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MEMORANDUM

TO: Iowa Board of Pharmacy

FROM: Compliance Officers

SUBJECT: Proposed revisions to USP Chapter 797 for sterile compounding

DATE: October 20, 2015

Proposed revision to USP Chapter 797 for sterile compounding will be published for comment on November 2, 2015 and comments will be accepted until January 31, 2016. Below is a brief summary of the proposed changes.

- Completely reorganizes the chapter and groups like sections together, eliminating redundancies, and clarify requirements. The sections are numbered.
- Replaces the “Low-, Medium-, and High-risk” level terminology with Category 1 and Category 2 risk levels. Category 1 CSPs have a shorter BUD and can be prepared in a segregated compounding area and Category 2 CSPs have a longer BUD and require a cleanroom environment.
- Information specific to hazardous drug handling is removed and replaced with a reference to USP Chapter 800.
- Introduces a new term “in-use time” that designates the time frame in which commercially available products used to prepare CSPs and CSPs must be used after being opened or punctured.
- Guidance is provided for sterility testing on batch sizes less than 40 and refers to a different USP Chapter for batch sizes greater than 40.
- Specifies that the chapter covers compounding for both humans and animals, preparation of proprietary bag and vial systems, and repackaging of commercially available products.
- Personnel qualifications become more strict (including visual observation of hand hygiene / garbing, gloved fingertip sampling, and MFT required quarterly regardless of category; requalification when there has been a 3 month or longer break from compounding).

- Environmental sampling requirements become more strict (including viable airborne particle monitoring and surface sampling at least monthly).
- “Immediate-use” is replaced with “Urgent-use”.
- Media-fill testing is simplified to require the most challenging compound the pharmacy makes with microbial growth medium substituted for the ingredients.
- If compounding Category 2 CSPs, the ante-area and buffer areas must be physically separate rooms with doors / walls.
- Cleaning and disinfecting frequencies stay consistent, but allows less frequent cleaning if compounding occurs less frequently; sporicidal agents are required weekly.
- Automatic compounding devices must have “accuracy assessment” each day used with daily record and weekly review of record required.
- Adds requirements for master formulation and compounding records.
- Enhances requirements for visual inspection of each injectable CSP prior to release.
- Records are required to be maintained for at least 3 years after the BUD.

Some potential questions / comments:

- Quarterly personnel monitoring requirements are significantly different; suggest annually for Category 1 and every 6 months for Category 2.
- Segregated compounding area (“SCA”) surfaces are required to be smooth, impervious, free from cracks and crevices, etc. but this area is not classified likely because it cannot meet these requirements.
- Cleaning tools are required to be sterile, including for SCA, but SCA is not classified and would not be able to maintain sterility.
- The chapter requires compounders to qualify the vendors it uses and that such “qualification must include an evaluation of the vendor’s reputation and reliability”. A reputation is completely subjective – who determines what is acceptable?
- The chapter specifically identifies that it covers compounding for animals and has an entire section on APIs; however, current law does not allow compounding for animals from bulk drug substances (although recently released guidance indicates that enforcement action may not be taken, in certain circumstances); how does a compounder reconcile the conflict in law?

BRIEFING

(797) Pharmaceutical Compounding—Sterile Preparations, *USP 39* page 626. It is proposed to revise this chapter to improve clarity, respond to stakeholder input, and reflect new science. Major edits to the chapter include:

1. Reorganized existing chapter to group similar topics together, eliminate redundancies, and clarify requirements. Key procedural information is placed in boxes so that it can be easily referenced and followed.
2. Collapsed compounded sterile preparations (CSP) microbial risk categories from three to two and changed terminology. No sterile compounding is inherently “low risk” and preparation of all CSPs must be done carefully. Categories were renamed neutrally as Category 1 and 2 CSPs, which are distinguished primarily by the conditions under which they are made and the time within which they are used. Category 1 CSPs have a shorter beyond use date (BUD) and may be prepared in a segregated compounding area; Category 2 CSPs have a longer BUD and must be prepared in a cleanroom environment.
3. Removed specific information on handling of hazardous drugs and added references to [Hazardous Drugs—Handling in Healthcare Settings \(800\)](#).
4. Introduced terminology for “in-use time” to refer to the time before which a conventionally manufactured product used to make a CSP must be used after it has been opened or punctured, or a CSP must be used after it has been opened or punctured.

Additionally, the chapter was revised to add requirements for maintaining master formulation and compounding records, provide guidance on use of isolators, and add guidance for sterility testing of CSP prepared in batch sizes of less than 40.

The proposed chapter is posted online at www.usp.org/usp-nf/notices/general-chapter-797-proposed-revision with line numbers. Please provide the line numbers corresponding to your comments when submitting comments to CompoundingSL@usp.org.

Additionally, minor editorial changes have been made to update the chapter to current *USP* style.

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<797> PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS

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 “official” and “article” in the *General Notices and Requirements*) 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) [•] (CN 1 May 2016)) 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 *General Notices and Requirements 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 (see *Preservation, Packaging, Storage, and Labeling* in the *General Notices and Requirements*) list the names and amounts or concentrations of all ingredients (see ^a *Labeling* (7) _(CN 1 May 2016)). 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.

CSP 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 *General Notices and Requirements*), for not more than 14 days at a cold temperature (see *General Notices and Requirements*), 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 *General Notices and Requirements*), for not more than 9 days at a cold temperature (see *General Notices and Requirements*), 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 *General Notices and Requirements*), for not more than 3 days at a cold temperature (see *General Notices and Requirements*), 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 $0.2\ \mu\text{m}$ or $0.22\ \mu\text{m}$ 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 $0.2\ \mu\text{m}$ or $0.22\ \mu\text{m}$ 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 verification⁴ (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 BSC³ 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

^a *Packaging and Storage Requirements* (659) (CN-1 May 2016) 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](#)) PEG 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* (1035)). 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 Prescription Compounding* (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 Sterilization and Sterility Assurance of Compendial Articles* (1211)) 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 *Sterilization and Sterility Assurance of Compendial Articles* (1211))—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 Sterilization and Sterility Assurance of Compendial Articles* (1211) 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 10^7 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 Sterilization and Sterility Assurance of Compendial Articles (1211)*). 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 $1.2 \mu\text{m}$ 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* (1035)) and other confirmation methods such as temperature-sensing devices (see *Sterilization and Sterility Assurance of Compendial Articles* (1211) 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* (1035)) and other confirmation methods such as temperature-sensing devices (see *Sterilization and Sterility Assurance of Compendial Articles* (1211) 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 *Sterilization and Sterility Assurance of Compendial Articles* (1211) 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.

