened ampuls, vial stoppers).~~
10. ~~The label of each multiple-dose vial (MDV) of allergen extracts as CSPs lists the name of one specific patient and a BUD and storage temperature range that is assigned based on manufacturers' recommendations or peer-reviewed publications.~~
11. ~~Single-dose allergen extracts as CSPs shall not be stored for subsequent additional use.~~

~~Personnel who compound allergen extracts as CSPs must be aware of greater potential risk of microbial and foreign material contamination when allergen extracts as CSPs are compounded in compliance with the foregoing criteria instead of the more rigorous standards in this chapter for *CSP Microbial Contamination Risk Levels*. Although contaminated allergen extracts as CSPs can pose health risks to patients when they are injected~~

~~intradermally or subcutaneously, these risks are substantially greater if the extract is inadvertently injected intravenously.~~

~~VERIFICATION OF COMPOUNDING ACCURACY AND STERILITY~~

~~The compounding procedures and sterilization methods for CSPs correspond to correctly designed and verified written documentation in the compounding facility. Verification requires planned testing, monitoring, and documentation to demonstrate adherence to environmental quality requirements, personnel practices, and procedures critical to achieving and maintaining sterility, accuracy, and purity of finished CSPs. For example, sterility testing (see *Test for Sterility of the Product To Be Examined* under *Sterility Tests* (71)) may be applied to specimens of low and medium risk level CSPs, and standard self-contained biological indicators (BI) shall be added to nondispensable specimens of high risk level CSPs before terminal sterilization for subsequent evaluation to determine whether the sterilization cycle was adequate (see *Biological Indicators for Sterilization* (1229.5)). Packaged and labeled CSPs shall be visually inspected for physical integrity and expected appearance, including final fill amount. The accuracy of identities, concentrations, amounts, and purities of ingredients in CSPs shall be confirmed by reviewing labels on packages, observing and documenting correct measurements with approved and correctly standardized devices, and reviewing information in labeling and certificates of analysis provided by suppliers. When the correct identity, purity, strength, and sterility of ingredients and components of CSPs cannot be confirmed (in cases of, for example, unlabeled syringes, opened ampuls, punctured stoppers of vials and bags, containers of ingredients with incomplete labeling), such ingredients and components shall be discarded immediately.~~

~~Some individual ingredients, such as bulk drug substances, are not labeled with expiration dates when they are stable indefinitely in their commercial packages under their labeled storage conditions. However, despite retaining full chemical stability, such ingredients may gain or lose moisture during storage and use. Changes in moisture content may require testing (see *Loss on Drying* (731)) to determine the correct amount to weigh for accurate content of active chemical moieties in CSPs (see *Pharmaceutical Calculations in Pharmacy Practice* (1160)).~~

~~Although not required, a quantitative stability-indicating chemical assay is recommended to ensure compounding accuracy of CSPs, especially those that contain drug ingredients with a narrow therapeutic plasma concentration range.~~

Sterilization Methods

~~The licensed healthcare professionals who supervise compounding shall be responsible for determining that the selected sterilization method (see *Methods of Sterilization* under *Sterility Assurance* (1211) (CN 1 May 2018)) both~~

sterilizes and maintains the strength, purity, quality, and packaging integrity of CSPs. The selected sterilization process is obtained from experience and appropriate information sources (e.g., see *Sterility Assurance (1211)* (CN 1 May 2018)) and, preferably, verified wherever possible to achieve sterility in the particular CSPs. General guidelines for matching CSPs and components to appropriate sterilization methods include the following:

1. CSPs have been ascertained to remain physically and chemically stable when subjected to the selected sterilization method.
2. Glass and metal devices may be covered tightly with aluminum foil, then exposed to dry heat in an oven at a mean temperature of 250° for 30 minutes to achieve sterility and depyrogenation (see *Dry-Heat Sterilization* under *Sterility Assurance (1211)* (CN 1 May 2018) and *Bacterial Endotoxins Test (85)*). Such items are either used immediately or stored until use in an environment suitable for compounding *Low-Risk Level CSPs* and *Medium-Risk Level CSPs*.
3. Personnel ascertain from appropriate information sources that the sterile microporous membrane filter used to sterilize CSP solutions, during either compounding or administration, is chemically and physically compatible with the CSP.

STERILIZATION OF HIGH-RISK LEVEL CSPS BY FILTRATION

Commercially available sterile filters shall be approved for human-use applications in sterilizing pharmaceutical fluids. Sterile filters used to sterilize CSPs shall be pyrogen free and have a nominal pore size of 0.2 or 0.22 µm. They shall be certified by the manufacturer to retain at least 10⁷ microorganisms of a strain of *Brevundimonas (Pseudomonas) diminuta* on each square centimeter of upstream filter surface area under conditions similar to those in which the CSPs will be sterilized (see *High-Risk Conditions in High-Risk Level CSPs*).

The compounding supervisor shall ensure, directly or from appropriate documentation, that the filters are chemically and physically stable at the pressure and temperature conditions to be used, that they have enough capacity to filter the required volumes, and that they will achieve sterility and maintain prefiltration pharmaceutical quality, including strength of ingredients of the specific CSP. The filter dimensions and liquid material to be sterile filtered shall permit the sterilization process to be completed rapidly, without the replacement of the filter during the process. When CSPs are known to contain excessive particulate matter, a prefilter of larger nominal pore size membrane is placed upstream from the sterilizing filter to remove gross particulate contaminants in order to maximize the efficiency of the sterilizing filter.

Filter units used to sterilize CSPs shall also be subjected to manufacturers' recommended integrity test, such as the bubble point test.

Compounding personnel shall ascertain that selected filters will achieve sterilization of the particular CSPs being sterilized. Large deviations from usual or expected chemical and physical properties of CSPs (e.g., water-miscible alcohols) may cause undetectable damage to filter integrity and shrinkage of microorganisms to sizes smaller than filter nominal pore size.

STERILIZATION OF HIGH-RISK LEVEL CSPS BY STEAM

The process of thermal sterilization employing saturated steam under pressure, or autoclaving, is the preferred method to terminally sterilize aqueous preparations that have been verified to maintain their full chemical and physical stability under the conditions employed (see *Steam Sterilization under Sterility Assurance (1211)* (CN 1-May-2018)). To achieve sterility, all materials are to be exposed to steam at 121° under a pressure of about 1 atmosphere or 15 psi for the duration verified by testing to achieve sterility of the items, which is usually 20 to 60 minutes for CSPs. An allowance shall be made for the time required for the material to reach 121° before the sterilization exposure duration is timed.

Not directly exposing items to pressurized steam may result in survival of microbial organisms and spores. Before their sterilization, plastic, glass, and metal devices are tightly wrapped in low-particle-shedding paper or fabrics or sealed in envelopes that prevent poststerilization microbial penetration. Immediately before filling ampuls and vials that will be steam sterilized, solutions are passed through a filter having a nominal pore size not larger than 1.2 µm for removal of particulate matter. Sealed containers shall be able to generate steam internally; thus, stoppered and crimped empty vials shall contain a small amount of moisture to generate steam.

The description of steam sterilization conditions and duration for specific CSPs shall be included in written documentation in the compounding facility. The effectiveness of steam sterilization shall be verified using appropriate BIs of *Bacillus stearothermophilus* (see *Biological Indicators for Sterilization (1229.5)*) and other confirmation methods such as temperature-sensing devices (see *Sterility Assurance (1211)* (CN 1-May-2018) and *Sterility Tests (71)*).

STERILIZATION OF HIGH-RISK LEVEL CSPS BY DRY HEAT

Dry heat sterilization is usually done as a batch process in an oven designed for sterilization. Heated filtered air shall be evenly distributed throughout the chamber by a blower device. The oven should be equipped with a system for controlling temperature and exposure period. Sterilization by dry heat requires higher temperatures and longer exposure times than does sterilization by steam. Dry heat shall be used only for those materials that cannot be sterilized by steam, when either the moisture would damage the material or the material is impermeable. During sterilization, sufficient space shall be left between materials to allow for good circulation of the hot air. The description of dry heat sterilization conditions and duration for specific CSPs shall be included in written documentation in the compounding

facility. The effectiveness of dry heat sterilization shall be verified using appropriate BIs of *Bacillus subtilis* (see *Biological Indicators for Sterilization* (1229.5)) and other confirmation methods such as temperature-sensing devices (see *Sterility Assurance* (1211))^(CN 1-May-2018) and *Sterility Tests* (71)). [NOTE—Dry heat sterilization may be performed at a lower temperature than may be effective for depyrogenation] -

Depyrogenation by Dry Heat

Dry heat depyrogenation shall be used to render glassware or containers such as vials free from pyrogens as well as viable microbes. A typical cycle would be 30 minutes at 250°. The description of the dry heat depyrogenation cycle and duration for specific load items shall be included in written documentation in the compounding facility. The effectiveness of the dry heat depyrogenation cycle shall be verified using endotoxin challenge vials (ECVs). The bacterial endotoxin test should be performed on the ECVs to verify that the cycle is capable of achieving a 3-log reduction in endotoxin (see *Sterility Assurance* (1211))^(CN 1-May-2018) and *Bacterial Endotoxins Test* (85)).

ENVIRONMENTAL QUALITY AND CONTROL

Achieving and maintaining sterility and overall freedom from contamination of a CSP is dependent on the quality status of the components incorporated, the process utilized, personnel performance, and the environmental conditions under which the process is performed. The standards required for the environmental conditions depend on the amount of exposure of the CSP to the immediate environment anticipated during processing. The quality and control of environmental conditions for each risk level of operation are explained in this section. In addition, operations using nonsterile components require the use of a method of preparation designed to produce a sterile preparation.

Exposure of Critical Sites

Maintaining the sterility and cleanliness (i.e., freedom from sterile foreign materials) of critical sites is a primary safeguard for CSPs. Critical sites are locations that include any component or fluid pathway surfaces (e.g., vial septa, injection ports, beakers) or openings (e.g., opened ampuls, needle hubs) exposed and at risk of direct contact with air (e.g., ambient room or HEPA filtered), moisture (e.g., oral and mucosal secretions), or touch contamination. The risk of, or potential for, critical sites to be contaminated with microorganisms and foreign matter increases with increasing exposed area of the critical sites, the density or concentration of contaminants, and exposure duration to worse than ISO Class 5 (see [Table 1](#)) air. Examples include an opened ampul or vial stopper on a 10-mL or larger vial or an

injection port on a package of intravenous solution having an area larger than the point of a needle or the tip of a syringe.

The nature of a critical site also affects the risk of contamination. The relatively rough, permeable surface of an elastomeric closure retains microorganisms and other contaminants after swabbing with a sterile 70% IPA pad more readily than does the smoother glass surface of the neck of an ampul. Therefore, the surface disinfection can be expected to be more effective for an ampul.

Protection of critical sites by precluding physical contact and airborne contamination shall be given the highest priority in sterile compounding practice. Airborne contaminants, especially those generated by sterile compounding personnel, are much more likely to reach critical sites than are contaminants that are adhering to the floor or other surfaces below the work level. Furthermore, large and high-density particles that are generated and introduced by compounding manipulations and personnel have the potential to settle on critical sites even when those critical sites are exposed within ISO Class 5 (see [Table 1](#)) air.

~~ISO Class 5 Air Sources, Buffer Areas, and Ante-Areas~~

The most common sources of ISO Class 5 (see [Table 1](#)) air quality for exposure of critical sites are horizontal and vertical LAFWs, CAIs, and CACIs. A clean room (see *Microbiological Control and Monitoring of Aseptic Processing Environments* (1116)) is a compounding environment that is supplied with HEPA or HEPA-filtered air that meets ISO Class 7 (see [Table 1](#)), the access to which is limited to personnel trained and authorized to perform sterile compounding and facility cleaning. A buffer area is an area that provides at least ISO Class 7 (see [Table 1](#)) air quality.

[Figure 1](#) is a conceptual representation of the placement of an ISO Class 5 (see [Table 1](#)) PEC in a segregated compounding area used for low-risk level CSPs with 12-hour or less BUD. This plan depicts the most critical operation area located within the PEC in a designated area (see definition of *Segregated Compounding Area*) separated from activities not essential to the preparation of CSPs. Placement of devices (e.g., computers, printers) and objects (e.g., carts, cabinets) that are not essential to compounding in the segregated area should be restricted or limited, depending on their effect on air quality in the ISO Class 5 (see [Table 1](#)) PEC.

Conceptual representation of USP Chapter <797> facility requirements

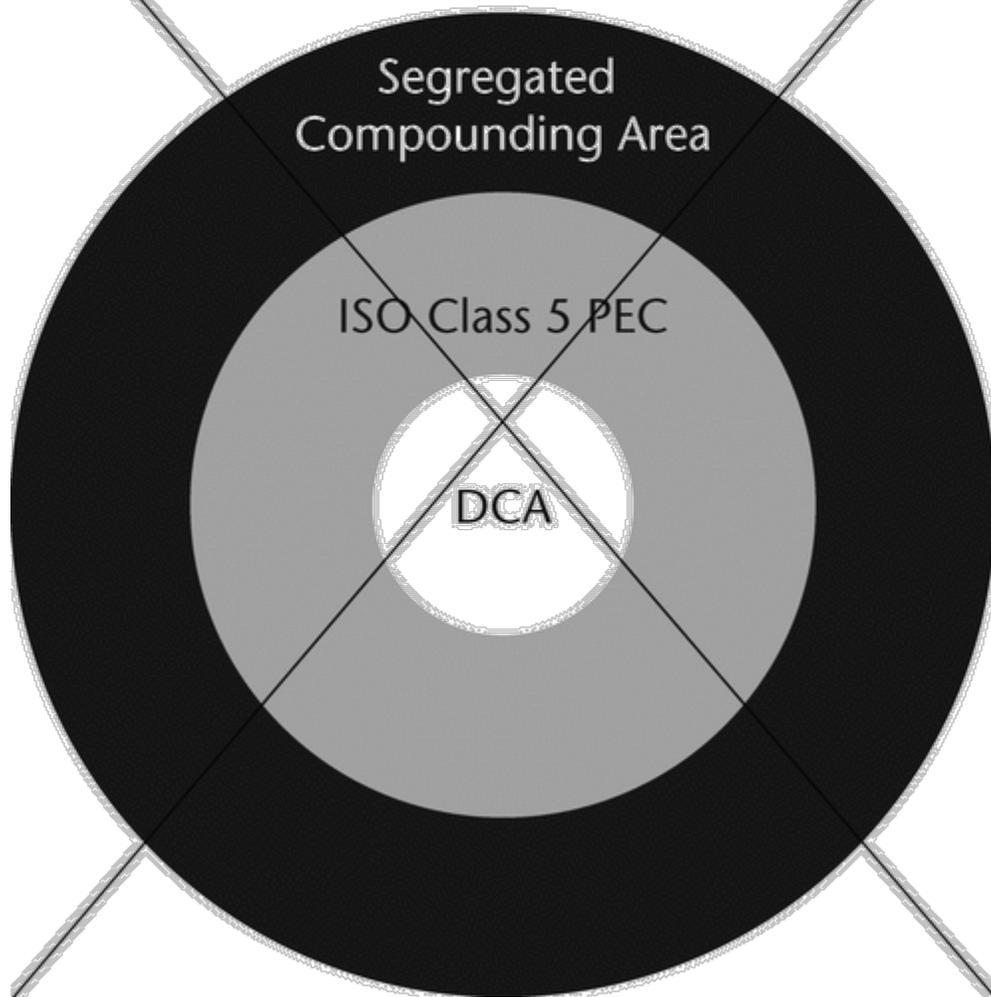


Figure 1. Conceptual representation of the placement of an ISO Class 5 PEC in a segregated compounding area used for low-risk level CSPs with 12-hour or less BUD.

[Figure 2](#) is a conceptual representation of the arrangement of a facility for preparation of CSPs categorized as low-, medium-, and high-risk level. The quality of the environmental air increases with movement from the outer boundary to the direct compounding area (DCA). Placement of devices in ante-areas and buffer areas is dictated by their effect on the designated environmental quality of atmospheres and surfaces, which shall be verified by monitoring (see *Viable and Nonviable Environmental Sampling (ES) Testing*). It is the responsibility of each compounding facility to ensure that each source of ISO Class 5 (see [Table 1](#)) environment for exposure of critical

sites and sterilization by filtration is properly located, operated, maintained, monitored, and verified.

Conceptual representation of USP Chapter <797> facility requirements

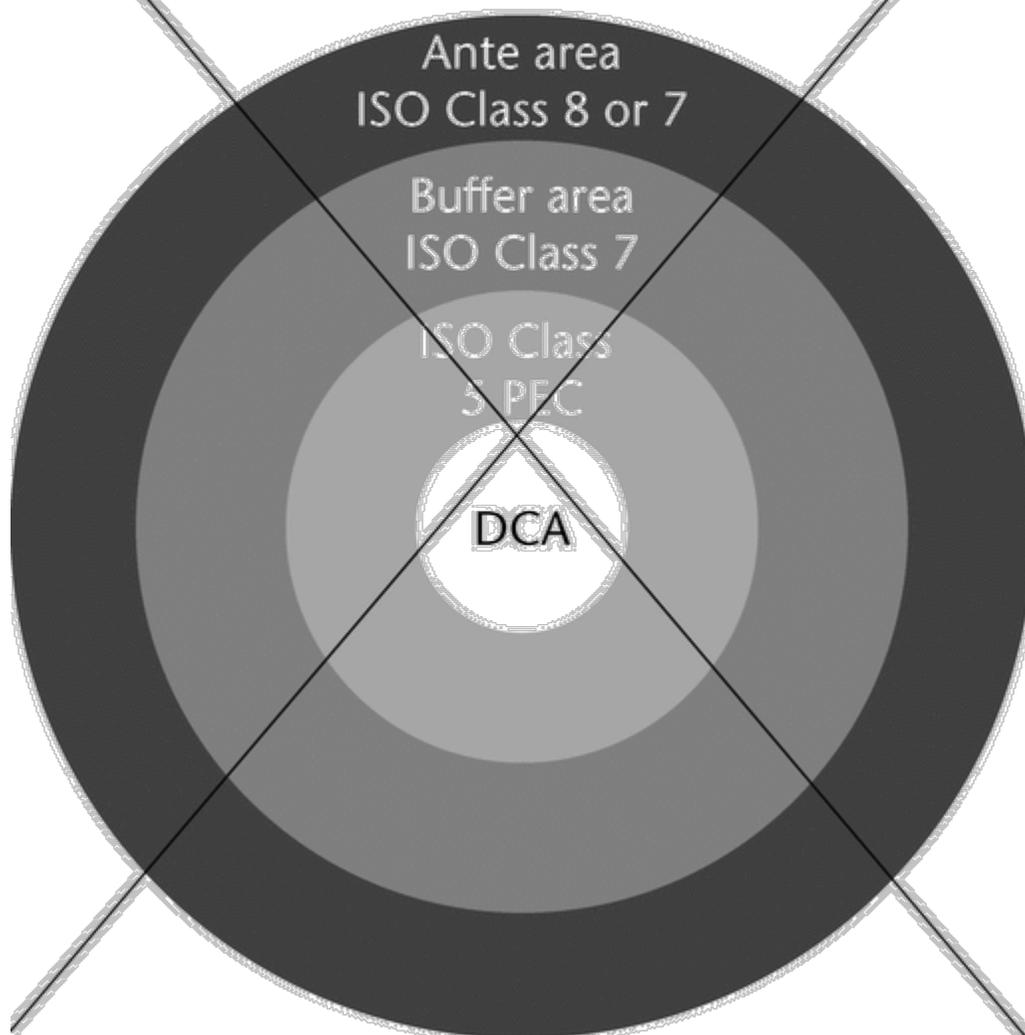


Figure 2. Conceptual representation of the arrangement of a facility for preparation of CSPs categorized as low-, medium-, and high-risk level.

Placement of devices (e.g., computers, printers) and objects (e.g., carts, cabinets) that are not essential to compounding in buffer areas is dictated by their effect on the required environmental quality of air atmospheres and surfaces, which shall be verified by monitoring (see *Viable and Nonviable Environmental Sampling (ES) Testing*). It is the responsibility of each compounding facility to ensure that each source of ISO Class 5 (see [Table 1](#)) environment for exposure of critical sites and sterilization by filtration is properly located, operated, maintained, monitored, and verified.

Facility Design and Environmental Controls

Compounding facilities are physically designed and environmentally controlled to minimize airborne contamination from contacting critical sites. These facilities shall also provide a comfortable and well-lighted working environment, which typically includes a temperature of 20° or cooler, to maintain comfortable conditions for compounding personnel to perform flawlessly when attired in the required aseptic compounding garb. PECs typically include, but are not limited to, LAFWs, BSCs, CAIs, and CACIs, which provide an ISO Class 5 (see [Table 1](#)) environment for the exposure of critical sites. PECs shall maintain ISO Class 5 (see [Table 1](#)) or better conditions for 0.5-µm particles (dynamic operating conditions) while compounding CSPs. Secondary engineering controls such as buffer areas and ante-areas generally serve as a core for the location of the PEC. Buffer areas are designed to maintain at least ISO Class 7 (see [Table 1](#)) conditions for 0.5-µm particles under dynamic conditions and ISO Class 8 (see [Table 1](#)) conditions for 0.5-µm and larger particles under dynamic conditions for the ante-areas. Airborne contamination control is achieved in the PEC through the use of HEPA filters. The airflow in the PEC shall be unidirectional (laminar flow), and because of the particle collection efficiency of the filter, the “first air” at the face of the filter is, for the purposes of aseptic compounding, free from airborne particulate contamination. HEPA-filtered air shall be supplied in critical areas (ISO Class 5, see [Table 1](#)) at a velocity sufficient to sweep particles away from the compounding area and maintain unidirectional airflow during operations. Proper design and control prevents turbulence and stagnant air in the critical area. In situ air pattern analysis via smoke studies shall be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions.

The principles of HEPA-filtered unidirectional airflow in the work environment shall be understood and practiced in the compounding process in order to achieve the desired environmental conditions. Policies and procedures for maintaining and working within the PEC area shall be written and followed. The policies and procedures will be determined by the scope and risk levels of the aseptic compounding activities utilized during the preparation of the CSPs. The CSP work environment is designed to have the cleanest work surfaces (PEC) located in a buffer area. The buffer area shall maintain at least ISO Class 7 (see [Table 1](#)) conditions for 0.5-µm and larger particles under dynamic operating conditions. The room shall be segregated from surrounding, unclassified spaces to reduce the risk of contaminants being blown, dragged, or otherwise introduced into the filtered unidirectional airflow environment, and this segregation shall be continuously monitored. For rooms providing a physical separation through the use of walls, doors, and pass-throughs, a minimum differential positive pressure of 0.02- to 0.05-inch water column is required. For buffer areas not physically separated

~~from the ante-areas, the principle of displacement airflow shall be employed. This concept utilizes a low pressure differential, high airflow principle. Using displacement airflow typically requires an air velocity of 40 ft per minute or more from the buffer area across the line of demarcation into the ante-area.~~

~~The displacement concept shall not be used for high-risk compounding.⁴ The PEC shall be placed within a buffer area in such a manner as to avoid conditions that could adversely affect their operation. For example, strong air currents from opened doors, personnel traffic, or air streams from the HVAC systems can disrupt the unidirectional airflow in open-faced workbenches. The operators may also create disruptions in airflow by their own movements and by the placement of objects onto the work surface. The PEC shall be placed out of the traffic flow and in a manner to avoid disruption from the HVAC system and room cross-drafts. Room air exchanges are typically expressed as ACPHs. Adequate HEPA-filtered airflow supplied to the buffer area and ante-area is required to maintain cleanliness classification during operational activity through the number of ACPHs. Factors that should be considered when determining air-change requirements include number of personnel working in the room and compounding processes that generate particulates, as well as temperature effects. An ISO Class 7 (see [Table 1](#)) buffer area and ante-area supplied with HEPA filtered air shall receive an ACPH of not less than 30. The PEC is a good augmentation to generating air changes in the air supply of an area but cannot be the sole source of HEPA-filtered air. If the area has an ISO Class 5 (see [Table 1](#)) recirculating device, a minimum of 15 ACPHs through the area supply HEPA filters is adequate, providing the combined ACPH is not less than 30. More air changes may be required, depending on the number of personnel and processes. HEPA-filtered supply air shall be introduced at the ceiling, and returns should be mounted low on the wall, creating a general top-down dilution of area air with HEPA-filtered make-up air. Ceiling-mounted returns are not recommended. All HEPA filters should be efficiency tested using the most penetrating particle size and should be leak tested at the factory and then leak tested again in situ after installation.⁵~~

~~Activities and tasks carried out within the buffer area shall be limited to only those necessary when working within a controlled environment. Only the furniture, equipment, supplies, and other material required for the compounding activities to be performed shall be brought into the area, and they shall be nonpermeable, nonshedding, cleanable, and resistant to disinfectants. Whenever such items are brought into the area, they shall first be cleaned and disinfected. Whenever possible, equipment and other items used in the buffer area shall not be taken out of the area except for calibration, servicing, or other activities associated with the proper maintenance of the item.~~

~~The surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets in the buffer area shall be smooth, impervious, free from cracks and~~

crevices, and nonshedding, thereby promoting cleanability and minimizing spaces in which microorganisms and other contaminants may accumulate. The surfaces shall be resistant to damage by disinfectant agents. Junctures of ceilings to walls shall be coved or caulked to avoid cracks and crevices where dirt can accumulate. If ceilings consist of inlaid panels, the panels shall be impregnated with a polymer to render them impervious and hydrophobic, and they shall be caulked around each perimeter to seal them to the support frame. Walls may be constructed of flexible material (e.g., heavy gauge polymer), panels locked together and sealed, or of epoxy-coated gypsum board. Preferably, floors are overlaid with wide sheet vinyl flooring with heat-welded seams and coving to the sidewall. Dust-collecting overhangs, such as ceiling utility pipes, and ledges, such as windowsills, should be avoided. The exterior lens surface of ceiling lighting fixtures should be smooth, mounted flush, and sealed. Any other penetrations through the ceiling or walls shall be sealed. The buffer area shall not contain sources of water (sinks) or floor drains. Work surfaces shall be constructed of smooth, impervious materials, such as stainless steel or molded plastic, so that they are easily cleaned and disinfected. Carts should be of stainless steel wire, nonporous plastic, or sheet metal construction with good quality, cleanable casters to promote mobility. Storage shelving, counters, and cabinets shall be smooth, impervious, free from cracks and crevices, nonshedding, cleanable, and disinfected; their number, design, and manner of installation shall promote effective cleaning and disinfection.

Placement of Primary Engineering Controls

PECs (LAFWs, BSCs, CAIs, and CACIs) shall be located within a restricted access ISO Class 7 (see [Table 1](#)) buffer area (see [Figure 1](#)), with the following CAI/CACI exceptions below:

- Only authorized personnel and materials required for compounding and cleaning shall be permitted in the buffer area.
- Presterilization procedures for high-risk level CSPs, such as weighing and mixing, shall be completed in no worse than an ISO Class 8 (see [Table 1](#)) environment.
- PECs shall be located out of traffic patterns and away from room air currents that could disrupt the intended airflow patterns.

CAIs and CACIs shall be placed in an ISO Class 7 (see [Table 1](#)) buffer area *unless* they meet all of the following conditions:

- The isolator shall provide isolation from the room and maintain ISO Class 5 (see [Table 1](#)) during dynamic operating conditions, including transferring ingredients, components, and devices into and out of the isolator and during preparation of CSPs.

- Particle counts sampled approximately 6 to 12 inches upstream of the critical exposure site shall maintain ISO Class 5 (see [Table 1](#)) levels during compounding operations.
- Not more than 3520 particles (0.5 µm and larger) per m³ shall be counted during material transfer, with the particle counter probe located as near to the transfer door as possible without obstructing the transfer.⁶

It is incumbent on the compounding personnel to obtain documentation from the manufacturer that the CAI/CACI will meet this standard when located in environments where the background particle counts exceed ISO Class 8 (see [Table 1](#)) for 0.5 µm and larger particles. When isolators are used for sterile compounding, the recovery time to achieve ISO Class 5 (see [Table 1](#)) air quality shall be documented and internal procedures developed to ensure that adequate recovery time is allowed after material transfer before and during compounding operations.

If the PEC is a CAI or CACI that does not meet the requirements above or is a LAFW or BSC that cannot be located within an ISO Class 7 (see [Table 1](#)) buffer area, then only low-risk level nonhazardous and radiopharmaceutical CSPs pursuant to a physician order for a specific patient may be prepared, and administration of the CSP shall commence within 12 hours of preparation or as recommended in the manufacturer's package insert, whichever is less.

~~Viable and Nonviable Environmental Sampling (ES) Testing~~

The ES program should provide information to staff and leadership to demonstrate that the PEC is maintaining an environment within the compounding area that consistently ensures acceptably low viable and nonviable particle levels. The compounding area includes the ISO Class 5 (see [Table 1](#)) PEC (LAFWs, BSCs, CAIs, and CACIs), buffer areas, ante-areas, and segregated compounding areas.

Environmental sampling shall occur as part a comprehensive quality management program and shall occur minimally under any of the following conditions:

- as part of the commissioning and certification of new facilities and equipment;
- following any servicing of facilities and equipment;
- as part of the re-certification of facilities and equipment (i.e., every 6 months);
- in response to identified problems with end products or staff technique; or
- in response to issues with CSPs, observed compounding personnel work practices, or patient-related infections (where the CSP is being considered as a potential source of the infection).

~~ENVIRONMENTAL NONVIABLE PARTICLE TESTING PROGRAM~~

~~A program to sample nonviable airborne particles differs from that for viable particles in that it is intended to directly measure the performance of the engineering controls used to create the various levels of air cleanliness, for example, ISO Class 5, 7, or 8 (see [Table 1](#)).~~

~~**Engineering Control Performance Verification**—PECs (LAFWs, BSCs, CAIs, and CACIs) and secondary engineering controls (buffer and ante-areas) are essential components of the overall contamination control strategy for aseptic compounding. As such, it is imperative that they perform as designed and that the resulting levels of contamination be within acceptable limits. Certification procedures such as those outlined in *Certification Guide for Sterile Compounding Facilities (CAG-003-2006)*[†] shall be performed by a qualified individual no less than every 6 months and whenever the device or room is relocated or altered or major service to the facility is performed.~~

~~**Total Particle Counts**—Certification that each ISO classified area, for example, ISO Class 5, 7, and 8 (see [Table 1](#)), is within established guidelines shall be performed no less than every 6 months and whenever the LAFW, BSC, CAI, or CACI is relocated or the physical structure of the buffer area or ante-area has been altered. Testing shall be performed by qualified operators using current, state-of-the-art electronic equipment with results of the following:~~

- ~~• ISO Class 5: not more than 3520 particles 0.5 μm and larger size per cubic meter of air for any LAFW, BSC, CAI, and CACI;~~
- ~~• ISO Class 7: not more than 352,000 particles of 0.5 μm size and larger per cubic meter of air for any buffer area;~~
- ~~• ISO Class 8: not more than 3,520,000 particles of 0.5 μm size and larger per cubic meter of air for any ante-area.~~

~~All certification records shall be maintained and reviewed by supervising personnel or other designated employees to ensure that the controlled environments comply with the proper air cleanliness, room pressures, and ACPHs.~~

~~PRESSURE DIFFERENTIAL MONITORING~~

~~A pressure gauge or velocity meter shall be installed to monitor the pressure differential or airflow between the buffer area and the ante-area and between the ante-area and the general environment outside the compounding area. The results shall be reviewed and documented on a log at least every work shift (minimum frequency shall be at least daily) or by a continuous recording device. The pressure between the ISO Class 7 (see [Table 1](#)) and the general pharmacy area shall not be less than 5 Pa (0.02 inch water column). In facilities where low- and medium-risk level CSPs are~~

prepared, differential airflow shall maintain a minimum velocity of 0.2 meters per second (40 feet per minute) between buffer area and ante-area.

~~ENVIRONMENTAL VIABLE AIRBORNE PARTICLE TESTING PROGRAM~~

~~The risk of contaminating a CSP prepared under low-risk level and medium-risk level conditions is highly dependent on proper hand hygiene and garbing practices, compounding personnel aseptic technique, and the presence of surface contamination, assuming that all work is performed in a certified and properly functioning ISO Class 5 (see [Table 1](#)) PEC and secondary engineering controls, ISO Class 7 (see [Table 1](#)) buffer area, and ISO Class 8 (see [Table 1](#)) ante-area. High-risk level CSPs pose the greatest threat to patients because compounding personnel are tasked with the requirement of processing nonsterile components and devices in order to achieve sterility.~~

~~A sampling program in conjunction with an observational audit is designed to evaluate the competency of compounding personnel work practices, allowing for the implementation of corrective actions on an ongoing basis (see *Personnel Training and Competency Evaluation of Garbing, Aseptic Work Practices and Cleaning/Disinfection Procedures*).~~

~~Sampling Plan~~—An appropriate environmental sampling plan shall be developed for airborne viable particles based on a risk assessment of compounding activities performed.

~~Selected sampling sites shall include locations within each ISO Class 5 (see [Table 1](#)) environment and in the ISO Class 7 and 8 (see [Table 1](#)) areas and in the segregated compounding areas at greatest risk of contamination (e.g., work areas near the ISO Class 5 [see [Table 1](#)] environment, counters near doors, pass-through boxes). The plan shall include sample location, method of collection, frequency of sampling, volume of air sampled, and time of day as related to activity in the compounding area and action levels.~~

~~Review of the data generated during a sampling event may detect elevated amounts of airborne microbial bioburden; such changes may be indicative of adverse changes within the environment. It is recommended that compounding personnel refer to *Microbiological Control and Monitoring of Aseptic Processing Environments* (1116) and the CDC's "Guidelines for Environmental Infection Control in Healthcare Facilities, 2003" for more information.~~

~~Growth Medium~~—A general microbiological growth medium such as Soybean-Casein Digest Medium shall be used to support the growth of bacteria. Malt extract agar or some other media that supports the growth of fungi shall be used in high-risk level compounding environments. Media used for surface sampling must be supplemented with additives to neutralize the effects of disinfecting agents (e.g., TSA with lecithin and polysorbate 80).

~~Viabile Air Sampling~~—Evaluation of airborne microorganisms using volumetric collection methods in the controlled air environments (LAFWs, CAIs, clean room or buffer areas, and ante-areas) shall be performed by properly trained individuals for all compounding risk levels.

Impaction shall be the preferred method of volumetric air sampling. Use of settling plates for qualitative air sampling may not be able to determine adequately the quality of air in the controlled environment. The settling of particles by gravity onto culture plates depends on the particle size and may be influenced by air movement. Consequently, the number of colony-forming units (cfu) on a settling plate may not always relate to the concentrations of viable particles in the sampled environment.

For low-, medium-, and high-risk level compounding, air sampling shall be performed at locations that are prone to contamination during compounding activities and during other activities such as staging, labeling, gowning, and cleaning. Locations shall include zones of air backwash turbulence within LAFW and other areas where air backwash turbulence may enter the compounding area (doorways, in and around ISO Class 5 [see [Table 1](#)] PEG and environments). Consideration should be given to the overall effect the chosen sampling method will have on the unidirectional airflow within a compounding environment.

For low-risk level CSPs with 12-hour or less BUD prepared in a PEG (LAFWs, BSCs, CAIs) that maintains an ISO Class 5 (see [Table 1](#)), air sampling shall be performed at locations inside the ISO Class 5 (see [Table 1](#)) environment and other areas that are in close proximity to the ISO Class 5 (see [Table 1](#)) environment during the certification of the PEG.

~~Air Sampling Devices~~—There are a number of manufacturers of electronic air sampling equipment. It is important that personnel refer to the manufacturer's recommended procedures when using the equipment to perform volumetric air sampling procedures. The instructions in the manufacturer's user's manual for verification and use of electric air samplers that actively collect volumes of air for evaluation must be followed. A sufficient volume of air (400 to 1000 liters) shall be tested at each location in order to maximize sensitivity. The volumetric air sampling devices need to be serviced and calibrated as recommended by the manufacturer.

It is recommended that compounding personnel also refer to *Methodology and Instrumentation for Quantitation of Viable Airborne Microorganisms under Microbiological Control and Monitoring of Aseptic Processing Environments* (1116), which provides more information on the use of volumetric air samplers and volume of air that should be sampled to detect environmental bioburden excursions.

~~Air Sampling Frequency and Process~~—Air sampling shall be performed at least semiannually (i.e., every 6 months) as part of the re-certification of facilities and equipment. If compounding occurs in multiple locations within

an institution (e.g., main pharmacy, satellites), environmental sampling is required for each individual compounding area. A sufficient volume of air shall be sampled and the manufacturer's guidelines for use of the electronic air sampling equipment followed. Any facility construction or equipment servicing may require that air sampling be performed during these events.

Incubation Period—At the end of the designated sampling or exposure period for air sampling activities, the microbial growth media plates are recovered and their covers secured (e.g., taped), and they are inverted and incubated at a temperature and for a time period conducive to multiplication of microorganisms. TSA should be incubated at 30° to 35° for 48 to 72 hours. Malt extract agar or other suitable fungal media should be incubated at 26° to 30° for 5 to 7 days. The number of discrete colonies of microorganisms are counted and reported as cfu and documented on an environmental sampling form. Counts from air sampling need to be transformed into cfu per cubic meter of air and evaluated for adverse trends.

Action Levels, Documentation, and Data Evaluation—The value of viable microbial sampling of the air in the compounding environment is realized when the data are used to identify and correct an unacceptable situation. Sampling data shall be collected and reviewed on a periodic basis as a means of evaluating the overall control of the compounding environment. If an activity consistently shows elevated levels of microbial growth, competent microbiology personnel shall be consulted.

Any cfu count that exceeds its respective action level (see [Table 2](#)) should prompt a re-evaluation of the adequacy of personnel work practices, cleaning procedures, operational procedures, and air filtration efficiency within the aseptic compounding location. An investigation into the source of the contamination shall be conducted. Sources could include HVAC systems, damaged HEPA filters, and changes in personnel garbing or work practices. The source of the problem shall be eliminated, the affected area cleaned, and resampling performed.

Counts of cfu are to be used as an approximate measure of the environmental microbial bioburden. Action levels are determined on the basis of cfu data gathered at each sampling location and trended over time. The numbers in [Table 2](#) should be used only as guidelines. Regardless of the number of cfu identified in the pharmacy, further corrective actions will be dictated by the identification of microorganisms recovered (at least the genus level) by an appropriate credentialed laboratory of any microbial bioburden captured as a cfu using an impaction air sampler. Highly pathogenic microorganisms (e.g., Gram-negative rods, coagulase positive staphylococcus, molds and yeasts) can be potentially fatal to patients receiving CSPs and must be immediately remedied, regardless of cfu count, with the assistance of a competent microbiologist, infection control professional, or industrial hygienist.

Table 2. Recommended Action Levels for Microbial Contamination*
 †(cfu per cubic meter [1000 liters] of air per plate)

Classification	Air Sample†
ISO Class 5	>1
ISO Class 7	>10
ISO Class 8 or worse	>100

* -Guidance for Industry—Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice—US HHS, FDA September 2004.