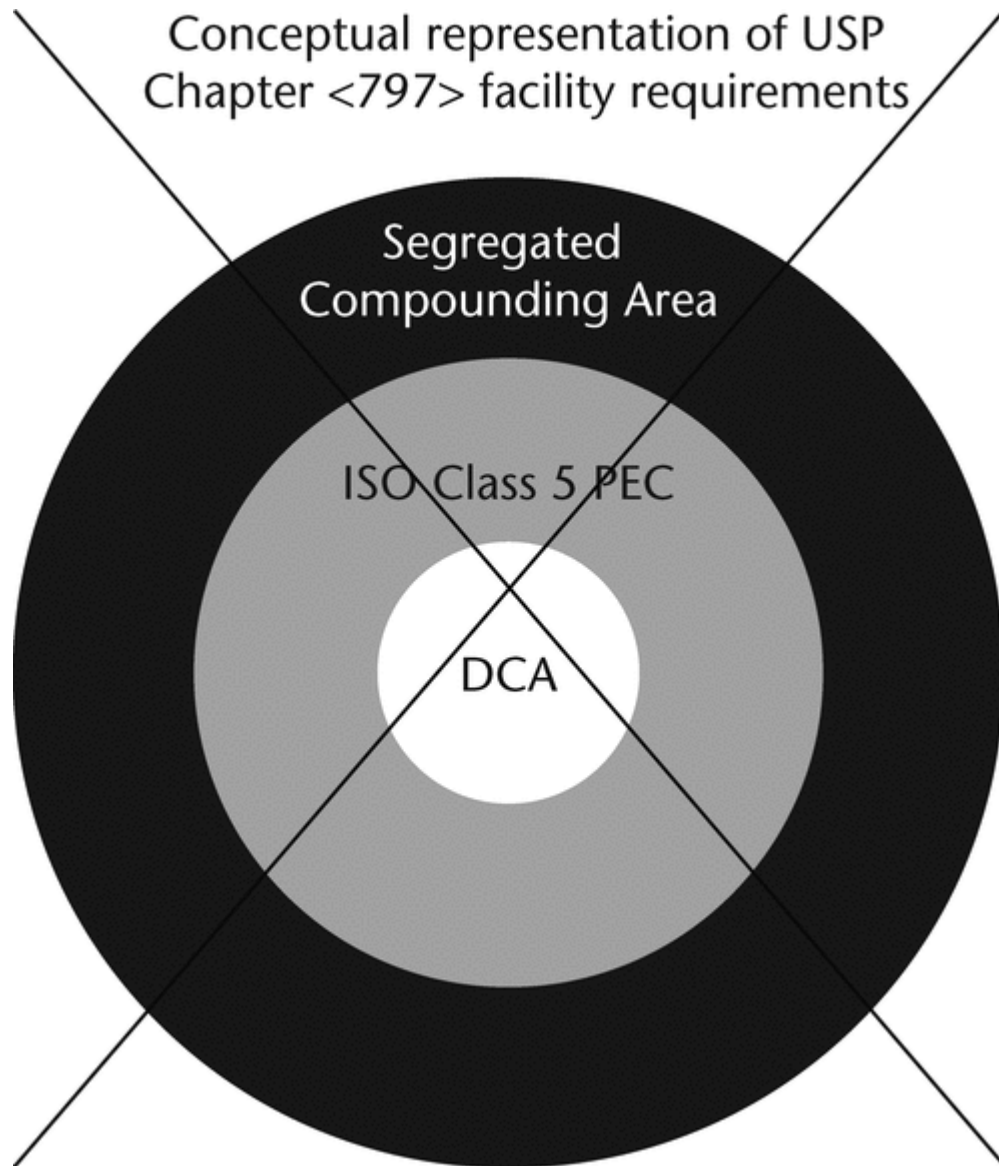


Figure 1. Conceptual representation of the placement of an ISO Class 5 PEC in a segregated compounding area used for low-risk level CSPs with 12-hour or less BUD.

[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

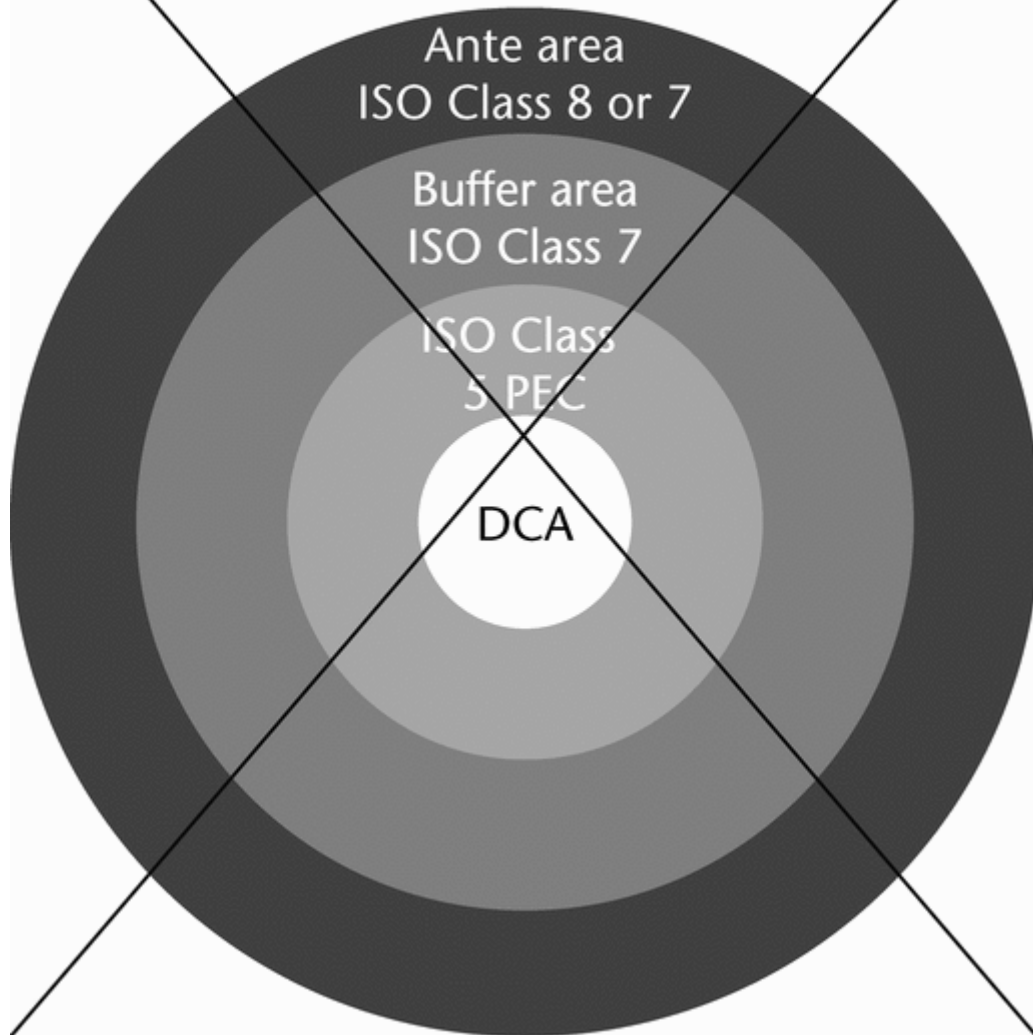


Figure 2. Conceptual representation of the arrangement of a facility for preparation of CSPs categorized as low-, medium-, and high-risk level.