Additional Personnel Requirements

Food, drinks, and materials exposed in patient care and treatment areas shall not enter ante-areas, buffer areas, or segregated compounding areas where components and ingredients of CSPs are present. When compounding activities require the manipulation of a patient's blood-derived or other biological material (e.g., radiolabeling a patient's or donor's white blood cells), the manipulations shall 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. Packaged compounding supplies and components, such as needles, syringes, tubing sets, and small- and large-volume parenterals, should be uncartoned and wiped down with a disinfectant that does not leave a residue (e.g., sterile 70% IPA), when possible in an ante-area of ISO Class 8 (see [Table 1](#)) air quality, before being passed into the buffer areas. Personnel hand hygiene and garbing procedures are also performed in the ante-area, which may contain a sink that enables hands-free use with a closed system of soap dispensing to minimize the risk of extrinsic contamination. There shall be some demarcation designation that separates the ante-area from the buffer area. Adequate provision for performing antiseptic hand cleansing using an alcohol-based surgical hand scrub with persistent activity followed by the donning of sterile gloves should be provided after entry into the buffer area.

Cleaning and Disinfecting the Compounding Area

Environmental contact is a major source of microbial contamination of CSPs. Consequently, scrupulous attention to cleaning and disinfecting the sterile compounding areas is required to minimize this as a source of CSP contamination.

The cleaning and disinfecting practices and frequencies in this section apply to ISO Class 5 (see [Table 1](#)) compounding areas for exposure of critical sites as well as buffer areas, ante-areas, and segregated compounding areas. Compounding personnel are responsible for ensuring that the frequency of

cleaning is in accordance with the requirements stated in [Table 3](#) and determining the cleaning and disinfecting products to be used (see [Appendix II](#)). Any organizational or institutional policies regarding disinfectant selection should be considered by compounding personnel. All cleaning and disinfecting practices and policies for the compounding of CSPs shall be included in written SOPs and shall be followed by all compounding personnel.

Table 3. Minimum Frequency of Cleaning and Disinfecting Compounding Areas

Site	Minimum Frequency
ISO Class 5 (see Table 1) Primary Engineering Control (e.g., LAFW, BSC, CAI, CACI)	At the beginning of each shift, before each batch, not longer than 30 minutes following the previous surface disinfection when ongoing compounding activities are occurring, after spills, and when surface contamination is known or suspected
Counters and easily cleanable work surfaces	Daily
Floors	Daily
Walls	Monthly
Ceilings	Monthly
Storage shelving	Monthly

The selection and use of disinfectants in healthcare facilities is guided by several properties, such as microbicidal activity, inactivation by organic matter, residue, and shelf life (see [Appendix II](#)). In general, highly toxic disinfectants, such as glutaraldehyde, are not used on housekeeping surfaces (e.g., floors, countertops). Many disinfectants registered by the EPA are one-step disinfectants. This means that the disinfectant has been formulated to be effective in the presence of light to moderate soiling without a pre-cleaning step.

Surfaces in LAFWs, BSCs, CAIs, and CACIs, which are intimate to the exposure of critical sites, require disinfecting more frequently than do housekeeping surfaces such as walls and ceilings. Disinfecting sterile compounding areas shall occur on a regular basis at the intervals noted in [Table 3](#) when spills occur, when the surfaces are visibly soiled, and when microbial contamination is known to have been or is suspected of having been introduced into the compounding areas.

When the surface to be disinfected has heavy soiling, a cleaning step is recommended prior to the application of the disinfectant. Trained compounding personnel are responsible for developing, implementing, and practicing the procedures for cleaning and disinfecting the DCAs written in the SOPs. Cleaning and disinfecting shall occur before compounding is

~~performed. Items shall be removed from all areas to be cleaned, and surfaces shall be cleaned by removing loose material and residue from spills; for example, water-soluble solid residues are removed with sterile water (for injection or irrigation) and low-shedding wipes. This shall be followed by wiping with a residue-free disinfecting agent such as sterile 70% IPA, which is allowed to dry before compounding begins.~~

~~Cleaning and disinfecting surfaces in the LAFWs, BSCs, CAIs, and CACIs are the most critical practices before the preparation of CSPs. Consequently, such surfaces shall be cleaned and disinfected frequently, including at the beginning of each work shift, before each batch preparation is started, every 30 minutes during continuous compounding periods of individual CSPs, when there are spills, and when surface contamination is known or suspected from procedural breaches.~~

~~Work surfaces in the ISO Class 7 (see [Table 1](#)) buffer areas and ISO Class 8 (see [Table 1](#)) ante-areas as well as segregated compounding areas shall be cleaned and disinfected at least daily, and dust and debris shall be removed when necessary from storage sites for compounding ingredients and supplies using a method that does not degrade the ISO Class 7 or 8 (see [Table 1](#)) air quality (see *Disinfectants and Antiseptics* (1072)).~~

~~Floors in the buffer or clean area, ante-area, and segregated compounding area are cleaned by mopping with a cleaning and disinfecting agent once daily at a time when no aseptic operations are in progress. Mopping shall be performed by trained personnel using approved agents and procedures described in the written SOPs. It is incumbent on compounding personnel to ensure that such cleaning is performed properly. In the buffer or clean area, ante-area, and segregated compounding area, walls, ceilings, and shelving shall be cleaned and disinfected monthly. Cleaning and disinfecting agents are to be used with careful consideration of compatibilities, effectiveness, and inappropriate or toxic residues (see *Appendix II*). Their schedules of use and methods of application shall be in accordance with written SOPs and followed by custodial or compounding personnel.~~

~~All cleaning materials, such as wipers, sponges, and mops, shall be nonshedding, preferably composed of synthetic micro fibers, and dedicated to use in the buffer or clean area, ante-area, and segregated compounding areas and shall not be removed from these areas except for disposal. Floor mops may be used in both the buffer or clean area and ante-area, but only in that order. Ideally, all cleaning tools are discarded after one use by collection in suitable plastic bags and removed with minimal agitation. If cleaning materials (e.g., mops) are reused, procedures shall be developed (based on manufacturers' recommendations) that ensure that the effectiveness of the cleaning device is maintained and that repeated use does not add to the bioburden of the area being cleaned.~~

~~Supplies and equipment removed from shipping cartons shall be wiped with a suitable disinfecting agent (e.g., sterile 70% IPA) delivered from a spray~~

bottle or other suitable delivery method. After the disinfectant is sprayed or wiped on a surface to be disinfected, the disinfectant shall be allowed to dry, during which time the item shall not be used for compounding purposes.

Wiping with small sterile 70% IPA swabs that are commercially available in individual foil-sealed packages (or a comparable method) is preferred for disinfecting entry points on bags and vials, allowing the IPA to dry before piercing stoppers with sterile needles and breaking necks of ampuls. The surface of the sterile 70% IPA swabs used for disinfecting entry points of sterile packages and devices shall not contact any other object before contacting the surface of the entry point. Sterile 70% IPA wetted gauze pads or other particle-generating material shall not be used to disinfect the sterile entry points of packages and devices.

When sterile supplies are received in sealed pouches designed to keep them sterile until opening, the sterile supplies may be removed from the covering pouches as the supplies are introduced into the ISO Class 5 (see [Table 1](#)) PEC (LAFW, BSC, CAI, CACI) without the need to disinfect the individual sterile supply items. No shipping or other external cartons may be taken into the buffer or clean area or segregated compounding area.

Personnel Cleansing and Garbing

The careful cleansing of hands and arms and the correct donning of PPE by compounding personnel constitute the first major step in preventing microbial contamination in CSPs. Personnel shall also be thoroughly competent and highly motivated to perform flawless aseptic manipulations with ingredients, devices, and components of CSPs. Squamous cells are normally shed from the human body at a rate of 10^6 or more per hour, and those skin particles are laden with microorganisms.^{8,9} When individuals are experiencing rashes, sunburn, weeping sores, conjunctivitis, active respiratory infection, as well as when they wear cosmetics, they shed these particles at even higher rates. Particles shed from compounding personnel pose an increased risk of microbial contamination of critical sites of CSPs. Therefore, compounding personnel with such conditions as mentioned above shall be excluded from working in ISO Class 5 (see [Table 1](#)) and ISO Class 7 (see [Table 1](#)) compounding areas until their conditions are remedied.

Before entering the buffer area or segregated compounding area (see *Low-Risk Level CSPs with 12-Hour or Less BUD*), compounding personnel shall remove personal outer garments (e.g., bandannas, coats, hats, jackets, scarves, sweaters, vests); all cosmetics, because they shed flakes and particles; and all hand, wrist, and other visible jewelry or piercings (e.g., earrings, lip or eyebrow piercings) that can interfere with the effectiveness of PPE (e.g., fit of gloves and cuffs of sleeves). The wearing of artificial nails or extenders is prohibited while working in the sterile compounding environment. Natural nails shall be kept neat and trimmed.

Personnel shall don the following PPE in an order that proceeds from those activities considered the dirtiest to those considered the cleanest. Garbing

~~activities considered the dirtiest include donning of dedicated shoes or shoe covers, head and facial hair covers (e.g., beard covers in addition to face masks), and face masks/eye shields. Eye shields are optional unless working with irritants such as germicidal disinfecting agents or when preparing hazardous drugs.~~

~~After donning dedicated shoes or shoe covers, head and facial hair covers, and face masks, a hand cleansing procedure shall be performed by removing debris from underneath fingernails using a nail cleaner under running warm water followed by vigorous hand washing. Hands and forearms shall be washed to the elbows for at least 30 seconds with soap (either nonantimicrobial or antimicrobial) and water while in the ante-area. The use of antimicrobial scrub brushes is not recommended because they can cause skin irritation and skin damage. Hands and forearms to the elbows will be completely dried using either lint-free disposable towels or an electronic hand dryer. After completion of hand washing, a nonshedding gown with sleeves that fit snugly around the wrists and enclosed at the neck is donned. Gowns designated for buffer area use shall be worn, and preferably they should be disposable. If reusable gowns are worn, they should be laundered appropriately for buffer area use.~~

~~Once inside the buffer area or segregated compounding area (see *Low-Risk Level CSPs with 12-Hour or Less BUD*), and prior to donning sterile powder-free gloves, antiseptic hand cleansing shall be performed using a waterless alcohol-based surgical hand scrub with persistent activity¹⁰ following manufacturers' recommendations. Hands are allowed to dry thoroughly before donning sterile gloves.~~

~~Sterile gloves shall be the last item donned before compounding begins. Gloves become contaminated when they contact nonsterile surfaces during compounding activities. Disinfection of contaminated gloved hands may be accomplished by wiping or rubbing sterile 70% IPA to all contact surface areas of the gloves and letting the gloved hands dry thoroughly. Only use gloves that have been tested for compatibility with alcohol disinfection by the manufacturer. Routine application of sterile 70% IPA shall occur throughout the compounding process and whenever nonsterile surfaces (e.g. vials, counter tops, chairs, carts) are touched. Gloves on hands shall also be routinely inspected for holes, punctures, or tears and replaced immediately if such are detected. Antiseptic hand cleansing shall be performed as indicated above. Compounding personnel shall be trained and evaluated in the avoidance of touching critical sites.~~

~~When compounding personnel exit the compounding area during a work shift, the exterior gown may be removed and retained in the compounding area if not visibly soiled, to be re-donned during that same work shift only. However, shoe covers, hair and facial hair covers, face masks/eye shields, and gloves shall be replaced with new ones before re-entering the compounding area, and proper hand hygiene shall be performed.~~

~~During high-risk compounding activities that precede terminal sterilization, such as weighing and mixing of nonsterile ingredients, compounding personnel shall be garbed and gloved the same as when performing compounding in an ISO Class 5 (see [Table 1](#)) environment. Properly garbed and gloved compounding personnel who are exposed to air quality that is either known or suspected to be worse than ISO Class 7 (see [Table 1](#)) shall re-garb PPE along with washing their hands properly, performing antiseptic hand cleansing with a waterless alcohol-based surgical hand scrub, and donning sterile gloves upon re-entering the ISO Class 7 (see [Table 1](#)) buffer area. When CAIs and CACIs are the source of the ISO Class 5 (see [Table 1](#)) environment, the garbing and gloving requirements for compounding personnel should be as described above, unless the isolator manufacturer can provide written documentation based on validated environmental testing that any component(s) of PPE or personnel cleansing are not required.~~

~~Personnel Training and Competency Evaluation of Garbing, Aseptic Work Practices, and Cleaning/Disinfection Procedures~~

~~Personnel who prepare CSPs shall be trained conscientiously and skillfully by expert personnel and through multimedia instructional sources and professional publications in the theoretical principles and practical skills of garbing procedures, aseptic work practices, achieving and maintaining ISO Class 5 (see [Table 1](#)) environmental conditions, and cleaning and disinfection procedures. This training shall be completed and documented before any compounding personnel begin to prepare CSPs. Compounding personnel shall complete didactic training, pass written competence assessments, undergo skill assessment using observational audit tools, and media-fill testing (see [Appendices III–V](#)).~~

~~Media-fill testing of aseptic work skills shall be performed initially before beginning to prepare CSPs and at least annually thereafter for low- and medium-risk level compounding and semiannually for high-risk level compounding.~~

~~Compounding personnel who fail written tests or observational audits or whose media-fill test vials have one or more units showing visible microbial contamination shall be re-instructed and re-evaluated by expert compounding personnel to ensure correction of all aseptic work practice deficiencies. Compounding personnel shall pass all evaluations prior to resuming compounding of sterile preparations. In addition to didactic evaluation and aseptic media fill, compounding personnel must demonstrate proficiency of proper hand hygiene, garbing, and consistent cleaning procedures.~~

~~In the event that cleaning and disinfecting procedures are also performed by other support personnel (e.g., institutional environmental services, housekeeping), thorough training of proper hand hygiene, garbing, and cleaning and disinfection procedures shall be done by a qualified aseptic compounding expert. After completion of training, support personnel shall~~

routinely undergo performance evaluation of proper hand hygiene, garbing, and all applicable cleaning and disinfecting procedures conducted by a qualified aseptic compounding expert.

~~COMPETENCY EVALUATION OF GARBING AND ASEPTIC WORK PRACTICE~~

The risk of contaminating a CSP prepared under low-risk level and medium-risk level conditions is highly dependent on proper hand hygiene and garbing practices, compounding personnel aseptic technique, and the presence of surface contamination, assuming that all work is performed in a certified and properly functioning ISO Class 5 (see [Table 1](#)) PEC and secondary engineering controls, ISO Class 7 (see [Table 1](#)) buffer area, and ISO Class 8 (see [Table 1](#)) ante-area. High-risk level CSPs pose the greatest threat to patients because compounding personnel are tasked with the requirement of processing nonsterile components and devices in order to achieve sterility. Compounding personnel shall be evaluated initially prior to beginning compounding CSPs and whenever an aseptic media fill is performed using a form such as the *Sample Form for Assessing Hand Hygiene and Garbing Related Practices of Compounding Personnel* (see [Appendix III](#)) and the personnel glove fingertip sampling procedures indicated below.

~~Aseptic Work Practice Assessment and Evaluation via Personnel Glove Fingertip Sampling~~—Sampling of compounding personnel glove fingertips shall be performed for all CSP risk level compounding because direct touch contamination is the most likely source of introducing microorganisms into CSPs prepared by humans. Glove fingertip sampling shall be used to evaluate the competency of personnel in performing hand hygiene and garbing procedures in addition to educating compounding personnel on proper work practices, which include frequent and repeated glove disinfection using sterile 70% IPA during actual compounding of CSPs. All personnel shall demonstrate competency in proper hand hygiene and garbing procedures and in aseptic work practices (e.g., disinfection of component surfaces, routine disinfection of gloved hands).

Sterile contact agar plates shall be used to sample the gloved fingertips of compounding personnel after garbing in order to assess garbing competency and after completing the media fill preparation (without applying sterile 70% IPA) in order to assess the adequacy of aseptic work practices prior to being initially allowed to prepare CSPs for human use and for more experienced personnel to maintain their qualifications to prepare CSPs for human use.

~~Garbing And Gloving Competency Evaluation~~—Compounding personnel shall be visually observed during the process of performing hand hygiene and garbing procedures (see *Personnel Cleansing and Garbing* under *Personnel Training and Evaluation in Aseptic Manipulation Skills* above). The visual observation shall be documented on a form such as the *Sample Form for Assessing Hand Hygiene and Garbing Related Practices of Compounding*

~~Personnel (see Appendix III) and maintained to provide a permanent record and long-term assessment of personnel competency.~~

~~**Gloved Fingertip Sampling**—All compounding personnel shall successfully complete an initial competency evaluation and gloved fingertip/thumb sampling procedure (zero cfu) no less than three times before initially being allowed to compound CSPs for human use. Immediately after the compounding employee completes the hand hygiene and garbing procedure (e.g., donning of sterile gloves prior to any disinfection with sterile 70% IPA), the evaluator will collect a gloved fingertip and thumb sample from both hands of the compounding employee onto appropriate agar plates by lightly pressing each fingertip into the agar. The plates will be incubated for the appropriate incubation period and at the appropriate temperature (see *Incubation Period*). After completing the initial gowning and gloving competency evaluation, re-evaluation of all compounding personnel for this competency shall occur at least annually for personnel who compound low- and medium-risk level CSPs and semi-annually for personnel who compound high-risk level CSPs using one or more sample collections during any media-fill test procedure before they are allowed to continue compounding CSPs for human use.~~

~~Immediately prior to sampling, gloves shall not be disinfected with sterile 70% IPA. Disinfecting gloves immediately before sampling will provide false negative results. Plates filled with nutrient agar with neutralizing agents such as lecithin and polysorbate 80 added shall be used when sampling personnel fingertips. Personnel shall “touch” the agar with the fingertips of both hands in separate plates in a manner to create a slight impression in the agar. The sampled gloves shall be immediately discarded and proper hand hygiene performed after sampling. The nutrient agar plates shall be incubated as stated below (see *Incubation Period*). Results should be reported separately as number of cfu per employee per hand (left hand, right hand). The cfu action level for gloved hands will be based on the total number of cfu on both gloves, not per hand.~~

~~**Incubation Period**—At the end of the designated sampling period for compounding personnel competency assessment activities (surface or personnel), the agar plates are recovered and covers secured and they are inverted and incubated at a temperature and for a time period conducive to multiplication of microorganisms. TSA with lecithin and polysorbate 80 shall be incubated at 30° to 35° for 48 to 72 hours.~~

~~**Aseptic Manipulation Competency Evaluation**—After successful completion of an initial Hand Hygiene and Garbing Competency Evaluation, all compounding personnel shall have their aseptic technique and related practice competency evaluated initially during the *Media-Fill Test Procedure* and subsequent annual or semi-annual *Media-Fill Test Procedures*. Records of these evaluations will be maintained using a form such as the *Sample*~~

~~Form for Assessing Aseptic Technique and Related Practices of Compounding Personnel (see Appendix IV) and maintained to provide a permanent record of and long-term assessment of personnel competency.~~

~~Media-Fill Test Procedure—The skill of personnel to aseptically prepare CSPs shall be evaluated using sterile fluid bacterial culture media-fill verification, (i.e., sterile bacterial culture medium transfer via a sterile syringe and needle). Media-fill testing is used to assess the quality of the aseptic skill of compounding personnel. Media-fill tests shall represent the most challenging or stressful conditions actually encountered by the personnel being evaluated when they prepare low- and medium-risk level CSPs and when sterilizing high-risk level CSPs. Media-fill challenge tests are also used to verify the capability of the compounding environment and processes to produce sterile preparations.~~

~~A commercially available sterile fluid culture media, such as Soybean-Casein Digest Medium (see *Sterility Tests* (71)), that is able to promote exponential colonization of bacteria that are most likely to be transmitted to CSPs from the compounding personnel and environment is commonly used. For high-risk level CSPs nonsterile commercially available Soybean-Casein Digest Medium may be used to make a 3% solution. Normal processing steps, including filter sterilization, shall be mimicked. Media-filled vials shall be incubated at 20° to 25° or at 30° to 35° for a minimum of 14 days. If two temperatures are used for incubation of media-filled samples, then these filled containers should be incubated for at least 7 days at each temperature (see *Microbiological Control and Monitoring of Aseptic Processing Environments* (1116)). Failure is indicated by visible turbidity in any one of the media-fill units on or before 14 days. Other methodologies recommended by a competent microbiologist to enhance recovery time and sensitivity to detect microbial contamination may be considered (see *CSP Microbial Contamination Risk Levels* for examples of media-fill procedures).~~

~~SURFACE CLEANING AND DISINFECTION SAMPLING AND ASSESSMENT~~

~~Surface sampling is an important component of the maintenance of a suitable microbially controlled environment for compounding CSPs, especially since transfer of microbial contamination from improperly disinfected work surfaces via inadvertent touch contact by compounding personnel can be a potential source of contamination into CSPs. It is useful for evaluating facility and work surface cleaning and disinfecting procedures and employee competency in work practices such as disinfection of component/vial surface cleaning. Surface sampling shall be performed in all ISO classified areas on a periodic basis. Sampling can be accomplished using contact plates or swabs, and it shall be done at the conclusion of compounding. Locations to be sampled shall be defined in a sample plan or on a form. The size of the plate to be used for each sampled location usually ranges from 24 to 30 cm². Contact plates are filled with general solid agar~~

growth medium and neutralizing agents above the rim of the plate, and they are used for sampling regular or flat surfaces. Swabs may be used for sampling irregular surfaces, especially for equipment (see *Microbiological Control and Monitoring of Aseptic Processing Environments* (1116)).

Cleaning and Disinfecting Competency Evaluation—Compounding personnel and other personnel responsible for cleaning shall be visually observed during the process of performing cleaning and disinfecting procedures, during initial personnel training on cleaning procedures, during changes in cleaning staff, and at the completion of any media-fill test procedure (see *Cleaning and Disinfecting of Compounding Areas*).

The visual observation shall be documented using a form such as the *Sample Form for Assessing Cleaning and Disinfection Procedures* (see *Appendix V*) and maintained to provide a permanent record and long-term assessment of personnel competency.

Surface Collection Methods—To sample surfaces using a contact plate, gently touch the sample area with the agar surface and roll the plate across the surface to be sampled. The contact plate will leave a growth media residue behind; therefore, immediately after sampling with the contact plate, the sampled area shall be thoroughly wiped with a nonshedding wipe soaked in sterile 70% IPA.

If an area is sampled via the swab method, collection of the sample is processed by using appropriate procedures that will result in the surface location equivalent to that of a contact plate. After swabbing the surface to be sampled, swabs are placed in an appropriate diluent; an aliquot is planted on or in the specified nutrient agar. Results should be reported as cfu per unit of surface area.

Action Levels, Documentation, and Data Evaluation

The value of viable microbial monitoring of gloved fingertips and surfaces of components and the compounding environment are realized when the data are used to identify and correct an unacceptable work practice. Sampling data shall be collected and reviewed on a routine basis as a means of evaluating the overall control of the compounding environment. If an activity consistently shows elevated levels of microbial growth, competent microbiology personnel shall be consulted.

Any cfu count that exceeds its respective action level (see [Table 4](#)) should prompt a re-evaluation of the adequacy of personnel work practices, cleaning procedures, operational procedures, and air filtration efficiency within the aseptic compounding location. An investigation into the source of the contamination shall be conducted. Sources could include HVAC systems, damaged HEPA filters, and changes in personnel garbing or working practices. The source of the problem shall be eliminated, the affected area cleaned, and resampling performed.

When gloved fingertip sample results exceed action levels after proper incubation, a review of hand hygiene and garbing procedures as well as glove and surface disinfection procedures and work practices shall be performed and documented. Employee training may be required to correct the source of the problem.

Counts of cfu are to be used as an approximate measure of the environmental microbial bioburden. Action levels are determined on the basis of cfu data gathered at each sampling location and trended over time. The numbers in [Table 4](#) should be used only as guidelines. Regardless of the number of cfu identified in the compounding facility, further corrective actions will be dictated by the identification of microorganisms recovered (at least the genus level) by an appropriate credentialed laboratory of any microbial bioburden captured as a cfu using an impaction air sampler. Highly pathogenic microorganisms (e.g., Gram-negative rods, coagulase positive staphylococcus, molds and yeasts) can be potentially fatal to patients receiving CSPs and shall be immediately remedied, regardless of cfu count, with the assistance of a competent microbiologist, infection control professional, or industrial hygienist.

Table 4. Recommended Action Levels for Microbial Contamination*

Classification	Fingertip Sample	Surface Sample (Contact Plate) (cfu per plate)
ISO Class 5	>3	>3
ISO Class 7	N/A	>5
ISO Class 8 or worse	N/A	>100

* -Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide to Good Manufacturing Practice for Medicinal Products Annexes PE 009-6, 5 April 2007.

~~SUGGESTED STANDARD OPERATING PROCEDURES (SOPS)~~

The compounding facility shall have written, properly approved SOPs designed to ensure the quality of the environment in which a CSP is prepared. The following procedures are recommended:-

1. Access to the buffer area is restricted to qualified personnel with specific responsibilities or assigned tasks in the compounding area.
2. All cartoned supplies are decontaminated in the area by removing them from shipping cartons and wiping or spraying them with a nonresidue-generating disinfecting agent while they are being transferred to a clean and properly disinfected cart or other conveyance for introduction into the buffer area. Manufacturers'

~~directions or published data for minimum contact time will be followed. Individual pouched sterile supplies need not be wiped because the pouches can be removed as these sterile supplies are introduced into the buffer area.~~

- ~~3. Supplies that are required frequently or otherwise needed close at hand but not necessarily needed for the scheduled operations of the shift are decontaminated and stored on shelving in the ante-area.~~
- ~~4. Carts used to bring supplies from the storeroom cannot be rolled beyond the demarcation line in the ante-area, and carts used in the buffer area cannot be rolled outward beyond the demarcation line unless cleaned and disinfected before returning.~~
- ~~5. Generally, supplies required for the scheduled operations of the shift are wiped down with an appropriate disinfecting agent and brought into the buffer area, preferably on one or more movable carts. Supplies that are required for back-up or general support of operations may be stored on the designated shelving in the buffer area, but excessive amounts of supplies are to be avoided.~~
- ~~6. Nonessential objects that shed particles shall not be brought into the buffer area, including pencils, cardboard cartons, paper towels, and cotton items (e.g., gauze pads).~~
- ~~7. Essential paper-related products (e.g., paper syringe overwraps, work records contained in a protective sleeve) shall be wiped down with an appropriate disinfecting agent prior to being brought into the buffer area.~~
- ~~8. Traffic flow in and out of the buffer area shall be minimized.~~
- ~~9. Personnel preparing to enter the buffer area shall remove all personal outer garments, cosmetics (because they shed flakes and particles), and all hand, wrist, and other visible jewelry or piercings that can interfere with the effectiveness of PPE.~~
- ~~10. Personnel entering the ante-area shall don attire as described in *Personnel Cleansing and Garbing and Personnel Training and Competency Evaluation of Garbing, Aseptic Work Practices and Cleaning/Disinfection Procedures*.~~
- ~~11. Personnel shall then thoroughly wash hands and forearms to the elbow with soap and water for at least 30 seconds. An air dryer or disposable nonshedding towels are used to dry hands and forearms after washing.~~
- ~~12. Personnel entering the buffer area shall perform antiseptic hand cleansing prior to donning sterile gloves using a waterless alcohol-based surgical hand scrub with persistent activity.~~
- ~~13. Chewing gum, drinks, candy, or food items shall not be brought into the buffer area or ante-area. Materials exposed in patient care and treatment areas shall never be introduced into areas where components and ingredients for CSPs are present.~~

14. ~~At the beginning of each compounding activity session, and whenever liquids are spilled, the surfaces of the direct compounding environment are first cleaned with USP Purified Water to remove water-soluble residues. Immediately thereafter, the same surfaces are disinfected with a nonresidue-generating agent using a nonlinting wipe.~~
15. ~~Primary engineering controls shall be operated continuously during compounding activity. When the blower is turned off and before other personnel enter to perform compounding activities, only one person shall enter the buffer area for the purposes of turning on the blower (for at least 30 minutes) and disinfecting the work surfaces.~~
16. ~~Traffic in the area of the DCA is minimized and controlled.~~
17. ~~Supplies used in the DCA for the planned procedures are accumulated and then decontaminated by wiping or spraying the outer surface with sterile 70% IPA or removing the outer wrap at the edge of the DCA as the item is introduced into the aseptic work area.~~
18. ~~All supply items are arranged in the DCA so as to reduce clutter and provide maximum efficiency and order for the flow of work.~~
19. ~~After proper introduction into the DCA of supply items required for and limited to the assigned operations, they are so arranged that a clear, uninterrupted path of HEPA-filtered air will bathe all critical sites at all times during the planned procedures. That is, no objects may be placed between the first air from HEPA filters and an exposed critical site.~~
20. ~~All procedures are performed in a manner designed to minimize the risk of touch contamination. Gloves are disinfected with adequate frequency with an approved disinfectant such as sterile 70% IPA.~~
21. ~~All rubber stoppers of vials and bottles and the necks of ampuls are disinfected by wiping with sterile 70% IPA and waiting for at least 10 seconds before they are used to prepare CSPs.~~
22. ~~After the preparation of every CSP, the contents of the container are thoroughly mixed and then inspected for the presence of particulate matter, evidence of incompatibility, or other defects.~~
23. ~~After procedures are completed, used syringes, bottles, vials, and other supplies are removed, but with a minimum of exit and re-entry into the DCA so as to minimize the risk of introducing contamination into the aseptic workspace.~~

ELEMENTS OF QUALITY CONTROL

~~A written description of specific training and performance evaluation program for individuals involved in the use of aseptic techniques for the preparation of sterile products shall be developed for each site. This program~~

~~equips personnel with the appropriate knowledge and trains them in the required skills necessary to perform the assigned tasks. Each person assigned to the aseptic area in the preparation of sterile products shall successfully complete specialized training in aseptic techniques and aseptic area practices prior to preparing CSPs (see *Personnel Training and Evaluation in Aseptic Manipulation Skills* and *Personnel Training and Competency Evaluation of Garbing, Aseptic Work Practices and Cleaning/Disinfection Procedures*).~~

~~Ingredients and Devices~~

~~Compounding personnel ascertain that ingredients for CSPs are of the correct identity and appropriate quality using the following information: vendor labels, labeling, certificates of analysis, direct chemical analysis, and knowledge of compounding facility storage conditions.~~

~~STERILE INGREDIENTS AND DEVICES~~

~~Commercially available sterile drug products, sterile ready-to-use containers, and devices are examples of sterile components. A written procedure for unit-by-unit physical inspection preparatory to use is followed to ensure that these components are sterile, free from defects, and otherwise suitable for their intended use.~~

~~NONSTERILE INGREDIENTS AND DEVICES~~

~~If any nonsterile components, including containers and ingredients, are used to make a CSP, such CSPs must be high risk. Nonsterile active ingredients and added substances or excipients for CSPs should preferably be official *USP* or *NF* articles. When nonofficial ingredients are used, they shall be accompanied by certificates of analysis from their suppliers to aid compounding personnel in judging the identity, quality, and purity in relation to the intended use in a particular CSP. Physical inspection of a package of ingredients is necessary in order to detect breaks in the container, looseness in the cap or closure, and deviation from the expected appearance, aroma, and texture of the contents.~~

~~Bulk or unformulated drug substances and added substances or excipients shall be stored in tightly closed containers under temperature, humidity, and lighting conditions that are either indicated in official monographs or approved by suppliers. The date of receipt by the compounding facility shall be clearly and indelibly marked on each package of ingredient. After receipt by the compounding facility, packages of ingredients that lack a supplier's expiration date cannot be used after 1 year unless either appropriate inspection or testing indicates that the ingredient has retained its purity and quality for use in CSPs.~~

~~Careful consideration and evaluation of nonsterile ingredient sources is especially warranted when the CSP will be administered into the vascular system, central nervous system, or eyes.~~

Upon receipt of each lot of the bulk drug substance or excipient used for CSPs, the individual compounding the preparation performs a visual inspection of the lot for evidence of deterioration, other types of unacceptable quality, and wrong identification. For bulk drug substances or excipients, visual inspection is performed on a routine basis as described in the written protocol.

Equipment

It is necessary that equipment, apparatus, and devices used to compound a CSP be consistently capable of operating properly and within acceptable tolerance limits. Written procedures outlining required equipment calibration, annual maintenance, monitoring for proper function, and controlled procedures for use of the equipment and specified time frames for these activities are established and followed. Routine maintenance and frequencies shall be outlined in these SOPs. Results from the equipment calibration, annual maintenance reports, and routine maintenance are kept on file for the lifetime of the equipment. Personnel are prepared through an appropriate combination of specific training and experience to operate or manipulate any piece of equipment, apparatus, or device they may use when preparing CSPs. Training includes gaining the ability to determine whether any item of equipment is operating properly or is malfunctioning.

~~VERIFICATION OF AUTOMATED COMPOUNDING DEVICES (ACDs) FOR PARENTERAL NUTRITION COMPOUNDING~~

~~ACDs for the preparation of parenteral nutrition admixtures are widely used by pharmacists in hospitals and other healthcare settings. They are designed to streamline the labor-intensive processes involved in the compounding of these multiple-component formulations by automatically delivering the individual nutritional components in a predetermined sequence under computerized control. Parenteral nutrition admixtures often contain 20 or more individual additives representing as many as 50 or more individual components (e.g., 15 to 20 crystalline amino acids, dextrose monohydrate, and lipids; 10 to 12 electrolyte salts; 5 to 7 trace minerals; and 12 vitamins). Thus, ACDs can provide improved accuracy and precision of the compounding process over the traditional manual compounding methods.~~

~~Accuracy~~

~~The accuracy of an ACD can be determined in various ways to ensure that the correct quantities of nutrients, electrolytes, or other nutritional components are delivered to the final infusion container. Initially, the ACD is tested for its volume and weight accuracy. For volume accuracy, a suitable volume of Sterile Water for Injection, USP, which represents a typical additive volume (e.g., 40 mL for small-volume range of 1 to 100 mL, 300 mL for large-volume range of 100 to 1000 mL), is programmed into the ACD~~

and delivered to the appropriate volumetric container. The compounding personnel should then consult *Volumetric Apparatus* (31) for appropriate parameters to assess the volumetric performance of the ACD. For gravimetric accuracy, the balance used in conjunction with the ACD is tested using various weight sizes that represent the amounts typically used to deliver the various additives. Compounding personnel should consult *Balances* (41) for acceptable tolerances of the weights used. In addition, the same volume of *Sterile Water for Injection* used to assess volumetric accuracy is then weighed on the balance used in conjunction with the ACD. For example, if 40 mL of water was used in the volumetric assessment, its corresponding weight should be about 40 g (assuming the relative density of water is 1.0). In addition, during the use of the ACD, certain additives, such as potassium chloride (corrected for density differences), can also be tested in the same manner as with an in-process test.

Finally, additional tests of accuracy may be employed that determine the content of certain ingredients in the final volume of the parenteral nutrition admixture. Generally, pharmacy departments do not have the capability to routinely perform chemical analyses such as analyses of dextrose or electrolyte concentrations. Consequently, hospital or institutional laboratories may be called upon to perform these quality assurance tests. However, the methods in such laboratories are often designed for biological, not pharmaceutical, systems. Thus, their testing procedures shall be verified to meet the *USP* requirements stated in the individual monograph for the component being tested. For example, under *Dextrose Injection*, the following is stated: It contains not less than 95.0% and not more than 105.0% of the labeled amount of $C_6H_{12}O_6 \cdot H_2O$. The hospital or institutional chemistry laboratories must validate their methods to apply to this range and correct for their typical measurement of anhydrous dextrose versus dextrose monohydrate. Similar ranges and issues exist, for example, for injections of calcium gluconate, magnesium sulfate, and potassium chloride. The critical point is the use of *USP* references and possible laboratory procedural differences.

Precision

The intermediate precision of the ACD can be determined on the basis of the day-to-day variations in performance of the accuracy measures. Thus, compounding personnel shall keep a daily record of the above-described accuracy assessments and review the results over time. This review shall occur at least at weekly intervals to avoid potentially clinically significant cumulative errors over time. This is especially true for additives with a narrow therapeutic index, such as potassium chloride.

FINISHED PREPARATION RELEASE CHECKS AND TESTS

The following quality metrics shall be performed for all CSPs before they are dispensed or administered.

~~Inspection of Solution Dosage Forms and Review of Compounding Procedures~~

All CSPs that are intended to be solutions shall be visually examined for the presence of particulate matter and not administered or dispensed when such matter is observed. The prescription orders, written compounding procedure, preparation records, and expended materials used to make CSPs at all contamination risk levels are inspected for accuracy of correct identities and amounts of ingredients, aseptic mixing and sterilization, packaging, labeling, and expected physical appearance before they are administered or dispensed.

~~PHYSICAL INSPECTION~~

Finished CSPs are individually inspected in accordance with written procedures after compounding. If not distributed promptly, these CSPs are individually inspected just prior to leaving the storage area. Those CSPs that are not immediately distributed are stored in an appropriate location as described in the written procedures. Immediately after compounding, and as a condition of release, each CSP unit, where possible, should be inspected against lighted white or black background or both for evidence of visible particulates or other foreign matter. Prerelease inspection also includes container closure integrity and any other apparent visual defect. CSPs with observed defects should be immediately discarded or marked and segregated from acceptable products in a manner that prevents their administration. When CSPs are not distributed promptly after preparation, a predistribution inspection is conducted to ensure that a CSP with defects, such as precipitation, cloudiness, and leakage, which may develop between the time of release and the time of distribution, is not released.