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 covered 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 disinfectable; 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 m^3 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 NONVIAIBLE 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)*⁷ 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 or 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).

Viable 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](#)] PEC 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 GSPs with 12-hour or less BUD prepared in a PEC (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 PEC.

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

Classification	Air Sample†
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

Site	Minimum Frequency
	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 10⁶ 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 GAGIs 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 Contamination⁵

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

⁵ - 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) _(CN 1 May 2016) 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 *General Notices and Requirements*) 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 Prescription Compounding* (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 *General Notices and Requirements*) will have an equivalent effect on the extent of hydrolysis of approximately 3 to 5 days in cold temperatures (see *General Notices and Requirements*).

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 *General Notices and Requirements*) 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 *General Notices and Requirements*). 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 *Expiration Date and Beyond-Use Date* under *Labeling* in the *General Notices and Requirements*). 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 *General Notices and Requirements*) 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 *Multiple-Dose Container* under *Preservation, Packaging, Storage, and Labeling* in the *General Notices and Requirements*) 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 *General Notices and Requirements*) 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.⁴⁴

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
AGPH	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
CAGI	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.⁴²

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 *General Notices and Requirements 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).⁴³

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 *General Notices and Requirements* 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.⁴ 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 *General Notices and Requirements* and ⁶(659)₂₀₁₆)^(CN-1-May-2016) 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.⁴²

Pharmacy Bulk Package: (see ⁶(659)₂₀₁₆)^(CN-1-May-2016) 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.⁴²

Single-Dose Container: (see *General Notices and Requirements* and ⁶⁵⁹) (CN 1 May 2016) A single-dose container is a single-unit container for articles (see *General Notices and Requirements*) 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.⁴³

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- μm 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- μm 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 covered 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 items 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° ± 2° 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 Properties¹

Chemical Category of Disinfectant							
		Isopropyl alcohol	Accelerated hydrogen peroxide	Quaternary Ammonium (e.g., dodecyl dimethyl ammonium chloride)	Phenolics	Chlorine (e.g., sodium hypochlorite)	Iodophors (e.g., povidone-iodine)
Concentration Used		60–95%	0.5% ²	0.4–1.6% aq	0.4–1.6% aq	100–5000 ppm	30–50 ppm
Microbial Inactivation ²	Bacteria	±	±	±	±	±	±
	Lipophilic viruses	±	±	±	±	±	±
	Hydrophilic viruses	±	±	±	±	±	±
	M.tuberculosis	±	±	±	±	±	±
	Mycotic agents (fungi)	±	±	±	±	±	±
	Bacterial Spores	=	=	=	=	±	=
Important Chemical & Physical Properties	Shelf life >1 week	±	±	±	±	±	±
	Corrosive or deleterious effects	±	=	=	=	±	±
	Non-evaporable	=	=	±	±	=	±

Chemical Category of Disinfectant

		Isopropyl alcohol	Accelerated hydrogen peroxide	Quaternary Ammonium (e.g., dodecyl dimethyl ammonium chloride)	Phenolics	Chlorine (e.g., sodium hypochlorite)	Iodophors (e.g., povidone-iodine)
Concentration Used		60–95%	0.5%³	0.4–1.6% aq	0.4–1.6% aq	100–5000 ppm	30–50 ppm
	residue						
	Inactivated by organic matter	±	±	±	±	±	±
	Skin irritant	±	=	±	±	±	±
	Eye irritant	±	=	±	±	±	±
	Respiratory irritant	=	=	=	=	±	=
	Systemic toxicity	±	=	±	±	±	±

Key to abbreviation and symbols: aq = diluted with water; ppm = parts per million; + = yes; = = no; ± = variable results.

¹ Modified from World Health Organization, Laboratory Bio Safety Manual 1983 and Rutala WA, "Antisepsis, disinfection and sterilization in the hospital and related institutions," *Manual of Clinical Microbiology*, American Society for Microbiology, Washington, DC, 1995, pages 227-245.

² Inactivation of the most common microorganisms (i.e., bacteria) occurs with a contact time of ≤1 minute; inactivation of spores requires longer contact times (e.g., 5-10 minutes for 5,000 ppm chlorine solution against *C. difficile* spores). Reference: Perez J, Springthorpe VS, Sattar SA, "Activity of selected oxidizing microbicides against the spores of *Clostridium difficile*: Relevance to environmental control," *American Journal of Infection Control*, August 2005, pages 320-325.

³ Accelerated hydrogen peroxide is a new generation of hydrogen peroxide-based germicides in which the potency and performance of the active ingredient 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.
	Does 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.
	Does beard cover if necessary.
	Does head cover assuring that all hair is covered.
	Does 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.
	Does 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.
	Does 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:	

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.*

	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

	<p>carts as needed to clean entire floor surface. Use of a microfiber cleaning system is an acceptable alternative to mops.</p>
	<p>In the ante-area, cleans sink and all contact surfaces; cleans floor with a disinfectant solution or uses microfiber cleaning system.</p>
Monthly Tasks:	
	<p>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.</p>
	<p>Cleans buffer area and ante-area ceiling, walls, and storage shelving with a disinfectant solution and a mop or uses a microfiber cleaning system.</p>
	<p>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.</p>
	<p>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.</p>
	<p>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.</p>
	<p>Cleans buffer area chairs, the interior and exterior of trash bins, and storage bins using disinfectant solution soaked lint free wipe.</p>
	<p>Documents all cleaning activities as to who performed such activities with date and time noted.</p>
<p>*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</p>	

corrections.

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

1. INTRODUCTION AND SCOPE

This chapter describes the minimum practices and quality standards to be followed when preparing compounded sterile human and animal drugs (compounded sterile preparations, or CSPs). These practices and standards must be used to prevent harm, including death, to human and animal patients that could result from 1) microbial contamination (nonsterility), 2) excessive bacterial endotoxins, 3) variability from the intended strength of correct ingredients, 4) chemical and physical contaminants, and/or 5) use of ingredients of inappropriate quality.

1.1 Scope

CSP AFFECTED

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

- Injections
- Aqueous bronchial inhalations
- Baths and soaks for live organs and tissues
- Irrigations for internal body cavities (i.e., any space that does not freely communicate with the environment outside of the body)
- Ophthalmics
- Implants

For the compounding of hazardous drugs, see [Hazardous Drugs—Handling in Healthcare Settings \(800\)](#).

PERSONNEL AND SETTINGS AFFECTED

This chapter applies to all persons who prepare CSPs (e.g., pharmacists, pharmacy technicians, physicians, veterinarians, and nurses) at all places where CSPs are prepared (e.g., hospitals and other healthcare institutions, patient treatment sites, infusion facilities, pharmacies, and physicians' or veterinarians' practice sites).

The compounding organization's leadership and all employees involved in preparing, storing, and transporting CSPs are responsible for 1) ensuring that the applicable practices and quality standards in this chapter are continually and consistently applied to their operations, and 2) proactively identifying and remedying potential problems within their operations.

SPECIFIC PRACTICES

Administration of medications: This chapter is not intended to address administration of sterile medications. Administration of sterile medications should be performed in accordance with the Centers for Disease Control and Prevention's Safe Injection Practices⁴ and the manufacturer's or compounder's labeling of the sterile medication.

Proprietary bag and vial systems: Docking and activation of proprietary bag and vial systems (e.g., ADD-Vantage®, Mini Bag Plus®, addEASE®) strictly in accordance

41 with the manufacturer's instructions for immediate administration to an individual patient
42 is not considered compounding. However, aseptic technique must be followed when
43 attaching the proprietary bag and vial system.

44 Docking of the proprietary bag and vial systems for future activation and administration
45 is considered compounding and must be performed in accordance with this chapter,
46 with the exception of *12. Establishing Beyond-Use Dates and In-Use Times*. Beyond-
47 use dates (BUDs) for proprietary bag and vial systems must be assigned in accordance
48 with the manufacturer's instructions provided in product labeling.

49 **Reconstitution or dilution:** Reconstituting or diluting a conventionally manufactured
50 sterile product with no intervening steps strictly in accordance with the manufacturer's
51 labeling for administration to an individual patient is not considered compounding.
52 However, aseptic technique must be followed during preparation, and procedures must
53 be in place to minimize the potential for contact with nonsterile surfaces and introduction
54 of particulate matter or biological fluids.

55 Any other reconstitution or dilution of a conventionally manufactured sterile product is
56 considered compounding and must be performed in accordance with this chapter.

57 **Repackaging:** Repackaging of a conventionally manufactured sterile product from its
58 original primary container into another primary container must be performed in
59 accordance with the requirements in this chapter for CSPs, including assignment of
60 BUDs and in-use times as described in *12. Establishing Beyond-Use Dates and In-Use*
61 *Times*.

62 **1.2 Factors Affecting the Risks Associated with CSPs**

63 CSPs can be compounded using only sterile starting ingredients or using some or all
64 nonsterile starting ingredients. If all of the components used to compound a drug are
65 sterile to begin with, the sterility of the components must be maintained during
66 compounding to produce a sterile compounded preparation. If one or more of the
67 starting components being used to compound is not sterile, the sterility of the
68 compounded preparation must be achieved through a sterilization process, such as
69 terminal sterilization in the final sealed container or sterile filtration, and then maintained
70 through subsequent manipulations of the preparation. When compounding with
71 nonsterile starting ingredients, the quality of the components and the effectiveness of
72 the sterilization step are particularly critical to achieving a sterile preparation. In all
73 cases, failure to achieve and/or maintain sterility of CSPs can lead to serious harm,
74 including death. Personnel engaged in compounding and handling CSPs must strictly
75 adhere to the standards in this chapter throughout the compounding process and until
76 the preparation reaches the intended patient(s).

77 The risks to the sterility associated with a particular CSP depend on a number of
78 factors, including the following:

- 79 • Batch size
- 80 • Complexity of the compounding process (e.g., number of manipulations involved;
81 whether starting with nonsterile or sterile components)

- 82 • Inherent nature of the drug being compounded (e.g., whether the drug is
83 susceptible to microbial growth; whether the preparation will be preservative
84 free)
- 85 • Complexity of the compounding operation (e.g., multiple people in the cleanroom
86 at the same time; multiple CSPs being prepared at the same time; activity in the
87 surrounding areas)
- 88 • Length of time between the start of compounding (including making a stock
89 solution) and administration of the drug to the patient

90 Ultimately, the risk to the population of patients is lower if the compounding is done for
91 an individual patient as compared to when the compounding is done in a batch for
92 multiple patients. When applying the standards in this chapter, the risks of a particular
93 compounding operation must be considered, and steps commensurate with these risks
94 must be taken to ensure a quality CSP.

95 1.3 Risk Categories

96 Consistent with this risk-based approach, this chapter distinguishes between two
97 categories of CSPs, Category 1 and Category 2, primarily by the conditions under which
98 they are made and the time within which they will be used. Category 1 CSPs are those
99 assigned a maximum BUD of 12 hours or less at controlled room temperature or 24
100 hours or less if refrigerated if made in accordance with all of the applicable standards for
101 Category 1 CSPs in this chapter. Category 2 CSPs are those that may be assigned a
102 BUD of greater than 12 hours at room temperature or greater than 24 hours if
103 refrigerated (see *12. Establishing Beyond-Use Dates and In-Use Times*) if made in
104 accordance with all of the applicable standards for Category 2 CSPs in this chapter.
105 See [Table 1](#) for a summary comparison of the minimum requirements in this chapter for
106 Category 1 and 2 CSPs.

107 This chapter describes minimum requirements that apply to compounding of all CSPs,
108 and also to repackaging of sterile products. If a compounder does not meet all of the
109 Category 2 requirements, the CSP or repackaged sterile product will be considered a
110 Category 1, and the shorter BUD applicable to Category 1 CSPs must be assigned. The
111 minimum requirements not specifically described as applicable to Category 1 or
112 Category 2, such as minimum training and competency testing and personal hygiene for
113 personnel, are applicable to compounding of all CSPs and repackaging of sterile
114 products.

115 **Table 1. Summary Comparison of Minimum Requirements for Category 1 and**
116 **Category 2 CSPs^a**

	Category 1 CSPs	Category 2 CSPs
Personnel Qualifications		
Visual observation of hand hygiene and garbing	Quarterly	Quarterly
Gloved fingertip sampling	Quarterly	Quarterly

	Category 1 CSPs	Category 2 CSPs
Media fill testing	Quarterly	Quarterly
Personal Protective Equipment		
See Table 2 .		
Buildings and Facilities		
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	Every 6 months
Environmental Monitoring		
Nonviable airborne monitoring	Every 6 months	Every 6 months
Viable airborne monitoring	Monthly	Monthly
Surface sampling	Monthly	Monthly
Release Testing		
Physical inspection	Required	Required
Sterility testing	Not required	Based on assigned BUD
Endotoxin testing	Not required	Required if prepared from nonsterile ingredient(s) ^b
BUD		
BUD assignment	≤12 hours at controlled room temperature or ≤24 hours if refrigerated	>12 hours at controlled room temperature or >24 hours if refrigerated
<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 See exemptions in <i>10.3 Bacterial Endotoxins Testing</i>.</p>		

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1.4 Urgent-Use CSPs

118 A CSP may be prepared in worse than International Organization for Standardization
119 (ISO) Class 5 air quality (see *4.1 Protection from Airborne Contaminants*) in rare
120 circumstances when a CSP is needed urgently (e.g., cardiopulmonary resuscitation) for
121 a single patient, and preparation of the CSP under conditions described for Category 1
122 or Category 2 would subject the patient to additional risk due to delays in therapy. In
123 these circumstances, the compounding procedure must be a continuous process not to
124 exceed 1 hour, and administration of the CSP must begin immediately upon completion
125 of preparation of the CSP. Aseptic technique must be followed during preparation, and
126 procedures must be in place to minimize the potential for contact with nonsterile
127 surfaces, introduction of particulate matter or biological fluids, and mix-ups with other
128 CSPs.