~~Compounding Accuracy Checks~~

Written procedures for double-checking compounding accuracy shall be followed for every CSP during preparation and immediately prior to release. The double-check system should meet state regulations and include label accuracy and accuracy of the addition of all drug products or ingredients used to prepare the finished product and their volumes or quantities. The used additive containers and, for those additives for which the entire container was not expended, the syringes used to measure the additive should be quarantined with the final products until the final product check is completed. Compounding personnel shall visually confirm that ingredients measured in syringes match the written order being compounded. Preferably, a person other than the compounder can verify that correct volumes of correct ingredients were measured to make each CSP. For

~~example, compounding personnel would pull the syringe plunger back to the volume measured.~~

~~When practical, the accuracy of measurements is confirmed by weighing a volume of the measured fluid, then calculating that volume by dividing the weight by the accurate value of the density, or specific gravity, of the measured fluid. Correct density or specific gravity values programmed in ACDs, which measure by weight using the quotient of the programmed volume divided by the density or specific gravity, shall be confirmed to be accurate before and after delivering volumes of the liquids assigned to each channel or port. These volume accuracy checks and the following additional safety and accuracy checks in this section shall be included in the SOP manual of the CSP facility.~~

Sterility Testing

~~All high-risk level CSPs that are prepared in groups of more than 25 identical individual single-dose packages (e.g., ampuls, bags, syringes, vials) or in multiple-dose vials (MDVs) for administration to multiple patients or that are exposed longer than 12 hours at 2° to 8° and longer than 6 hours at warmer than 8° before they are sterilized shall meet the sterility test (see *Sterility Tests* (71)) before they are dispensed or administered. The *Membrane Filtration* method is the method of choice where feasible (e.g., components are compatible with the membrane). A method not described in the *USP* may be used if verification results demonstrate that the alternative is at least as effective and reliable as the *USP Membrane Filtration* method or the *USP Direct Inoculation of the Culture Medium* method where the *Membrane Filtration* method is not feasible.~~

~~When high-risk level CSPs are dispensed before receiving the results of their sterility tests, there shall be a written procedure requiring daily observation of the incubating test specimens and immediate recall of the dispensed CSPs when there is any evidence of microbial growth in the test specimens. In addition, the patient and the physician of the patient to whom a potentially contaminated CSP was administered are notified of the potential risk. Positive sterility test results should prompt a rapid and systematic investigation of aseptic technique, environmental control, and other sterility assurance controls to identify sources of contamination and correct problems in the methods or processes.~~

Bacterial Endotoxin (Pyrogen) Testing

~~All high-risk level CSPs, except those for inhalation and ophthalmic administration, that are prepared in groups of more than 25 identical individual single-dose packages (e.g., ampuls, bags, syringes, vials) or in MDVs for administration to multiple patients or that are exposed longer than 12 hours at 2° to 8° and longer than 6 hours at warmer than 8° before they are sterilized shall be tested to ensure that they do not contain excessive bacterial endotoxins (see *Bacterial Endotoxins Test* (85) and *Pyrogen Test*~~

~~{151}). In the absence of a bacterial endotoxins limit in the official monograph or other CSP formula source, the CSP shall not exceed the amount of USP Endotoxin Units (per hour per kilogram of body weight or square meters of body surface area) specified in *Bacterial Endotoxins Test* {85} referenced above for the appropriate route of administration.~~

~~**Identity and Strength Verification of Ingredients**~~

~~Compounding facilities shall have at least the following written procedures for verifying the correct identity and quality of CSPs before they are dispensed and administered:~~

- ~~1. That labels of CSPs bear correct names and amounts or concentrations of ingredients, the total volume, the BUD, the appropriate route(s) of administration, the storage conditions, and other information for safe use.~~
- ~~2. That there are correct identities, purities, and amounts of ingredients by comparing the original written order with the written compounding record for the CSP.~~
- ~~3. That correct fill volumes in CSPs and correct quantities of filled units of the CSPs were obtained. When the strength of finished CSPs cannot be confirmed to be accurate, based on the above three inspections, the CSPs shall be assayed by methods that are specific for the active ingredients.~~

~~**STORAGE AND BEYOND-USE DATING**~~

~~BUDs for compounded preparations are usually assigned on the basis of professional experience, which should include careful interpretation of appropriate information sources for the same or similar formulations (see *Stability Criteria and Beyond-Use Dating* under *Pharmaceutical Compounding—Nonsterile Preparations* {795}). BUDs for CSPs are rarely based on preparation-specific chemical assay results, which are used with the Arrhenius equation to determine expiration dates (see *Labeling* {7}, *Expiration Date and Beyond-Use Date*)[•] (CN 1-May-2018) for manufactured products. The majority of CSPs are aqueous solutions in which hydrolysis of dissolved ingredients is the most common chemical degradation reaction. The extent of hydrolysis and other heat-catalyzed degradation reactions at any particular time point in the life of a CSP represents the thermodynamic sum of exposure temperatures and durations. Such lifetime stability exposure is represented in the mean kinetic temperature calculation (see *Pharmaceutical Calculations in Pharmacy Practice* {1160}). Drug hydrolysis rates increase exponentially with arithmetic temperature increase; thus, exposure of a beta-lactam antibiotic solution for 1 day at controlled room temperature (see *Packaging and Storage Requirements* {659})[•] (CN 1-May-2018)~~

will have an equivalent effect on the extent of hydrolysis of approximately 3 to 5 days in cold temperatures (see *•Packaging and Storage Requirements (659)*).^{•(CN 1-May-2018)}

Personnel who prepare, dispense, and administer CSPs shall store them strictly in accordance with the conditions stated on the label of ingredient products and finished CSPs. When CSPs are known to have been exposed to temperatures warmer than the warmest labeled limit or to temperatures exceeding 40° (see *•Packaging and Storage Requirements (659)*).^{•(CN 1-May-2018)} for more than 4 hours, such CSPs should be discarded unless direct assay data or appropriate documentation confirms their continued stability.

Determining Beyond-Use Dates

BUDs and expiration dates are not the same (see *•Packaging and Storage Requirements (659)*).^{•(CN 1-May-2018)} Expiration dates for the chemical and physical stability of manufactured sterile products are determined from results of rigorous analytical and performance testing, and they are specific for a particular formulation in its container and at stated exposure conditions of illumination and temperature. When CSPs deviate from conditions in the approved labeling of manufactured products contained in CSPs, compounding personnel may consult the manufacturer of particular products for advice on assigning BUDs based on chemical and physical stability parameters. BUDs for CSPs that are prepared strictly in accordance with manufacturers' product labeling shall be those specified in that labeling or from appropriate literature sources or direct testing. BUDs for CSPs that lack justification from either appropriate literature sources or by direct testing evidence shall be assigned as described in *Stability Criteria and Beyond-Use Dating* under *Pharmaceutical Compounding—Nonsterile Preparations (795)*.

In addition, compounding personnel may refer to applicable publications to obtain relevant stability, compatibility, and degradation information regarding the drug or its congeners. When assigning a beyond-use date, compounding personnel should consult and apply drug-specific and general stability documentation and literature where available, and they should consider the nature of the drug and its degradation mechanism, the container in which it is packaged, the expected storage conditions, and the intended duration of therapy (see *•Labeling (7)*, *Expiration Date and Beyond-Use Date*).^{•(CN 1-May-2018)} Stability information must be carefully interpreted in relation to the actual compounded formulation and conditions for storage and use. Predictions based on other evidence, such as publications, charts, and tables, would result in theoretical BUDs. Theoretically predicted beyond-use dating introduces varying degrees of assumptions and, hence, a likelihood of error or at least inaccuracy. The degree of error or inaccuracy would be dependent on the extent of differences between the CSPs' characteristics (e.g., composition, concentration of ingredients, fill volume, container type and material) and the characteristics of the products from which stability data or information is

to be extrapolated. The greater the doubt of the accuracy of theoretically predicted beyond-use dating, the greater the need to determine dating periods experimentally. Theoretically predicted beyond-use dating periods should be carefully considered for CSPs prepared from nonsterile bulk active ingredients having therapeutic activity, especially where these CSPs are expected to be compounded routinely. When CSPs will be distributed to and administered in residential locations other than healthcare facilities, the effect of potentially uncontrolled and unmonitored temperature conditions shall be considered when assigning BUDs. It must be ascertained that CSPs will not be exposed to warm temperatures (see *Packaging and Storage Requirements (659)*)[•] (CN 1 May 2018) unless the compounding facility has evidence to justify stability of CSPs during such exposure.

It should be recognized that the truly valid evidence of stability for predicting beyond-use dating can be obtained only through product-specific experimental studies. Semiquantitative procedures such as thin-layer chromatography (TLC) may be acceptable for many CSPs. However, quantitative stability-indicating assays such as high-performance liquid chromatographic (HPLC) assays would be more appropriate for certain CSPs. Examples include CSPs with a narrow therapeutic index, where close monitoring or dose titration is required to ensure therapeutic effectiveness and to avoid toxicity; where a theoretically established beyond-use dating period is supported by only marginal evidence; or where a significant margin of safety cannot be verified for the proposed beyond-use dating period. In short, because beyond-use dating periods established from product-specific data acquired from the appropriate instrumental analyses are clearly more reliable than those predicted theoretically, the former approach is strongly urged to support dating periods exceeding 30 days.

To ensure consistent practices in determining and assigning BUDs, the compounding facility should have written policies and procedures governing the determination of the BUDs for all compounded products. When attempting to predict a theoretical BUD, a compounded or an admixed preparation should be considered as a unique system that has physical and chemical properties and stability characteristics that differ from its components. For example, antioxidant, buffering, or antimicrobial properties of a sterile vial for injection (SVI) might be lost upon its dilution, with the potential of seriously compromising the chemical stability of the SVI's active ingredient or the physical or microbiological stability of the SVI formulation in general. Thus, the properties stabilized in the SVI formulation usually cannot be expected to be carried over to the compounded or admixed preparation. Preparation-specific, experimentally determined stability data evaluation protocols are preferable to published stability information.

Compounding personnel who assign BUDs to CSPs when lacking direct chemical assay results must critically interpret and evaluate the most appropriate available information sources to determine a conservative and

safe BUD. The SOP manual of the compounding facility and each specific CSP formula record shall describe the general basis used to assign the BUD and storage conditions.

When manufactured MDVs (see *•Packaging and Storage Requirements (659), Multiple-dose container*)^{•(CN 1-May-2018)} of sterile ingredients are used in CSPs, the stoppers of the MDVs are inspected for physical integrity and disinfected by wiping with a sterile 70% IPA swab before each penetration with a sterile withdrawal device. When contaminants or abnormal properties are suspected or observed in MDVs, such MDVs shall be discarded. The BUD after initially entering or opening (e.g., needle puncturing) multiple-dose containers is 28 days (see *Antimicrobial Effectiveness Testing (51)*) unless otherwise specified by the manufacturer.

Proprietary Bag and Vial Systems

The sterility storage and stability beyond-use times for attached and activated (where activated is defined as allowing contact of the previously separate diluent and drug contents) container pairs of drug products for intravascular administration (e.g., ADD-Vantage[®], Mini Bag Plus[®]) shall be applied as indicated by the manufacturer. In other words, follow manufacturers' instructions for handling and storing ADD-Vantage[®], Mini Bag Plus[®], Add A Vial[®], Add-Ease[®] products, and any others.

Monitoring Controlled Storage Areas

To ensure that product potency is retained through the manufacturer's labeled expiration date, compounding personnel shall monitor the drug storage areas within the compounding facility. Controlled temperature areas in compounding facilities include controlled room temperature, 20° to 25° with mean kinetic temperature 25°; controlled cold temperature, 2° to 8° with mean kinetic temperature 8°; cold temperature, 2° to 8°; freezing temperature, -25° and -10° (see *•Packaging and Storage Requirements (659)*)^{•(CN 1-May-2018)} if needed to achieve freezing, and the media-specific temperature range for microbial culture media. A controlled temperature area shall be monitored at least once daily and the results documented on a temperature log. Additionally, compounding personnel shall note the storage temperature when placing the product into or removing the product from the storage unit in order to monitor any temperature aberrations. Suitable temperature recording devices may include a calibrated continuous recording device or a National Institute of Standards and Technology (NIST) calibrated thermometer that has adequate accuracy and sensitivity for the intended purpose, and it shall be properly calibrated at suitable intervals. If the compounding facility uses a continuous temperature recording device, compounding personnel shall verify at least once daily that the recording device itself is functioning properly.

The temperature sensing mechanisms shall be suitably placed in the controlled temperature storage space to reflect accurately its true

temperature. In addition, the compounding facility shall adhere to appropriate procedures of all controlled storage spaces to ensure that such spaces are not subject to significantly prolonged temperature fluctuations as may occur, for example, by leaving a refrigerator door open too long.

~~MAINTAINING STERILITY, PURITY, AND STABILITY OF DISPENSED AND DISTRIBUTED CSPS~~

This section summarizes the responsibilities of compounding facilities for maintaining quality and control of CSPs that are dispensed and administered within their parent healthcare organizations.

Compounding personnel shall ensure proper storage and security of CSPs prepared by or dispensed from the compounding facility until either their BUDs are reached or they are administered to patients. In fulfilling this general responsibility, the compounding facility is responsible for the proper packaging, handling, transport, and storage of CSPs prepared by or dispensed from it, including the appropriate education, training, and supervision of compounding personnel assigned to these functions. The compounding facility should assist in the education and training of noncompounding personnel responsible for carrying out any aspect of these functions.

Establishing, maintaining, and ensuring compliance with comprehensive written policies and procedures encompassing these responsibilities is a further responsibility of the compounding facility. Where noncompounding personnel are assigned tasks involving any of these responsibilities, the policies and procedures encompassing those tasks should be developed by compounding supervisors. The quality and control activities related to distribution of CSPs are summarized in the following five subsections. Activities or concerns that should be addressed as the compounding facility fulfills these responsibilities are as follows.

~~Packaging, Handling, and Transport~~

Inappropriate processes or techniques involved with packaging, handling, and transport can adversely affect quality and package integrity of CSPs. Although compounding personnel routinely perform many of the tasks associated with these functions, some tasks, such as transport, handling, and placement into storage, may be fulfilled by noncompounding personnel who are not under the direct administrative control of the compounding facility. Under these circumstances, appropriate SOPs shall be established by the compounding facility with the involvement of other departments or services whose personnel are responsible for carrying out those CSP-related functions for which the compounding facility has a direct interest. The performance of the noncompounding personnel is monitored for compliance to established policies and procedures.

The critical requirements that are unique to CSPs and that are necessary to ensure CSP quality and packaging integrity shall be addressed in SOPs. For example, techniques should be specified to prevent the depression of syringe plungers or dislodging of syringe tips during handling and transport. Additionally, disconnection of system components (e.g., where CSPs are dispensed with administration sets attached to them) shall be prevented through the BUD of the CSP. Foam padding or inserts are particularly useful where CSPs are transported by pneumatic tube systems. Regardless of the methods used, the compounding facility must evaluate their effectiveness and the reliability of the intended protection. Evaluation should be continuous—for example, through a surveillance system, including a system of problem reporting to the compounding facility.

Inappropriate transport and handling can adversely affect the quality of certain CSPs having unique stability concerns. For example, the physical shaking that might occur during pneumatic tube transport or undue exposure to heat or light must be addressed on a preparation-specific basis. Alternative transport modes or special packaging measures might be needed for the proper assurance of quality of these CSPs. The use of tamper-evident closures and seals on CSP ports can add an additional measure of security to ensure product integrity regardless of the transport method used.

Chemotoxic and other hazardous CSPs require safeguards to maintain the integrity of the CSP and to minimize the exposure potential of these products to the environment and to personnel who may come in contact with them. Transportation by pneumatic tube should be discouraged because of potential breakage and contamination. Special requirements associated with the packaging, transport, and handling of these agents include the prevention of accidental exposures or spills and the training of personnel in the event of an exposure or spill. Examples of special requirements of these agents also include exposure-reducing strategies such as the use of Luer lock syringes and connections, syringe caps, the capping of container ports, sealed plastic bags, impact-resistant containers, and cautionary labeling.

Use and Storage

The compounding facility is responsible for ensuring that CSPs in the patient-care setting maintain their quality until administered. The immediate labeling of the CSP container will display prominently and understandably the requirements for proper storage and expiration dating. Delivery and patient-care setting personnel shall be properly trained to deliver the CSP to the appropriate storage location. Outdated and unused CSPs shall be returned to the compounding facility for disposition.

SOPs must exist to ensure that storage conditions in the patient-care setting are suitable for the CSP-specific storage requirements. Procedures include daily monitoring and documentation of drug storage refrigerators to ensure temperatures between 2° and 8° and the monthly inspection of all drug storage locations by compounding personnel. Inspections shall confirm

~~compliance with appropriate storage conditions, separation of drugs and food, proper use of MDVs, and the avoidance of using single-dose products as MDVs. CSPs, as well as all other drug products, shall be stored in the patient-care area in such a way as to secure them from unauthorized personnel, visitors, and patients.~~

~~Readying for Administration~~

~~Procedures essential for generally ensuring quality, especially sterility assurance, when readying a CSP for its subsequent administration include proper hand washing, aseptic technique, site care, and change of administration sets. Additional procedures may also be essential for certain CSPs, devices, or techniques. Examples where such special procedures are needed include in-line filtration, the operation of automated infusion control devices, and the replenishment of CSPs into the reservoirs of implantable or portable infusion pumps. When CSPs are likely to be exposed to warmer than 30° for more than 1 hour during their administration to patients, the maintenance of their sterility and stability should be confirmed from either relevant and reliable sources or direct testing.~~

~~Redispensed CSPs~~

~~The compounding facility shall have the sole authority to determine when unopened, returned CSPs may be redispensed. Returned CSPs may be redispensed only when personnel responsible for sterile compounding can ensure that such CSPs are sterile, pure, and stable (contain labeled strength of ingredients). The following may provide such assurance: the CSPs were maintained under continuous refrigeration and protected from light, if required, and no evidence of tampering or any readying for use outside the compounding facility exists. Assignment of new storage times and BUDs that exceed the original dates for returned CSPs is permitted only when there is supporting evidence from sterility testing and quantitative assay of ingredients. Thus, initial preparation and thaw times should be documented and reliable measures should have been taken to prevent and detect tampering. Compliance with all procedures associated with maintaining product quality is essential. The CSPs shall not be redispensed if there is not adequate assurance that preparation quality and packaging integrity (including the connections of devices, where applicable) were continuously maintained between the time the CSPs left and the time they were returned. Additionally, CSPs shall not be redispensed if redispensing cannot be supported by the originally assigned BUD.~~

~~Education and Training~~

~~The assurance of CSPs' quality and packaging integrity is highly dependent on the proper adherence of all personnel to the pertinent SOPs. Compounding personnel shall design, implement, and maintain a formal education, training, and competency assessment program that encompasses~~

~~all the functions and tasks addressed in the foregoing sections and all personnel to whom such functions and tasks are assigned. This program includes the assessment and documentation of procedural breaches, administration mishaps, side effects, allergic reactions, and complications associated with dosage or administration, such as extravasation. This program should be coordinated with the institution's adverse events and incident reporting programs.~~

~~Packing and Transporting CSPs~~

~~The following sections describe how to maintain sterility and stability of CSPs until they are delivered to patient care locations for administration.~~

~~PACKING CSPS FOR TRANSIT~~

~~When CSPs are distributed to locations outside the premises in which they are compounded, compounding personnel select packing containers and materials that are expected to maintain physical integrity, sterility, and stability of CSPs during transit. Packing is selected that simultaneously protects CSPs from damage, leakage, contamination, and degradation, and protects personnel who transport packed CSPs from harm. The SOP manual of the compounding facility specifically describes appropriate packing containers and insulating and stuffing materials, based on information from product specifications, vendors, and experience of compounding personnel. Written instructions that clearly explain how to safely open containers of packed CSPs are provided to patients and other recipients.~~

~~TRANSIT OF CSPS~~

~~Compounding facilities that ship CSPs to locations outside their own premises shall select modes of transport that are expected to deliver properly packed CSPs in undamaged, sterile, and stable condition to recipients.~~

~~Compounding personnel should ascertain that temperatures of CSPs during transit by the selected mode will not exceed the warmest temperature specified on the storage temperature range on CSP labels. It is recommended that compounding personnel communicate directly with the couriers to learn shipping durations and exposure conditions that CSPs may encounter.~~

~~Compounding personnel shall include specific handling and exposure instructions on the exteriors of containers packed with CSPs to be transported and obtain reasonable assurance of compliance therewith from transporters. Compounding personnel shall periodically review the delivery performance of couriers to ascertain that CSPs are being efficiently and properly transported.~~

~~Storage in Locations Outside Compounding Facilities~~

~~Compounding facilities that ship CSPs to patients and other recipients outside their own premises shall ascertain or provide, whichever is appropriate, the following assurances:~~

- ~~1. Labels and accessory labeling for CSPs include clearly readable BUDs, storage instructions, and disposal instructions for out-of-date units.~~
- ~~2. Each patient or other recipient is able to store the CSPs properly, including the use of a properly functioning refrigerator and freezer if CSPs are labeled for such storage.~~

~~PATIENT OR CAREGIVER TRAINING~~

~~A formal training program is provided as a means to ensure understanding and compliance with the many special and complex responsibilities placed on the patient or caregiver for the storage, handling, and administration of CSPs. The instructional objectives for the training program include all home care responsibilities expected of the patient or caregiver and is specified in terms of patient or caregiver competencies.~~

~~Upon the conclusion of the training program, the patient or caregiver should, correctly and consistently, be able to do the following:~~

- ~~1. Describe the therapy involved, including the disease or condition for which the CSPs are prescribed, goals of therapy, expected therapeutic outcome, and potential side effects of the CSPs.~~
- ~~2. Inspect all drug products, CSPs, devices, equipment, and supplies on receipt to ensure that proper temperatures were maintained during transport and that goods received show no evidence of deterioration or defects.~~
- ~~3. Handle, store, and monitor all drug products, CSPs, and related supplies and equipment in the home, including all special requirements related to same.~~
- ~~4. Visually inspect all drug products, CSPs, devices, and other items the patient or caregiver is required to use immediately prior to administration in a manner to ensure that all items are acceptable for use. For example, CSPs must be free from leakage, container cracks, particulates, precipitate, haziness, discoloration, or other deviations from the normal expected appearance, and the immediate packages of sterile devices must be completely sealed, with no evidence of loss of package integrity.~~
- ~~5. Check labels immediately prior to administration to ensure the right drug, dose, patient, and time of administration.~~
- ~~6. Clean the in-home preparation area, scrub hands, use proper aseptic technique, and manipulate all containers, equipment, apparatus, devices, and supplies used in conjunction with administration.~~

7. ~~Employ all techniques and precautions associated with CSP administration; for example, preparing supplies and equipment, handling of devices, priming the tubing, and discontinuing an infusion.~~
8. ~~Care for catheters, change dressings, and maintain site patency as indicated.~~
9. ~~Monitor for and detect occurrences of therapeutic complications such as infection, phlebitis, electrolyte imbalance, and catheter misplacement.~~
10. ~~Respond immediately to emergency or critical situations such as catheter breakage or displacement, tubing disconnection, clot formation, flow blockage, and equipment malfunction.~~
11. ~~Know when to seek and how to obtain professional emergency services or professional advice.~~
12. ~~Handle, contain, and dispose of wastes, such as needles, syringes, devices, biohazardous spills or residuals, and infectious substances.~~

~~Training programs include a hands-on demonstration and practice with actual items that the patient or caregiver is expected to use, such as CSP containers, devices, and equipment. The patient or caregiver practices aseptic and injection technique under the direct observation of a health professional.~~

~~The compounding facility, in conjunction with nursing or medical personnel, is responsible for ensuring initially and on an ongoing basis that the patient or caregiver understands, has mastered, and is capable of and willing to comply with all of these home care responsibilities. This is achieved through a formal, written assessment program. All specified competencies in the patient or caregiver training program are formally assessed. The patient or caregiver is expected to demonstrate to appropriate healthcare personnel mastery of assigned activities before being allowed to administer CSPs unsupervised by a health professional.~~

~~Printed material such as checklists or instructions provided during training may serve as continuing post-training reinforcement of learning or as reminders of specific patient or caregiver responsibilities. Post-training verbal counseling can also be used periodically, as appropriate, to reinforce training and to ensure continuing correct and complete fulfillment of responsibilities.~~

~~PATIENT MONITORING AND ADVERSE EVENTS REPORTING~~

~~Compounding facilities shall clinically monitor patients treated with CSPs according to the regulations and guidelines of their respective state healthcare practitioner licensure boards or of accepted standards of practice. Compounding facilities shall provide patients and other recipients of CSPs~~

with a way to address their questions and report any concerns that they may have with CSPs and their administration devices.

The SOP manuals of compounding facilities shall describe specific instructions for receiving, acknowledging, and dating receipts, and for recording, or filing, and evaluating reports of adverse events and of the quality of preparation claimed to be associated with CSPs. Reports of adverse events with CSPs shall be reviewed promptly and thoroughly by compounding supervisors to correct and prevent future occurrences. Compounding personnel are encouraged to participate in adverse event reporting and product defects programs of the FDA and USP.

QUALITY ASSURANCE (QA) PROGRAM

A provider of CSPs shall have in place a formal QA program intended to provide a mechanism for monitoring, evaluating, correcting, and improving the activities and processes described in this chapter. Emphasis in the QA program is placed on maintaining and improving the quality of systems and the provision of patient care. In addition, the QA program ensures that any plan aimed at correcting identified problems also includes appropriate follow-up to make certain that effective corrective actions were performed.¹¹

Characteristics of a QA program include the following:

1. Formalization in writing;
2. Consideration of all aspects of the preparations and dispensing of products as described in this chapter, including environmental testing and verification results;
3. Description of specific monitoring and evaluation activities;
4. Specification of how results are to be reported and evaluated;
5. Identification of appropriate follow-up mechanisms when action limits or thresholds are exceeded; and
6. Delineation of the individuals responsible for each aspect of the QA program.

In developing a specific plan, focus is on establishing objective, measurable indicators for monitoring activities and processes that are deemed high risk, high volume, or problem prone. In general, the selection of indicators and the effectiveness of the overall QA program is reassessed on an annual basis.

ABBREVIATIONS AND ACRONYMS

ACD	automated compounding device
ACPH	air changes per hour

ALARA	as low as reasonably achievable
ASHRAE	American Society of Heating, Refrigerating and Air-Conditioning Engineers
BI	biological indicator
BSC	biological safety cabinet
BUD	beyond-use date
CACI	compounding aseptic containment isolator
CAI	compounding aseptic isolator
CDC	Centers for Disease Control and Prevention
CETA	Controlled Environment Testing Association
cfu	colony-forming unit(s)
CSP	compounded sterile preparation
CSTD	closed-system vial transfer device
DCA	direct compounding area
ECV	endotoxin challenge vial
EU	Endotoxin Unit
FDA	Food and Drug Administration
HEPA	high efficiency particulate air
HICPAC	Healthcare Infection Control Practices Advisory Committee
HVAC	heating, ventilation, and air conditioning
IPA	isopropyl alcohol
ISO	International Organization for Standardization
LAFW	laminar airflow workbench
MDVs	multiple-dose vials
MMWR	Morbidity and Mortality Weekly Report
NIOSH	National Institute for Occupational Safety and Health
NIST	National Institute of Standards and Technology
PEC	primary engineering control
PET	positron emission tomography
PPE	personnel protective equipment
psi	pounds per square inch
QA	quality assurance
SOP	standard operating procedure
SVI	sterile vial for injection

TSA	trypticase soy agar
USP	United States Pharmacopeia

GLOSSARY

Ante-Area: ~~An ISO Class 8 (see [Table 1](#)) or better area where personnel hand hygiene and garbing procedures, staging of components, order entry, CSP labeling, and other high-particulate-generating activities are performed. It is also a transition area that (1) provides assurance that pressure relationships are constantly maintained so that air flows from clean to dirty areas and (2) reduces the need for the heating, ventilating, and air-conditioning (HVAC) control system to respond to large disturbances.¹²~~

Aseptic Processing: ~~(see *Microbiological Control and Monitoring of Aseptic Processing Environments* {1116}) A mode of processing pharmaceutical and medical products that involves the separate sterilization of the product and of the package (containers, closures, or packaging material for medical devices) and the transfer of the product into the container and its closure under at least ISO Class 5 (see [Table 1](#)) conditions.~~

Beyond-Use Date (BUD): ~~(see [Labeling](#) {7}• (CN 1, May 2018) and *Pharmaceutical Compounding—Nonsterile Preparations* {795}) For the purpose of this chapter, the date or time after which a CSP shall not be stored or transported. The date is determined from the date or time the preparation is compounded.~~

Biological Safety Cabinet (BSC): ~~A ventilated cabinet for CSPs, personnel, product, and environmental protection having an open front with inward airflow for personnel protection, downward high-efficiency particulate air (HEPA)-filtered laminar airflow for product protection, and HEPA-filtered exhausted air for environmental protection.~~

Buffer Area: ~~An area where the primary engineering control (PEC) is physically located. Activities that occur in this area include the preparation and staging of components and supplies used when compounding CSPs.~~

Clean Room: ~~(see *Microbiological Control and Monitoring of Aseptic Processing Environments* {1116} and also the definition of *Buffer Area*) A room in which the concentration of airborne particles is controlled to meet a specified airborne particulate cleanliness class. Microorganisms in the environment are monitored so that a microbial level for air, surface, and personnel gear are not exceeded for a specified cleanliness class.~~

Compounding Aseptic Containment Isolator (CACI): ~~A compounding aseptic isolator (CAI) designed to provide worker protection from exposure to undesirable levels of airborne drug throughout the compounding and~~

material transfer processes and to provide an aseptic environment for compounding sterile preparations. Air exchange with the surrounding environment should not occur unless the air is first passed through a microbial retentive filter (HEPA minimum) system capable of containing airborne concentrations of the physical size and state of the drug being compounded. Where volatile hazardous drugs are prepared, the exhaust air from the isolator should be appropriately removed by properly designed building ventilation.

Compounding Aseptic Isolator (CAI): A form of isolator specifically designed for compounding pharmaceutical ingredients or preparations. It is designed to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer processes. Air exchange into the isolator from the surrounding environment should not occur unless the air has first passed through a microbially retentive filter (HEPA minimum).¹³

Critical Area: An ISO Class 5 (see [Table 1](#)) environment.

Critical Site: A location that includes any component or fluid pathway surfaces (e.g., vial septa, injection ports, beakers) or openings (e.g., opened ampuls, needle hubs) exposed and at risk of direct contact with air (e.g., ambient room or HEPA filtered), moisture (e.g., oral and mucosal secretions), or touch contamination. Risk of microbial particulate contamination of the critical site increases with the size of the openings and exposure time.

Direct Compounding Area (DCA): A critical area within the ISO Class 5 (see [Table 1](#)) primary engineering control (PEC) where critical sites are exposed to unidirectional HEPA-filtered air, also known as first air.

Disinfectant: An agent that frees from infection, usually a chemical agent but sometimes a physical one, and that destroys disease-causing pathogens or other harmful microorganisms but may not kill bacterial and fungal spores. It refers to substances applied to inanimate objects.

First Air: The air exiting the HEPA filter in a unidirectional air stream that is essentially particle free.

Hazardous Drugs: Drugs are classified as hazardous if studies in animals or humans indicate that exposures to them have a potential for causing cancer, development or reproductive toxicity, or harm to organs. (See current NIOSH publication.)

Labeling: [see [Labeling \(7\)](#) (CN 1-May-2018) and 21 USC 321 (k) and (m)] A term that designates all labels and other written, printed, or graphic matter on an immediate container of an article or preparation or on, or in, any package or wrapper in which it is enclosed, except any outer shipping

container. The term "label" designates that part of the labeling on the immediate container.

Media-Fill Test: ~~(see *Microbiological Control and Monitoring of Aseptic Processing Environments* {1116})~~ A test used to qualify aseptic technique of compounding personnel or processes and to ensure that the processes used are able to produce sterile product without microbial contamination. During this test, a microbiological growth medium such as Soybean Casein Digest Medium is substituted for the actual drug product to simulate admixture compounding.[†] The issues to consider in the development of a media-fill test are media-fill procedures, media selection, fill volume, incubation, time and temperature, inspection of filled units, documentation, interpretation of results, and possible corrective actions required.

Multiple-Dose Container: ~~(see •• (CN-1-May-2018) {659})~~ A multiple-unit container for articles or preparations intended for parenteral administration only and usually containing antimicrobial preservatives. The beyond-use date (BUD) for an opened or entered (e.g., needle punctured) multiple-dose container with antimicrobial preservatives is 28 days (see *Antimicrobial Effectiveness Testing* {51}), unless otherwise specified by the manufacturer.

Negative Pressure Room: A room that is at a lower pressure than the adjacent spaces and, therefore, the net flow of air is *into* the room.^{†2}

Pharmacy Bulk Package: ~~(see {659})~~ A container of a sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for infusion or, through a sterile transfer device, for the filling of empty sterile syringes. The closure shall be penetrated only one time after constitution with a suitable sterile transfer device or dispensing set, which allows measured dispensing of the contents. The pharmacy bulk package is to be used only in a suitable work area such as a laminar flow hood (or an equivalent clean air compounding area).

Where a container is offered as a pharmacy bulk package, the label shall (a) state prominently "Pharmacy Bulk Package—Not for Direct Infusion," (b) contain or refer to information on proper techniques to help ensure safe use of the product, and (c) bear a statement limiting the time frame in which the container may be used once it has been entered, provided it is held under the labeled storage conditions.

Primary Engineering Control (PEC): A device or room that provides an ISO Class 5 (see [Table 1](#)) environment for the exposure of critical sites when compounding CSPs. Such devices include, but may not be limited to, laminar airflow workbenches (LAFWs), biological safety cabinets (BSCs), compounding aseptic isolators (CAIs), and compounding aseptic containment isolators (CACIs).

Preparation: ~~A preparation, or a CSP, that is a sterile drug or nutrient compounded in a licensed pharmacy or other healthcare-related facility pursuant to the order of a licensed prescriber; the article may or may not contain sterile products.~~

Product: ~~A commercially manufactured sterile drug or nutrient that has been evaluated for safety and efficacy by the FDA. Products are accompanied by full prescribing information, which is commonly known as the FDA-approved manufacturer's labeling or product package insert.~~

Positive Pressure Room: ~~A room that is at a higher pressure than the adjacent spaces and, therefore, the net airflow is *out of* the room.¹²~~

Single-Dose Container: ~~(see ~~§ 659~~ (CN 1-May-2018)) A single-dose container is a single-unit container for articles (see *General Notices* ~~§ 659~~ (CN 1-May-2018)) or preparations intended for parenteral administration only. It is intended for a single use. A single-dose container is labeled as such. Examples of single-dose containers include prefilled syringes, cartridges, fusion-sealed containers, and closure-sealed containers when so labeled.~~

Segregated Compounding Area: ~~A designated space, either a demarcated area or room, that is restricted to preparing low-risk level CSPs with 12-hour or less BUD. Such area shall contain a device that provides unidirectional airflow of ISO Class 5 (see [Table 1](#)) air quality for preparation of CSPs and shall be void of activities and materials that are extraneous to sterile compounding.~~

Sterilizing Grade Membranes: ~~Membranes that are documented to retain 100% of a culture of 10^7 microorganisms of a strain of *Brevundimonas (Pseudomonas) diminuta* per square centimeter of membrane surface under a pressure of not less than 30 psi (2.0 bar). Such filter membranes are nominally at 0.22- μm or 0.2- μm nominal pore size, depending on the manufacturer's practice.~~

Sterilization by Filtration: ~~Passage of a fluid or solution through a sterilizing grade membrane to produce a sterile effluent.~~

Terminal Sterilization: ~~The application of a lethal process (e.g., steam under pressure or autoclaving) to sealed containers for the purpose of achieving a predetermined sterility assurance level of usually less than 10^{-6} , or a probability of less than one in one million of a nonsterile unit.¹³~~

Unidirectional Flow (see footnote 3): ~~An airflow moving in a single direction in a robust and uniform manner and at sufficient speed to reproducibly sweep particles away from the critical processing or testing area.~~

APPENDICES

Appendix I. Principal Competencies, Conditions, Practices, and Quality Assurances That Are Required († “shall”) and Recommended (‡ “should”) in USP Chapter (797)

NOTE—This tabular appendix selectively abstracts and condenses the full text of (797) for rapid reference only. Compounding personnel are responsible for reading, understanding and complying with the full text and all official USP terminology, content, and conditions therein.

INTRODUCTION

‡ Chapter purpose is to prevent harm and death to patients treated with CSPs.

† Chapter pertains to preparation, storage, and transportation, but not administration, of CSPs.

† Personnel and facilities to which (797) applies; therefore, for whom and which it may be enforced by regulatory and accreditation authorities.

† Types of preparations designated to be CSPs according to their physical forms, and their sites and routes of administration to patients.

† Compounding personnel must be meticulously conscientious to preclude contact contamination of CSPs both within and outside ISO Class 5 areas.

ORGANIZATION

† All compounding personnel shall be responsible for understanding fundamental practices and precautions within USP (797), for developing and implementing appropriate procedures, and for continually evaluating these procedures and the quality of final CSPs to prevent harm.

RESPONSIBILITY OF COMPOUNDING PERSONNEL

† Practices and quality assurances required to prepare, store, and transport CSPs that are sterile, and acceptably accurate, pure, and stable.

CSP MICROBIAL CONTAMINATION RISK LEVELS

† Proper training and evaluation of personnel, proper cleansing and garbing of personnel, proper cleaning and disinfecting of compounding work environments, and proper maintenance and monitoring of controlled environmental locations (all of which are detailed in their respective sections).

Low-Risk Level CSPs

† Aseptic manipulations within an ISO Class 5 environment using three or fewer sterile products and entries into any container.

~~† In absence of passing sterility test, store not more than 48 hours at controlled room temperature, 14 days at cold temperature, and 45 days in solid frozen state at -25° to -10° or colder.~~

~~† Media-fill test at least annually by compounding personnel.~~

~~Low-Risk Level CSPs with 12-Hour or Less BUD~~

~~† Fully comply with all four specific criteria.~~

~~‡ Sinks should not be located adjacent to the ISO Class 5 primary engineering control.~~

~~‡ Sinks should be separated from the immediate area of the ISO Class 5 primary engineering control device.~~

~~Medium-Risk Level CSPs~~

~~† Aseptic manipulations within an ISO Class 5 environment using prolonged and complex mixing and transfer, more than three sterile products and entries into any container, and pooling ingredients from multiple sterile products to prepare multiple CSPs.~~

~~† In absence of passing sterility test, store not more than 30 hours at controlled room temperature, 9 days at cold temperature, and 45 days in solid frozen state at -25° to -10° or colder.~~

~~† Media-fill test at least annually by compounding personnel.~~

~~High-Risk Level CSPs~~

~~† Confirmed presence of nonsterile ingredients and devices, or confirmed or suspected exposure of sterile ingredients for more than one hour to air quality inferior to ISO Class 5 before final sterilization.~~

~~† Sterilization method verified to achieve sterility for the quantity and type of containers.~~

~~† Meet allowable limits for bacterial endotoxins.~~

~~† Maintain acceptable strength and purity of ingredients and integrity of containers after sterilization.~~

~~† In absence of passing sterility test, store not more than 24 hours at controlled room temperature, 3 days at cold temperature, and 45 days in solid frozen state at -25° to -10° or colder.~~

~~† Media-fill test at least semiannually by compounding personnel.~~

PERSONNEL TRAINING AND EVALUATION IN ASEPTIC MANIPULATIONS SKILLS

~~† Pass didactic, practical skill assessment and media-fill testing initially, followed by an annual assessment for a low- and medium-risk level compounding and semi-annual assessment for high-risk level compounding.~~

~~† Compounding personnel who fail written tests, or whose media-fill test~~

vials result in gross microbial colonization, shall be immediately reinstructed and re-evaluated by expert compounding personnel to ensure correction of all aseptic practice deficiencies.

IMMEDIATE-USE CSPs

† Fully comply with all six specified criteria.

SINGLE-DOSE AND MULTIPLE-DOSE CONTAINERS

† Beyond use date 28 days, unless specified otherwise by the manufacturer, for closure sealed multiple dose containers after initial opening or entry.

† Beyond use time of 6 hours, unless specified otherwise by the manufacturer, for closure sealed single dose containers in ISO Class 5 or cleaner air after initial opening or entry.

† Beyond use time of 1 hour for closure sealed single dose containers after being opened or entered in worse than ISO Class 5 air.

† Storage of opened single dose ampuls is not permitted.

HAZARDOUS DRUGS AS CSPs

† Appropriate personnel protective equipment.

† Appropriate primary engineering controls (BSCs and CACIs) are used for concurrent personnel protection and exposure of critical sites.

† Hazardous drugs shall be stored separately from other inventory in a manner to prevent contamination and personnel exposure.

† At least 0.01 inch water column negative pressure and 12 air changes per hour in non-cleanrooms in which CACIs are located.

† Hazardous drugs shall be handled with caution at all times using appropriate chemotherapy gloves during receiving, distribution, stocking, inventorying, preparing for administration, and disposal.

† Hazardous drugs shall be prepared in an ISO Class 5 environment with protective engineering controls in place, and following aseptic practices specified for the appropriate contamination risk levels.

† Access to drug preparation areas shall be limited to authorized personnel.

† A pressure indicator shall be installed that can readily monitor room pressurization, which is documented daily.

† Annual documentation of full training of personnel regarding storage, handling, and disposal of hazardous drugs.

† When used, a CSTD shall be used in an ISO Class 5 primary engineering control device.

† At least 0.01 inch water column negative pressure is required for compounding of hazardous drugs.