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1.5 Roadmap through Chapter

The chapter is organized as follows:

- [1. Introduction and Scope](#)
 - [2. Personnel Qualifications—Training, Evaluation, and Requalification](#)
 - [3. Personal Hygiene and Personal Protective Equipment](#)
 - [4. Buildings and Facilities](#)
 - [5. Environmental Monitoring](#)
 - [6. Cleaning and Disinfecting Compounding Areas](#)
 - [7. Equipment and Components](#)
 - [8. Sterilization and Depyrogenation](#)
 - [9. SOPs and Master Formulation and Compounding Records](#)
 - [10. Release Testing](#)
 - [11. Labeling](#)
 - [12. Establishing Beyond-Use Dates and In-Use Times](#)
 - [13. Quality Assurance and Quality Control](#)
 - [14. CSP Storage, Handling, Packaging, and Transport](#)
 - [15. Complaint Handling and Adverse Event Reporting](#)
 - [16. Documentation](#)
 - [17. Radiopharmaceuticals as CSPs](#)
- [Glossary](#)
[Appendices](#)
[Appendix 1. Acronyms](#)
[Appendix 2. Common Disinfectants Used in Health Care for Inanimate Surfaces and Noncritical Devices, and Their Microbial Activity and Properties](#)

2. PERSONNEL QUALIFICATIONS—TRAINING, EVALUATION, AND REQUALIFICATION

Because the failure of compounding personnel to follow procedures and adhere to quality standards poses the greatest risk of CSP contamination, all personnel involved in the preparation and handling of CSPs must be trained and qualified and must undergo annual refresher training and requalification in appropriate sterile compounding standards and practices. Training, qualification, and requalification of personnel must be documented.

Each compounding facility must develop a written training program that describes the required training, the frequency of training, and the process for evaluating the performance of individuals involved in sterile compounding. This program should equip personnel with the appropriate knowledge and train them in the required skills necessary to perform their assigned tasks. This section describes the minimum qualifications for personnel preparing and handling CSPs, including the training, evaluation, and requalification of such personnel.

Separate from the formal competency testing and requalification described in this section, supervisors of compounding personnel should observe compounding activities on a daily basis and take immediate corrective action if deficient practices are observed.

2.1 Demonstrating Proficiency in Core Competencies

174 Before beginning to prepare CSPs, personnel must complete training and be able to
175 demonstrate proficiency in the theoretical principles and hands-on skills of sterile
176 manipulations and in achieving and maintaining appropriate environmental conditions.
177 Successful completion must be demonstrated through written testing and hands-on
178 demonstration of skills. Proficiency must be demonstrated in at least the following core
179 competencies:

- 180 • Hand hygiene and garbing
- 181 • Cleaning and disinfection
- 182 • Measuring and mixing
- 183 • Aseptic manipulation
- 184 • Proper cleanroom behavior
- 185 • Methods of sterilization and depyrogenation, if applicable
- 186 • Use of equipment
- 187 • Documentation of the compounding process (e.g., master formulation and
188 compounding records)
- 189 • Understanding the direction of the HEPA-filtered unidirectional airflow within the
190 ISO Class 5 area
- 191 • Proper use of PECs
- 192 • The potential impact of personnel activities such as moving materials into and out
193 of the compounding area

194 The following sections describe in detail the competency testing that must be conducted
195 initially for all sterile compounding personnel in garbing and hand hygiene and aseptic
196 manipulation, and the requirements for retraining and requalification.

197 **2.2 Competency Testing in Garbing and Hand Hygiene**

198 Gloved fingertip/thumb sampling is important because direct touch contamination is
199 the most likely source of microorganisms. Gloved fingertip sampling evaluates a
200 compounding person's competency in correctly performing hand hygiene and garbing
201 (see [Box 2-1](#)). All persons performing compounding must successfully complete an
202 initial competency evaluation, including visual observation and gloved fingertip/thumb
203 sampling [zero colony-forming units (CFUs)] no fewer than three times before being
204 allowed to compound CSPs, to demonstrate that they can perform the procedure
205 consistently. After the initial competency evaluation, compounding personnel must
206 successfully complete gloved fingertip/thumb sampling quarterly (no more than a total of
207 three CFUs). Each fingertip/thumb evaluation must occur after separate, full hand
208 hygiene and garbing procedures.

209 Compounding personnel must be visually observed by competent personnel while
210 performing hand hygiene and garbing procedures (see *3. Personal Hygiene and*
211 *Personal Protective Equipment*). The visual audit must be documented and the
212 documentation maintained to provide a permanent record and long-term assessment of
213 personnel competency.

214 Sampling must be performed on sterile gloves inside of an ISO Class 5 PEC. If
215 conducting gloved fingertip/thumb sampling in a Restricted Access Barrier System
216 (RABS) [e.g., Compounding Aseptic Isolator (CAI) or Compounding Aseptic
217 Containment Isolator (CACI)] or an isolator, samples must be taken from the sterile

218 gloves placed over the gauntlet gloves. In addition, gloved fingertip/thumb sampling
219 must be performed after completing the media-fill preparation without applying sterile
220 alcohol or any other agent that could interfere with the ability of the gloved fingertip test
221 to assess the adequacy of aseptic work practices.

222 **Box 2-1 Gloved Fingertip Sampling and Testing Procedures**

- Use two plates filled with nutrient agar containing neutralizing agents (e.g., lecithin and polysorbate 80) in a size range of 24- to 30-cm² in size.
- Do NOT disinfect gloves with sterile 70% isopropyl alcohol (IPA) or any other disinfectant immediately before touching the agar plate because this could cause a false-negative result.
- Collect a gloved fingertip and thumb sample from both hands by lightly pressing each fingertip into the agar. Use a separate plate for each hand.
- Re-cover the agar plates without further contact with agar. Label the plates with a personnel identifier, right or left hand, date, and time.
- Immediately discard the gloves after sampling.
- Invert the plates and incubate them at a temperature and for a time period conducive to multiplication of microorganisms (e.g., 20°–35° for 5 days).
- Record the number of CFU per hand (left hand, right hand).
- Determine whether the CFU action level for gloved hands (i.e., zero CFU initially or three CFU thereafter) is exceeded by counting the total number of CFUs on both gloves, not per hand.