~~‡ Negative-pressure buffer area is not required for low-volume compounding operations when CSTD is used in BSC or CACI.~~

~~‡ Compounding personnel of reproductive capability shall confirm in writing that they understand the risks of handling hazardous drugs.~~

~~‡ Disposal of all hazardous drug wastes shall comply with all applicable federal and state regulations.~~

~~‡ Total external exhaust of primary engineering controls.~~

~~‡ Assay of surface wipe samples every 6 months.~~

~~RADIOPHARMACEUTICALS AS CSPs~~

~~‡ Positron Emission Tomography is according to USP chapter <823>.~~

~~‡ Appropriate primary engineering controls and radioactivity containment and shielding.~~

~~‡ Radiopharmaceuticals compounded from sterile components, in closed sterile containers, with volume of 100 mL or less for a single-dose injection or not more than 30 mL taken from a multiple-dose container shall be designated as and conform to the standards for low-risk level CSPs.~~

~~‡ Radiopharmaceutical vials, designed for multi-use, compounded with technetium-99m, exposed to ISO Class 5 environment and punctured by needles with no direct contact contamination may be used up to the time indicated by manufacturers' recommendations.~~

~~‡ Location of primary engineering controls permitted in ISO Class 8 controlled environment.~~

~~‡ Technetium-99m/Molybdenum-99 generators used according to manufacturer, state, and federal requirements.~~

~~‡ Radiopharmaceuticals prepared as low-risk level CSPs with 12-hour or less BUD shall be prepared in a segregated compounding area.~~

~~‡ Materials and garb exposed in patient-care and treatment area shall not cross a line of demarcation into the segregated compounding area.~~

~~‡ Technetium-99m/Molybdenum-99 generators must be eluted in ISO Class 8 conditions.~~

~~‡ Segregated compounding area will be designated with a line of demarcation.~~

~~‡ Storage and transport of properly shielded vials of radiopharmaceutical CSPs may occur in a limited access ambient environment without a specific ISO class designation.~~

~~ALLERGEN EXTRACTS AS CSPs~~

~~‡ Allergen extracts as CSPs are not subject to the personnel, environmental, and storage requirements for all CSP Microbial Contamination Risk Levels~~

when certain criteria are met.

VERIFICATION OF COMPOUNDING ACCURACY AND STERILITY

† Review labels and document correct measurements, aseptic manipulations, and sterilization procedures to confirm correct identity, purity, and strength of ingredients in, and sterility of, CSPs.

‡ Assay finished CSPs to confirm correct identity and, or, strength of ingredients.

‡ Sterility test finished CSPs.

Sterilization Methods

† Verify that methods achieve sterility while maintaining appropriate strength, purity, quality, and packaging integrity.

‡ Prove effectiveness by USP chapter (71), equivalent, or superior sterility testing.

Sterilization of High-Risk Level CSPs by Filtration

† Nominal 0.2- μ m pore size sterile membranes that are chemically and physically compatible with the CSP.

† Complete rapidly without filter replacement.

† Subject filter to manufacturer's recommended integrity test (e.g., bubble point test) after filtering CSPs.

Sterilization of High-Risk Level CSPs by Steam

† Test to verify the mass of containers to be sterilized will be sterile after the selected exposure duration in the particular autoclave.

† Ensure live steam contacts all ingredients and surfaces to be sterilized.

† Pass solutions through a 1.2- μ m or smaller nominal pore size filter into final containers to remove particulates before sterilization.

† Heated filtered air shall be evenly distributed throughout the chamber by a blower device.

† Dry heat shall only be used for those materials that cannot be sterilized by steam, when the moisture would either damage or be impermeable to the materials.

† Sufficient space shall be left between materials to allow for good circulation of the hot air.

† The description of dry heat sterilization conditions and duration for specific CSPs shall be included in written documentation in the compounding facility. The effectiveness of dry heat sterilization shall be verified using appropriate biological indicators and other confirmation.

‡ The oven should be equipped with a system for controlling temperature and exposure period.

~~Depyrogenation by Dry Heat~~

~~† Dry heat depyrogenation shall be used to render glassware or containers, such as vials free from pyrogens as well as viable microbes.~~

~~† The description of the dry heat depyrogenation cycle and duration for specific load items shall be included in written documentation in the compounding facility.~~

~~† The effectiveness of the dry heat depyrogenation cycle shall be verified using endotoxin challenge vials (ECVs).~~

~~‡ The bacterial endotoxin test should be performed on the ECVs to verify the cycle is capable of achieving a 3-log reduction in endotoxin.~~

~~ENVIRONMENTAL QUALITY AND CONTROL~~

~~Exposure of Critical Sites~~

~~† ISO Class 5 or better air.~~

~~† Preclude direct contact (e.g., touch and secretions) contamination.~~

~~ISO Class 5 Air Sources, Buffer Areas, and Ante-Areas~~

~~† A buffer area is an area that provides at least ISO Class 7 air quality.~~

~~† New representations of facility layouts.~~

~~† Each compounding facility shall ensure that each source of ISO Class 5 environment for exposure of critical sites and sterilization by filtration is properly located, operated, maintained, monitored, and verified.~~

~~† Devices (e.g., computers and printers) and objects (e.g., carts and cabinets) can be placed in buffer areas and shall be verified by testing or monitoring.~~

~~Viable and Nonviable Environmental Sampling (ES) Testing~~

~~† Environmental sampling shall occur as part a comprehensive quality management program and shall occur minimally when several conditions exist.~~

~~‡ The ES program should provide information to staff and leadership to demonstrate that the engineering controls are maintaining an environment within the compounding area that consistently maintains acceptably low viable and nonviable particle levels.~~

~~Environmental Nonviable Particle Testing Program~~

~~† Certification and testing of primary (LAFWs, BSCs, CAIs and CACIs) and secondary engineering controls (buffer and ante areas) shall be performed by a qualified individual no less than every six months and whenever the device or room is relocated, altered, or major service to the facility is performed. Certification procedures such as those outlined in the CETA Certification Guide for Sterile Compounding Facilities (CAG-003-2006) shall~~

be used.

Total Particle Counts

† Certification that each ISO classified area (e.g., ISO Class 5, 7 and 8) is within established guidelines shall be performed no less than every 6 months and whenever the LAFW, BSC, CAI, or CACI is relocated or the physical structure of the buffer room or ante-area has been altered.

† Testing shall be performed by qualified operators using current, state-of-the-art electronic equipment with results meeting ISO Class 5, 7, or 8 depending on the requirements of the area.

† All certification records shall be maintained and reviewed by supervising personnel or other designated employee to ensure that the controlled environments comply with the proper air cleanliness, room pressures, and air changes per hour.

Pressure Differential Monitoring

† A pressure gauge or velocity meter shall be installed to monitor the pressure differential or airflow between the buffer area and ante-area, and the ante-area and the general environment outside the compounding area.

† The results shall be reviewed and documented on a log at least every work shift (minimum frequency shall be at least daily) or by a continuous recording device.

† The pressure between the ISO Class 7 and general pharmacy area shall not be less than 5 Pa (0.02 inch water column (w.c.)).

† In facilities where low- and medium-risk level CSPs are prepared, differential airflow shall maintain a minimum velocity of 0.2 meter/second (40 fpm) between buffer area and ante-area.

Environmental Viable Airborne Particle Testing Program—Sampling Plan

† An appropriate environmental sampling plan shall be developed for airborne viable particles based on a risk assessment of compounding activities performed.

† Selected sampling sites shall include locations within each ISO Class 5 environment and in the ISO Class 7 and 8 areas, and the segregated compounding areas at greatest risk of contamination (e.g., work areas near the ISO Class 5 environment, counters near doors, pass-through boxes).

† The plan shall include sample location, method of collection, frequency of sampling, volume of air sampled, and time of day as related to activity in the compounding area and action levels.

‡ It is recommended that compounding personnel refer to USP Chapter *Microbiological Control and Monitoring of Aseptic Processing Environments* (1116) and the CDC Guidelines for Environmental Infection Control in

Healthcare Facilities-2003 for more information.

Growth Media

† A general microbiological growth medium such as Soybean-Casein Digest Medium (also known as trypticase soy broth (TSB) or agar (TSA)) shall be used to support the growth of bacteria.

† Malt extract agar (MEA) or some other media that supports the growth of fungi shall be used in high-risk level compounding environments.

† Media used for surface sampling shall be supplemented with additives to neutralize the effects of disinfecting agents (e.g., TSA with lecithin and polysorbate 80).

Viable Air Sampling

† Evaluation of airborne microorganisms using volumetric collection methods in the controlled air environments shall be performed by properly trained individuals for all compounding risk levels.

† Impaction shall be the preferred method of volumetric air sampling.

† For low-, medium-, and high-risk level compounding, air sampling shall be performed at locations that are prone to contamination during compounding activities and during other activities like staging, labeling, gowning, and cleaning.

† Locations shall include zones of air backwash turbulence within laminar airflow workbench and other areas where air backwash turbulence may enter the compounding area.

† For low-risk level CSPs with 12-hour or less BUD, air sampling shall be performed at locations inside the ISO Class 5 environment and other areas that are in close proximity to the ISO class 5 environment, during the certification of the primary engineering control.

‡ Consideration should be given to the overall effect the chosen sampling method will have on the unidirectional airflow within a compounding environment.

Air Sampling Devices

† The instructions in the manufacturer's user manual for verification and use of electric air samplers that actively collect volumes of air for evaluation shall be followed.

† A sufficient volume of air (400-1000 liters) shall be tested at each location in order to maximize sensitivity.

‡ It is recommended that compounding personnel also refer to USP Chapter <1116>, which can provide more information on the use of volumetric air samplers and volume of air that should be sampled to detect environmental bioburden excursions.

Air Sampling Frequency and Process

† Air sampling shall be performed at least semiannually (i.e. every 6 months), as part of the re-certification of facilities and equipment for area where primary engineering controls are located.

† A sufficient volume of air shall be sampled and the manufacturer's guidelines for use of the electronic air sampling equipment followed.

‡ Any facility construction or equipment servicing may require the need to perform air sampling during these events.

Incubation Period

† The microbial growth media plates used to collect environmental sampling are recovered, covers secured (e.g., taped), inverted, and incubated at a temperature and for a time period conducive to multiplication of microorganisms.

† The number of discrete colonies of microorganisms shall be counted and reported as colony-forming units (cfu) and documented on an environmental monitoring form. Counts from air monitoring need to be transformed into cfu/cubic meter of air and evaluated for adverse trends.

‡ TSA should be incubated at $35^{\circ} \pm 2^{\circ}$ for 2–3 days.

‡ MEA or other suitable fungal media should be incubated at $28^{\circ} \pm 2^{\circ}$ for 5–7 days.

Action Levels, Documentation and Data Evaluation

† Sampling data shall be collected and reviewed on a periodic basis as a means of evaluating the overall control of the compounding environment.

† Competent microbiology personnel shall be consulted if an environmental sampling consistently shows elevated levels of microbial growth.

† An investigation into the source of the environmental contamination shall be conducted.

‡ Any cfu count that exceeds its respective action level should prompt a re-evaluation of the adequacy of personnel work practices, cleaning procedures, operational procedures, and air filtration efficiency within the aseptic compounding location.

‡ Table titled, Recommended Action Levels for Microbial Contamination should only be used as a guideline

Facility Design and Environmental Controls

† Compounding facilities are physically designed and environmentally controlled to minimize airborne contamination from contacting critical sites.

† Compounding facilities shall provide a comfortable and well-lighted working environment, which typically includes a temperature of 20° or cooler to maintain comfortable conditions for compounding personnel when

attired in the required aseptic compounding garb.
† Primary engineering controls provide unidirectional (i.e., laminar) HEPA air at a velocity sufficient to prevent airborne particles from contacting critical sites.
† In situ air pattern analysis via smoke studies shall be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions.
† Policies and procedures for maintaining and working within the primary engineering control area shall be written and followed. The policies and procedures will be determined by the scope and risk levels of the aseptic compounding activities used during the preparation of the CSPs.
† The principles of HEPA-filtered unidirectional airflow in the work environment shall be understood and practiced in the compounding process in order to achieve the desired environmental conditions.
† Clean rooms for nonhazardous and nonradioactive CSPs are supplied with HEPA that enters from ceilings with return vents low on walls, and that provides not less than 30 air changes per hour.
† Buffer areas maintain 0.02- to 0.05-inch water column positive pressure, and do not contain sinks or drains.
† Air velocity from buffer rooms or zones to ante-areas is at least 40 feet/minute.
† The primary engineering controls shall be placed within a buffer area in such a manner as to avoid conditions that could adversely affect their operation.
† The primary engineering controls shall be placed out of the traffic flow and in a manner to avoid disruption from the HVAC system and room cross-drafts.
† HEPA-filtered supply air shall be introduced at the ceiling.
† All HEPA filters shall be efficiency tested using the most penetrating particle size and shall be leak tested at the factory and then leak tested again in situ after installation.
† Activities and tasks carried out within the buffer area shall be limited to only those necessary when working within a controlled environment.
† Only the furniture, equipment, supplies, and other material required for the compounding activities to be performed shall be brought into the room.
† Surfaces and essential furniture in buffer rooms or zones and clean rooms shall be nonporous, smooth, nonshedding, impermeable, cleanable, and resistant to disinfectants.
† The surfaces of ceilings, walls, floors, fixtures, shelving, counters, and

cabinets in the buffer area shall be smooth, impervious, free from cracks and crevices, and nonshedding, thereby promoting cleanability, and minimizing spaces in which microorganisms and other contaminants may accumulate.

† The surfaces shall be resistant to damage by disinfectant agents.

† Junctures of ceilings to walls shall be coved or caulked to avoid cracks and crevices where dirt can accumulate.

† Ceiling tiles shall be caulked around each perimeter to seal them to the support frame.

† The exterior lens surface of ceiling lighting fixtures shall be smooth, mounted flush, and sealed.

† Any other penetrations through the ceiling or walls shall be sealed.

† The buffer area shall not contain sources of water (sinks) or floor drains. Work surfaces shall be constructed of smooth, impervious materials, such as stainless steel or molded plastic, so that they are easily cleaned and disinfected.

† Carts shall be of stainless steel wire, nonporous plastic, or sheet metal construction with good quality, cleanable casters to promote mobility.

† Storage shelving, counters, and cabinets shall be smooth, impervious, free from cracks and crevices, nonshedding, cleanable, and disinfectable.

† Their number, design, and manner of installation the itmes above shall promote effective cleaning and disinfection.

‡ If ceilings consist of inlaid panels, the panels should be impregnated with a polymer to render them impervious and hydrophobic.

‡ Dust-collecting overhangs, such as ceiling utility pipes, or ledges, such as windowsills, should be avoided.

‡ Air returns should be mounted low on the wall creating a general top-down dilution of room air with HEPA-filtered make-up air.

Placement of Primary Engineering Controls Within ISO Class 7 Buffer Areas

† Primary engineering controls for nonhazardous and nonradioactive CSPs are located in buffer areas, except for CAIs that are proven to maintain ISO Class 5 air when particle counts are sampled 6 to 12 inches upstream of critical site exposure areas during performance of normal inward and outward transfer of materials, and compounding manipulations when such CAIs are located in air quality worse than ISO Class 7.

† Presterilization procedures for high-risk level CSPs, such as weighing and mixing, shall be completed in no worse than an ISO Class 8 environment.

† Primary engineering controls shall be located out of traffic patterns and away from room air currents that could disrupt the intended airflow patterns.

† When isolators are used for sterile compounding, the recovery time to achieve ISO Class 5 air quality shall be documented and internal procedures developed to ensure that adequate recovery time is allowed after material transfer before and during compounding operations.

† When compounding activities require the manipulation of a patient's blood-derived or other biological material (e.g., radiolabeling a patient's or a donor's white blood cells), the manipulations shall be clearly separated from routine material-handling procedures and equipment used in CSP preparation activities, and they shall be controlled by specific standard operating procedures in order to avoid any cross-contamination.

† Food, drinks, and items exposed in patient care areas, and unpacking of bulk supplies and personnel cleansing and garbing are prohibited from buffer areas or rooms.

† Demarcation designation between buffer areas or rooms and ante-areas.

† Antiseptic hand cleansing and sterile gloves in buffer areas or rooms.

‡ Packaged compounding supplies and components, such as needles, syringes, tubing sets, and small- and large-volume parenterals, should be uncartoned and wiped down with a disinfectant that does not leave a residue (e.g., sterile 70% IPA) when possible in an ante-area, of ISO Class 8 air quality, before being passed into the buffer areas.

~~Cleaning and Disinfecting the Sterile Compounding Areas~~

† Trained personnel write detailed procedures including cleansers, disinfectants, and non-shedding wipe and mop materials.

† Cleaning and disinfecting surfaces in the LAFWs, BSCs, CAIs, and CACIs shall be cleaned and disinfected frequently, including at the beginning of each work shift, before each batch preparation is started, every 30 minutes during continuous compounding periods of individual CSPs, when there are spills, and when surface contamination is known or suspected from procedural breaches.

† Trained compounding personnel are responsible for developing, implementing, and practicing the procedures for cleaning and disinfecting the DCAs written in the SOPs.

† Cleaning and disinfecting shall occur before compounding is performed. Items shall be removed from all areas to be cleaned, and surfaces shall be cleaned by removing loose material and residue from spills, e.g., water-soluble solid residues are removed with Sterile Water (for Injection or Irrigation) and low-shedding wipes. This shall be followed by wiping with a residue-free disinfecting agent, such as sterile 70% IPA, which is allowed to dry before compounding begins.

† Work surfaces in ISO Class 7 and 8 areas and segregated compounding areas are cleaned at least daily.

~~† Dust and debris shall be removed when necessary from storage sites for compounding ingredients and supplies, using a method that does not degrade the ISO Class 7 or 8 air quality.~~

~~† Floors in ISO Class 7 and 8 areas are cleaned daily when no compounding occurs.~~

~~† IPA (70% isopropyl alcohol) remains on surfaces to be disinfected for at least 30 seconds before such surfaces are used to prepare CSPs.~~

~~† Emptied shelving, walls, and ceilings in ante-areas are cleaned and disinfected at least monthly.~~

~~† Mopping shall be performed by trained personnel using approved agents and procedures described in the written SOPs.~~

~~† Cleaning and disinfecting agents, their schedules of use and methods of application shall be in accordance with written SOPs and followed by custodial and/or compounding personnel.~~

~~† All cleaning materials, such as wipers, sponges, and mops, shall be nonshedding, preferably composed of synthetic micro fibers, and dedicated to use in the buffer area, or ante-area, and segregated compounding areas and shall not be removed from these areas except for disposal.~~

~~† If cleaning materials are reused (e.g., mops), procedures shall be developed (based on manufacturer recommendations) that ensure that the effectiveness of the cleaning device is maintained and repeated use does not add to the bioburden of the area being cleaned.~~

~~† Supplies and equipment removed from shipping cartons shall be wiped with a suitable disinfecting agent (e.g., sterile 70% IPA) delivered from a spray bottle or other suitable delivery method.~~

~~† After the disinfectant is sprayed or wiped on a surface to be disinfected, the disinfectant shall be allowed to dry, and during this time the item shall not be used for compounding purposes.~~

~~† Sterile 70% IPA wetted gauze pads or other particle-generating material shall not be used to disinfect the sterile entry points of packages and devices.~~

~~Personnel Cleansing and Garbing~~

~~† Personnel shall also be thoroughly competent and highly motivated to perform flawless aseptic manipulations with ingredients, devices, and components of CSPs.~~

~~† Personnel with rashes, sunburn, weeping sores, conjunctivitis, active respiratory infection, and cosmetics are prohibited from preparing CSPs.~~

~~† Compounding personnel shall remove personal outer garments; cosmetics; artificial nails; hand, wrist, and body jewelry that can interfere with the fit of gowns and gloves; and visible body piercing above the neck.~~

† Order of compounding garb and cleansing in ante-area: shoes or shoe covers, head and facial hair covers, face mask, fingernail cleansing, hand and forearm washing and drying; non-shedding gown.

† Order of cleansing and gloving in buffer room or area: hand cleansing with a persistently active alcohol-based product with persistent activity; allow hands to dry; don sterile gloves.

† Routinely disinfect gloves with sterile 70% IPA after contacting nonsterile objects.

† Inspect gloves for holes and replace when breaches are detected.

† Personnel repeat proper procedures after they are exposed to direct contact contamination or worse than ISO Class 8 air.

† These requirements are exempted only for immediate-use CSPs and CAIs for which manufacturers provide written documentation based on validated testing that such personnel practices are not required to maintain sterility in CSPs.

Personnel Training and Competency Evaluation of Garbing, Aseptic Work Practices and Cleaning/Disinfection Procedures

† Personnel who prepare CSPs shall be trained conscientiously and skillfully by expert personnel, multi-media instructional sources, and professional publications in the theoretical principles and practical skills of garbing procedures, aseptic work practices, achieving and maintaining ISO Class 5 environmental conditions, and cleaning and disinfection procedures.

† This training shall be completed and documented before any compounding personnel begin to prepare CSPs.

† Compounding personnel shall complete didactic training, pass written competence assessments, undergo skill assessment using observational audit tools, and media-fill testing.

† Media-fill testing of aseptic work skills shall be performed initially before beginning to prepare CSPs and at least annually thereafter for low- and medium-risk level compounding; and semiannually for high-risk level compounding.

† Compounding personnel who fail written tests, observational audits, or whose media-fill test vials have one or more units showing visible microbial contamination, shall be reinstructed and re-evaluated by expert compounding personnel to ensure correction of all aseptic work practice deficiencies.

† Compounding personnel shall pass all evaluations prior to resuming compounding of sterile preparations.

† Compounding personnel must demonstrate proficiency of proper hand hygiene, garbing, and consistent cleaning procedures in addition to didactic

evaluation and aseptic media fill.

† Cleaning and disinfecting procedures performed by other support personnel shall be thoroughly trained in proper hand hygiene, and garbing, cleaning, and disinfection procedures by a qualified aseptic compounding expert.

† Support personnel shall routinely undergo performance evaluation of proper hand hygiene, garbing, and all applicable cleaning and disinfecting procedures conducted by a qualified aseptic compounding expert.

Competency Evaluation of Garbing and Aseptic Work Practices

† Compounding personnel shall be evaluated initially prior to beginning compounding CSPs and whenever an aseptic media fill is performed using a Sample Form for Assessing Hand Hygiene and Garbing Related Practices of Compounding Personnel and the personnel glove fingertip sampling procedures.

Aseptic Work Practice Assessment and Evaluation via Personnel Glove Fingertip Sampling

† Monitoring of compounding personnel glove fingertips shall be performed for all CSP risk level compounding.

† Glove fingertip sampling shall be used to evaluate the competency of personnel in performing hand hygiene and garbing procedures in addition to educating compounding personnel on proper work practices.

† All personnel shall demonstrate competency in proper hand hygiene and garbing procedures in addition to aseptic work practices.

† Sterile contact agar plates shall be used to sample the gloved fingertips of compounding personnel after garbing to assess garbing competency and after completing the media-fill preparation.

† Gloves shall not be disinfected with sterile 70% IPA immediately prior to sampling.

Garbing and Gloving Competency Evaluation

† Compounding personnel shall be visually observed during the process of performing hand hygiene and garbing procedures.

† The visual observation shall be documented on a Sample Form for Assessing Hand Hygiene and Garbing Related Practices of Compounding Personnel and maintained to provide a permanent record of and long-term assessment of personnel competency.

Gloved Fingertip Sampling

† Immediately after the compounder completes the hand hygiene and garbing procedure, the evaluator shall collect a gloved fingertip and thumb sample from both hands of the compounder onto appropriate agar plates by

lightly pressing each finger tip into the agar.

† The plates shall be incubated for the appropriate incubation period and at the appropriate temperature.

† All employees shall successfully complete an initial competency evaluation and gloved fingertip/thumb sampling procedure (0 cfu) no less than three times before initially being allowed to compound CSPs for human use.

† After completing the initial gowning and gloving competency evaluation, re-evaluation of all compounding personnel shall occur at least annually for low- and medium-risk level CSPs and semiannually for high-risk level CSPs before being allowed to continue compounding CSPs.

† Gloves shall not be disinfected with sterile 70% IPA prior to testing.

† The sampled gloves shall be immediately discarded and proper hand hygiene performed after sampling. The nutrient agar plates shall be incubated as stated below.

† The cfu action level for gloved hands shall be based on the total number of cfu on both gloves and not per hand.

‡ Results should be reported separately as number of cfu per employee per hand (left hand, right hand).

Incubation Period

† At the end of the designated sampling period, the agar plates are recovered, covers secured, inverted and incubated at a temperature and for a time period conducive to multiplication of microorganisms. Trypticase soy agar (TSA) with lecithin and polysorbate 80 shall be incubated at $35^{\circ} \pm 2^{\circ}$ for 2-3 days.

Aseptic Manipulation Competency Evaluation

† All compounding personnel shall have their aseptic technique and related practice competency evaluated initially during the media-fill test procedure and subsequent annual or semiannual media-fill test procedures on the Sample Form for Assessing Aseptic Technique and Related Practices of Compounding Personnel.

Media-Fill Test Procedure

† The skill of personnel to aseptically prepare CSPs shall be evaluated using sterile fluid bacterial culture media-fill verification.

† Media-filled vials shall be incubated within a range of $35^{\circ} \pm 2^{\circ}$ for 14 days.

Surface Cleaning and Disinfection Sampling and Assessment

† Surface sampling shall be performed in all ISO classified areas on a periodic basis and can be accomplished using contact plates and/or swabs and shall be done at the conclusion of compounding.

† Locations to be sampled shall be defined in a sample plan or on a form.

Cleaning and Disinfecting Competency Evaluation

† Compounding personnel and other personnel responsible for cleaning shall be visually observed during the process of performing cleaning and disinfecting procedures during initial personnel training on cleaning procedures, changes in cleaning staff and at the completion of any Media-Fill Test Procedure.

† Visual observation shall be documented on a Sample Form for Assessing Cleaning and Disinfection Procedures and maintained to provide a permanent record of, and long-term assessment of, personnel competency.

Surface Collection Methods

† Immediately after sampling a surface with the contact plate, the sampled area shall be thoroughly wiped with a non-shedding wipe soaked in sterile 70% IPA.

‡ Results should be reported as cfu per unit of surface area.

Action Levels, Documentation, and Data Evaluation

† Environmental sampling data shall be collected and reviewed on a routine basis as a means of evaluating the overall control of the compounding environment.

† If an activity consistently shows elevated levels of microbial growth, competent microbiology personnel shall be consulted.

† An investigation into the source of the contamination shall be conducted.

† When gloved fingertip sample results exceeds action levels after proper incubation, a review of hand hygiene and garbing procedures as well as glove and surface disinfection procedures and work practices shall be performed and documented.

‡ Any cfu count that exceeds its respective action level should prompt a re-evaluation of the adequacy of personnel work practices, cleaning procedures, operational procedures, and air filtration efficiency within the aseptic compounding location.

SUGGESTED STANDARD OPERATING PROCEDURES

† All facilities are required to have these, and they must include at least the items enumerated in this section.

FINISHED PREPARATION RELEASE CHECKS AND TESTS

Inspection of Solution Dosage Forms and Review of Compounding Procedures

† Review procedures and documents to ensure sterility, purity, correct identities and amounts of ingredients, and stability.

† Visually inspect for abnormal particulate matter and color, and intact containers and seals.

Sterility Testing

† High-risk level CSPs prepared in batches of more than 25 identical containers, or exposed longer than 12 hours at 2° to 8°, and 6 hours at warmer than 8° before being sterilized.

Bacterial Endotoxin (Pyrogen) Testing

† High-risk level CSPs, excluding those for inhalation and ophthalmic administration, prepared in batches of more than 25 identical containers, or exposed longer than 12 hours at 2° to 8°, and 6 hours at warmer than 8°, before being sterilized.

Identity and Strength Verification of Ingredients

† Written procedures to verify correct identity, quality, amounts, and purities of ingredients used in CSPs.

† Written procedures to ensure labels of CSPs contain correct names and amounts or concentrations of ingredients, total volumes, beyond-use dates, storage conditions, and route(s) of administration.

STORAGE AND BEYOND-USE DATING

Determining Beyond-Use Dates

† Use the general criteria in USP <795> in the absence of direct stability-indicating assays or authoritative literature that supports longer durations.

MAINTAINING STERILITY, PURITY, AND STABILITY OF DISPENSED AND DISTRIBUTED CSPs

† Written procedures for proper packaging, storage, and transportation conditions to maintain sterility, quality, purity, and strength of CSPs.

Redispensed CSPs

† When sterility, and acceptable purity, strength, and quality can be ensured.

† Assignment of sterility storage times and stability beyond-use dates that occur later than those of originally dispensed CSPs must be based on results of sterility testing and quantitative assay of ingredients.

Packaging and Transporting CSPs

† Packaging maintains physical integrity, sterility, stability, and purity of CSPs.

† Modes of transport that maintain appropriate temperatures and prevent damage to CSPs.

PATIENT OR CAREGIVER TRAINING

‡ Multiple-component formal training program to ensure patients and caregivers understand the proper storage, handling, use, and disposal of CSPs.

PATIENT MONITORING AND ADVERSE EVENTS REPORTING

‡ Written standard procedures describe means for patients to ask questions and report concerns and adverse events with CSPs, and for compounding supervisors to correct and prevent future problems.

‡ Adverse events and defects with CSPs reported to FDA's MedWatch and USP's MEDMARX programs.

GLOSSARY

‡ Twenty-eight terms are defined and integral to complying with USP (797).

Appendix II. Common Disinfectants Used in Health Care for Inanimate Surfaces and Noncritical Devices, and Their Microbial Activity and Properties*

Chemical Category of Disinfectant

	Isopropyl alcohol	Accelerated hydrogen peroxide	Quaternary Ammonium (e.g., dodecyl dimethyl ammonium chloride)	Phenolics	Chlorine (e.g., sodium hypochlorite)
	60–95%	0.5%^a	0.4–1.6% aq	0.4–1.6% aq	100–5000 ppm
Bacteria	+	+	+	+	+
Lipophilic viruses	+	+	+	+	+
Hydrophilic viruses	±	+	±	±	+
M.tuberculosis	+	+	±	+	+
Mycotic agents (fungi)	+	+	+	+	+
Bacterial Spores	–	–	–	–	+
Shelf life >1 week	+	+	+	+	+

Chemical Category of Disinfectant

	Isopropyl alcohol	Accelerated hydrogen peroxide	Quaternary Ammonium (e.g., dodecyl dimethyl ammonium chloride)	Phenolics	Chlorine (e.g., sodium hypochlorite)
	60-95%	0.5%^a	0.4-1.6% aq	0.4-1.6% aq	100-5000 ppm
Corrosive or deleterious effects	±	-	-	-	±
Non-evaporable residue	-	-	+	+	-
Inactivated by organic matter	+	±	+	±	+
Skin irritant	±	-	+	+	+
Eye irritant	+	-	+	+	+
Respiratory irritant	-	-	-	-	+
Systemic toxicity	+	-	+	+	+

and symbols: aq = diluted with water; ppm = parts per million; + = yes; - = no; ± = variable results

World Health Organization, Laboratory Bio-Safety Manual 1983 and Rutala WA, "Antisepsis, disinfection and sterilization in health care-related institutions," *Manual of Clinical Microbiology*, American Society for Microbiology, Washington, DC, 2003, pp 103-110.

The most common microorganism (i.e., bacteria) occurs with a contact time of ≤1 minute; inactivation times (e.g., 5-10 minutes for 5,000 ppm chlorine solution against *C. difficile* spores). Reference: Perez J, et al. "Efficacy of selected oxidizing microbicides against the spores of *Clostridium difficile*: Relevance to environmental disinfection." *Journal of Infection Control*, August 2005, pages 320-325.

Accelerated hydrogen peroxide is a new generation of hydrogen peroxide-based germicides in which the potency and speed of action have been enhanced and accelerated through the use of appropriate acids and detergents.

Appendix III. Sample Form for Assessing Hand Hygiene and Garbing Related Practices of Compounding Personnel

Printed name and position/title of person assessed:	
Name of facility or location:	
<p>Hand Hygiene and Garbing Practices: The qualified evaluator will check each space for which the person being assessed has acceptably completed the described activity, prints N/A if the activity is not applicable to the assessment session or N/O if the activity was not observed.*</p>	
	Presents in a clean appropriate attire and manner.
	Wears no cosmetics or jewelry (watches, rings, earrings, etc. piercing jewelry included) upon entry into ante-areas.
	Brings no food or drinks into or stored in the ante-areas or buffer areas.
	Is aware of the line of demarcation separating clean and dirty sides and observes required activities.
	Dons shoe covers or designated clean area shoes one at a time, placing the covered or designated shoe on clean side of the line of demarcation, as appropriate.
	Dons beard cover if necessary.
	Dons head cover assuring that all hair is covered.
	Dons face mask to cover bridge of nose down to include chin.
	Performs hand hygiene procedure by wetting hands and forearms and washing using soap and warm water for at least 30 seconds.
	Dries hands and forearms using lint-free towel or hand dryer.
	Selects the appropriate sized gown examining for any holes, tears, or other defects.
	Dons gown and ensures full closure.
	Disinfects hands again using a waterless alcohol-based surgical hand scrub with persistent activity and allows hands to dry

	thoroughly before donning sterile gloves.
	Dons appropriate sized sterile gloves ensuring that there is a tight fit with no excess glove material at the fingertips.
	Examines gloves ensuring that there are no defects, holes, or tears.
	While engaging in sterile compounding activities, routinely disinfects gloves with sterile 70% IPA prior to work in the direct compounding area (DCA) and after touching items or surfaces that may contaminate gloves.
	Removes PPE on the clean side of the ante-area.
	Removes gloves and performs hand hygiene.
	Removes gown and discards it, or hangs it on hook if it is to be reused within the same work day.
	Removes and discards mask, head cover, and beard cover (if used).
	Removes shoe covers or shoes one at a time, ensuring that uncovered foot is placed on the dirty side of the line of demarcation and performs hand hygiene again. (Removes and discards shoe covers every time the compounding area is exited).

~~*The person assessed is immediately informed of all unacceptable activities (i.e., spaces lacking check marks, N/A, or N/O) and shown and informed of specific corrections.~~

Signature of Person Assessed	Printed Name	Date
Signature of Qualified Evaluator	Printed Name	Date

Appendix IV. Sample Form for Assessing Aseptic Technique and Related Practices of Compounding Personnel

Printed name and position/title of person assessed:	
Name of facility or location:	
<p>Aseptic Technique, Safety, and Quality Assurance Practices: The qualified evaluator checks each space for which the person being assessed has acceptably completed the described activity, prints N/A if the activity is not applicable to the assessment session or N/O if the activity was not observed.*</p>	
	Completes the Hand Hygiene and Garbing Competency Assessment Form.
	Performs proper hand hygiene, garbing, and gloving procedures according to SOPs.
	Disinfects ISO Class 5 device surfaces with an appropriate agent.
	Disinfects components/vials with an appropriate agent prior to placing into ISO Class 5 work area.
	Introduces only essential materials in a proper arrangement in the ISO Class 5 work area.
	Does not interrupt, impede, or divert flow of first-air to critical sites.
	Ensures syringes, needles, and tubing remain in their individual packaging and are only opened in ISO Class 5 work area.
	Performs manipulations only in the appropriate DCA of the ISO Class 5 device.
	Does not expose critical sites to contact contamination or worse than ISO Class 5 air.
	Disinfects stoppers, injection ports, and ampul necks by wiping with sterile 70% IPA and allows sufficient time to dry.
	Affixes needles to syringes without

	contact contamination.
	Punctures vial stoppers and spikes infusion ports without contact contamination.
	Labels preparation(s) correctly.
	Disinfects sterile gloves routinely by wiping with sterile 70% IPA during prolonged compounding manipulations.
	Cleans, sets up, and calibrates automated compounding device (e.g., "TPN compounder") according to manufacturer's instructions.
	Disposes of sharps and waste according to institutional policy or recognized guidelines.

***The person assessed is immediately informed of all unacceptable activities (i.e., spaces lacking check marks, N/A, or N/O) and shown and informed of specific corrections:**

Signature of Person Assessed	Printed Name	Date
Signature of Qualified Evaluator	Printed Name	Date

Appendix V. Sample Form for Assessing Cleaning and Disinfection Procedures

Printed name and position/title of person assessed:	
Name of facility or location:	
Cleaning and Disinfection Practices: The qualified evaluator will check each space for which the person being assessed has acceptably completed the described activity, prints N/A if the activity is not applicable to the assessment session or N/O if the activity was not observed.*	
Daily Tasks:	
	Prepares correct concentration of disinfectant solution according to

	manufacturer's instructions.
	Uses appropriately labeled container for the type of surface to be cleaned (floor, wall, production bins, etc.).
	Documents disinfectant solution preparation.
	Follows garbing procedures when performing any cleaning activities.
	At the beginning of each shift, cleans all ISO Class 5 devices prior to compounding in the following order: walls, IV bar, automated compounders, and work surface.
	Uses a lint free wipe soaked with sterile 70% IPA or other approved disinfectant solution and allows to dry completely.
	Removes all compounder components and cleans all ISO Class 5 areas as stated above at the end of each shift.
	Cleans all counters and easily cleanable work surfaces.
	Mops floors, using the mop labeled "floors," starting at the wall opposite the room entry door; mops floor surface in even strokes toward the operator. Moves carts as needed to clean entire floor surface. Use of a microfiber cleaning system is an acceptable alternative to mops.
	In the ante-area, cleans sink and all contact surfaces; cleans floor with a disinfectant solution or uses microfiber cleaning system.
Monthly Tasks:	
	Performs monthly cleaning on a designated day. Prepares a disinfectant solution as stated in daily tasks that is appropriate for the surfaces to be cleaned.
	Cleans buffer area and ante-area ceiling, walls, and storage shelving with a disinfectant solution and a mop or uses a microfiber cleaning system.
	Once ISO Class 5 area is clean, cleans compounding room ceiling, followed by walls

	and ending with the floor. Uses appropriate labeled mops or microfiber cleaning system.
	Cleans all buffer area totes and storage shelves by removing contents and using a germicidal detergent soaked lint free wipe, cleans the inside surfaces of the tote and then the entire exterior surfaces of the tote. Allows totes to dry. Prior to replacing contents into tote, wipes tote with sterile 70% IPA to remove disinfectant residue. Uses new wipe as needed.
	Cleans all buffer area carts by removing contents and using germicidal detergent soaked lint free wipe, cleans all carts starting with the top shelf and top of post, working down to wheels. Cleans the under side of shelves in a similar manner. Uses a new wipe for each cart. Allows to dry. Wipes carts with sterile 70% IPA wetted lint free wipe to remove any disinfectant residue. Uses new wipe as needed.
	Cleans buffer area chairs, the interior and exterior of trash bins, and storage bins using disinfectant solution soaked lint free wipe.
	Documents all cleaning activities as to who performed such activities with date and time noted.

***The person assessed is immediately informed of all unacceptable activities (i.e., spaces lacking check marks, N/A, or N/O) and shown and informed of specific corrections:**

Signature of Person Assessed	Printed Name	Date
Signature of Qualified Evaluator	Printed Name	Date

1 ■ 1. INTRODUCTION AND SCOPE

2 This chapter describes the minimum standards to be followed when
3 preparing compounded sterile human and animal drugs [compounded sterile
4 preparations (CSPs)] based on current scientific information and best
5 practices for sterile compounding. Sterile compounding is defined as
6 combining, admixing, diluting, pooling, reconstituting, repackaging, or
7 otherwise altering a drug or bulk drug substance to create a sterile
8 medication. Preparing a conventionally manufactured sterile product in
9 accordance with the directions contained in approved labeling provided by
10 the product's manufacturer is not compounding as long as the product is
11 prepared for an individual patient and follows the provisions for
12 administration below.

13 For the purposes of this chapter, administration means the direct and
14 immediate application of a conventionally manufactured product or a CSP to
15 a patient by injecting, infusing, or otherwise providing a sterile medication in
16 its final form. For guidance on administration of CSPs, see the Centers for
17 Disease Control and Prevention's (CDC) *Safe Injection Practices to Prevent*
18 *Transmission of Infections to Patients*. Administration of medication,
19 including withdrawal of doses, is out of the scope of this chapter.
20 Administration of medication should follow the manufacturer's or
21 compounder's labeling of the sterile medication. Additionally, the preparation
22 of non-hazardous CSPs for administration must follow applicable
23 jurisdictional laws and regulations (e.g., labeling).

24 Preparation of non-hazardous CSPs for a single patient using only sterile
25 starting ingredients when administration will begin within 1 hour of
26 beginning the preparation (e.g., within 1 hour of initial entry into or
27 puncture of a single-dose container) is not required to meet the standards in
28 this chapter. Any unused starting ingredient that is not labeled as a multiple-
29 dose container must be discarded after preparation is complete. Additionally,
30 preparation of sterile medications for immediate administration should be
31 performed in accordance with evidence-based information for physical and
32 chemical compatibility of the drugs administered.

33 Aseptic technique must be followed for preparing any sterile medication.
34 Procedures must be in place to minimize the potential for contact with
35 nonsterile surfaces, introduction of particulate matter or biological fluids, and
36 mix-ups with other products or CSPs.

37 The requirements in this chapter must be followed to minimize harm,
38 including death, to human and animal patients that could result from 1)
39 microbial contamination (nonsterility), 2) excessive bacterial endotoxins, 3)
40 variability from the intended strength of correct ingredients, 4) physical and
41 chemical incompatibilities, 5) chemical and physical contaminants, and/or 6)
42 use of ingredients of inappropriate quality.

44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82

1.1 Scope

CSPS AFFECTED

The requirements in this chapter must be met to ensure the sterility of any CSP. Although the list below is not exhaustive, the following must be sterile:

- Injections, including infusions
- Irrigations for internal body cavities (i.e., any space that does not normally communicate with the environment outside of the body such as the bladder cavity or peritoneal cavity). [NOTE—Irrigations for the mouth, rectal cavity, and sinus cavity are not required to be sterile.]
- Ophthalmic dosage forms
- Preparations for pulmonary inhalation. [NOTE—Nasal dosage forms intended for local application are not required to be sterile.]
- Baths and soaks for live organs and tissues
- Implants

Compounding of sterile hazardous drugs (HDs) must additionally comply with [Hazardous Drugs—Handling in Healthcare Settings \(800\)](#).

Compounding of radiopharmaceuticals is subject to the requirements in [Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging \(825\)](#).

Handling of blood components—which are specific elements of blood such as red and white blood cells, platelets, or plasma—should additionally comply with jurisdictional standards and guidelines such as the CDC Biosafety in Microbiological and Biomedical Laboratories (BMBL).

Compounding using biological products requires special considerations because these products are particularly susceptible to microbiological growth and chemical and physical degradation.

PERSONNEL AND SETTINGS AFFECTED

This chapter describes the minimum requirements that apply to all persons who prepare CSPs in all places where CSPs are prepared. This includes, but is not limited to, pharmacists, technicians, physicians, veterinarians, dentists, naturopaths, chiropractors, and nurses in all places including, but not limited to, hospitals and other healthcare institutions, patient treatment sites, infusion facilities, pharmacies, and physicians' or veterinarians' practice sites.

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. *USP* has no role in enforcement.

Repackaging: Repackaging of a sterile product or preparation from its original container into another container must be performed in accordance with the requirements in this chapter for CSPs. If there is evidence or documentation [e.g., Food and Drug Administration (FDA) Guidance] for a shorter beyond-use date (BUD), the shorter BUD must be used.

Proprietary bag and vial systems: Docking and activation of proprietary bag and vial systems (e.g., ADD-Vantage, Mini Bag Plus, addEASE) in accordance with the manufacturer's instructions for immediate administration to an individual patient is not considered compounding and may be performed outside of an International Organization for Standardization (ISO) 5 environment. However, aseptic technique must be followed when attaching the proprietary bag and vial system.

Docking of the proprietary bag and vial systems for future activation and administration is considered compounding and must be performed in accordance with this chapter, with the exception of *12. Establishing Beyond-Use Dates*. BUDs for proprietary bag and vial systems must not be longer than those specified in the manufacturer's labeling.

Allergenic extracts: Licensed allergenic extracts are mixed and diluted to prepare prescription sets for administration to patients. A prescription set is a vial or set of vials of premixed licensed allergenic extracts for subcutaneous immunotherapy diluted with an appropriate diluent. Because of certain characteristics of allergenic extracts and allergy practice, preparation of allergenic extract prescription sets is not subject to the requirements in this chapter that are applicable to other sterile CSPs. The standards for compounding allergenic extracts are in *18. Compounding Allergenic Extracts* and are applicable only when:

1. The compounding process involves simple transfer via sterile needles and syringes of conventionally manufactured sterile allergen products and appropriate conventionally manufactured sterile added substances, and
2. Manipulations are limited to penetrating disinfected stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile vials

Otherwise, compounding of allergenic extracts prescription sets must meet the requirements for Category 1 or 2 CSPs, which are described in this chapter.

1.2 Factors Affecting the Risks Associated with CSPs

CSPs can be compounded either by using only sterile starting ingredients or by using some or all nonsterile starting ingredients. If all of the components

123 used to compound a drug are sterile to begin with, the sterility of the
 124 components must be maintained during compounding to produce a sterile
 125 compounded preparation. If one or more of the starting components being
 126 used to compound is not sterile, the sterility of the compounded preparation
 127 must be achieved through a sterilization process, such as terminal
 128 sterilization in the final sealed container, or sterile filtration, and then
 129 maintained through subsequent manipulations of the preparation. When
 130 compounding with nonsterile starting ingredients, the quality of the
 131 components and the effectiveness of the sterilization step are critical to
 132 achieving a sterile preparation. Personnel must adhere to the requirements
 133 in this chapter throughout the compounding process.

1.3 CSP Categories

135 This chapter distinguishes two categories of CSPs, Category 1 and Category
 136 2, primarily based on the conditions under which they are made, the
 137 probability for microbial growth, and the time period within which they must
 138 be used. Category 1 CSPs are those assigned a BUD of 12 hours or less at
 139 controlled room temperature or 24 hours or less when refrigerated if made
 140 in accordance with all of the applicable requirements for Category 1 CSPs in
 141 this chapter. Category 2 CSPs are those that may be assigned a BUD of
 142 greater than 12 hours at controlled room temperature or greater than 24
 143 hours if refrigerated (see *12. Establishing Beyond-Use Dates*) if made in
 144 accordance with all of the applicable requirements for Category 2 CSPs in
 145 this chapter. See [Table 1](#) for a summary of the minimum requirements in
 146 this chapter for Category 1 and 2 CSPs.

147 This chapter describes minimum requirements that apply to compounding
 148 of all CSPs. The minimum requirements that are not specifically described as
 149 applicable to Category 1 or Category 2, such as minimum training,
 150 competency testing, and personal hygiene for personnel, are applicable to
 151 the compounding of all CSPs.

Table 1. Summary of Minimum Requirements for Category 1 and Category 2 CSPs^a

	Category 1 CSPs	Category 2 CSPs
Personnel Qualifications		
Visual observation of hand hygiene and garbing	Every 6 months	Every 6 months
Gloved fingertip and thumb sampling	Every 6 months	Every 6 months
Media fill testing	Every 6 months	Every 6 months
Requalification	Every 12 months	Every 12 months

Buildings and Facilities		
Placement of the primary engineering control (PEC)	Not required to be placed in a classified area	Required to be placed in a classified area
Recertification	Every 6 months for the PEC	Every 6 months for the PEC and secondary engineering control (SEC)
Nonviable airborne monitoring	Every 6 months	Every 6 months
Microbiological Air and Surface Monitoring		
Viable air sampling	Every 6 months	Every 6 months
Surface sampling	Monthly	Monthly
Release Testing		
Visual inspection	Required	Required
Sterility testing	Not required	Based on assigned BUD
Endotoxin testing	Not required	Based on assigned BUD (e.g., if sterility testing is required) and if prepared from nonsterile ingredient(s) ^b
BUD		
BUD assignment	≤12 hours at controlled room temperature or ≤24 hours if refrigerated (see Table 11)	>12 hours at controlled room temperature or >24 hours if refrigerated (see Table 12)
<p>^a This table summarizes the requirements that apply specifically to Category 1 and Category 2 CSPs. There are numerous requirements in the chapter that are not summarized in this table because they apply to all CSPs, regardless of whether they are Category 1 or Category 2.</p> <p>^b Except for inhalation and topical ophthalmic preparations, Category 2 CSPs assigned a BUD that requires sterility testing and those made from one or more nonsterile ingredient(s) or components(s) must be tested to ensure that they do not contain excessive bacterial endotoxins (see 10.3 Bacterial Endotoxins Testing).</p>		

155
156
157
158
159
160
161
162

2. PERSONNEL QUALIFICATIONS—TRAINING, EVALUATION, AND REQUALIFICATION

All personnel involved in the compounding of CSPs must be initially trained and qualified by demonstrating proficiency in compounding CSPs. Personnel must complete requalification every 12 months in appropriate sterile compounding principles and practices. Training, evaluation, and requalification of personnel must be documented.

163 Each compounding facility must develop a written training program that
164 describes the required training, the frequency of training, and the process
165 for evaluating the performance of individuals involved in preparing CSPs.
166 This program should equip personnel with the appropriate knowledge and
167 train them in the required skills necessary to perform their assigned tasks.

168 **2.1 Demonstrating Proficiency in Core Competencies**

169 Before beginning to prepare CSPs independently, all compounding
170 personnel must complete training and be able to demonstrate knowledge of
171 theoretical principles and proficiency of skills for performing sterile
172 manipulations and achieving and maintaining appropriate environmental
173 conditions. Competency must be demonstrated in at least the following:

- 174 • Hand hygiene
- 175 • Garbing
- 176 • Cleaning and disinfection
- 177 • Calculations, measuring, and mixing
- 178 • Aseptic technique
- 179 • Achieving and/or maintaining sterility and apyrogenicity
- 180 • Use of equipment
- 181 • Documentation of the compounding process (e.g., master formulation
182 and compounding records)
- 183 • Principles of high-efficiency particulate air (HEPA)-filtered
184 unidirectional airflow within the ISO Class 5 area
- 185 • Proper use of primary engineering control (PECs)
- 186 • Principles of movement of materials and personnel within the
187 compounding area

188 All compounding personnel must demonstrate competency through written
189 testing and proficiency through hands-on demonstration of skills every 12
190 months. Any other personnel handling CSPs and/or accessing the
191 compounding area must complete training and demonstrate competency in
192 maintaining the quality of the environment in which they are performing
193 their assigned task. The designated person must ensure that any person
194 who enters the sterile compounding area maintains the quality of the
195 environment.

196 **2.2 Demonstrating Competency in Garbing and Hand Hygiene**

197 All compounding personnel must be visually observed every 6 months by a
198 qualified person while performing hand hygiene and garbing procedures (see
199 *3. Personal Hygiene and Garbing*). The visual audit must be documented and
200 the documentation maintained to provide a record of personnel competency.

201 Gloved fingertip and thumb sampling is important because direct touch
202 contamination is the most likely source of microorganisms. Initial gloved
203 fingertip and thumb sampling evaluates a compounder's competency in

204 correctly performing hand hygiene and garbing (see [Box 2-1](#)). Before being
 205 allowed to independently compound, all compounders must successfully
 206 complete an initial competency evaluation, including visual observation and
 207 gloved fingertip and thumb sampling, no fewer than 3 separate times. Each
 208 fingertip and thumb evaluation must occur after performing a separate and
 209 complete hand hygiene and full garbing procedure. After the initial
 210 competency evaluation, compounding personnel must successfully complete
 211 gloved fingertip and thumb sampling every 6 months after completing the
 212 media-fill test. Successful completion of initial gloved fingertip and thumb
 213 sampling is defined as zero colony-forming units (cfu). Successful
 214 completion of subsequent gloved fingertip and thumb sampling after media-
 215 fill testing is defined as ≤ 3 cfu. Action levels for gloved fingertip and thumb
 216 sampling results are shown in [Table 2](#).

217 **Table 2. Action Levels for Gloved Fingertip and Thumb Sampling^a**

Gloved Fingertip and Thumb Sampling	Action Levels (total number of cfu on both hands)
Initial sampling after garbing	≥ 1
Subsequent sampling after media-fill testing (every 6 months)	> 3
^a Action levels are based on the total cfu count on both hands.	

218 Initial gloved fingertip and thumb sampling must be performed on donned
 219 sterile gloves in the ISO Class 7 buffer room or segregated compounding
 220 area (SCA). Subsequent gloved fingertip and thumb sampling must be
 221 performed on donned sterile gloves inside of an ISO Class 5 PEC. If
 222 conducting gloved fingertip and thumb sampling in a compounding aseptic
 223 isolator (CAI), compounding aseptic containment isolator (CACI), or an
 224 isolator, samples must be taken from the sterile gloves placed over the
 225 gauntlet gloves.

226 **Box 2-1. Gloved Fingertip and Thumb Sampling Procedures**

- Use one sampling device per hand (e.g., plates, paddles, or slides) containing general microbial growth agar [e.g., trypticase soy agar (TSA)] supplemented with neutralizing additives (e.g., lecithin and polysorbate 80) as this agar supports both bacterial and fungal growth.
- Label each contact sampling device with a personnel identifier, whether it was from the right or left hand, and the date and time of sampling.
- Do not disinfect gloves immediately before touching the sampling device because this could cause a false-negative result.
- Using a separate sampling device for each hand, collect a gloved fingertip and thumb sample from both hands by rolling finger pads

and thumb pad over the agar surface.

- Incubate the sampling device at a temperature of 30°–35° for no less than 48 hours and then at 20°–25° for no less than 5 additional days. If using plates or slides, invert them during incubation to prevent condensate from dropping onto the agar and affecting the accuracy of the cfu reading.
- Record the number of cfu per hand (left hand, right hand).
- Determine whether the cfu action level is exceeded by counting the total number of cfu on both hands.

227

2.3 Competency Testing in Aseptic Manipulation

228

After successful completion of the initial hand hygiene and garbing competency evaluation, all compounding personnel must have their sterile technique and related practices evaluated during a media-fill test (see [Box 2-2](#)). When performing a media-fill test, use the most difficult and challenging compounding procedures and processing conditions encountered by the person during a work shift (e.g., the most manipulations, most complex flow of materials, longest time to compound, size of batch), replacing all the components used in the CSPs with soybean–casein digest media.

237

If using a commercial sterile microbial growth medium, either verify that the growth medium is growth promoting (see [Sterility Tests \(71\)](#), [Culture Media and Incubation Temperatures](#), [Growth Promotion Test of Aerobes, Anaerobes, and Fungi](#)), or obtain a certificate of analysis (COA) from the supplier of the growth medium to ensure that it will support the growth of microorganisms. Store microbial growth media in accordance with manufacturer instructions and use before the expiration date. If preparing a sterile microbial growth medium in-house, the growth promotion capability of the medium must be demonstrated for each batch and documented (see [\(71\)](#)).

247

Failure is indicated by visible turbidity or other visual manifestations of growth in the medium in one or more container–closure unit(s) on or before the end of the incubation period. Investigate media-fill failures to determine possible causes (e.g., sterilizing filter failure).

251

Evaluation results must be documented and the documentation maintained to provide a record and long-term assessment of personnel competency. Documentation must at a minimum include the name of the person evaluated, evaluation date/time, media and components used including expiration date and lot number, the results, and the signatures of the person evaluated and the observer.

257

Box 2-2. Media-Fill Testing Procedures

- If all of the starting components are sterile to begin with, manipulate

them in a manner that simulates sterile-to-sterile compounding activities, and transfer the sterile soybean–casein digest media into the same types of container–closure systems commonly used at the facility. Do not further dilute the media unless specified by the manufacturer.

- If some of the starting components are nonsterile to begin with, use a nonsterile soybean–casein digest powder to make a solution. The solution must be prepared according to [Sterility Tests \(71\)](#), [Culture Media and Incubation Temperatures](#). Manipulate it in a manner that simulates nonsterile-to-sterile compounding activities.
- Once the compounding simulation is completed and the final containers are filled with the test media, incubate them in an incubator for 7 days at 20°–25° followed by 7 days at 30°–35° to detect a broad spectrum of microorganisms. Failure is indicated by visible turbidity or other visual manifestations of growth in the media in one or more container–closure unit(s) on or before 14 days.

258

2.4 Reevaluation, Retraining, and Requalification

259

REQUALIFICATION AFTER FAILURE

260 Personnel who fail the visual observation of hand hygiene, garbing, and/or
261 aseptic technique; gloved fingertip and thumb sampling; and/or media-fill
262 testing must successfully pass reevaluations in the deficient area(s) before
263 they can resume compounding of sterile preparations. The designated
264 person must identify the cause of failure and determine appropriate
265 retraining requirements. All failures, retraining, and reevaluations must be
266 documented.

267

REQUALIFICATION PROGRAM

268 Compounding personnel must successfully complete requalification every
269 12 months in the core competencies listed in *2.1 Demonstrating Proficiency
270 in Core Competencies*. Successful completion must be demonstrated through
271 written testing and hands-on demonstration of skills.

272

TIMING OF REEVALUATION AND REQUALIFICATION

273 **Visual observation:** Compounding personnel must be visually observed
274 while performing hand hygiene and garbing procedures initially, and then at
275 least every 6 months.

276 **Gloved fingertip and thumb sampling:** Compounding personnel must
277 perform fingertip and thumb sampling 3 times initially and then every 6
278 months (in conjunction with media-fill testing).

279 **Media-fill testing:** After initial qualification, conduct a media-fill test of all
280 personnel engaged in compounding CSPs at least every 6 months (in
281 conjunction with gloved fingertip and thumb sampling).

282 **Cleaning and disinfecting:** Retrain and requalify personnel in cleaning
283 and disinfecting compounding areas in conjunction with any change(s) in
284 cleaning and disinfecting procedures.

285 **After a pause in compounding:** Personnel who have not compounded
286 CSPs in more than 6 months must be requalified in all core competencies
287 before they may resume compounding duties.

288

289

3. PERSONAL HYGIENE AND GARBING

290 Personal hygiene and garbing are essential to maintaining microbial control
291 of the environment. Most microorganisms detected in cleanrooms are
292 transferred from individuals. Squamous cells are normally shed from the
293 human body at a rate of 10^6 or more per hour, and those skin particles are
294 covered with microorganisms.¹² To minimize contamination of the
295 environment and CSPs, individuals entering a compounding area must be
296 properly garbed and must maintain proper personal hygiene.

297 Individuals that may have a higher risk of contaminating the CSP and the
298 environment (e.g., personnel with rashes, sunburn, recent tattoos, oozing
299 sores, conjunctivitis, or active respiratory infection) must report these
300 conditions to their supervisor. The designated person is responsible for
301 evaluating whether these individuals should be excluded from working in
302 compounding areas before their conditions have resolved because of the risk
303 of contaminating the CSP and the environment.

304

3.1 Personnel Preparation

305 Individuals entering a compounding area must take appropriate steps to
306 minimize microbial contamination of the environment and the CSPs,
307 including hand hygiene (3.2 *Hand Hygiene*), garbing (3.3 *Garbing*
308 *Requirements*), and consideration of needed materials to be brought into the
309 compounding area. Before entering a compounding area, individuals must
310 remove any items that are not easily cleanable or that are not necessary for
311 compounding. At a minimum, individuals must:

- 312 • Remove personal outer garments.
- 313 • Remove all cosmetics because they shed flakes and particles.
- 314 • Remove all hand, wrist, and other exposed jewelry including piercings
315 that could interfere with the effectiveness of garbing (e.g., the fit of
316 gloves, cuffs of sleeves, and eye protection) or otherwise increase the
317 risk of contamination of the CSP. Cover any jewelry that cannot be
318 removed.
- 319 • Not wear ear buds or headphones.

- 320 • Not bring electronic devices that are not necessary for compounding or
321 other required tasks into the compounding area.
322 • Keep nails clean and neatly trimmed to minimize particle shedding and
323 avoid glove punctures. Nail polish, artificial nails, and extenders must
324 not be worn.

325 Additional restrictions on items may be necessary based on the risk of
326 contaminating the environment and the CSP.

327 **3.2 Hand Hygiene**

328 Hand hygiene must be performed before entering a compounding area (see
329 [Box 3-1](#)). Alcohol hand sanitizers alone are not sufficient for washing hands
330 and forearms. All hygiene products must be used sequentially and not
331 concurrently because of potential chemical incompatibilities and adverse
332 dermatologic reactions. Brushes must not be used for hand hygiene because
333 of the potential for skin irritation and increased bacterial shedding. Hand
334 driers must not be used because of the risk of creating air turbulence and
335 circulating contamination in the compounding area.

336 Perform hand hygiene after donning shoe covers, head and facial hair
337 covers, and a face mask. [NOTE—The order of garbing must be determined
338 by the facility and documented in the facility's standard operating procedure
339 (SOP).] After hands are washed and dried, don remaining garb except sterile
340 gloves, and then perform hand antisepsis using an alcohol-based hand rub
341 with persistent antimicrobial activity immediately before donning sterile
342 gloves. [NOTE—Soap must not be added to a partially empty soap dispenser.
343 This practice of "topping off" dispensers can lead to bacterial contamination
344 of soap.]

345 **Box 3-1. Hand Hygiene Procedures**

- Remove debris from underneath fingernails under warm running water using a disposable nail cleaner. Wash hands and forearms up to the elbows with soap and water for at least 30 seconds.
- Dry hands and forearms to the elbows completely with low-lint disposable towels or wipes.
- Apply an alcohol-based hand rub with persistent antimicrobial activity to dry skin, following the manufacturer's instructions for application times, and use a sufficient amount of product to keep the hands wet for the duration of the application time.
- Allow hands to dry thoroughly before donning sterile gloves.

346 **3.3 Garbing Requirements**

347 Personnel intending to enter a buffer room or SCA must be properly
348 garbed. Garb must be put on in an order that reduces the risk of

349 contamination. The order of garbing must be determined by the facility and
350 documented in the facility's SOP. Donning and doffing garb must not occur in
351 the ante-room or the SCA at the same time. The minimum garbing
352 requirements for preparing CSPs include:

- 353 • Non-cotton, low-lint garment with sleeves that fit snugly around the
354 wrists and that is enclosed at the neck
- 355 • Low-lint, disposable covers for shoes
- 356 • Low-lint, disposable covers for head that cover the ears and forehead
- 357 • Face mask
- 358 • Low-lint, disposable covers for all facial hair
- 359 • Sterile gloves
- 360 • If using a restricted-access barrier system (RABS), such as a CAI or
361 CACI, disposable gloves (e.g., cotton, either nonsterile or sterile)
362 must be worn inside gauntlet gloves and sterile gloves must worn
363 over gauntlet gloves

364 Gowns and other garb must be stored in a manner that minimizes
365 contamination (e.g., away from sinks to avoid splashing). Garb must be
366 replaced immediately if it becomes visibly soiled or if its integrity is
367 compromised. When personnel exit the compounding area, garb cannot be
368 reused and must be discarded.

369 If compounding an HD, appropriate personal protective equipment (PPE)
370 must be worn in accordance with [\(800\)](#).

371 GLOVES

372 Gloves must be sterile and powder free. Application of sterile 70%
373 isopropyl alcohol (IPA) to gloves must occur throughout the compounding
374 process and whenever nonsterile surfaces (e.g., vials, counter tops, chairs,
375 or carts) are touched. Contaminated gloved hands can be disinfected by
376 rubbing sterile 70% IPA onto all contact surface areas of the gloves and
377 letting the gloves dry thoroughly.

378 Gloves on hands and gauntlet sleeves on RABS and isolators must be
379 inspected routinely for holes, punctures, or tears and must be replaced
380 immediately if such defects are detected.

381

382 4. FACILITIES AND ENGINEERING CONTROLS

383 Sterile compounding facilities must be designed, outfitted, and maintained
384 properly to minimize the risk of contamination of CSPs. The required air
385 quality must be achieved and maintained through PECs and secondary
386 engineering controls (SECs). The ante-room, buffer room, and SCA must be
387 separated from areas not directly related to compounding and must be
388 appropriately controlled to achieve and maintain the required air quality
389 classifications. The design of the facility should take into account the number

390 of personnel and their movements, and the equipment, supplies, and
391 components to maintain and facilitate the maintenance of air quality. The
392 number of operations being performed, the equipment (e.g., PECs, carts,
393 computers, etc.), the personnel in the compounding area (and in adjacent
394 areas), and the complexity of the compounding procedures are critical
395 considerations for maintaining control of environmental conditions in the
396 facility.

397 4.1 Protection from Airborne Contaminants

398 Sterile compounding facilities must be designed to minimize the risk of
399 airborne contamination of the area in which sterile compounding occurs.
400 Proper design and controls are required to minimize the risk that CSPs will
401 be exposed to airborne contaminants that may cause microbial
402 contamination.

403 AIR QUALITY STANDARDS

404 The ISO standards for air quality in controlled environments are provided in
405 [Table 3](#) and referenced throughout this chapter.

406 **Table 3. ISO Classification of Particulate Matter in Room Air^a**

ISO Class	Particle Count ^b /m ³
3	35.2
4	352
5	3520
6	35,200
7	352,000
8	3,520,000

^a Adapted from ISO 14644-1, Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness by particle concentration.

^b Limits for number of particles $\geq 0.5 \mu\text{m}$ measured under dynamic operating conditions.

407 DESIGN REQUIREMENTS TO MAINTAIN AIR QUALITY

408 Facilities used for compounding CSPs must be designed so that air quality
409 improves with movement through separate operational areas to the PEC.
410 Classified areas in which the air quality is controlled (see [Table 3](#)) include
411 ante-rooms, buffer rooms, and PECs.

- 412 • Ante-rooms providing access to positive pressure buffer rooms must
413 meet at least ISO Class 8 classification. Ante-rooms providing access
414 to negative pressure buffer rooms must meet at least ISO Class 7
415 classification (see [800](#)). Typically, personnel hand hygiene and
416 garbing procedures, staging of components, and other activities that
417 potentially generate higher levels of particulates are performed in the

418 ante-room. Ante-rooms are also transition areas to ensure that
419 proper air classification and pressure relationships are maintained
420 between designated areas.

- 421 • A buffer room must meet at least ISO Class 7 air quality. Activities in
422 the buffer room must be controlled to minimize any effects on air
423 quality in the area where CSPs are prepared.
- 424 • CSPs must be prepared in an ISO Class 5 or better PEC.

425 If compounding only Category 1 CSPs, the PEC may be placed in an
426 unclassified SCA.

427 **4.2 Facility Design and Environmental Controls**

428 In addition to minimizing airborne contamination, sterile compounding
429 facilities must be designed and controlled to provide a well-lighted and
430 comfortable working environment (see [Physical Environments That Promote
431 Safe Medication Use \(1066\)](#)). The cleanroom suite should be continuously
432 maintained at a temperature of 20° or cooler and a relative humidity below
433 60% to minimize the risk for microbial proliferation and provide comfortable
434 conditions for compounding personnel attired in the required garb. The
435 temperature and humidity must be monitored in the cleanroom suite each
436 day that compounding is performed, either manually or by a continuous
437 recording device, and the results must be readily retrievable, reviewed by
438 the designated person, and documented. Temperature and humidity in the
439 cleanroom suite must be controlled through an efficient heating, ventilation,
440 and air conditioning (HVAC) system. Free-standing humidifiers/dehumidifiers
441 and air conditioners must not be used within the classified area.
442 Temperature monitoring devices must be verified for accuracy at least every
443 12 months or as required by the manufacturer.

444 A person or persons must be designated as the person responsible for
445 ensuring that each area related to CSP preparation meets the classified air
446 quality standard appropriate for the activities to be conducted in that area.
447 They must also ensure that the ISO Class 5 areas are located, operated,
448 maintained, monitored, and certified to have appropriate air quality.

449 **TYPES OF SECS AND DESIGN**

450 The PEC must be located in an SEC, which may be either a cleanroom suite
451 (buffer room with ante-room) or an SCA (see *Appendix 2: Example Designs
452 for Sterile Non-Hazardous Compounding Areas* for examples of facility
453 designs).

454 **Cleanroom suite:** The ISO-classified ante-room must be separated from
455 the surrounding unclassified areas of the facility by fixed walls and doors,
456 and controls must be in place to minimize the flow of lower-quality air into
457 the more controlled areas. Air supplied to the cleanroom suite must be
458 introduced through HEPA filters that are located in the ceiling of the buffer
459 and ante-rooms. Returns must be low on the wall unless a visual smoke

460 study demonstrates dilution of particles and sweeping out of particles from
461 the entire room. This smoke study must be repeated whenever a change to
462 the placement of the PEC within the room is made. The classified rooms
463 must be equipped with a pressure-differential monitoring system. The ante-
464 room must have a line of demarcation to separate the clean side from the
465 dirty side. The ante-room is entered through the dirty side, and the clean
466 side is the area closest to the buffer room. Required garb must be worn on
467 the clean side of the line of demarcation (see 3. *Personal Hygiene and*
468 *Garbing*).

469 **Segregated compounding area (SCA):** A PEC may be located within an
470 unclassified area, without an ante-room or buffer room. This type of design
471 is called an SCA. Only Category 1 CSPs can be compounded in an SCA. The
472 SCA must be located away from unsealed windows, doors that connect to
473 the outdoors, and traffic flow, all of which may adversely affect the air
474 quality in the PEC. An SCA must not be located adjacent to environmental
475 control challenges (e.g., restrooms, warehouses, or food preparation areas).
476 The impact of activities that will be conducted around or adjacent to the SCA
477 must be considered carefully when designing such an area. A visible
478 perimeter must establish the boundaries of the SCA.

479 The PEC must be located in the buffer room of the cleanroom suite or the
480 SCA in a manner that minimizes conditions that could increase the risk of
481 microbial contamination. For example, strong air currents from opened
482 doors, personnel traffic, or air streams from the HVAC system(s) can disrupt
483 the unidirectional airflow of an open-faced PEC such as a laminar airflow
484 workbench (LAFW). Access to the SEC must be restricted to authorized
485 personnel and required materials.

486 It is also critical to control materials (e.g., supplies and equipment) as they
487 move from classified areas of lower quality to those of higher quality (e.g.,
488 ISO Class 8 ante-room to ISO Class 7 buffer room to ISO Class 5 PEC) to
489 minimize the influx of contaminants. Airlocks and interlocking doors can be
490 used to facilitate better control of air balance between areas of differing ISO
491 classification (e.g., between the buffer room and ante-room), or between a
492 classified area and an unclassified area (e.g., between the ante-room and an
493 unclassified area such as a hallway). If a pass-through is used, both doors
494 must never be opened at the same time, and doors should be interlocking.

495 Due to the interdependence of the various rooms or areas that make up a
496 sterile compounding facility, it is essential to carefully define and control the
497 dynamic interactions permitted between areas and rooms. When designing
498 doors, consider the placement of door closures, door surfaces, and the
499 movement of the doors, all of which can affect airflow. Seals and sweeps
500 should not be installed at doors between buffer and ante-rooms. Access
501 doors should be hands-free. Tacky surfaces must not be used in ISO-
502 classified areas.

503 THE CSP COMPOUNDING ENVIRONMENT

504 The PEC must be certified to meet ISO Class 5 or better conditions (see
505 [Table 3](#)) during dynamic operating conditions and must be designed to
506 prevent contamination during compounding of CSPs.

507 Unidirectional airflow must be maintained in the PEC. HEPA-filtered air
508 must be supplied to the PEC at a velocity sufficient to sweep particles away
509 from critical sites and maintain unidirectional airflow during operations.
510 Proper design, control, and use minimize turbulence and creation of eddies
511 or stagnant air in the PEC.

512 TYPES OF PECS AND PLACEMENT

513 Proper placement of the PEC is critical to ensuring an ISO Class 5
514 environment for preparing CSPs. Placement of the PEC must allow for
515 cleaning around the PEC. See [Table 4](#) for a summary of minimum
516 requirements for the placement of PECs for preparing non-HD CSPs.

517 Types of PEC and their placement include:

518 **Laminar airflow system (LAFS):** An LAFS provides an ISO Class 5 or
519 better environment for sterile compounding. The LAFS provides
520 unidirectional HEPA-filtered airflow that is designed to prevent contamination
521 of a sterile compounding environment. The unidirectional airflow within the
522 LAFS helps protect the direct compounding area (DCA) from process-
523 generated contamination (e.g., opening wrappings of sterile containers,
524 compounder movement, etc.) as well as from outside sources.

525 *Types of LAFS:* Examples of LAFS include LAWFs, integrated vertical
526 laminar flow zones (IVLFZs), and biological safety cabinets (BSCs).

527 LAMINAR AIRFLOW WORKBENCH (LAFW): An LAFW is a device that provides an
528 ISO Class 5 or better environment for sterile compounding. The LAFW
529 provides either horizontal or vertical unidirectional HEPA-filtered airflow.
530 [NOTE—An LAFW must not be used for preparation of antineoplastic and/or
531 active pharmaceutical ingredient (API) HDs (see [800](#)).]

532 INTEGRATED VERTICAL LAMINAR FLOW ZONE (IVLFZ): An IVLFZ is a designated ISO
533 Class 5 area serving as the PEC within an ISO Class 7 or cleaner buffer
534 room. In the IVLFZ, unidirectional airflow is created by placing HEPA filters
535 in the ceiling over stainless steel work tables. The unidirectional HEPA-
536 filtered zone must be separated from the ISO Class 7 area with a physical
537 barrier located at the ceiling to direct the airflow downward over the work
538 area to separate the DCA from potential sources of contamination. [NOTE—
539 Smoke studies have shown that it is difficult to achieve this type of design
540 and also achieve and maintain unidirectional airflow under dynamic
541 operating conditions.] [NOTE—A IVLFZ must not be used for preparation of
542 antineoplastic and/or API HDs (see [800](#)).]

543 CLASS II BIOLOGICAL SAFETY CABINET (BSC): A Class II BSC is a ventilated cabinet
544 with an open front and inward and downward unidirectional HEPA-filtered
545 airflow and HEPA-filtered exhaust. The BSC is designed to provide worker
546 protection from exposure to airborne drugs and to provide an ISO Class 5 or
547 better environment for preparing CSPs. [NOTE—The exhaust air from the BSC
548 must be externally vented for preparation of antineoplastic and/or API HDs
549 (see [\(800\)](#)).]

550 *Placement of LAFS:* The LAFS must be located out of traffic patterns and
551 away from room air currents that could disrupt the intended airflow patterns
552 inside the PEC. If used to prepare only Category 1 CSPs, the ISO Class 5 PEC
553 may be located in an unclassified SCA. If used to prepare Category 2 CSPs,
554 the LAFS must be located within a cleanroom suite with an ISO Class 7 or
555 better buffer room and ISO Class 8 or better ante-room. A dynamic airflow
556 smoke pattern test must be performed initially and at least every 6 months
557 to ensure that 1) the LAFS is properly placed into the facility, and 2)
558 compounders understand how to utilize the unidirectional airflow to maintain
559 first air in the DCA.

560 **Restricted-access barrier system (RABS):** A RABS is an enclosure that
561 provides HEPA-filtered ISO Class 5 unidirectional air. It allows for the ingress
562 and/or egress of materials through defined openings that have been
563 designed and validated to preclude the transfer of contamination, and that
564 generally are not to be opened during compounding operations.

565 *Types of RABS:* Examples of RABS include CAIs and CACIs. In a CAI or
566 CACI, glove ports are used to provide physical separation between the
567 surrounding area and the aseptic manipulations.

568 COMPOUNDING ASEPTIC ISOLATOR (CAI): A CAI is designed for compounding non-
569 HD CSPs. It is designed to maintain an ISO Class 5 environment throughout
570 the compounding and material transfer processes. Air exchange into the CAI
571 from the surrounding environment must not occur unless the air has first
572 passed through a HEPA filter.

573 COMPOUNDING ASEPTIC CONTAINMENT ISOLATOR (CACI): A CACI is designed to
574 provide worker protection from exposure to undesirable levels of airborne
575 drug throughout the compounding and material transfer processes, and to
576 maintain an ISO Class 5 environment for compounding sterile HD
577 preparations (see [\(800\)](#)). Air exchange with the surrounding environment
578 must not occur unless it is first passed through a HEPA filter capable of
579 containing airborne concentrations of the physical size and state of the drug
580 being compounded.

581 *Placement of RABS:* If used to prepare only Category 1 CSPs, the ISO Class
582 5 environment may be achieved by placing the RABS in an unclassified SCA.
583 If used to prepare Category 2 CSPs, the RABS must be located within a

584 cleanroom suite with an ISO Class 7 or better buffer room and an ISO Class
585 8 or better ante-room.

586 All transport ports on the RABS must be closed during compounding. When
587 a RABS is used, the recovery time after opening to achieve ISO Class 5 air
588 quality must be documented, and internal procedures must be developed to
589 ensure that adequate recovery time is allowed after opening and closing the
590 RABS, both before and during compounding operations. An airflow smoke
591 pattern test must be performed under dynamic operating conditions initially
592 and at least every 6 months to ensure that the RABS is properly integrated
593 into the facility and that the compounder understands how to utilize the
594 unidirectional airflow to maintain first air in the DCA. For placement of a
595 CACI used for the preparation of antineoplastic and/or API HDs, see [\(800\)](#).

596 **Isolator:** An isolator provides isolation from the surrounding area and
597 maintains ISO Class 5 air quality during dynamic operating conditions. A CAI
598 or CACI is not an isolator. An isolator comprises four elements (see ISO
599 14644-7):

- 600 1. Controlled workspace: This is the defined volume that is created by
601 using a combination of aerodynamic and physical means of
602 separation, in order to achieve the necessary means of assurance of
603 maintaining separation.
- 604 2. Transfer device(s): This is the means whereby materials are
605 transferred in and out of the work zone. There is a range of transfer
606 devices including simple doors, air-purged transfer chambers, and
607 double door transport ports. It should be possible to demonstrate
608 that unfiltered air from the environment cannot enter the isolator
609 during decontamination or compounding procedures.
- 610 3. Access device(s): This is the means whereby the activity or process
611 in the work zone is carried out. Access devices include gloves and
612 gauntlets for the operator and/or remote controlled robotic devices.
- 613 4. Decontamination system: This is the means of decontaminating the
614 isolator itself and materials entering and leaving it using a generator
615 that distributes a sporicidal agent throughout the chamber.

616 *Placement of Isolators:* An isolator used to prepare only Category 1 CSPs
617 can be placed in an unclassified SCA. If the isolator is used to prepare
618 Category 2 CSPs, the area surrounding the isolator must at minimum be
619 placed in an ISO Class 8 or better air quality buffer room. [NOTE—An ante-
620 room is not required when using an isolator.] A dynamic airflow smoke
621 pattern test must be performed initially and at least every 6 months to
622 ensure that the isolator is properly placed into the facility and that the
623 designated person and compounder understand how to utilize the
624 unidirectional airflow to maintain first air in the DCA. For placement of an
625 isolator used for the preparation of HDs, see [\(800\)](#).

626
627

Table 4. Summary of Minimum Requirements for Placement of PEC for Compounding Non-HD CSPs^a

PEC Type	Device Type	Placement for Compounding Category 1CSPs	Placement for Compounding Category 2 CSPs
LAFS	LAFW	Unclassified SCA	ISO Class 7 positive pressure buffer room with an ISO Class 8 positive pressure ante-room
	IVLFZ	N/A ^b	ISO Class 7 positive pressure buffer room with an ISO Class 8 positive pressure ante-room
	BSC	Unclassified SCA	ISO Class 7 positive pressure buffer room with an ISO Class 8 positive pressure ante-room
RABS	CAI or CACI	Unclassified SCA	ISO Class 7 positive pressure buffer room with an ISO Class 8 positive pressure ante-room
Isolator	Isolator	Unclassified SCA	ISO Class 8 positive pressure room
^a For compounding HDs, refer to (800) .			
^b An IVLFZ must not be used in an unclassified area.			