223 **2.3 Competency Testing in Aseptic Manipulation**

224 After successful completion of the initial hand hygiene and garbing competency
225 evaluation, all sterile compounding personnel must have their sterile technique and
226 related practices evaluated during a media-fill test (see [Box 2-2](#)). Evaluation results
227 must be documented and the documentation maintained to provide a permanent record
228 and long-term assessment of personnel competency.

229 **Box 2-2 Media-Fill Testing Procedures**

- When performing these testing procedures, 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), replacing all the components used in the CSPs with microbial growth medium.
- Include all normal processing steps and incorporate worst-case conditions, including sterilizing filtration if used.
- Do not interrupt the test once it has begun, unless the normal work day involves interruptions.
- If all of the starting components are sterile to begin with, transfer sterile fluid microbial culture medium, such as sterile soybean-casein digest, into the same types of container–closure systems commonly used at the facility to evaluate a person’s skill at aseptically processing CSPs into finished dosage forms.
- If some of the starting components are nonsterile to begin with, use a nonsterile commercially available medium, such as soybean-casein digest powder, to make a 3% solution. Prepare the nonsterile culture medium according to the manufacturer’s instructions and manipulate it in a manner that reflects nonsterile-to-sterile compounding activities.
- Incubate media-filled vials at 20°–35° for a minimum of 14 days. If two temperatures are used for incubation of media-filled samples, incubate the filled containers for at least 7 days at the lower temperature (20°–25°) followed by 7 days at 30°–35°. 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 14 days. Investigate media-fill failures to determine possible causes (e.g., sterilizing filter failure). Document and discuss investigational findings with personnel before any re-testing.
- If using a purchased pre-prepared microbial growth medium, either verify that the growth medium is growth promoting, or obtain a certificate of analysis (COA) from the supplier of the growth medium to ensure that it will support the growth of microorganisms.
- If using a microbial growth medium prepared in-house, the growth promotion capability of the medium must be demonstrated and documented (see [Sterility Tests \(71\)](#)).
- Always store microbial growth media in accordance with manufacturer instructions and use them before their expiration date.

230

2.4 Reevaluation, Retraining, and Requalification

231

REQUALIFICATION AFTER FAILURE

232

Persons who fail written tests; visual observation of hand hygiene, garbing, and aseptic technique; gloved fingertip/thumb sampling; or media-fill tests must undergo immediate requalification through additional training by competent compounding

233

personnel. Personnel who fail visual observation of hand hygiene, garbing, and aseptic technique; gloved fingertip/thumb sampling; or media-fill tests must pass three

234

235

236

237 successive reevaluations in the deficient area before they can resume compounding of
238 sterile preparations.

239 REFRESHER TRAINING PROGRAM

240 Compounding personnel must successfully complete annual refresher training in the
241 core competencies listed in *2.1 Demonstrating Proficiency in Core Competencies*.
242 Successful completion must be demonstrated through written testing and hands-on
243 demonstration of skills.

244 TIMING OF REEVALUATION AND REQUALIFICATION

245

- 246 • Visual observation—Compounding personnel must be visually observed while
247 performing hand hygiene and garbing procedures initially and then at least
248 quarterly.
- 249 • Gloved fingertip sampling—Compounding personnel must perform
250 fingertip/thumb sampling three times initially and then quarterly to confirm their
251 competency and work practices. Fingertip sampling conducted as part of a
252 routine media-fill test can be counted in fulfilling these reevaluation
253 requirements.
- 254 • Media-fill testing—After initial qualification, conduct media-fill tests of all
255 personnel engaged in compounding CSPs at least quarterly to evaluate aseptic
256 technique and requalify them.
- 257 • Cleaning and disinfecting—Retrain and requalify personnel in cleaning and
258 disinfecting compounding areas after a change in cleaning and disinfecting
259 procedures.
- 260 • After a pause in compounding—Personnel who have not compounded CSPs in
261 more than 3 months must be requalified in all core competencies before
262 resuming compounding duties.

263 If compounding is done less frequently than the frequencies specified above (e.g.,
264 quarterly), personnel reevaluation and requalification must occur before each
265 compounding session begins.

266

267 **3. PERSONAL HYGIENE AND PERSONAL PROTECTIVE EQUIPMENT**

268 Because personnel preparing CSPs are the most likely cause of CSP contamination,
269 compounding personnel must maintain proper personal hygiene and use personal
270 protective equipment (PPE).

271 Personnel suffering from rashes, sunburn, oozing tattoos or sores, conjunctivitis, active
272 respiratory infection, or other active communicable disease must be excluded from
273 working in compounding areas until their conditions are resolved.

274

3.1 Personnel Preparation

275 Compounding personnel must take appropriate steps to prevent microbial
276 contamination of CSPs. Squamous cells are normally shed from the human body at a
277 rate of 10⁶ or more per hour, and those skin particles are laden with microorganisms.^{2,3}
278 Before entering a designated compounding area, compounding staff must remove any

279 items that are not easily cleanable and that are not necessary for compounding. For
280 example, personnel must:

- 281 • Remove personal outer garments (e.g., bandanas, coats, hats, jackets, scarves,
282 sweaters, and vests)
- 283 • Remove all cosmetics because they shed flakes and particles
- 284 • Remove all hand, wrist, and other exposed jewelry or piercings (e.g., rings,
285 watches, bracelets, earrings, and lip or eyebrow rings) that can interfere with
286 the effectiveness of PPE (e.g., fit of gloves, cuffs of sleeves, and eye
287 protection). Cover any jewelry that cannot be removed (e.g., surgically
288 implanted jewelry)
- 289 • Remove ear buds, headphones, and cell phones, or other similar devices
- 290 • Keep natural nails clean and neatly trimmed to minimize particle shedding and
291 avoid glove punctures. Nail polish, artificial nails, and extenders must be
292 removed.

293 **3.2 Hand Hygiene**

294 Hand hygiene is required before initiating any compounding activities and when re-
295 entering the ante-area after a break in compounding activity. After donning shoe covers,
296 head and facial hair covers, and face masks, hand hygiene must be conducted (see
297 [Box 3-1](#)). Hands must be washed with unscented soap and water. Alcohol hand
298 sanitizers alone are not sufficient. Do not combine antimicrobial soaps and handrubs
299 with alcohol-based products because of potential adverse dermatologic reactions.
300 Brushes are not recommended for hand hygiene because of the potential for skin
301 irritation and increased bacterial shedding. Dry hands and forearms with either low-lint
302 disposable towels or wipes. After hands are washed and dried, perform hand antisepsis
303 using a suitable alcohol-based handrub with sustained antimicrobial activity immediately
304 before donning sterile gloves. Follow the manufacturer's instructions for application
305 times, and apply the product to dry hands only. [NOTE—Soap must not be added to a
306 partially empty soap dispenser. This practice of "topping off" dispensers can lead to
307 bacterial contamination of soap.]