628 If a robotic enclosure is used as the PEC, a dynamic smoke visualization
629 test must be performed initially and every 6 months thereafter to ensure
630 that it is properly integrated into the facility, that there is no turbulence or
631 refluxing at any critical site, that room air does not enter the PEC where
632 sterile products and/or preparations may be exposed, and that all processes
633 can be performed without introducing contamination to the DCA(s).

AIR EXCHANGE REQUIREMENTS

634 For cleanroom suites, adequate HEPA-filtered airflow to the buffer room(s)
635 and ante-room(s) is required to maintain the appropriate ISO classification
636 during compounding activities. Airflow is measured in terms of the number
637 of air changes per hour (ACPH). The ACPH may need to be higher to
638 maintain the required ISO classification and microbial state of control
639 depending on these factors: number of personnel permitted to work in the
640 area, number of particulates that may be generated from activities and
641 processes in the area, the equipment located in the room, the room
642 pressure, and the effects of temperature. See [Table 5](#) for a summary of
643 ACPH requirements for non-HD sterile compounding areas.

644 A minimum of 30 total HEPA-filtered ACPH must be supplied to ISO Class 7
645 rooms:
646

- 647 • The total HEPA-filtered air change rate must be adequate to maintain
648 ISO Class 7 during dynamic operating conditions considering the
649 factors listed above
- 650 • At least 15 ACPH of the total air change rate in a room must come
651 from the HVAC through HEPA filters located in the ceiling
- 652 • The HEPA-filtered air from the PEC, when added to the HVAC-supplied
653 HEPA-filtered air, increases the total HEPA-filtered ACPH to at least
654 30 ACPH
- 655 • If the PEC is used to meet the minimum total ACPH requirements, the
656 PEC must not be turned off except for maintenance
- 657 • The ACPH from HVAC, ACPH contributed from the PEC, and the total
658 ACPH must be documented on the certification report

659 A minimum of 20 ACPH of HEPA-filtered air must be supplied to ISO Class 8
660 rooms from the HVAC through HEPA filters that are located in the ceiling:

- 661 • The total HEPA-filtered air change rate must be adequate to maintain
662 ISO Class 8 under dynamic operating conditions considering the
663 factors listed above
- 664 • Ante-rooms where activity levels are high may require more HEPA-
665 filtered ACPH to maintain ISO Class 8 under dynamic operating
666 conditions
- 667 • The total ACPH must be documented on the certification report

668 **Table 5. Summary of ACPH Requirements for Non-HD Sterile**
669 **Compounding Areas**

Compounding Area	ACPH Requirement
Unclassified SCA	No requirement
ISO Class 7 room(s)	≥30 ACPH
ISO Class 8 room(s)	≥20 ACPH

670 ESTABLISHING AND MAINTAINING PRESSURE DIFFERENTIALS
671 Continuous differential positive pressure is required to minimize airflow
672 from an area with lower air-quality classification to an area of higher air-
673 quality classification. In a cleanroom suite, a minimum differential positive
674 pressure of 0.02-inch water column is required between each ISO classified
675 area (e.g., between the buffer room and ante-room). The pressure
676 differential between the ante-room and the unclassified area must not be
677 less than 0.02-inch water column. No pressure differential is required
678 between the SCA and the surrounding area. See [\(800\)](#) for pressure
679 requirements for compounding HD CSPs.

680 In a cleanroom suite, a pressure differential monitoring system must be
681 used to continuously monitor the pressure differential between the ante-
682 room(s) and buffer room(s) and between the ante-room and the general

683 environment outside the classified room(s) or area(s). The results from the
684 pressure monitoring system must be reviewed and documented at least daily
685 on the days when compounding is occurring. All pressure monitoring devices
686 must be tested for accuracy and performance at least every 6 months.

687 FACILITIES PREPARING CSPS FROM NONSTERILE STARTING 688 INGREDIENT(S) OR COMPONENT(S)

689 If preparing a Category 2 CSP from nonsterile ingredient(s) or
690 components(s), presterilization procedures, such as weighing and mixing,
691 must be completed in no worse than an ISO Class 8 environment.
692 Presterilization procedures must be performed in a containment ventilated
693 enclosure (CVE), BSC, or CACI to minimize the risk of airborne
694 contamination. Presterilization procedures must not adversely affect the
695 required air quality of the SEC as demonstrated during certification under
696 dynamic operating conditions. Personnel must follow the hygiene and
697 garbing requirements as described in 3. *Personal Hygiene and Garbing*
698 during presterilization procedures.

699 **4.3 Creating Areas to Achieve Easily Cleanable Conditions**

700 CLEANROOM SUITE

701 The surfaces of ceilings, walls, floors, doors, door frames, fixtures,
702 shelving, work surfaces, counters, and cabinets in the classified area must
703 be smooth, impervious, free from cracks and crevices, and non-shedding so
704 they can be easily cleaned and disinfected and to minimize spaces in which
705 microorganisms and other contaminants can accumulate. Surfaces should be
706 resistant to damage by cleaning agents, disinfectants, and tools used to
707 clean. Junctures between the ceiling and the walls and between the walls
708 and the floor must be sealed to eliminate cracks and crevices where dirt can
709 accumulate. If ceilings consist of inlaid panels, the panels must be caulked
710 or otherwise sealed and secured around each panel to seal them to the
711 support frame. Ceiling panels must be washable, scrubbable and soil
712 resistant, and designed for use in a cleanroom environment.

713 Walls must be constructed of, or may be covered with, durable material
714 (e.g., epoxy painted walls or heavy-gauge polymer) and the integrity of the
715 surface must be maintained. Panels must be joined together and sealed to
716 each other and the support structure. Floors must be smooth, sealed (e.g.,
717 with continuous, welded seams), and impervious. Floors must include coving
718 to the sidewall. Classified areas should minimize dust-collecting overhangs
719 such as utility pipes and ledges such as windowsills. If overhangs or ledges
720 are present, they must be easily cleanable. The exterior lens surface of
721 ceiling light fixtures must be smooth, mounted flush, and sealed. Any other
722 penetrations through the ceiling or walls must be sealed.

723

724 SCA

725 The SCA and all surfaces (e.g., walls, floors, counters, and equipment) in
726 the SCA must be clean, uncluttered, and dedicated to compounding.
727 Surfaces in the SCA should be smooth, impervious, free from cracks and
728 crevices, and non-shedding so they can be easily cleaned and disinfected
729 and to minimize spaces in which microorganisms and other contaminants
730 can accumulate. Surfaces should be resistant to damage by cleaning agents,
731 disinfectants, and tools used to clean. Dust-collecting overhangs such as
732 utility pipes and ledges such as windowsills should be minimized. If
733 overhangs or ledges are present, they must be easily cleanable.

734 4.4 Water Sources

735 The facility where CSPs are prepared must be designed so that activities
736 such as hand hygiene and garbing will not adversely affect the ability of the
737 PEC to function as designed. Sinks should enable hands-free use with a
738 closed system of soap (i.e., non-refillable container) to minimize the risk of
739 extrinsic contamination. In facilities with a cleanroom suite, the sink used for
740 hand hygiene may be placed either inside or outside of the ante-room. The
741 buffer room must not contain sink(s), eyewash(es), shower(s), or floor
742 drain(s). The ante-room must not contain floor drain(s). If installed,
743 sprinkler systems should be recessed and covered, and must be easily
744 cleanable. In a facility with an SCA design, the sink must be accessible but
745 located at least 1 meter away from the PEC. The sink must not be located
746 inside the perimeter of the SCA.

747 4.5 Placement and Movement of Materials

748 Only furniture, equipment, and other materials necessary for performing
749 compounding activities are permitted in the classified area or SCA, and they
750 should be low-shedding and easily cleaned and disinfected. Their number,
751 design, location, and manner of installation must not impact environmental
752 air quality and must promote effective cleaning and disinfecting. Certain
753 items are not permitted on the clean side of ante-room(s) and in buffer
754 room(s), including, but not limited to, corrugated cardboard, external
755 shipping containers, and nonessential paper (e.g., paper towels and tissues).

756 Carts used to transport components or equipment into classified areas
757 must be constructed from nonporous materials with cleanable casters and
758 wheels to promote mobility and ensure ease of cleaning and disinfection. All
759 items must be wiped with low-lint wipers and an appropriate disinfectant by
760 personnel wearing gloves before they are brought into the clean side of
761 ante-room(s), placed into pass-through(s), or brought inside the perimeter
762 of the SCA. In a cleanroom suite, carts must not be moved from the dirty
763 side to the clean side of the ante-room unless the entire cart, including
764 casters, is cleaned and disinfected.

765 Only equipment necessary for performing compounding activities is
766 permitted in the PEC. Proper placement of equipment in a PEC must be

767 verified by a smoke visualization study under dynamic operating conditions
768 to verify that there is minimal disruption in airflow. Equipment and other
769 items used in a classified area or an SCA should not be removed except for
770 calibration, servicing, cleaning, or other activities associated with
771 maintenance. If removed, these items must be cleaned and disinfected
772 before they are returned to the classified area or inside the perimeter of the
773 SCA.

774 **4.6 Certification and Recertification**

775 Before a compounding area is used to compound either Category 1 or
776 Category 2 CSPs, it must be certified using procedures in the current
777 Controlled Environment Testing Association (CETA) certification guide for
778 *Sterile Compounding Facilities* or an equivalent guideline. Certification
779 indicates that the compounding area is meeting its design and air quality
780 specifications (see [Table 3](#)). It is important to place special emphasis on
781 certifying the ISO Class 5 areas.

782 Certification of the classified areas including the PEC must be performed
783 initially, and recertification must be performed at least every 6 months and
784 must include:

- 785 • Airflow testing: Airflow testing is performed to determine acceptability
786 of the air velocity and volume, the air exchange rate, and the room
787 pressure cascade to ensure that air consistently flows from clean to
788 dirty areas, and that the appropriate quality of air is maintained
789 under dynamic operating conditions. The ACPH from HVAC, ACPH
790 contributed from the PEC, and the total ACPH must be documented
791 on the certification report.
- 792 • HEPA filter integrity testing: HEPA filters must be leak tested at the
793 factory and then leak tested again after installation and as part of
794 recertification.
- 795 • Total particle count testing (see *Monitoring Air Quality for Nonviable*
796 *Airborne Particles*): Total particle count testing must be performed
797 under dynamic operating conditions using current, state-of-the-art
798 electronic equipment.
- 799 • Smoke visualization studies: Smoke visualization studies must be
800 performed for each PEC during dynamic operating conditions to
801 demonstrate unidirectional airflow and sweeping action over and
802 away from the preparation(s).

803 Classified areas must additionally be recertified if there are changes to the
804 area such as redesign, construction, or replacement or relocation of any
805 PEC, or alteration in the configuration of the room that could affect airflow or
806 air quality.

807 All certification and recertification records must be reviewed by the
808 designated person to ensure that the classified environments comply with

809 the minimum requirements in this chapter. Records must be maintained in
810 accordance with the requirements in *17. Documentation*.

811 A corrective action plan must be implemented and documented in response
812 to any out-of-range results.

813 MONITORING AIR QUALITY FOR NONVIABLE AIRBORNE PARTICLES

814 It is imperative that all engineering control equipment function as designed
815 and that the levels of nonviable airborne particles remain within acceptable
816 limits during compounding (see [Table 3](#)). A monitoring program for
817 nonviable airborne particles must be developed and implemented to
818 measure the performance of the engineering controls that are being used to
819 provide the specified levels of air cleanliness (e.g., in the ISO Class 5 PEC
820 and ISO Class 7 and 8 rooms).

821 NONVIABLE AIR SAMPLING—TIMING AND LOCATIONS

822 Total nonviable airborne particle count testing must be conducted in all
823 classified areas during dynamic operating conditions at least every 6
824 months.

825 Nonviable air sampling sites must be selected in all classified areas.
826 Measurements of nonviable airborne particles must be taken in each PEC at
827 locations where there is greatest risk to the exposed CSPs, containers, and
828 closures. When conducting sampling of the PEC, care should be taken to
829 avoid disturbing the unidirectional airflow within the PEC. All sampling sites
830 and procedures must be described in the facility's SOP. Measurements of
831 nonviable airborne particles in other classified areas, including the buffer
832 room(s) and ante-room(s), should be taken at representative locations that
833 reflect the quality of air in the room(s).

834 DATA EVALUATION AND ACTION LEVELS

835 If levels measured during the nonviable air sampling program exceed the
836 criteria in [Table 3](#) for the ISO classification of the area sampled, the cause
837 must be investigated and corrective action taken. Some examples of
838 corrective action include process or facility improvements or HEPA filter
839 replacement or repair. The extent of the investigation should be consistent
840 with the deviation and should include an evaluation of trends.

841

842 **5. MICROBIOLOGICAL AIR AND SURFACE MONITORING**

843 An effective air and surface monitoring program provides information on
844 the environmental quality of the compounding area. In addition, an effective
845 air and surface monitoring program identifies environmental quality trends
846 over time, identifies potential routes of contamination, and allows for
847 implementation of corrective actions to minimize the risk of CSP
848 contamination. Sterile compounding facilities must develop and implement
849 written procedures for air and surface monitoring (see *9. SOPs and Master
850 Formulation and Compounding Records*). All air and surface monitoring

851 procedures, the test results, and the corrective actions must be documented,
852 and the records must be maintained in accordance with the requirements in
853 *17. Documentation.*

854 **5.1 General Monitoring Requirements**

855 The microbiological air and surface monitoring program must include 1)
856 viable impact volumetric airborne particulate sampling, and 2) surface
857 sampling. The goals of an air and surface monitoring program are to
858 determine whether contamination is present at unacceptable levels and to
859 assess whether proper personnel practices are being followed, cleaning and
860 disinfecting agents are effective, and environmental quality is maintained.

861 The air and surface monitoring program involves the collection and
862 evaluation of samples from various air and surface locations to detect
863 airborne and surface contaminants. The data from airborne and surface
864 sampling are then used to assess risks for contamination, potential routes of
865 contamination, and the adequacy of cleaning and disinfection agents and
866 procedures. Regular review of the sampling data must be performed to
867 detect trends such as elevated levels of microbial bioburden, elevated levels
868 of nonviable particulates, or other adverse changes within the environment.

869 In addition, results from air and surface sampling must be reviewed in
870 conjunction with personnel data (i.e., training records, visual observations,
871 competency assessments) to assess the state of control and to identify
872 potential risks of contamination. Prompt corrective action in response to any
873 adverse findings is essential to maintain the necessary environmental quality
874 for preparation of CSPs. Data must also be reviewed following corrective
875 actions to confirm that the actions taken have been effective in achieving the
876 required air and surface quality levels (see [Table 3](#), [Table 6](#), and [Table 7](#)).

877 Air and surface monitoring must be performed initially for sterile
878 compounding facilities to establish a baseline level of environmental quality.
879 After initial sampling, the environment in which sterile compounding
880 activities are performed must be monitored according to the minimum
881 frequencies described in this section to ensure that the environment remains
882 suitable for sterile compounding. Evaluating results collected over a period of
883 time can be useful in identifying trends or determining that a significant
884 change has occurred, even when the results fall within the specified limits.

885 Air and surface monitoring must be conducted during dynamic operating
886 conditions to confirm that the required environmental quality in classified
887 areas is maintained. In addition to the specific sampling frequencies
888 described in this section, sampling must be performed in any of the following
889 circumstances:

- 890 • In conjunction with the certification of new facilities and equipment
- 891 • After any servicing of facilities or equipment (see *4. Facilities and*
892 *Engineering Controls*)

- 893 • In response to identified problems (e.g., positive growth in sterility
894 tests of CSPs)
- 895 • In response to identified trends (e.g., repeated positive gloved
896 fingertip and thumb sampling results, failed media fill testing, or
897 repeated observations of air or surface contamination)
- 898 • In response to changes that could impact the sterile compounding
899 environment (e.g., change to cleaning agents)

900 The air and surface monitoring program must be clearly described in the
901 facility's SOPs, which must include a diagram of the sampling locations,
902 procedures for collecting samples, frequency of sampling, size of samples
903 (e.g., surface area, volume of air), time of day of sampling in relation to
904 activities in the compounding area, and action levels that will trigger
905 corrective action.

906 The times and locations of sampling should be carefully selected based on
907 their relationship to the activities performed in the area. It is important to
908 obtain samples from locations that pose the highest possible risk of
909 contamination to the CSP and that are likely to be representative of the
910 conditions throughout the area. To obtain air and surface samples that are
911 representative of the typical compounding conditions at the facility, air and
912 surface sampling must be conducted during dynamic operating conditions in
913 all PECs and classified rooms. However, the monitoring program must be
914 designed and conducted in a manner that minimizes the chance that the
915 sampling itself will contribute to contamination of the CSP or the
916 environment.

917 It is important that personnel be trained in the proper operation of the air
918 and surface sampling equipment to ensure accurate and reproducible
919 sampling. All air sampling devices must be serviced and calibrated as
920 recommended by the manufacturer.

921 **5.2 Monitoring Air Quality for Viable Airborne Particles**

922 A monitoring program for viable airborne particles must be developed and
923 implemented to assess microbiological air quality in all classified areas.

924 **VIABLE AIR SAMPLING—TIMING AND LOCATIONS**

925 Volumetric active air sampling of all classified areas using an impaction
926 device must be conducted in each classified area [e.g., ISO Class 5 PEC and
927 ISO Class 7 and 8 room(s)] during dynamic operating conditions at least
928 every 6 months. Air sampling sites must be selected in all classified areas.

929 When conducting sampling of the PEC, care should be taken to avoid
930 disturbing unidirectional airflow. See [Box 5-1](#) for active air sampling
931 procedures. A general microbiological growth medium that supports the
932 growth of bacteria and fungi must be used (e.g., TSA medium). COAs from
933 the manufacturer must verify that the medium meets the expected growth
934 promotion, pH, and sterilization requirements. Samples must be incubated in

935 a calibrated incubator at temperatures that will promote growth of bacteria
936 and fungi. The incubator temperature must be monitored during incubation,
937 either manually or by a continuous recording device, and the results must be
938 reviewed and documented. The microbiological incubator must be placed in a
939 location outside of the sterile compounding area. All air sampling activities
940 must be performed by trained individuals.

941 **Box 5-1. Active Air Sampling Procedures for Viable Airborne**
942 **Monitoring**

- Follow the manufacturer's instructions for operation of the active air sampling device, including placement of media.
- Using the sampling device, test at least 1 cubic meter or 1000 liters of air from each location sampled.
- At the end of the sampling, retrieve the media plates/devices and cover them.
- Invert the media and incubate at 30°–35° for no less than 48 hours. Examine for growth. Record the total number of discrete colonies of microorganisms on each plate as cfu per cubic meter of air on an environmental sampling form based on sample type (i.e., viable air), sample location, and sample date.
- Then incubate the inverted media at 20°–25° for no less than 5 additional days. Examine the media plates for growth. Record the total number of discrete colonies of microorganisms on each plate as cfu per cubic meter of air on an environmental sampling form based on sample type (i.e., viable air), sample location, and sample date.
- Alternatively, two pieces of media may be collected for each sample location and incubated concurrently in separate incubators at 30°–35° for no less than 5 days and at 20°–25° for no less than 5 days. Record the total number of discrete colonies of microorganisms on each plate as cfu per cubic meter of air on an environmental sampling form based on sample type (i.e., viable air), sample location, and sample date.

943 **DATA EVALUATION AND ACTION LEVELS**

944 Evaluate cfu counts against the action levels in [Table 6](#), and examine
945 counts in relation to previous data to identify adverse results or trends. If
946 two pieces of media are collected at a single location, all recovered growth
947 on each is documented and action levels are applied to each device. If levels
948 measured during the viable air monitoring program exceed the levels in
949 [Table 6](#) for the ISO classification levels of the area sampled, the cause must
950 be investigated and corrective action must be taken. The corrective action
951 plan must be dependent on the cfu count and the microorganism recovered.
952 Some examples of corrective action include process or facility improvements,
953 personnel training, cleaning and disinfecting, or HEPA filter replacement

954 and/or repair. The extent of the investigation should be consistent with the
955 deviation and should include an evaluation of trends. The corrective action
956 plan must be documented. If levels measured during viable air sampling
957 exceed the levels in [Table 6](#), the genus of any microorganism recovered
958 must be identified (see [Microbial Characterization, Identification, and Strain](#)
959 [Typing \(1113\)](#)) with the assistance of a microbiologist.

960 **Table 6. Action Levels for Viable Airborne Particle Air Sampling^a**

ISO Class	Air Sampling Action Levels [cfu per cubic meter (1000 liters) of air per plate]
5	> 1
7	> 10
8	> 100

^a Adapted from *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*. U.S. Department of Health and Human Services, FDA, September 2004.

961 **5.3 Monitoring Surfaces for Viable Particles**

962 Surface sampling is an important tool used to assist in maintenance of a
963 suitably controlled environment for compounding CSPs, especially because
964 transfer of microbial contamination from improperly disinfected work
965 surfaces via inadvertent touch contact by compounding personnel is a
966 potential source of contamination of CSPs. Surface sampling is useful for
967 evaluating facility cleaning and material handling procedures, work surface
968 cleaning and disinfecting procedures, and personnel competency in work
969 practices such as cleaning and disinfecting of component and/or vial
970 surfaces. All sampling sites and procedures must be described in the
971 facility's SOP.

972 SURFACE SAMPLING: TIMING AND LOCATIONS

973 Surface sampling of all classified areas must be conducted at least
974 monthly. Surface sampling for microbial contamination must be performed in
975 all classified areas (see [Microbiological Control and Monitoring of Aseptic](#)
976 [Processing Environments \(1116\)](#)). Each classified area must be sampled,
977 including the following:

- 978 • The interior of the PEC and the equipment contained in it
- 979 • Staging or work area(s) near the PEC
- 980 • Frequently touched surfaces
- 981 • Pass-through chamber(s)

982 When conducted, surface sampling must be performed at the end of the
983 compounding activities or shift, but before the area has been cleaned and
984 disinfected.

985
986
987
988
989
990
991
992
993
994
995
996
997
998
999

SAMPLING PROCEDURES

Surface sampling devices (e.g., plates, paddles, or slides) containing microbial growth media must be used for sampling flat surfaces. COAs from the manufacturer must verify that the devices meet the expected growth promotion, pH, and sterilization requirements. Surface sampling devices must contain general microbial growth media (e.g., TSA) supplemented with neutralizing additives (e.g., lecithin and polysorbate 80) to neutralize the effects of any residual disinfecting agents. If used, contact plates must have a raised convex surface. Sterile swabs wetted with sterile water or a sterile neutralizing buffer may be used when sampling irregular surfaces and difficult-to-reach locations, such as crevices, corners, and spaces between surfaces. After sampling, the sampled area must be thoroughly cleaned and disinfected (see 6. *Cleaning and Disinfecting Compounding Areas*).

See [Box 5-2](#) for the procedures for surface sampling on flat surfaces and [Box 5-3](#) for the procedures for surface sampling on irregular surfaces.

1000

Box 5-2. Using Devices for Flat Surface Sampling

- Remove the cover from the contact sampling device. Using a rolling motion, firmly press the media surface onto the surface to be sampled. The contact sampling device will leave a residue of growth medium on the sample site. After sampling, use a low-lint sterile wiper to thoroughly clean the sampled area with sterile 70% IPA.
- Cover each contact sampling device. If using plates, invert the plates.
- Incubate the contact sampling devices at 30°–35° for no less than 48 hours. Examine for growth. Record the total number of discrete colonies of microorganisms on each plate as cfu per sample on an environmental sampling form based on sample type (i.e., surface), sample location, and sample date.
- Incubate the contact sampling device at 20°–25° for no less than 5 additional days. Examine the device for growth. Record the total number of discrete colonies of microorganisms (cfu per sample) on the environmental sampling record based on sample type (i.e., surface), sample location, and sample date.
- Alternatively, two devices may be collected for each sample location and incubated concurrently in separate incubators at 30°–35° for no less than 5 days and at 20°–25° for no less than 5 days. Record the total number of discrete colonies of microorganisms (cfu/sample) on the environmental sampling record based on sample type (i.e., surface), sample location, and sample date.

1001

Box 5-3. Using Devices for Irregular Surface Sampling

- Sterile swabs wetted with sterile water or a sterile neutralizing buffer should be used.

- If using the neutralizing buffer, the residue must be removed from the surface after sampling using sterile 70% IPA. Swabs sampled with sterile water must be processed with a neutralizing buffer or plated in a neutralizing medium.
- After swabbing the area, place the swab in appropriate diluent or sterile packaging until it can be processed. The swab must be processed using a diluent and an extraction step to aid in the removal of any microorganisms from the swab.
- Plate all or a portion of the diluent in TSA (or TSA with neutralizers). If the diluent is diluted, the dilution factor must be applied to the raw count to determine the actual total microbial count.
- Incubate the plates at 30°–35° for no less than 48 hours. Examine for growth. Record the total number of discrete colonies of microorganisms on each plate as cfu per sample on an environmental sampling form based on sample type (i.e., surface), sample location, and sample date.
- Incubate the plates at 20°–25° for no less than 5 additional days. Examine for growth. Record the total number of discrete colonies of microorganisms on each plate as cfu per sample on the environmental sampling form based on sample type (i.e., surface), sample location, and sample date.
- Alternatively, two devices may be collected for each area and incubated concurrently in separate incubators at 30°–35° for no less than 5 days and at 20°–25° for no less than 5 days. Record the total number of discrete colonies of microorganisms on each plate as cfu per sample on the environmental sampling form based on sample type (i.e., surface), sample location, and sample date.

1002

DATA EVALUATION AND ACTION LEVELS

1003

Evaluate cfu counts against the action levels in [Table 7](#), and examine

1004

counts in relation to previous data to identify adverse results or trends. If

1005

two devices were collected at a single location, all recovered growth on each

1006

is documented and action levels are applied to each device. If levels

1007

measured during surface sampling exceed the levels in [Table 7](#) for the ISO

1008

classification levels of the area sampled, the cause must be investigated and

1009

corrective action must be taken. The corrective action plan must be

1010

dependent on the cfu count and the microorganism recovered. Some

1011

examples of corrective action include process or facility improvements,

1012

personnel training, cleaning and disinfecting, or HEPA filter replacement

1013

and/or repair. The extent of the investigation should be consistent with the

1014

deviation and should include an evaluation of trends. The corrective action

1015

plan must be documented. If levels measured during surface sampling

1016 exceed the levels in [Table 7](#), the genus of any microorganism recovered
1017 must be identified (see [1113](#)) with the assistance of a microbiologist.

1018 **Table 7. Action Levels for Surface Sampling**

ISO Class	Surface Sampling Action Levels (cfu/device or swab)
5	>3
7	>5
8	>50

1019
1020 **6. CLEANING AND DISINFECTING COMPOUNDING AREAS**

1021 Cleaning and disinfecting are important because surfaces in classified areas
1022 and SCA are a potential source of microbial contamination of CSPs. The
1023 process of cleaning involves removing organic and inorganic materials from
1024 surfaces, usually with a manual or mechanical process and a cleaning agent.
1025 The process of disinfecting involves destruction of microorganisms, usually
1026 with a chemical agent. Surfaces must be cleaned prior to being disinfected
1027 unless an Environmental Protection Agency (EPA) registered one-step
1028 disinfectant cleaner is used to accomplish both the cleaning and disinfection
1029 in one step. Some EPA registered one-step disinfectant cleaners may have
1030 sporicidal properties.

1031 Cleaning and disinfecting surfaces must occur at the minimum frequencies
1032 specified in [Table 8](#) or, if compounding is not performed daily, cleaning and
1033 disinfecting must be completed before initiating compounding. Cleaning and
1034 disinfecting must be repeated when spills occur; when surfaces, floors, and
1035 walls are visibly soiled; and when contamination is known or suspected in
1036 the compounding areas.

1037 All cleaning and disinfecting activities must be performed by trained and
1038 appropriately garbed personnel using facility-approved agents and
1039 procedures, which must be described in written SOPs. Cleaning must be
1040 performed in the direction of clean to dirty areas. The frequency, method(s),
1041 and location(s) of cleaning and disinfection agent use must be established in
1042 written SOPs, in accordance with the manufacturer's instructions, and must
1043 be followed by all cleaning personnel. The manufacturer's directions or
1044 published data for the minimum contact time must be followed for the
1045 cleaning, disinfecting, and sporicidal agents used. All cleaning and
1046 disinfecting activities must be documented.

1047 **Table 8. Minimum Frequency for Cleaning and Disinfecting Surfaces**
1048 **and Applying Sporicidals in Classified Areas and within the Perimeter**
1049 **of the SCA**

1050

Site	Cleaning	Disinfecting	Applying Sporicidal
PEC(s) and equipment inside the PEC(s)	The horizontal work surface at the beginning and end of each shift, after spills, and when surface contamination is known or suspected. The ceiling, walls, bars and any equipment inside the PEC on each day that compounding is performed and when contamination is known or suspected.	Disinfect all interior surfaces of the PEC at the beginning and end of each shift, after spills, and when surface contamination is known or suspected. Disinfect the horizontal work surface at least every 30 minutes while compounding if the compounding process takes 30 minutes or less. If the compounding process of a single batch or preparation takes more than 30 minutes, compounding must not be disrupted and the work surface of the PEC must be disinfected immediately after compounding.	Monthly
Surfaces of sink(s)	Daily	Daily ^a	Monthly
Pass-through(s)	Daily	Daily ^a	Monthly
Work surface(s) outside the PEC	Daily	Daily ^a	Monthly
Floor(s)	Daily	Daily ^a	Monthly
Wall(s), door(s), and door frame(s)	Monthly	Monthly ^a	Monthly
Ceiling(s)	Monthly	Monthly ^a	Monthly
Storage shelving and storage bins	Monthly	Monthly ^a	Monthly
^a Many disinfectants registered by the EPA are one-step cleaning and			

disinfecting agents, which means that the disinfectant has been formulated to be effective in the presence of light to moderate soiling without a separate cleaning step.

6.1 Cleaning, Disinfecting, and Sporidical Agents

Cleaning and disinfecting agents must be selected and used with careful consideration of compatibilities, effectiveness, and inappropriate or toxic residues or fumes. 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 (see and [Disinfectants and Antiseptics \(1072\)](#)). After the disinfectant is applied and wiped on the surface to be disinfected, the disinfectant must be allowed to dwell for the minimum contact time specified by the manufacturer, during which time the surface cannot be disturbed. Sporidical agents, shown to be effective against *Bacillus* species, must be used at least monthly to disinfect all surfaces in classified and SCAs. The disinfecting agents (e.g., 70% IPA) used in the ISO 5 PEC must be sterile. See [Table 9](#) for a summary of the purposes of the cleaning, disinfectant, and sporidical agents.

Table 9. Purpose of Cleaning, Disinfecting, and Sporidical Agents

Type of Agent	Purpose
Cleaning agent	An agent for the removal of residues (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.
Disinfectant	A chemical or physical agent used on inanimate surfaces and objects to destroy fungi, viruses, and bacteria. Sporidical disinfectant agents are considered a special class of disinfectants that also are effective against bacterial endospores.
Sporidical agent	A chemical or physical agent that destroys bacterial and fungal spores when used at a sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.

6.2 Cleaning Supplies

All cleaning supplies (e.g., wipers, sponges, and mop heads) with the exception of tool handles and holders must be low-linting. Wipers, sponges, and mop heads should be disposable. If disposable cleaning supplies are used, they must be discarded after each cleaning activity. Reusable cleaning tools must be made of cleanable materials (e.g., no wooden handles) and must be cleaned before and after each use. 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. They must be discarded after an appropriate amount of time, to be determined based on the condition of the tools. Dispose of cleaning supplies used in the classified areas and SCAs in a

1079 manner that minimizes the potential for dispersing contaminants into the air
1080 (e.g., with minimal agitation, away from work surfaces).

1081 **6.3 Cleaning and Disinfecting the PEC**

1082 Clean and disinfect the PEC at the minimum frequencies specified in [Table](#)
1083 [8](#). See [Box 6-1](#) for procedures for cleaning and disinfecting the PEC. If the
1084 PEC contains a removable work tray, all sides of the work tray and the area
1085 underneath the work tray must be cleaned and disinfecting at least monthly.

1086 **Box 6-1. Procedures for Cleaning and Disinfecting the PEC**

- Remove any particles, debris, or residue with an appropriate solution (e.g., [Sterile Water for Injection](#) or [Sterile Water for Irrigation](#)) using sterile, low-lint wipers.
- Apply a cleaning agent (e.g., EPA-registered one-step disinfectant cleaner).
- Disinfect with a sterile disinfectant (e.g., sterile 70% IPA).
- Allow the surface to dry completely before beginning compounding.
- The PEC must be wiped with a sporicidal agent at least monthly.

1087 **6.4 Cleaning and Disinfecting Compounding Supplies for the** 1088 **Classified Areas and SCAs**

1089 No shipping carton(s) or other corrugated or uncoated cardboard are
1090 allowed in the classified area or SCA. Before compounding supplies are
1091 introduced into a classified area or SCA, they must be wiped with a
1092 sporicidal agent or sterile disinfectant (e.g., sterile 70% IPA) using low-lint
1093 wipers. After the sporicidal or sterile disinfectant is applied and wiped on the
1094 surface, the agent must be allowed to dwell for the minimum contact time
1095 specified by the manufacturer, during which time the item cannot be
1096 disturbed. The agent used for wiping the packaging must not alter the
1097 product label.

1098 Any item to be transferred into the PEC must be wiped with a sporicidal
1099 agent or sterile disinfectant (e.g., sterile 70% IPA) using low-lint wipers. The
1100 agent must be allowed to dwell for the minimum contact time specified by
1101 the manufacturer, during which time the item cannot be disturbed. The
1102 agent used for wiping the packaging must not alter the product label.

1103 **6.5 Disinfecting Critical Sites within the PEC**

1104 Critical sites (e.g., vial stoppers, ampule necks, and intravenous bag
1105 septums) must be disinfected by wiping them with sterile 70% IPA in the
1106 PEC. The critical site must be wiped in one direction ensuring that both
1107 chemical and mechanical actions are used to remove contaminants. The
1108 sterile 70% IPA must be allowed to dry before entering or puncturing
1109 stoppers/septums with sterile needles or breaking the necks of ampules.

1111 **7. EQUIPMENT, SUPPLIES, AND COMPONENTS**

1112 **7.1 Equipment**

1113 PECs are described in *Types of PECs and Placement*. Other equipment used
1114 in compounding CSPs [e.g., automated compounding devices (ACDs),
1115 repeater pumps, and balances] should be of suitable composition such that
1116 the surfaces that contact components are not reactive or sorptive.
1117 Equipment that must be brought into classified areas must be wiped with
1118 disinfectant using low-lint wipers.

1119 Equipment must be placed in a manner that facilitates sterile compounding
1120 operations. The equipment must be capable of operating properly and within
1121 required performance parameters. Compounding personnel must establish
1122 and follow SOPs for the calibration, maintenance, cleaning, and use of the
1123 equipment based on the manufacturer's recommendations. Personnel must
1124 maintain records from equipment calibration, verification, and maintenance
1125 in accordance with the requirements in *17. Documentation*.

1126 ACDs, repeater pumps, and other similar equipment are designed to assist
1127 in the compounding of preparations by delivering specific volumes of
1128 solution(s) automatically under computerized control.

1129 Before using ACDs, repeater pumps, or other similar equipment,
1130 compounding personnel must conduct an accuracy assessment before the
1131 first use and again each day the equipment is used to compound CSPs. The
1132 precision of the equipment can be monitored based on an assessment of
1133 day-to-day variations in its accuracy measures. Compounding personnel
1134 must keep a daily record of the accuracy measurements on the days the
1135 equipment is in use. Corrective actions must be implemented if accuracy
1136 measurements are outside the manufacturer's specification.

1137 **7.2 Supplies**

1138 Supplies (e.g., beakers, utensils, needles, syringes, filters, and tubing sets)
1139 should be of suitable composition such that the surfaces that contact
1140 components are not reactive or sorptive. Supplies in direct contact with the
1141 CSP must be sterile and depyrogenated. When sterile supplies are received
1142 in sealed pouches designed to keep them sterile until opening, the sterile
1143 supplies may be removed from the covering pouches as the supplies are
1144 introduced into the ISO Class 5 PEC without the need to disinfect the
1145 individual sterile supply items.

1146 **7.3 Components**

1147 Compounding personnel must follow facility SOPs, which must address the
1148 selection, receipt, evaluation, handling, storage, and documentation of all
1149 CSP components, including all ingredients, containers, and closures.
1150 Packages of components that must be brought into classified areas must be
1151 wiped with a sporicidal agent or sterile disinfectant using low-lint wipers.

1152 **COMPONENT SELECTION**

1153 Conventionally manufactured sterile products should be used when
1154 available and appropriate for the intended CSP. All APIs must be

1155 accompanied by a COA that includes the specifications and test results and
1156 shows that the API meets the specifications of the *USP–NF* monograph, if
1157 one exists. All other ingredients must be accompanied by documentation
1158 (e.g., COA, labeling) that includes the specifications and shows that the
1159 ingredient meets the specifications.

1160 In the US, APIs used in compounding must be obtained from an FDA-
1161 registered facility and must comply with the criteria in the *USP–NF*
1162 monograph, if one exists. All ingredients other than API(s) should preferably
1163 be obtained from an FDA-registered facility and must comply with the
1164 criteria in the *USP–NF* monograph, if one exists. If ingredients other than
1165 APIs (e.g., excipients and preservatives) cannot be obtained from an FDA-
1166 registered facility, the designated person must select an acceptable and
1167 reliable source (see [Good Distribution Practices for Bulk Pharmaceutical
1168 Excipients \(1197\)](#)). The compounding facility must establish the identity,
1169 strength, purity, and quality of the ingredients obtained from that supplier
1170 by reasonable means. Reasonable means may include visual inspections,
1171 evaluation of a COA supplied by the manufacturer, and/or verification by
1172 analytically testing a sample to determine conformance with the COA or
1173 other specifications.

1174 Each lot of commercially available sterile, depyrogenated containers and
1175 container–closure systems must be accompanied by a COA or other
1176 documentation showing conformance with established specifications (i.e.,
1177 sterility and depyrogenation requirements). If sterilization and
1178 depyrogenation of supplies or container–closure systems are performed on
1179 site, the efficacy of each process must be established and documented (see
1180 [Sterilization of Compendial Articles \(1229\)](#)).

1181 COMPONENT RECEIPT

1182 Upon receipt of each lot of a component, the external packaging must be
1183 examined for evidence of deterioration and other aspects of unacceptable
1184 quality. Facility personnel must verify the labeling and condition of the
1185 component, [e.g., whether the outer packaging is damaged and whether
1186 temperature-sensing indicators show that the component has been exposed
1187 to excessive temperature(s)].

1188 Any component found to be of unacceptable quality must be promptly
1189 rejected, clearly labeled as rejected, and segregated to prevent use before
1190 appropriate disposal. Any other lots of that component from that vendor
1191 must be examined to determine whether other lots have the same defect.

1192 The date of receipt by the compounding facility must be clearly marked on
1193 each API or inactive ingredient package that lacks a vendor expiration date.
1194 Packages of ingredients (i.e., API and inactive ingredients) that lack a
1195 vendor’s expiration date must be assigned a conservative expiration date,
1196 not to exceed 1 year after receipt by the compounding facility.

1197

1198 **COMPONENT EVALUATION BEFORE USE**

1199 Compounding personnel must ascertain before use that ingredients for
1200 CSPs are of the correct identity, appropriate quality, within expiry date, and
1201 have been stored under appropriate conditions. The following information
1202 should be used to make this determination: prescription or medication order,
1203 compounding record, master formulation record (if used), vendor labels,
1204 COAs of API(s) and inactive ingredient(s), product labeling of conventionally
1205 manufactured sterile products, labeling of CSPs, and documentation of the
1206 compounding facility storage conditions and practices.

1207 All components must be re-inspected before use. All packages must be re-
1208 inspected to detect container breaks, looseness of the cap or closure, and
1209 deviation from the expected appearance, aroma, and texture of the contents
1210 that might have occurred during storage. Sterile container–closures must be
1211 visually re-inspected to ensure that they are free from defects that could
1212 compromise sterility and are otherwise suitable for their intended use.

1213 If components intended for use in preparing CSPs do not meet expected
1214 quality attributes, they must be promptly rejected, clearly labeled as
1215 rejected, and segregated to prevent use before disposal.

1216 **COMPONENT HANDLING AND STORAGE**

1217 All components must be handled and stored in a manner that prevents
1218 contamination, mix-ups, and deterioration. Ingredients must be stored in
1219 closed containers under temperature, humidity, and lighting conditions
1220 consistent with those indicated in official monographs or specified by the
1221 suppliers and/or manufacturer.

1222

1223 **8. STERILIZATION AND DEPYROGENATION**

1224 When selecting the sterilization method for CSPs prepared from one or
1225 more nonsterile starting components, personnel must take into consideration
1226 the nature of the component(s), their physical and chemical properties, and
1227 the intended container–closure system. The sterilization method used must
1228 sterilize the CSP without degrading its physical and chemical stability (e.g.,
1229 affecting its strength, purity, and quality) or the packaging integrity. See
1230 also the [\(1229\)](#) family of chapters.

1231 The following must be considered when selecting an appropriate
1232 sterilization method:

- 1233 • Terminal sterilization (e.g., dry heat, steam, or irradiation) is the
1234 preferred method unless the specific CSP or container–closure system
1235 cannot tolerate terminal sterilization
- 1236 • Steam sterilization is not an option if moisture, pressure, or the
1237 temperatures used would degrade the CSP or if there is insufficient
1238 moisture to sterilize the CSP within the final, sealed container–closure
1239 system (e.g., anhydrous oils and solid CSPs)

- 1240 • Filtration is not an option when compounding a suspension if the
1241 suspended drug particles are removed by the filter being used

1242 CSPs that are terminally sterilized (e.g., dry heat, steam, or irradiation)
1243 must use a process intended to achieve a sterility assurance level (SAL) of
1244 10^{-6} . An SAL of 10^{-6} is equivalent to a probability that 1 unit in a million is
1245 nonsterile. An SAL value cannot be applied to CSPs that are aseptically filled
1246 into a sterile container following sterilization by filtration because
1247 sterilization by filtration is not terminal sterilization.

1248 A description of the terminal sterilization and depyrogenation process,
1249 including the temperature, pressure (if applicable), duration, permissible
1250 load conditions for each cycle, and results of biological indicators must be
1251 included in the facility's SOPs.

1252 SOPs must include training of personnel on all sterilization methods and
1253 equipment used by the facility. In addition, the SOPs must include a
1254 schedule and method for establishing and verifying the effectiveness of the
1255 terminal sterilization and depyrogenation methods selected, as well as the
1256 methods for maintaining and cleaning the sterilizing and depyrogenation
1257 equipment.

1258 **8.1 Depyrogenation**

1259 See [Dry Heat Depyrogenation \(1228.1\)](#). Dry heat depyrogenation must be
1260 used to render glassware, metal, and other thermostable containers and
1261 components pyrogen-free. Depyrogenation processes typically operate at a
1262 range of temperatures, from approximately 170° up to about 400° ,
1263 depending on the exposure time (e.g., a cycle might hold the items at 250°
1264 for 30 minutes to achieve sterility and depyrogenation). The duration of the
1265 exposure period must include sufficient time for the items to reach the
1266 depyrogenation temperature. The items must remain at the depyrogenation
1267 temperature for the duration of the depyrogenation period.

1268 The effectiveness of the dry heat depyrogenation cycle must be established
1269 initially and verified annually using endotoxin challenge vials (ECVs) to
1270 demonstrate that the cycle is capable of achieving a ≥ 3 -log reduction in
1271 endotoxins (see [Bacterial Endotoxins Test \(85\)](#)). This verification must be
1272 documented.

1273 Items that are not thermostable must be depyrogenated by rinsing with
1274 sterile, pyrogen-free water and then thoroughly drained or dried
1275 immediately before use in compounding.

1276 **8.2 Sterilization by Filtration**

1277 See [Sterilizing Filtration of Liquids \(1229.4\)](#). Sterilizing filters must be
1278 sterile, depyrogenated, and have a nominal pore size of $0.22\ \mu\text{m}$ or smaller.
1279 They must be certified by the manufacturer to retain at least 10^7
1280 microorganisms of a strain of *Brevundimonas diminuta* per square
1281 centimeter of upstream filter surface area under conditions similar to those

1282 in which the CSPs will be filtered (i.e., pressure, flow rate, and volume
1283 filtered).

1284 The designated person must ensure—from available published information,
1285 from supplier documentation, or through direct challenge (e.g., filtering the
1286 CSP)—that the filters 1) are chemically and physically compatible with all
1287 ingredients in the CSP (e.g., water-miscible alcohols may damage filter
1288 integrity); 2) are chemically stable at the pressure and temperature
1289 conditions that will be used; and 3) have enough capacity to filter the
1290 required volumes. The filter dimensions and the CSP to be sterilized by
1291 filtration should permit the sterilization process to be completed without the
1292 need for replacement of the filter during the process. Filter units used to
1293 sterilize CSPs must be subjected to the manufacturers' recommended
1294 integrity testing, such as a post-use bubble point test. If multiple filters are
1295 required for the compounding process, each of the filters must pass a filter-
1296 integrity test.

1297 When CSPs are known to contain excessive particulate matter, a
1298 prefiltration step must be performed using a filter of larger nominal pore size
1299 (e.g., 1.2 μm) or a separate filter of larger nominal pore size should be
1300 placed upstream of (i.e., prior to) the sterilizing filter to remove gross
1301 particulate contaminants before the CSP is passed through the sterilizing-
1302 grade filter. Excessive particulate matter requiring a prefiltration step could
1303 potentially be a signal of an inappropriate formulation, and therefore the
1304 formulation and the process should be assessed and, if necessary, modified.
1305 CSPs that were prepared using a filter that failed integrity tests must be
1306 discarded or resterilized by filtration.

1307

8.3 Sterilization by Steam Heat

1308 Temperatures used to achieve sterilization by steam heat are lower than
1309 those used to achieve depyrogenation. The process of thermal sterilization
1310 using saturated steam under pressure (i.e., autoclaving) is the preferred
1311 method for terminal sterilization of aqueous CSPs in their final, sealed
1312 container–closure system (see [Steam Sterilization by Direct Contact \(1229.1\)](#)).
1313 Steam sterilization is not an option if moisture, pressure, or the
1314 temperatures used would degrade the CSP.

1315 To achieve sterility when steam sterilization is used, all materials must be
1316 directly exposed to steam under adequate pressure for the length of time
1317 necessary, as determined by use of appropriate biological indicators, to
1318 render the items sterile (e.g., between 20 and 60 minutes at 121° saturated
1319 steam under a pressure of 15 psi, depending on the volume or size of the
1320 CSP being sterilized). The duration of the exposure period must include
1321 sufficient time for the entire contents of the CSP and other items to reach
1322 the sterilizing temperature. The CSP and other items must remain at the
1323 sterilizing temperature for the duration of the sterilization period.

1324 CSPs must be placed in the autoclave to allow steam to reach the CSPs
1325 without entrapment of air. Flat, stainless steel trays with low sides or

1326 ventilated bottoms will permit steam contact. When preparing items for
1327 steam sterilization, the items must be wrapped in low-lint protective fabric
1328 or paper or sealed in envelopes that will permit steam penetration and that
1329 are designed to prevent post-sterilization microbial contamination. For CSPs,
1330 immediately before filling ampules and vials that will be steam sterilized,
1331 solutions must be passed through a filter with a nominal pore size of not
1332 larger than 1.2 µm for removal of particulate matter.

1333 Sealed containers must be able to generate steam internally. Stopped
1334 and crimped empty vials must contain a small amount of sterile water to
1335 generate steam. Deep containers, such as beakers and graduated cylinders,
1336 must be inverted or placed on their sides at a downward-sloping angle to
1337 minimize air entrapment and to facilitate condensate drainage, or must have
1338 a small amount of sterile water placed in them before steam sterilization.
1339 Porous materials and those items with occluded pathways (e.g., tubing)
1340 must only be sterilized by steam if the autoclave chamber has suitable
1341 cycles for dry goods, such as a pre-vacuum process to remove air before
1342 steam is sent into the chamber. Elastomeric closures and many other dry
1343 goods will need a drying cycle after steam exposure to remove condensed or
1344 absorbed moisture.

1345 The effectiveness of steam sterilization must be verified and documented
1346 with each sterilization run or load by using appropriate biological indicators,
1347 such as spores of *Geobacillus stearothermophilus*, ATCC 12980, ATCC 7953,
1348 or equivalent (see [Biological Indicators for Sterilization \(1229.5\)](#)), and other
1349 confirmation methods such as physicochemical indicators and integrators
1350 (see [Physicochemical Integrators and Indicators for Sterilization \(1229.9\)](#)).

1351 The steam supplied must be free of contaminants and generated using
1352 water per the manufacturer's recommendation. A calibrated data recorder or
1353 chart must be used to monitor each cycle and to examine for cycle
1354 irregularities (e.g., deviations in temperature or pressure). The date, run,
1355 and load numbers of the steam sterilizer used to sterilize a CSP must be
1356 documented in the compounding record.

1357 **8.4 Sterilization by Dry Heat**

1358 Dry heat may be used for those items that cannot be sterilized by steam or
1359 other means, when either the moisture would damage the material or the
1360 wrapping material is impermeable (see [Dry Heat Sterilization \(1229.8\)](#)).

1361 Sterilization by dry heat requires higher temperatures and longer exposure
1362 times than sterilization by steam. The duration of the exposure period must
1363 include sufficient time for the entire contents of CSPs and other items to
1364 reach the sterilizing temperature. The CSP and other items must remain at
1365 the sterilizing temperature for the duration of the sterilization period.

1366 Dry heat sterilization is usually done in an oven designed for sterilization at
1367 a temperature of 160° or higher. If lower temperatures are used, they must
1368 be shown to achieve effective sterilization (see [Dry Heat Sterilization \(1229.8\)](#), [Validation of Dry Heat Sterilization, Biological Indicators](#)).

1370 Heated air must be evenly distributed throughout the chamber, which is
1371 typically accomplished by an air blower. The calibrated oven must be
1372 equipped with temperature controls and a timer. During sterilization,
1373 sufficient space must be left between materials to allow for circulation of the
1374 hot air. A calibrated data recorder or chart must be used to monitor each
1375 cycle and the data must be reviewed to identify cycle irregularities (e.g.,
1376 deviations in temperature or exposure time).

1377 The effectiveness of the dry heat sterilization method must be validated,
1378 verified, and documented with each sterilization run or load using
1379 appropriate biological indicators such as spores of *Bacillus atrophaeus*, ATCC
1380 9372 (see [\(1229.5\)](#)), and other confirmation methods (e.g., temperature-
1381 sensing devices). The date, run, and load numbers of the dry heat oven
1382 used to sterilize a CSP must be documented in the compounding record.

1383

1384 **9. SOPS AND MASTER FORMULATION AND COMPOUNDING RECORDS**

1385

9.1 Creating and Following SOPs

1386 Facilities that prepare CSPs must develop SOPs for the compounding
1387 process and other support activities. A designated person must ensure that
1388 SOPs are appropriate and are implemented, which includes ensuring that
1389 personnel demonstrate competency in performing every procedure that
1390 relates to their job function. A designated person must follow up to ensure
1391 that corrective actions are taken if problems, deviations, failures, or errors
1392 are identified. The corrective action must be documented.

1393 All personnel who perform or oversee compounding or support activities
1394 must be trained in the SOPs. All compounding personnel must:

- 1395 • Be able to recognize potential problems, deviations, failures, or errors
1396 associated with preparing a CSP (e.g., those related to equipment,
1397 facilities, materials, personnel, the compounding process, or testing)
1398 that could potentially result in contamination or other adverse impact
1399 on CSP quality
- 1400 • Report any problems, deviations, or errors to the designated person

1401 SOPs must be reviewed at least every 12 months by the designated person
1402 to ensure that they reflect current practices, and the review must be
1403 documented. Any changes or alterations to an SOP must be made only by a
1404 designated person and must be documented. Revisions to SOPs must be
1405 communicated to all personnel involved in these processes and procedures,
1406 and personnel should document acknowledgement of the communication.

1407

9.2 Creating Master Formulation Records

1408 A Master Formulation Record must be created for CSPs prepared in a batch
1409 for more than 1 patient, or for CSPs prepared from nonsterile ingredient(s).

1410 Any changes or alterations to the Master Formulation Record must be made
1411 only by a designated person. Any change(s) must be documented with the
1412 date and time the change was made and the identity of the person who
1413 made the change. [Box 9-1](#) lists the information that must be included in a
1414 Master Formulation Record.

1415

Box 9-1. Master Formulation Records

A Master Formulation Record must include at least the following information:

- Name, strength or activity, and dosage form of the CSP
- Identities and amounts of all ingredients
- Type and size of container–closure system(s)
- Complete instructions for preparing the CSP, including equipment, supplies, a description of the compounding steps, and any special precautions
- Physical description of the final CSP
- BUD and storage requirements
- Reference source to support the stability of the CSP

If applicable, the Master Formulation Record must also include:

- Quality control (QC) procedures (e.g., pH testing, filter integrity testing)
- Sterilization method (e.g., steam, dry heat, irradiation, or filter)
- Other information needed to describe the compounding process and ensure repeatability (e.g., adjusting pH and tonicity)

1416

9.3 Creating Compounding Records

1417 A Compounding Record must be created for all CSPs. The Compounding
1418 Record must be created by the compounder preparing the CSP to document
1419 the compounding process or repackaging process. A Compounding Record
1420 may be in the form of a prescription or medication order, compounding log,
1421 or label. If an ACD, repeater pump, workflow management system, or other
1422 similar equipment is used, the required information in the compounding
1423 record may be stored electronically as long as it is retrievable and contains
1424 the required information (see [Box 9-2](#)). A Master Formulation Record can
1425 serve as the basis for preparing the Compounding Record. For example, a
1426 copy of the Master Formulation Record can be made that contains spaces for

1427 recording the information needed to complete the Compounding Record. [Box](#)
1428 [9-2](#) lists the information that must be included in a Compounding Record.

1429 **Box 9-2. Compounding Records**

Compounding Records must include at least the following information:

- Name, strength or activity, and dosage form of the CSP
- Date and time of preparation of the CSP
- Assigned internal identification number (e.g., prescription, order, or lot number)
- Identity of all individuals involved in each step (e.g., technician or pharmacist)
- Name, vendor or manufacturer, lot number, and expiration date for each ingredient
- Weight or volume of each ingredient
- Total quantity compounded
- Assigned BUD and storage requirements

If applicable, the Compounding Record must also include:

- Master Formulation Record reference for the CSP
- Calculations made to determine and verify quantities and/or concentrations of components
- Results of QC procedures (e.g., visual inspection, filter integrity testing, pH testing)

1430

1431

10. RELEASE TESTING

1432 All release testing procedures (e.g., visual inspections and testing) must be
1433 included in the facility's documentation (see 9. *SOPs and Master Formulation*
1434 *and Compounding Records*). Any out-of-specification results must be
1435 investigated, and the corrective action plan must be implemented and
1436 documented as part of the quality assurance (QA) and QC program (see 15.
1437 *Quality Assurance and Quality Control*).

1438

10.1 Visual Inspection

1439 At the completion of compounding, before release and dispensing, the CSP
1440 must be visually inspected to determine whether the physical appearance of
1441 the CSP is as expected (e.g., it is inspected for evidence of inappropriate
1442 visible particulates or other foreign matter, discoloration, or other defects).
1443 The CSP must be visually inspected to confirm that the CSP and its labeling

1444 match the prescription or medication order. The inspection also must include
1445 a visual inspection of container–closure integrity (e.g., checking for leakage,
1446 cracks in the container, or improper seals). CSPs with observed defects must
1447 be discarded, or marked and segregated from acceptable units in a manner
1448 that prevents them from being released or dispensed.

1449 When a CSP will not be released or dispensed promptly after preparation, a
1450 visual inspection must be conducted immediately before it is released or
1451 dispensed to make sure that the CSP does not exhibit any defects, such as
1452 precipitation, cloudiness, or leakage, which could develop during storage. A
1453 CSP with such defects must be immediately discarded, or marked and
1454 segregated from acceptable units in a manner that prevents it from being
1455 released or dispensed. Any defect may indicate sterility or stability problems
1456 that should be investigated to determine the cause (see *15. Quality*
1457 *Assurance and Quality Control*).

1458 **10.2 Sterility Testing**

1459 Sterility testing is not required for Category 1 CSPs (see [Table 11](#)). If a
1460 Category 2 CSP is assigned a BUD that requires sterility testing (see [Table](#)
1461 [12](#)), the testing must be performed according to [\(71\)](#) or a validated
1462 alternative method (see [Validation of Alternative Microbiological Methods](#)
1463 [\(1223\)](#)) that is non-inferior to [\(71\)](#) testing.

1464 If sterility testing is performed, the minimum quantity of each container to
1465 be tested for each medium is specified in [Sterility Tests \(71\), Table 2](#), and
1466 the number of containers required to be tested in relation to the batch size is
1467 specified in [Sterility Tests \(71\), Table 3](#). Deviations from the batch sizes
1468 specified in [Sterility Tests \(71\), Table 3](#) are allowable as described below:

- 1469 • If the number of CSPs to be compounded in a single batch is less than
1470 the number of CSPs needed for testing as specified in [Sterility Tests](#)
1471 [\(71\), Table 3](#), additional units must be compounded to be able to
1472 perform sterility testing.
- 1473 • If between 1 and 39 CSPs are compounded in a single batch, the
1474 sterility testing must be performed on a number of units equal to
1475 10% of the number of CSPs prepared, rounded up to the next whole
1476 number. For example:
 - 1477 • If 1 CSP is compounded, 10% of 1 rounded up to the next
1478 whole number would indicate that 1 additional CSP must be
1479 prepared for sterility testing.
 - 1480 • If 39 CSPs are compounded, 10% of 39 rounded up to the
1481 next whole number would indicate that 4 additional CSPs must
1482 be prepared for sterility testing.

1483 If more than 40 CSPs are prepared in a single batch, the sample sizes
1484 specified in [Sterility Tests \(71\), Table 3](#) must be used.

1485 If sterility testing is performed according to [Sterility Tests \(71\)](#), a [\(71\)](#),
1486 [Method Suitability Test](#) must be performed to ensure that contamination can
1487 be recovered. If performing sterility testing according to [\(71\)](#), the [\(71\)](#), [Test](#)
1488 [for Sterility of the Product to be Examined, Membrane Filtration](#) method is
1489 the method of choice when the CSP formulation permits. The preferred
1490 alternative is the [\(71\)](#), [Test for Sterility of the Product to be Examined,](#)
1491 [Direct Inoculation of the Culture Medium](#) method. If an alternative method is
1492 used for sterility testing, the method must be validated (see [\(1223\)](#)) and
1493 demonstrated to be suitable for that CSP formulation.

1494 Sterility tests resulting in failures must prompt an investigation into the
1495 possible causes and must include identification of the microorganism, as well
1496 as an evaluation of the sterility testing procedure, compounding facility,
1497 process, and/or personnel that may have contributed to the failure. The
1498 source(s) of the contamination, if identified, must be corrected, and the
1499 facility must determine whether the conditions causing the sterility failure
1500 affect other CSPs. The investigation and resulting corrective actions must be
1501 documented.

1502 **10.3 Bacterial Endotoxins Testing**

1503 Except for inhalation and topical ophthalmic preparations, Category 2 CSPs
1504 made from one or more nonsterile ingredient(s) or component(s) and
1505 assigned a BUD that requires sterility testing (see [Table 12](#)) must be tested
1506 to ensure that they do not contain excessive bacterial endotoxins (see [\(85\)](#)).
1507 [NOTE—CSPs that are assigned a BUD that does not require sterility testing
1508 are not required to be tested for bacterial endotoxins.] In the absence of a
1509 bacterial endotoxins limit in an official monograph or other CSP formula
1510 source, the CSP must not exceed the endotoxins limit calculated as
1511 described in [\(85\)](#) for the appropriate route of administration. See also
1512 [Guidelines on Endotoxins Test \(1085\)](#).

1513 **11. LABELING**

1514
1515 CSPs must be labeled with legible identifying information to prevent errors
1516 during storage, dispensing, and use. The term labeling designates all labels
1517 and other written, printed, or graphic matter on an article's immediate
1518 container or on, or in, any package or wrapper in which it is enclosed, except
1519 any outer shipping container. The term label designates that part of the
1520 labeling that is on the immediate container. See [Labeling \(7\)](#).

1521 The label on the immediate container of the CSP must, at a minimum,
1522 display prominently and legibly the following information:

- 1523 • Assigned internal identification number (e.g., prescription, order, or lot
1524 number)
- 1525 • Active ingredient(s) and their amounts, activities, or concentrations
- 1526 • Storage conditions if other than controlled room temperature

- 1527 • Date prepared
- 1528 • BUD
- 1529 • Indication that the preparation is compounded

1530 The label on the immediate container of the CSP must additionally display
1531 prominently the following information:

- 1532 • Route of administration if it is not obvious from the container, or when
1533 necessary for the safe use of the CSP
- 1534 • Total amount or volume if it is not obvious from the container
- 1535 • If it is a multiple-dose container, a statement stating such
- 1536 • Contact information of the compounding facility if the CSP is to be sent
1537 outside of the facility in which it was compounded

1538 Additionally, the labeling of the CSP must provide any applicable special
1539 handling instructions or warning statements.

1540 Labeling procedures must be followed as described in the facility's SOPs to
1541 prevent labeling errors and CSP mix-ups. The label of the CSP must be
1542 verified to ensure that it conforms with the:

- 1543 1. Prescription or medication order;
- 1544 2. Master Formulation Record, if required (see 9.2 *Creating Master*
1545 *Formulation Records*); and
- 1546 3. Compounding Record (see 9.3 *Creating Compounding Records*)

1547 All labels must also comply with applicable jurisdictional laws and
1548 regulations.

1550 **12. ESTABLISHING BEYOND-USE DATES**

1551 **12.1 Terminology**

1552 Each CSP label must state the date, or the hour and date, beyond which
1553 the preparation must not be used or administration must not begin, and
1554 after which time the preparation must be discarded. The BUD is determined
1555 from the date/time that preparation of the CSP is initiated. The BUD is not
1556 intended to limit the time during which the CSP is administered (e.g.,
1557 infused).

1558 BUDs and expiration dates are not the same. An expiration date identifies
1559 the time during which a conventionally manufactured product, active
1560 ingredient, or excipient can be expected to meet the requirements of a
1561 compendial monograph, if one exists, provided it is kept under the
1562 prescribed storage conditions. The expiration date limits the time during
1563 which the conventionally manufactured product, API, or excipient may be
1564 dispensed or used (see [Labeling \(7\)](#), [Labels and Labeling for Products and](#)
1565 [Other Categories, Expiration Date and Beyond-Use Date](#)). Expiration dates

1566 are assigned by manufacturers based on analytical and performance testing
 1567 of the sterility, chemical and physical stability, and packaging integrity of the
 1568 product. Expiration dates are specific for a particular formulation in its
 1569 container and at stated exposure conditions of illumination and temperature.
 1570 See [Table 10](#) for a summary of terms.

1571 **Table 10. Summary of Terms**

Term	Definition	Applicability
Beyond-Use Date	Either the date or hour and date after which a CSP must not be used or administration must not begin. The BUD is determined from the date/time that preparation of the CSP is initiated.	Applies to all CSPs
Expiration Date	The time during which a product can be expected to meet the requirements of the compendial monograph, if one exists, provided it is kept under the prescribed storage conditions.	Applies to all conventionally manufactured products, APIs, and excipients

1572 **12.2 Parameters to Consider in Establishing a BUD**

1573 Multiple factors that affect sterility and chemical and physical stability must
 1574 be considered when establishing BUDs for CSPs. BUDs should be established
 1575 conservatively for CSPs to ensure that the drug maintains its required
 1576 characteristics (i.e., stability and sterility) until its BUD.

1577 When establishing a BUD for a CSP, compounders must consider factors
 1578 that may affect stability, including but not limited to:

- 1579 • The chemical and physical properties of the drug and/or its formulation
- 1580 • The compatibility of the container–closure system with the finished
- 1581 preparation (e.g., leachables, interactions, and storage conditions)

1582 The BUDs for CSPs in [Table 11](#) and [Table 12](#) are based primarily on factors
 1583 that affect the achievement and maintenance of sterility, which include, but
 1584 are not limited to, the following:

- 1585 • Environment in which the CSP is prepared (e.g., PEC in a cleanroom
- 1586 suite or SCA)
- 1587 • Aseptic preparation and sterilization method
- 1588 • Components and ingredients (e.g., sterile or nonsterile starting
- 1589 ingredients)
- 1590 • Whether or not sterility testing is performed
- 1591 • Storage conditions (e.g., packaging and temperature)

1592 **12.3 Establishing a BUD for a CSP**

1593 BUDs for CSPs must be established in accordance with [Table 11](#) for
1594 Category 1 CSPs and [Table 12](#) for Category 2 CSPs. One day is equivalent to
1595 24 hours.

1596 The BUDs in [Table 11](#) and [Table 12](#) for CSPs are based on the risk of
1597 microbial contamination or not achieving sterility despite implementation of
1598 the requirements in this chapter. Therefore, it is assumed that the CSP
1599 formulation will remain chemically and physically stable, and its packaging
1600 will maintain its integrity for the duration of the BUD.

1601 A shorter BUD is required when the stability of the CSP or its components
1602 is less than the hours or days stated in [Table 11](#) or [Table 12](#). Additionally,
1603 the BUD must not exceed the shortest remaining expiration date or BUD of
1604 any of the starting components, regardless of the source.

1605 [Table 11](#) establishes the longest permitted BUDs for Category 1 CSPs.
1606 Category 1 CSPs may be prepared in an SCA or cleanroom suite (see [4.2](#)
1607 *Facility Design and Environmental Controls*).

1608 **Table 11. BUDs for Category 1 CSPs**

	Storage Conditions	
	Controlled Room Temperature (20°–25°)	Refrigerator (2°–8°)
BUD	≤12 hours	≤24 hours

1609 [Table 12](#) establishes BUDs for Category 2 CSPs, based on the following
1610 factors affecting sterility:

- 1611 • Aseptic preparation and sterilization method
- 1612 • Starting components
- 1613 • Sterility testing
- 1614 • Storage conditions

1615 Category 2 CSPs must be prepared in a cleanroom suite (see [4.2 Facility](#)
1616 *Design and Environmental Controls*).

1617 ASEPTIC PREPARATION AND STERILIZATION METHOD

1618 A CSP may be prepared by the following methods (see [8. Sterilization and](#)
1619 *Depyrogenation*):

- 1620 1. **Aseptic preparation**, which includes either 1) compounding with
1621 only sterile starting ingredient(s), or 2) compounding with nonsterile
1622 ingredient(s) followed by sterilization by filtration. [NOTE—Sterilization
1623 by filtration is not a form of terminal sterilization.]
- 1624 2. **Terminal sterilization**, which includes compounding with sterile
1625 and/or nonsterile starting ingredient(s) and subsequent sterilization
1626 with a process intended to achieve an SAL of 10^{-6} (e.g., dry heat,
1627 steam, or irradiation).

1628 Terminal sterilization is the preferred method of sterilization, unless the
1629 specific CSP or container–closure system cannot tolerate terminal
1630 sterilization. [Table 12](#) allows for longer BUDs for CSPs that are terminally
1631 sterilized than for aseptically prepared CSPs because terminal sterilization
1632 using a verified method provides reasonable assurance that a CSP will be
1633 sterile.

1634 STARTING COMPONENTS

1635 The use of one or more nonsterile starting component(s) is a risk factor to
1636 be considered when preparing a CSP. A longer BUD is permitted in [Table 12](#)
1637 for CSPs that are aseptically prepared from conventionally manufactured
1638 sterile starting component(s) than from one or more nonsterile starting
1639 component(s).

1640 STERILITY TESTING

1641 Sterility testing (see *10.2 Sterility Testing*) of a CSP can provide additional
1642 assurance of the absence of contamination, although passing a sterility test
1643 does not guarantee that all units of a batch of CSPs are sterile because
1644 contamination may not be uniformly distributed throughout the batch. A
1645 longer BUD is permitted in [Table 12](#) if sterility testing results are within
1646 acceptable limits.

1647 STORAGE CONDITIONS

1648 Storage in colder conditions [i.e., in a refrigerator or freezer (see [Packaging
1649 and Storage Requirements \(659\)](#))] has been shown to slow the growth of
1650 most microorganisms. However, the chemical and physical stability of the
1651 CSP and its components must be considered when storing in colder
1652 conditions (e.g., some formulations may precipitate when stored in a
1653 refrigerator or freezer). A longer BUD is permitted in [Table 12](#) for CSPs
1654 stored in colder conditions than for CSPs stored at controlled room
1655 temperature.

1656 If the CSP will be stored in a frozen state, the container–closure system
1657 must be able to withstand the physical stress (i.e., without breaking or
1658 cracking) during storage in a freezer. The CSP must be thawed in
1659 appropriate conditions to avoid compromising the physical and chemical
1660 stability of the preparation and its components (e.g., do not heat in a
1661 microwave). Once the CSP is thawed, the CSP must not be re-frozen.

1662 CSPs may be stored under different storage conditions before they are
1663 used (e.g., CSPs may first be frozen, and then thawed in the refrigerator,
1664 and finally kept at controlled room temperature before administration). The
1665 storage time of a CSP must not exceed the original BUD placed on the CSP
1666 for its labeled storage condition, and BUDs must not be additive. For
1667 example, a CSP cannot be stored for 45 days in a freezer, then 3 days
1668 refrigerated, and then 1 day at controlled room temperature for a total of 49
1669 days. Once a CSP has been stored under a condition that would require a

1670 shorter BUD (i.e., controlled room temperature), the CSP must be used
 1671 within the timeframe for that storage condition (in this example, 1 day).

1672 **Table 12. BUDs for Category 2 CSPs**

Preparation Characteristics		Storage Conditions		
Sterilization Method	Sterility Testing Performed and Passed	Controlled Room Temperature (20°–25°)	Refrigerator (2°–8°)	Freezer (–25° to –10°)
Aseptically prepared CSPs	No	Prepared from one or more nonsterile starting component(s): 1 day	Prepared from one or more nonsterile starting component(s): 4 days	Prepared from one or more nonsterile starting component(s): 45 days
		Prepared from only sterile starting components: 4 days	Prepared from only sterile starting components: 9 days	Prepared from only sterile starting components: 45 days
	Yes	30 days	45 days	60 days
Terminally sterilized CSPs	No	14 days	28 days	45 days
	Yes	45 days	60 days	90 days

1673 **12.4 Multiple-Dose CSPs**

1674 A compounded multiple-dose container is designed to contain more than
 1675 one dose, intended to be entered or penetrated multiple times, and usually
 1676 contains a preservative. The presence of a preservative may inhibit the
 1677 growth of microorganisms and minimize the risk of contamination. The use
 1678 of preservatives must be appropriate for the CSP formulation and the route
 1679 of administration. For example, the preservative must not be inactivated by
 1680 any ingredients in the CSP and some preservatives are not always
 1681 appropriate for the patient (e.g., neonates) or route of administration (e.g.,
 1682 intrathecal or ophthalmic injections). The use of preservatives, however,
 1683 must not be considered a substitute for aseptic technique.

1684 A multiple-dose CSP must be prepared as a Category 2 CSP. A multiple-
 1685 dose CSP must additionally pass antimicrobial effectiveness testing in
 1686 accordance with [Antimicrobial Effectiveness Testing \(51\)](#). The compounder
 1687 may rely on 1) antimicrobial effectiveness testing that it conducts (or
 1688 contracts for) once for each formulation in the particular container–closure
 1689 system in which it will be packaged or 2) antimicrobial effectiveness testing

1690 results published in peer-reviewed literature sources if the CSP formulation
1691 (including any preservative) and container–closure system are exactly the
1692 same as those tested.

1693 After a multiple-dose container is initially entered or punctured, the
1694 multiple-dose container must not be used for longer than the assigned BUD
1695 or 28 days if supported by antimicrobial effectiveness testing results (see
1696 [\(51\)](#)) on the CSP, whichever is shorter.

1697 The container–closure system used to package the multiple-dose CSP must
1698 be evaluated for and conform to container–closure integrity (see [\(1207\)](#)).

1699 The container–closure integrity test needs to be conducted only once on
1700 each formulation and fill volume in the particular container–closure system
1701 in which the multiple-dose CSP will be packaged.

1702

1703 **13. USE OF CONVENTIONALLY MANUFACTURED PRODUCTS**

1704 This section addresses the time within which an entered or punctured
1705 conventionally manufactured product must be used.

1706 **13.1 Use of Conventionally Manufactured Single-Dose Containers**

1707 A conventionally manufactured single-dose container is designed for use
1708 with a single patient as a single injection/infusion (see [Packaging and](#)
1709 [Storage Requirements \(659\)](#), [General Definitions](#), [Injection Packaging](#)
1710 [Systems](#)). A conventionally manufactured single-dose container is a
1711 container–closure system that holds a sterile medication for parenteral
1712 administration (injection or infusion) that is not required to meet the
1713 antimicrobial effectiveness testing requirements. If a single-dose vial is
1714 entered or punctured in worse than an ISO Class 5 air, it must be used
1715 within 1 hour or by the end of the case in which it will be used, and any
1716 remaining contents must be discarded. If a single-dose vial is entered or
1717 punctured only in an ISO Class 5 or cleaner air, it may be used up to 6 hours
1718 after initial entry or puncture. Opened single-dose ampuls must not be
1719 stored for any time period.

1720 **13.2 Use of Conventionally Manufactured Multiple-Dose Containers**

1721 A conventionally manufactured multiple-dose container is intended to
1722 contain more than one dose of a drug product (see [Packaging and Storage](#)
1723 [Requirements \(659\)](#), [General Definitions](#), [Injection Packaging Systems](#)).
1724 Once initially entering or puncturing the multiple-dose container, the
1725 multiple-dose container must not be used for more than 28 days (see [\(51\)](#))
1726 unless otherwise specified by the manufacturer on the labeling.

1727 **13.3 Use of a Conventionally Manufactured Pharmacy Bulk Package**

1728 A conventionally manufactured pharmacy bulk package is a container of a
1729 sterile product for parenteral use that contains many single doses. The
1730 contents are intended for use in a pharmacy admixture program and are

1731 restricted to the sterile preparation of admixtures for infusion or, through a
1732 sterile transfer device, for the filling of empty sterile containers. The
1733 pharmacy bulk package must be used according to the manufacturer's
1734 labeling (see [Packaging and Storage Requirements \(659\)](#), [General](#)
1735 [Definitions](#), [Injection Packaging Systems](#)). The pharmacy bulk package is to
1736 be used only in an ISO Class 5 PEC.

1737

1738

14. USE OF CSPS AS COMPONENTS

1739 This section addresses the time within which an entered or punctured CSP
1740 must be used.

1741

14.1 Use of Compounded Single-Dose Containers

1742 A compounded single-dose container is intended for one-time
1743 administration (e.g., injection, infusion, case) for a single patient. If a
1744 compounded single-dose container is entered or punctured only in ISO Class
1745 5 or cleaner air, it may be used for up to 6 hours after initial entry or
1746 puncture. The remainder must be discarded. The compounded single-dose
1747 container must be stored in conditions applicable to that CSP (e.g.,
1748 refrigerator, controlled room temperature).

1749

14.2 Use of Compounded Stock Solutions

1750 A compounded stock solution is a sterile mixture of components that is
1751 used to prepare CSP(s). The compounded stock solution must be stored
1752 according to storage conditions for the BUD assigned. The compounded
1753 stock solution must only be entered or punctured in an ISO Class 5 or
1754 cleaner air. It may be used for up to 6 hours after initial entry or puncture.
1755 The remainder must be discarded.

1756

14.3 Use of Compounded Multiple-Dose Containers

1757 After a multiple-dose container is initially entered or punctured, the
1758 multiple-dose container must not be used for longer than the assigned BUD
1759 (see *Multiple-Dose CSPs*) or 28 days if supported by antimicrobial
1760 effectiveness testing results (see [\(51\)](#)) on the CSP, whichever is shorter.

1761

1762

15. QUALITY ASSURANCE AND QUALITY CONTROL

1763 QA is a system of procedures, activities, and oversight that ensures that
1764 the compounding process consistently meets quality standards. QC is the
1765 sampling, testing, and documentation of results that, taken together, ensure
1766 that specifications have been met before release of the CSP. See [Quality](#)
1767 [Assurance in Pharmaceutical Compounding \(1163\)](#).

1768 A facility's QA and QC programs must be formally established and
1769 documented in SOPs that ensure that all aspects of the preparation of CSPs
1770 are conducted in accordance with the requirements in this chapter and

1771 applicable jurisdictional laws and regulations. A designated person must
1772 ensure that the facility has formal, written QA and QC programs that
1773 establish a system of:

- 1774 1. Adherence to procedures
- 1775 2. Prevention and detection of errors and other quality problems
- 1776 3. Evaluation of complaints and adverse events
- 1777 4. Appropriate investigations and corrective actions

1778 The SOPs must describe the roles, duties, and training of the personnel
1779 responsible for each aspect of the QA program. The overall QA and QC
1780 program must be reviewed at least once every 12 months by the designated
1781 person. The results of the review must be documented and appropriate
1782 action must be taken if needed.

1783 **15.1 Notification About and Recall of Out-of-Specification Dispensed** 1784 **CSPs**

1785 If a CSP is dispensed or administered before the results of release testing
1786 are known, the facility must have procedures in place to:

- 1787 1. Immediately notify the prescriber of a failure of specifications with
1788 the potential to cause patient harm (e.g., sterility, strength, purity,
1789 bacterial endotoxin, or other quality attributes), and
- 1790 2. Determine whether a recall is necessary

1791 The SOP for recall of out-of-specification dispensed CSPs must contain:

- 1792 • Procedures to determine the severity of the problem and the urgency
1793 for implementation and completion of the recall
- 1794 • Procedures to determine the distribution of any affected CSP, including
1795 the date and quantity of distribution
- 1796 • Procedures to identify patients who have received the CSP
- 1797 • Procedures for disposition and reconciliation of the recalled CSP

1798 The sterile compounding facility must document the implementation of the
1799 recall procedures. The recall must be reported to appropriate regulatory
1800 bodies as required by applicable jurisdictional laws and regulations (e.g.,
1801 state board of pharmacy, state health department).