308 **Box 3-1 Hand Hygiene Procedures**

- Remove debris from underneath fingernails, if present, using a nail cleaner under warm running water.
- Wash hands and forearms up to the elbows with unscented soap and water for at least 30 seconds.
- Dry hands and forearms to the elbows completely with low-lint disposable towels or wipes.
- Immediately prior to donning sterile gloves, apply a suitable alcohol-based handrub with sustained antimicrobial activity, 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.

309

3.3. Garb and Glove Requirements

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The garb and glove requirements for CSPs depend on the category of CSP and type of PEC used. [Table 2](#) summarizes the minimum garb and glove requirements for CSPs.

311

Table 2. Minimum Garb and Glove Requirements

312

CSP Category	PEC type	Minimum Requirement
Category 1	Any	<ul style="list-style-type: none"> • Non-cotton, low-lint, disposable gown or coveralls • Low-lint, disposable covers for shoes • Low-lint, disposable covers for head and facial hair that cover the ears and forehead • Sterile gloves and sterile sleeves^a
Category 2	Laminar airflow system (LAFS) and biological safety cabinet (BSC)	<ul style="list-style-type: none"> • Non-cotton, low-lint, disposable gowns or coveralls • Low-lint, disposable covers for shoes • Low-lint, disposable covers for head and facial hair that cover the ears and forehead • Mask • Sterile gloves and sterile sleeves^a • Eye shield is optional
Category 2	RABS (CAI or CACI) or isolator	<ul style="list-style-type: none"> • Non-cotton, low-lint, disposable gowns or coveralls • Low-lint, disposable covers for shoes and hair • Sterile gloves

^a If a sterile gown is used, the use of sterile sleeves is optional.

313

Personnel intending to enter a buffer area or segregated compounding area must put on protective clothing. Protective clothing must be put on in an order that eliminates the greatest risk of contamination. As noted previously, put on shoe covers, head and facial hair covers, face masks, and gown, before completing hand cleansing procedures and then put on sterile gloves and sterile sleeves (if used). If sterile gowns are used, put on sterile gloves and gowns after hand cleansing procedures. Garbing and degarbing should not occur in the ante-area at the same time.

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GOWNS

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Visibly soiled gowns must be changed immediately. Gowns and other garbing items must be segregated and stored before use in an enclosure to prevent contamination (e.g., away from sinks to avoid splashing). Coveralls and sterile gowns must not be reused.

321

322

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GLOVES

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326 Gloves must be sterile and powder free. Use only gloves that have been tested by the
327 manufacturer for compatibility with alcohol disinfection. Before putting on gloves,
328 perform hand hygiene as described in [Box 3-1](#). Hands must be completely dry before
329 putting on sterile gloves. Unless donning a sterile gown, sterile gloves must be the last
330 item put on before handling anything in the buffer or segregated compounding area and
331 before compounding begins in the PEC. If donning a sterile gown, put on the gloves
332 first, then the sterile gown.

333 Routine application of sterile 70% IPA to gloves must occur throughout the
334 compounding process and whenever nonsterile surfaces (e.g., vials, counter tops,
335 chairs, carts) are touched. Contaminated gloved hands can be disinfected by rubbing
336 sterile 70% IPA solution onto all contact surface areas of the gloves and letting the
337 gloved hands dry thoroughly.

338 Gloves on hands and gauntlet sleeves on RABS and isolators must be inspected
339 routinely by the personnel using them for holes, punctures, or tears and must be
340 replaced immediately if such defects are detected. Sterile gloves must be placed over
341 the gauntlet gloves of the RABS and isolators.

342 EXITING AND REENTERING COMPOUNDING AREAS

343 When compounding personnel exit the buffer or segregated compounding area during
344 a work shift, a nonsterile gown can be removed and retained in the ante or segregated
345 compounding area if not visibly soiled, to be re-donned during that same work shift only.
346 Coveralls and sterile gowns may not be reused and must be replaced with new ones.
347 Shoe covers, hair and facial hair covers, face masks, head covering, gloves, and
348 sleeves may not be reused and must be replaced with new ones. Goggles must be
349 either sterilized or disinfected with sterile 70% IPA before each use. Hand hygiene must
350 be performed before resuming sterile compounding.

351 COMPOUNDING HAZARDOUS DRUGS

352 For PPE requirements when handling hazardous drugs, refer to [\(800\)](#).

353

354

4. BUILDINGS AND FACILITIES

355 Buildings and facilities in which compounding will be taking place must be designed,
356 built, outfitted, and maintained properly to prevent airborne contamination of CSPs.
357 Areas related to compounding operations in such facilities (i.e., ante-area, buffer area,
358 segregated compounding area, and PEC) must be separated from areas not directly
359 related to compounding and must be appropriately controlled to achieve and maintain
360 required air quality classification levels (see [Table 3](#)), depending on the nature of the
361 operation being performed in the specific area.

362 A facility's design must ensure that the movement of personnel, equipment, and
363 components into and out of the compounding area does not disrupt air quality in the
364 area or create a route of contamination. The number of operations being performed, the
365 number of personnel in the compounding area (and in adjacent areas), and the
366 complexity of the compounding procedures are critical factors that determine whether a
367 facility will be able to maintain control of environmental conditions. All of these factors
368 must be taken into account when designing and outfitting a facility in which sterile
369 compounding will be performed.

370 This section describes applicable air quality standards and the appropriate design of
371 buildings and facilities intended for the preparation of CSPs. It describes in detail the
372 materials to be used and the steps to be taken in designing facilities to ensure suitable
373 conditions. This section also discusses the environmental controls that must be in place
374 to ensure achievement and maintenance of sterility for CSPs.

375 4.1 Protection from Airborne Contaminants

376 Buildings and facilities used in compounding must be designed to prevent airborne
377 contamination of the area in which sterile compounding occurs. Without proper design
378 and controls, airborne contaminants are likely to reach the area where compounding
379 occurs, increasing the risk that CSPs will be exposed to microbial contamination.

380 APPLICABLE AIR QUALITY STANDARDS

381 The internationally accepted standards for air quality in controlled environments are
382 described in [Table 3](#) and referenced throughout this chapter.

383 **Table 3. ISO Classification of Particulate Matter in Room Air**

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

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

384 DESIGN REQUIREMENTS TO MAINTAIN AIR QUALITY

385 For compounding Category 1 or 2 CSPs, buildings and facilities intended for
386 compounding CSPs must be designed so that air quality increases with movement
387 through separate operational areas to the PEC. Separate areas of operation must be
388 appropriately controlled, depending on the necessary level of air quality. Classified
389 areas in which the air quality is controlled include ante-areas, buffer areas, and PECs.