1802 **15.2 Complaint Handling**

1803 Compounding facilities must develop and implement SOPs for handling
1804 complaints. Complaints may include, but are not limited to, concerns or
1805 reports on the quality, labeling, or possible adverse reactions related to a
1806 specific CSP.

1807 A designated person must review all complaints to determine whether the
1808 complaint indicates a potential quality problem with the CSP. If it does, a
1809 thorough investigation into the cause of the problem must be initiated and
1810 completed. The investigation must consider whether the quality problem
1811 extends to other CSPs. Corrective action, if necessary, must be implemented
1812 for all potentially affected CSPs. Consider whether to initiate a recall of
1813 potentially affected CSPs and whether to cease sterile compounding
1814 processes until all underlying problems have been identified and corrected.

1815 A readily retrievable written or electronic record of each complaint must be
1816 kept by the facility, regardless of the source of the complaint (e.g., email,
1817 telephone, mail). The record must contain the name of the complainant, the
1818 date the complaint was received, the nature of the complaint, and the
1819 response to the complaint. In addition, to the extent that the information is
1820 known, the following should be recorded: the name and strength of the CSP
1821 and the assigned internal identification number (e.g., prescription, order, or
1822 lot number).

1823 The record must also include the findings of any investigation and any
1824 follow-up. Records of complaints must be easily retrievable for review and
1825 evaluation for possible trends and must be retained in accordance with the
1826 record-keeping requirements in *17. Documentation*. A CSP that is returned
1827 in connection with a complaint must be quarantined until it is destroyed after
1828 completion of the investigation and in accordance with applicable
1829 jurisdictional laws and regulations.

1830 **15.3 Adverse Event Reporting**

1831 Adverse events potentially associated with the quality of CSPs must be
1832 reported in accordance with facility SOPs and all applicable jurisdictional laws
1833 and regulations. In addition, adverse events potentially associated with the
1834 quality of the CSP should be reported to the applicable jurisdictional
1835 regulatory body (e.g., state boards of pharmacy, state health departments,
1836 FDA's MedWatch program for human drugs, or FDA Form 1932a for animal
1837 drugs).

1838 **16. CSP STORAGE, HANDLING, PACKAGING, SHIPPING, AND** 1839 **TRANSPORT**

1841 Processes and techniques for storing, handling, packaging, and
1842 transporting CSPs must be outlined in SOPs. Personnel who will be storing,
1843 handling, packaging, and transporting CSPs within the facility must be
1844 trained in accordance with the relevant SOPs, and the training must be
1845 documented.

1846 **16.1 Handling and Storing CSPs**

1847 CSPs must be handled in a manner that maintains CSP quality and
1848 packaging integrity. To help ensure that CSP quality is maintained during

1849 storage at the compounding facility, personnel must monitor conditions in
1850 the storage areas. A controlled temperature area (see [\(659\)](#)) must be
1851 established and monitored to ensure that the temperature remains within
1852 the appropriate range for the CSP (see *4.2 Facility Design and Environmental*
1853 *Controls*).

1854 The compounding facility must detect and minimize temperature excursions
1855 that are outside the temperature limits within the controlled temperature
1856 areas. When it is known that a CSP has been exposed to temperatures either
1857 below or above the storage temperature limits for the CSP, a designated
1858 person must determine (e.g., by consulting literature or analytical testing)
1859 whether the CSP is expected to retain its integrity or quality. If this cannot
1860 be determined, it must be discarded.

1861 **16.2 Packaging of CSPs**

1862 Packaging materials should protect CSPs from damage, leakage,
1863 contamination, degradation, and adsorption while preventing inadvertent
1864 exposure to transport personnel. The facility must select appropriate
1865 shipping containers and packaging materials based on the product
1866 specifications, information from vendors, and the mode of transport.
1867 Compounding personnel must monitor the effectiveness and reliability of the
1868 packaging materials.

1869 Alternative modes of transport and/or special packaging (e.g., tamper-
1870 evident closures) may be needed to protect the quality of CSPs. If the CSP is
1871 sensitive to light, light-resistant packaging materials must be used. In some
1872 cases, the CSP must be packaged in a special container (e.g., a cooler) to
1873 protect it from temperature fluctuations.

1874 **16.3 Shipping and Transporting CSPs**

1875 Compounding personnel must select modes of transport that are expected
1876 to deliver properly packed CSPs in an undamaged, sterile, and stable
1877 condition. Inappropriate transport can adversely affect the quality of CSPs.
1878 For example, preparation-specific considerations should be given to physical
1879 shaking that might occur during pneumatic tube transport or undue
1880 exposure to heat, cold, or light. When shipping or transporting CSPs that
1881 require special handling (e.g., CSPs with stability concerns), personnel must
1882 include specific handling instructions on the exterior of the container.

1883

1884

17. DOCUMENTATION

1885 All facilities where CSPs are prepared must have and maintain written or
1886 electronic documentation to demonstrate compliance with the requirements
1887 in this chapter. This documentation must include, but is not limited to, the
1888 following:

- 1889 • Personnel training, competency assessments, and qualification records
- 1890 including corrective actions for any failures
- 1891 • Certification reports, including corrective actions for any failures
- 1892 • Environmental air and surface monitoring procedures and results
- 1893 • Equipment records (e.g., calibration, verification, and maintenance
- 1894 reports)
- 1895 • Receipt of components
- 1896 • SOPs, Master Formulation Records (when used), and Compounding
- 1897 Records
- 1898 • Release testing records
- 1899 • Information related to complaints and adverse events
- 1900 • Investigations and corrective actions

1901 Documentation must comply with all applicable jurisdictional laws and
1902 regulations. Records must be legible and stored in a manner that prevents
1903 their deterioration and/or loss. All required compounding records for a
1904 particular CSP (e.g., Master Formulation Record, Compounding Record, and
1905 release testing results) must be readily retrievable for at least 3 years after
1906 preparation or as required by jurisdictional laws and regulations, whichever
1907 is longer.

1908
1909

18. COMPOUNDING ALLERGENIC EXTRACTS

1910 Licensed allergenic extracts are defined as single-dose or multiple-dose
1911 preparations and dilutions for subcutaneous immunotherapy. Licensed
1912 allergenic extracts are routinely mixed and diluted into prescription sets for
1913 an individual patient, even though these allergenic extract combinations are
1914 not specified in the approved licenses for the licensed biological products
1915 [e.g., Biological License Applications (BLA)]. Because patients must be
1916 maintained on a maintenance dose of prepared concentrated allergenic
1917 extracts for a period of time longer than the BUDs specified for Category 1
1918 and Category 2, longer BUDs are required for prescription sets to achieve
1919 effective therapy.

1920 Allergenic extracts prescription sets must follow standards at least as
1921 stringent as those in this section:

1922 Personnel Qualifications

1923

1924 1. A designated person with training and expertise in allergen
1925 immunotherapy is responsible for ensuring that personnel who will be
1926 preparing allergen immunotherapy are trained, evaluated, and
1927 supervised.

1928 2. Before beginning to independently prepare allergen extracts, all
1929 compounding personnel must complete training and be able to
1930 demonstrate knowledge of theoretical principles and skills for sterile
1931 compounding.

- 1932 3. Annual personnel training and competency must be documented.
1933 Personnel must demonstrate proficiency in these procedures by
1934 passing a written exam before they can be allowed to compound
1935 allergenic extract prescription sets.
1936 4. Compounding personnel must have their hand hygiene and garbing
1937 procedures evaluated using gloved fingertip and thumb sampling (see
1938 [Box 2-1](#)) 3 times before beginning to prepare prescription sets, and
1939 then at least annually thereafter.
1940 5. Compounding personnel must have their sterile technique and
1941 related practices evaluated annually as demonstrated by successful
1942 completion of a media-fill test (see [Box 2-2](#)).
1943 6. Personnel who fail competency evaluations must successfully pass
1944 reevaluations in the deficient area(s) before they can resume
1945 compounding of allergenic extract prescription sets. The designated
1946 person must identify the cause of failure and determine appropriate
1947 retraining requirements.
1948 7. Personnel who have not compounded an allergenic extract
1949 prescription set in more than 6 months must be evaluated in all core
1950 competencies before resuming compounding duties.

1951 **Personnel Hygiene and Garbing**

- 1952
1953 8. Before beginning compounding of allergen immunotherapy
1954 prescription sets, personnel must perform hand hygiene procedures
1955 (see [Box 3-1](#)).
1956 9. Compounding personnel must do the:

1957 A. Powder-free sterile gloves
1958 B. Non-cotton, low-lint garment with sleeves that fit snugly
1959 around the wrists and that is enclosed at the neck
1960 C. Face mask
1961 D. Low-lint, disposable cover for head and if applicable,
1962 disposable cover for facial hair

1963
1964 10. Compounding personnel must disinfect their gloves throughout
1965 the process by rubbing sterile 70% IPA onto all surfaces of the gloves
1966 and letting the gloves dry thoroughly.

1967 **Facilities**

- 1968
1969 11. The compounding process must occur in an ISO Class 5 PEC or in
1970 a dedicated allergenic extracts compounding area (AECA). The PEC or
1971 AECA used to compound prescription sets must be located away from
1972 unsealed windows, doors that connect to the outdoors, and traffic

1973 flow, all of which may adversely affect the air quality. Neither a PEC
1974 nor an AECA may be located adjacent to environmental control
1975 challenges (e.g., restrooms, warehouses, or food preparation areas).
1976 The PEC or the work surfaces in the AECA must be located at least 1
1977 meter away from a sink. The impact of activities that will be
1978 conducted around or adjacent to the PEC or AECA must be considered
1979 carefully when designing such an area.

- 1980 A. If used, the PEC must be certified every 6 months (see 4.6
1981 *Certification and Recertification*).
- 1982 B. If used, a visible perimeter must establish the boundaries of
1983 the AECA.
- 1984 I. Access to the AECA during compounding must be
1985 restricted to authorized personnel.
- 1986 II. During compounding activities, no other activity is
1987 permitted in the AECA.
- 1988 III. The surfaces of ceilings, walls, floors, fixtures,
1989 shelving, counters, and cabinets in the AECA must be
1990 cleanable and must be kept clean.
- 1991 IV. Carpet is not allowed in the AECA.
- 1992 V. Surfaces should be resistant to damage by cleaning
1993 and sanitizing agents.
- 1994 VI. The surfaces in the AECA upon which the allergenic
1995 extract prescription sets are prepared must be smooth,
1996 impervious, free from cracks and crevices, and non-
1997 shedding to allow for easy cleaning and disinfecting.
- 1998 VII. Dust-collecting overhangs such as utility pipes, ledges,
1999 and windowsills should be minimized. If overhangs or
2000 ledges are present, they must be easily cleanable.
- 2001 VIII. The AECA must be designed and controlled to provide a
2002 well-lighted working environment, with temperature
2003 and humidity controls for the comfort of compounding
2004 personnel wearing the required garb.

2005

2006 **Cleaning and Disinfecting**

2007

2008 12. In a PEC, all interior surfaces of the PEC must be cleaned and
2009 disinfected at the beginning and end of each shift of compounding,
2010 when there are spills, and when surface contamination is known or
2011 suspected. The horizontal work surface must be disinfected between
2012 each prescription set.

2013 13. In an AECA, all work surfaces in the AECA where direct
2014 compounding is occurring must be cleaned and disinfected at the

2015 beginning and end of each shift of compounding; between each
2016 prescription set; when there are spills; and when surface
2017 contamination is known or suspected.
2018 14. Vial stoppers on packages of conventionally manufactured sterile
2019 ingredients must be disinfected by careful wiping with sterile 70%
2020 IPA swabs to ensure that the critical sites are wet and allowed to dry
2021 before they are used to compound allergenic extracts prescription
2022 sets.

2023 **Establishing BUDs**

2024
2025 15. The BUD for the prescription set must be no later than the
2026 earliest expiration date of any allergenic extract or any diluent that is
2027 part of the prescription set, and the BUD must not exceed 1 year
2028 from the date the prescription set is mixed or diluted.

2029 **Labeling**

2030
2031 16. The label of each vial of an allergenic extract prescription set
2032 must display the following prominently and understandably:

- 2033 A. Patient name
2034 B. Type and fractional dilution of each vial, with a corresponding
2035 vial number
2036 C. BUD
2037 D. Identity of the compounder and date of preparation
2038 E. Storage conditions

2039

2040 **Shipping and Transport**

2041
2042 17. If shipping or transporting allergenic extract prescription sets,
2043 compounding personnel must select modes of transport that are
2044 expected to deliver properly packed prescription sets in an
2045 undamaged, sterile, and stable condition. Inappropriate transport can
2046 adversely affect the quality of allergenic extract prescription sets.
2047 18. When shipping or transporting allergenic extract prescription sets
2048 that require special handling, personnel must include specific
2049 handling instructions on the exterior of the container.

2050 **Documentation**

2051
2052 19. All facilities where allergen extract prescription sets are prepared
2053 must have and maintain written or electronic documentation to
2054 include, but not limited to, the following:

- 2055 A. SOPs describing all aspects of the compounding process
2056 B. Personnel training records, competency assessments, and
2057 qualification records including corrective actions for any
2058 failures
2059 C. Certification reports of the PEC, if used, including corrective
2060 actions for any failures
2061 D. Temperature logs for the refrigerator(s)
2062 E. Cleaning logs
2063 F. Compounding records for individual allergenic extract
2064 prescription sets (see [Box 18-1](#))
2065 G. Information related to complaints and adverse events
2066 H. Investigations and corrective actions

2067

2068 **Box 18-1. Compounding Records for Individual Allergenic Extract**
2069 **Prescription Sets**

Compounding Records must include at least the following information:

- Name, concentration, volume, vendor or manufacturer, lot number, and expiration date for each ingredient
- Date and time of preparation of the allergenic extract
- Assigned internal identification number
- Identity of all individuals involved in each step
- Total quantity compounded
- Assigned BUD
- Documentation of results of QC procedures (e.g., visual inspection, second verification of quantities)

2070

2071

GLOSSARY

2072 **Administration:** The direct and immediate application of a conventionally
2073 manufactured product or a CSP to a patient by injecting, infusing, or
2074 otherwise providing a sterile medication in its final form.

2075 **Airlock:** A space with interlocked doors, constructed to maintain air
2076 pressure control when items move between two adjoining areas (generally
2077 with different air cleanliness standards). The intent of an airlock is to
2078 prevent ingress of particulate matter and microbial contamination from a
2079 lesser-controlled area.

2080 **Allergenic extract prescription set:** Combinations of licensed allergenic
2081 extracts which would be mixed and diluted to provide subcutaneous
2082 immunotherapy to an individual patient, even though these allergenic

2083 extract combinations are not specified in the approved BLAs for the licensed
2084 biological products.

2085 **Allergenic extracts:** Biological substances used for the diagnosis and/or
2086 treatment of allergic diseases such as allergic rhinitis, allergic sinusitis,
2087 allergic conjunctivitis, bee venom allergy, and food allergy.

2088 **Ante-room:** An ISO Class 8 or cleaner room with fixed walls and doors
2089 where personnel hand hygiene, garbing procedures, and other activities that
2090 generate high particulate levels are performed. The ante-room is the
2091 transition room between the unclassified area of the facility and the buffer
2092 room.

2093 **Aseptic processing or preparation:** A process by which separate, sterile
2094 components (e.g., drugs, containers, or closures) are brought together
2095 under conditions that maintain their sterility. The components can either be
2096 purchased as sterile or, when starting with nonsterile components, can be
2097 separately sterilized prior to combining (e.g., by membrane filtration,
2098 autoclave).

2099 **Aseptic technique:** A type of technique used to keep objects and areas
2100 free of microorganisms and thereby minimize infection risk to the patient. It
2101 is accomplished through practices that maintain the microbe count at an
2102 irreducible minimum.

2103 **Batch:** More than 1 unit of CSP prepared in a single process and intended
2104 to have uniform characteristics and quality, within specified limits.

2105 **Beyond-use date (BUD):** Either the date or hour and date after which a
2106 CSP must not be used or administration must not begin. The BUD is
2107 determined from the date/time that preparation of the CSP is initiated.

2108 **Blood components:** Any therapeutic constituent of blood that is
2109 separated by physical or mechanical means (e.g., red cells, platelets,
2110 plasma). It is not intended to capture plasma-derived products.

2111 **Buffer room:** An ISO Class 7 or cleaner room with fixed walls and doors
2112 where PEC(s) that generate and maintain an ISO Class 5 environment are
2113 physically located. The buffer room may only be accessed through the ante-
2114 room.

2115 **Category 1 CSP:** A CSP that is assigned a BUD of 12 hours or less at
2116 controlled room temperature or 24 hours or less refrigerated that is
2117 compounded in accordance with all applicable requirements for Category 1
2118 CSPs in this chapter.

2119 **Category 2 CSP:** A CSP that is assigned a BUD of greater than 12 hours
2120 at controlled room temperature or greater than 24 hours refrigerated that is

2121 compounded in accordance with all applicable requirements for Category 2
2122 CSPs in this chapter.

2123 **Certificate of analysis (COA):** A report from the supplier of a
2124 component, container, or closure that accompanies the supplier's material
2125 and contains the specifications and results of all analyses and a description
2126 of the material.

2127 **Class II biological safety cabinet (BSC):** A ventilated cabinet with an
2128 open front and inward and downward unidirectional HEPA-filtered airflow and
2129 HEPA-filtered exhaust. A BSC used to prepare a CSP must be capable of
2130 providing an ISO Class 5 environment for preparation of the CSP.

2131 **Classified area:** An area that maintains an air quality classification based
2132 on the ISO (see also the definition for *ISO class*).

2133 **Cleaning agent:** An agent for the removal of residues (e.g., dirt, debris,
2134 microbes, and residual drugs or chemicals) from surfaces.

2135 **Cleanroom suite:** A classified area that consists of both an ante-room
2136 and buffer room.

2137 **Component:** Any ingredient used in the compounding of a preparation,
2138 including any active ingredient, added substance, and the container–closure
2139 system used to package the preparation.

2140 **Compounded sterile preparation (CSP):** A preparation intended to be
2141 sterile that is created by combining, admixing, diluting, pooling,
2142 reconstituting, repackaging, or otherwise altering a drug product or bulk
2143 drug substance.

2144 **Compounding:** The process of combining, admixing, diluting, pooling,
2145 reconstituting, repackaging, or otherwise altering a drug or bulk drug
2146 substance to create a sterile medication. Preparing a conventionally
2147 manufactured sterile product in accordance with the directions contained in
2148 approved labeling provided by the product's manufacturer is not
2149 compounding as long as the product is prepared for an individual patient and
2150 follows the provisions for administration.

2151 **Compounding area:** The area where compounding is occurring (i.e., a
2152 cleanroom suite or SCA).

2153 **Compounding aseptic containment isolator (CACI):** A type of RABS
2154 that uses HEPA filtration to provide an ISO Class 5 unidirectional air
2155 environment designed for the compounding of sterile HDs.

2156 **Compounding aseptic isolator (CAI):** A type of RABS that uses HEPA
2157 filtration to provide an ISO Class 5 unidirectional air environment designed
2158 for compounding of sterile non-HDs.

2159 **Compounded stock solution:** A sterile mixture of components that is
2160 used to compound finished CSPs.

2161 **Container–closure system:** The sum of packaging components that
2162 together contain and protect the dosage form. This includes primary
2163 packaging components and secondary packaging components, if the latter
2164 are intended to provide additional protection.

2165 **Conventionally manufactured product:** A pharmaceutical dosage form,
2166 usually the subject of an FDA-approved application, and manufactured under
2167 current good manufacturing practice conditions.

2168 **Critical site:** A location that includes any component or fluid pathway
2169 surfaces (e.g., vial septa, injection ports, and beakers) or openings (e.g.,
2170 opened ampules and needle hubs) that are exposed and at risk of direct
2171 contact with air (e.g., ambient room or HEPA filtered), moisture (e.g., oral
2172 and mucosal secretions), or touch contamination.

2173 **Designated person:** One or more individuals assigned to be responsible
2174 and accountable for the performance and operation of the compounding
2175 facility and personnel in the preparation of CSPs.

2176 **Detergent:** A cleaning agent comprised of a hydrophilic component and a
2177 lipophilic component. There are four types of detergents: anionic, cationic,
2178 amphoteric, and non-ionic.

2179 **Direct compounding area (DCA):** A critical area within the ISO Class 5
2180 PEC where critical sites are exposed to unidirectional HEPA-filtered air, also
2181 known as first air.

2182 **Disinfectant:** A chemical or physical agent used on inanimate surfaces
2183 and objects to destroy fungi, viruses, and bacteria. Sporocidal disinfectant
2184 agents are considered a special class of disinfectants that also are effective
2185 against bacterial endospores.

2186 **Dynamic operating conditions:** Conditions in the SCA or cleanroom
2187 suite in which operating personnel are present and performing actual or
2188 simulated compounding operations.

2189 **Expiration date:** The time during which a product can be expected to
2190 meet the requirements of the compendial monograph, if one exists, provided
2191 that the product is kept under the prescribed storage conditions.

2192 **Filter integrity test:** A test (e.g., bubble point test) of the integrity of a
2193 sterilizing grade filter performed after the filtration process to detect whether
2194 the integrity of the filter has been compromised.

2195 **First air:** The air exiting the HEPA filter in a unidirectional air stream.

2196 **Formulation:** The specific qualitative and quantitative composition of the
2197 final CSP.

2198 **Garb:** Items such as gloves, gowns, shoe covers, head and facial hair
2199 covers, masks, and other items designed to reduce particle-shedding from
2200 personnel and minimize the risk of contamination of CSP(s).

2201 **Garment:** Gowns or coveralls.

2202 **Germicidal detergent:** See the definition for *One-step disinfection*.

2203 **Hazardous drug (HD):** Any drug identified by at least one of the
2204 following six criteria: carcinogenicity, teratogenicity or developmental
2205 toxicity, reproductive toxicity in humans, organ toxicity at low dose in
2206 humans or animals, genotoxicity, or new drugs that mimic existing HDs in
2207 structure or toxicity.

2208 **High-efficiency particulate air (HEPA) filtration:** Being, using, or
2209 containing a filter designed to remove 99.97% of airborne particles
2210 measuring 0.3-micron or greater in diameter passing through it.

2211 **ISO class:** An air-quality classification from the International Organization
2212 for Standardization.

2213 **Isolator:** An enclosure that provides HEPA-filtered ISO Class 5
2214 unidirectional air operated at a continuously higher pressure than its
2215 surrounding environment and is decontaminated using an automated
2216 system. It uses only decontaminated interfaces or rapid transfer ports for
2217 materials transfer. [NOTE—A CAI or CACI is not an isolator.]

2218 **Label:** A display of written, printed, or graphic matter on the immediate
2219 container of any article.

2220 **Labeling:** All labels and other written, printed, or graphic matter that are
2221 1) on any article or any of its containers or wrappers, or 2) accompanying
2222 such an article.

2223 **Laminar airflow system (LAFS):** A device or zone within a buffer area
2224 that provides an ISO Class 5 or better air quality environment for sterile
2225 compounding. The system provides a unidirectional HEPA-filtered airflow.

2226 **Laminar airflow workbench (LAFW):** A device that is a type of LAFS
2227 that provides an ISO Class 5 or better air quality environment for sterile
2228 compounding. The device provides a unidirectional HEPA-filtered airflow.

2229 **Line of demarcation:** A visible line on the floor that separates the clean
2230 and dirty sides of the ante-room.

2231 **Low-lint wiper:** A wiper exhibiting few, if any, fibers or other
2232 contamination, visible without magnification, which is separate from, or
2233 easily removed from, the wiper material in a dry condition.

2234 **Media fill test:** A simulation used to qualify processes and personnel
2235 engaged in sterile compounding to ensure that the processes and personnel
2236 are able to prepare CSPs without contamination.

2237 **Multiple-dose container:** A container of sterile medication for parenteral
2238 administration (e.g., injection or infusion) that is designed to contain more
2239 than one dose of the medication. A multiple-dose container is usually
2240 required to meet the antimicrobial effectiveness testing criteria. See
2241 [Container Content for Injections \(697\), Determination of Volume of Injection](#)
2242 [in Containers, Multi-Dose Containers.](#)

2243 **One-step disinfectant:** A product with an EPA-registered claim that it
2244 can clean and disinfect a non-porous surface in the presence of light to
2245 moderate organic soiling without a separate cleaning step.

2246 **Outsourced sterile product:** A sterile product compounded by an FDA-
2247 registered 503B outsourcing facility.

2248 **Pass-through:** An enclosure with sealed doors on both sides that may be
2249 interlocked. The pass-through is positioned between two spaces for the
2250 purpose of minimizing particulate transfer while moving materials from one
2251 space to another.

2252 **Perimeter:** A visible line on the floor that defines the boundaries of the
2253 SCA or AECA.

2254 **Pharmacy bulk package:** A conventionally manufactured sterile product
2255 for parenteral use that contains many single doses intended for use in a
2256 pharmacy admixture program. A pharmacy bulk package may either be used
2257 to prepare admixtures for infusion or, through a sterile transfer device, for
2258 filling sterile containers.

2259 **Positive-pressure room:** A room that is maintained at higher pressure
2260 than the adjacent spaces, and therefore the net airflow is out of the room.

2261 **Preservative:** A substance added to inhibit microbial growth.

2262 **Primary engineering control (PEC):** A device or zone that provides an
2263 ISO Class 5 air quality environment for sterile compounding.

2264 **Pyrogen:** A substance that induces a febrile reaction in a patient.

2265 **Quality assurance (QA):** A system of procedures, activities, and
2266 oversight that ensures that the compounding process consistently meets
2267 quality standards.

2268 **Quality control (QC):** The sampling, testing, and documentation of
2269 results that, taken together, ensure that specifications have been met before
2270 release of the CSP.

2271 **Reconstitution:** The process of adding a diluent to a solid conventionally
2272 manufactured product to prepare a sterile solution or suspension.

2273 **Release testing:** Testing performed to ensure that a preparation meets
2274 appropriate quality characteristics.

2275 **Repackaging:** The act of removing a sterile product or preparation from
2276 its original primary container and placing it into another primary container,
2277 usually of smaller size without further manipulation.

2278 **Restricted-access barrier system (RABS):** An enclosure that provides
2279 HEPA-filtered ISO Class 5 unidirectional air that allows for the ingress and/or
2280 egress of materials through defined openings that have been designed and
2281 validated to preclude the transfer of contamination, and that generally are
2282 not to be opened during operations. Examples of RABS include CAIs and
2283 CACIs.

2284 **Secondary engineering control (SEC):** The area where the PEC is
2285 placed (e.g., a cleanroom suite or an SCA). It incorporates specific design
2286 and operational parameters required to minimize the risk of contamination
2287 within the compounding area.

2288 **Segregated compounding area (SCA):** A designated, unclassified
2289 space, area, or room with a defined perimeter that contains a PEC and is
2290 suitable for preparation of Category 1 CSPs only.

2291 **Single-dose containers:** A container of sterile medication for parenteral
2292 administration (e.g., injection or infusion) that is designed for use with a
2293 single patient as a single injection/infusion. A single-dose container usually
2294 does not contain a preservative.

2295 **Sporicidal agent:** A chemical or physical agent that destroys bacterial
2296 and fungal spores when used in sufficient concentration for a specified
2297 contact time. It is expected to kill all vegetative microorganisms.

2298 **Stability:** The extent to which a product or preparation retains physical
2299 and chemical properties and characteristics within specified limits throughout
2300 its expiration or BUD.

2301 **Sterility:** The absence of viable microorganisms.

2302 **Sterility assurance level (SAL):** The probability of an item being
2303 nonsterile after it has been exposed to a validated sterilization process. An
2304 SAL value can only be applied to terminal sterilization.

2305 **Sterilization by filtration:** Passage of a gas or liquid through a
2306 sterilizing-grade membrane to yield filtrates that are sterile.

2307 **Sterilizing-grade membranes:** Filter membranes that are documented
2308 to retain 100% of a culture of 10^7 microorganisms of a strain of

2309 *Brevundimonas diminuta* per square centimeters of membrane surface under
2310 a pressure of not less than 30 psi. Such filter membranes are nominally
2311 0.22-µm or 0.2-µm pore size.

2312 **Terminal sterilization:** The application of a lethal process (e.g., dry heat,
2313 steam, irradiation) to sealed containers for the purpose of achieving a
2314 predetermined SAL of greater than 10⁻⁶ or a probability of less than one in
2315 one million of a nonsterile unit.

2316 **Two-step disinfectant:** An EPA-registered disinfectant that must be used
2317 after a separate cleaning step. The surface must be cleaned to remove
2318 soiling prior to application of the disinfectant product.

2319 **Unclassified space:** A space not required to meet any air cleanliness
2320 classification based on the ISO.

2321 **Unidirectional airflow:** Air within a PEC moving in a single direction in a
2322 uniform manner and at sufficient velocity to sweep particles away from the
2323 DCA.

2324 **Workflow management system:** Technology comprised of hardware
2325 and software that allows for automation to assist in the verification of
2326 components of, and preparation of, CSPs and to document components and
2327 processes.

2328 **Verify:** To confirm that a method, process, system, or equipment will
2329 perform as expected under the conditions of actual use.

2330

2331

APPENDICES

2332

Appendix 1: Acronyms

2333

ACD	Automated compounding device
ACPH	Air changes per hour
AECA	Allergenic extracts compounding area
API	Active pharmaceutical ingredient
BLA	Biological License Application
BMBL	Biosafety in Microbiological and Biomedical Laboratories
BSC	Biological safety cabinet
BUD	Beyond-use date
CACI	Compounding aseptic containment isolator
CAI	Compounding aseptic isolator
CDC	Centers for Disease Control and Prevention
CETA	Controlled Environment Testing Association
CFU	Colony-forming units
COA	Certificate of analysis

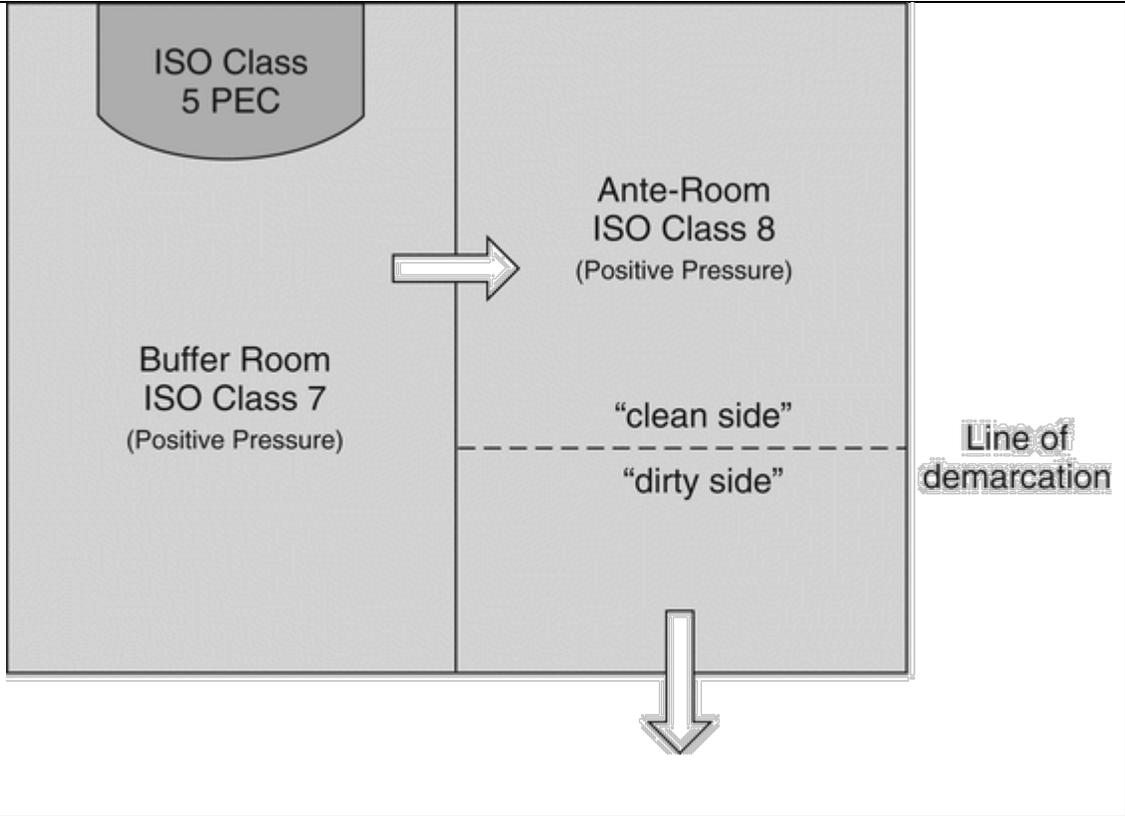
CSP	Compounded sterile preparation
CVE	Containment ventilated enclosure
DCA	Direct compounding area
ECV	Endotoxin challenge vial
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
HDs	Hazardous drugs
HEPA	High-efficiency particulate air
HVAC	Heating, ventilation, and air conditioning
IPA	Isopropyl alcohol
ISO	International Organization for Standardization
IVLFZ	Integrated vertical laminar flow zone
LAFS	Laminar airflow system
LAFW	Laminar airflow workbench
PEC	Primary engineering control
PPE	Personal protective equipment
QA	Quality assurance
QC	Quality control
RABS	Restricted-access barrier system
SAL	Sterility assurance level
SCA	Segregated compounding area
SEC	Secondary engineering control
SOP	Standard operating procedure
TSA	Trypticase soy agar

2334
2335

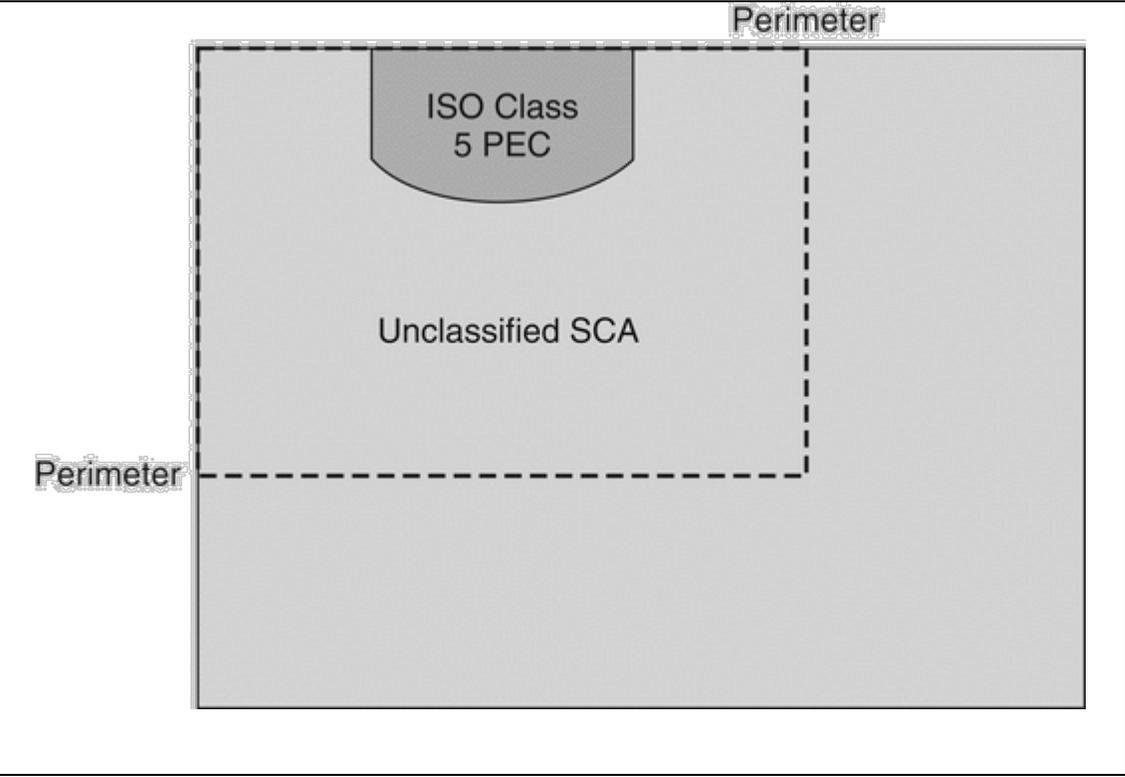
Appendix 2: Example Designs for Sterile Non-Hazardous Drug Compounding Areas^a

Type of Facility Design	Example Design
-------------------------	----------------

Cleanroom suite^a



SCA



^a For examples of designs for hazardous drug compounding areas, see [Hazardous Drugs—Handling in Healthcare Settings \(800\), Appendix 2: Examples of Designs for Hazardous Drug Compounding Areas](#).

^b The arrows indicate the direction of airflow.

- 2336 ■ ^{2S(USP42)}
2337 ⁺ U.S. Food and Drug Administration, Guidance for Industry, *Sterile Drug*
2338 *Products Produced by Aseptic Processing—Current Good Manufacturing*
2339 *Practice*, September 2004.
2340 ^² Guidelines for Environmental Infection Control in Health-Care Facilities,
2341 Recommendations of CDC and the Healthcare Infection Control Practices
2342 Advisory Committee (HICPAC), MMWR, vol. 52, no. RR-10, June 6, 2003,
2343 figure 3, pg. 12.
2344 ^³ NSF/ANSI 49.
2345 ^⁴ ISO 14644-4:2001 Cleanrooms and associated controlled environments—
2346 Design, construction, and start-up, *Case Postale 56*, CH-1211 Geneva 20,
2347 Switzerland, tel. +41 22 749 01 11.
2348 ^⁵ By definition (IEST RP CC 001.4), HEPA filters are a minimum of 99.97%
2349 efficient when tested using 0.3-µm thermally generated particles and a
2350 photometer or rated at their most penetrating particle size using a particle
2351 counter.
2352 ^⁶ Sample procedures are detailed in CETA Applications Guide CAG-002-
2353 2006—section 2.09.
2354 ^⁷ Controlled Environment Testing Association, 1500 Sunday Drive, Ste. 102,
2355 Raleigh, NC 27607; www.CETAinternational.org.
2356 ^⁸ Agalloco J, Akers JE. Aseptic Processing: A Vision of the Future.
2357 *Pharmaceutical Technology*, 2005. Aseptic Processing supplement, s16.
2358 ^⁹ Eaton T. Microbial Risk Assessment for Aseptically Prepared Products. *Am*
2359 *Pharm Rev.* 2005; 8 (5, Sep/Oct): 46–51.
2360 ^{¹⁰} *Guideline for Hand Hygiene in Health care Settings*, MMWR, October 25,
2361 2002, vol. 51, No. RR-16 available on the Internet at
2362 <http://www.cdc.gov/handhygiene/>.
2363 ^{¹¹} The use of additional resources, such as the Accreditation Manual for
2364 Home Care from the Joint Commission on Accreditation of Healthcare
2365 Organizations, may prove helpful in the development of a QA plan.
2366 ^{¹²} See American Society of Heating, Refrigerating and Air Conditioning
2367 Engineers, Inc. (ASHRAE), *Laboratory Design Guide*.
2368 ^{¹³} *CETA Applications Guide for the Use of Compounding Isolators in*
2369 *Compounding Sterile Preparations in Healthcare Facilities*, CAG-001-2005,
2370 Controlled Environment Testing Association (CETA), November 8, 2005.
2371 ■ ¹ Agalloco J, Akers JE. Aseptic processing: a vision of the future. *Pharm*
2372 *Technol.* 2005; Aseptic Processing supplement, s16. ■ ^{2S(USP42)}
2373 ■ ² Eaton T. Microbial risk assessment for aseptically prepared products. *Am*
2374 *Pharm Rev.* 2005; 8(5): 46–51. ■ ^{2S(USP42)}