- 390 • Ante-areas must meet at least ISO Class 8 standards. Typically, personnel hand
391 hygiene and garbing procedures, staging of components, order entry, CSP
392 handling, and other activities that potentially generate high levels of particulates
393 are performed in this area. Ante-areas are also transition areas to ensure that
394 proper air pressure relationships are maintained between designated areas.
- 395 • A buffer area must provide at least ISO Class 7 air quality. Activities in this area
396 must be especially carefully controlled to avoid affecting the air quality in the
397 area where CSP preparation occurs.
- 398 • Areas intended for CSP preparation must meet ISO Class 5 standards. ISO
399 Class 5 standards are achieved through use of a PEC, such as a LAFS, BSC,
400 CAI, CACI, or isolator.

401 A PEC used for compounding may be placed in an unclassified, segregated
402 compounding area (see below) if only Category 1 CSPs are compounded in the PEC.

403 **4.2 Facility Design and Environmental Controls**

404 In addition to minimizing airborne contamination and protecting CSPs, compounding
405 facilities must be designed and controlled to provide a well-lit and comfortable working
406 environment, with appropriate temperature and humidity for compounding personnel
407 wearing the required garb. The room must be maintained at a temperature of 20° or
408 cooler and a humidity below 60% at all times. Temperature and humidity must be
409 controlled through an efficient heating, ventilation, and air conditioning (HVAC) system
410 rather than through use of humidifiers and dehumidifiers, which can contain standing
411 water that can contribute to microbial contamination.

412 It is the responsibility of compounding facility management to ensure that each
413 operational area related to CSP preparation meets the ISO-classified air quality
414 standard appropriate for the activities to be conducted there and, specifically, that the
415 ISO Class 5 areas are optimally located, operated, maintained, monitored, and verified
416 to have appropriate air quality.

417 **DESIGN OF A COMPOUNDING FACILITY**

418 A compounding facility generally consists of separate, designated operational clean
419 areas, including an ante-area, a buffer area, and a PEC, or a segregated compounding
420 area containing a PEC where CSPs are prepared. See *Placement and Use of Primary*
421 *Engineering Controls* for the requirements for a segregated compounding area. The
422 ante-area must be separated from the surrounding, unclassified sections of the building
423 to reduce the risk of contaminants being blown, dragged, tracked, or otherwise
424 introduced into the high-efficiency particulate air (HEPA)-filtered clean environment.
425 This separation must be continuously maintained and monitored (see 5. *Environmental*
426 *Monitoring*). When compounding Category 2 CSPs, the ISO Class 8 ante-area and the
427 ISO Class 7 buffer area must be separate rooms, with walls and doors between them
428 and controls to prevent the flow of lower-quality air into the more controlled areas.

429 The PEC must be located in the buffer area or the segregated compounding area so
430 as to avoid conditions that could adversely affect their separate operations. For
431 example, strong air currents from opened doors, personnel traffic, or air streams from
432 the HVAC system(s) can disrupt the unidirectional airflow of an open-faced PEC such
433 as a laminar airflow workbench (LAFW). Compounding personnel can also create
434 disruptions in airflow by their own movements adjacent to the PEC, their manipulations
435 within the PEC, and by placing objects onto work surfaces within the PEC. Access of
436 personnel to controlled areas must be limited. For example, only authorized personnel
437 and materials required for compounding and cleaning should be permitted in the buffer
438 area.

439 Due to the interdependence of the various rooms or areas that make up a
440 compounding facility, it is essential to carefully define and control the dynamic
441 interactions permitted between areas and rooms. When designing doors, consider door
442 closures, door surfaces, and the swing of the door, all of which can affect airflow.

443 Airlocks and interlocking doors can be used to facilitate better control of air balance
444 between a higher classified area and an area of lesser air quality (e.g., between the
445 buffer area and ante-area), or between a classified area and an unclassified area (e.g.,

446 between the ante-area and an uncontrolled area such as a hallway). If a pass-through is
447 used, it must only be opened one door at a time; both doors must never be opened at
448 the same time.

449 It is critical to adequately control materials (e.g., supplies, equipment, and utensils) as
450 they move from lesser to higher classified areas to prevent the influx of contaminants.
451 For this reason, when designing a facility, consider the movement of materials.

452 When designing the facility, consider whether all materials used can be easily cleaned.
453 Avoid using door seals and sweeps that are difficult to clean. Hands-free access doors
454 are preferred. Do not use tacky mats in ISO-classified areas.

455 THE CSP PROCESSING ENVIRONMENT

456 All CSPs must be prepared in a PEC, which provides an ISO Class 5 environment
457 (with the exception of Urgent-Use CSPs, see *1.4 Urgent-Use CSPs*). The compounding
458 environment must continuously meet ISO Class 5 or better conditions for 0.5- μ m
459 particles and must exclude microbial contamination during compounding of CSPs
460 (typical operating conditions).

461 HEPA filters and unidirectional (laminar) airflow are used to maintain the appropriate
462 airborne particulate classification of the area. Unidirectional airflow must be maintained
463 in the PEC at all times. HEPA-filtered air must be supplied to the PEC at a velocity
464 sufficient to sweep particles away from critical sites and maintain unidirectional airflow
465 during operations. Proper design and control prevents turbulence and creation of eddies
466 or stagnant air in the PEC.

467 Air must be introduced through HEPA filters located at the ceiling of the buffer area
468 containing the PEC, and returns should be mounted low on the wall, creating a general
469 top-down dilution of area air through HEPA-filtered air.

470 PLACEMENT AND USE OF PRIMARY ENGINEERING CONTROLS

471 Proper placement of the PEC is critical to ensuring an ISO Class 5 environment for
472 compounding CSPs.

473 **LAFS:** Provides an ISO Class 5 or better environment for sterile compounding. A
474 LAFS provides smooth, unidirectional HEPA-filtered airflow that is designed to prevent
475 contamination of a sterile compounding environment. The LAFS can consist of either a
476 LAFW or a HEPA filter alone creating an ISO Class 5 zone within an ISO Class 7 room,
477 as long as unidirectional airflow is maintained.

478 The LAFS must be located out of traffic patterns and away from room air currents that
479 could disrupt the intended airflow patterns. If used to prepare only Category 1 CSPs, the
480 ISO Class 5 environment can be obtained by placing a LAFW in a segregated
481 compounding area. If used to prepare Category 2 CSPs, the LAFS must be located
482 within a restricted access buffer area with an ISO Class 7 or better air quality.

483 **BSC:** A ventilated cabinet with an open front and inward and downward HEPA-filtered
484 airflow and HEPA-filtered exhaust. A BSC must be located out of traffic patterns and
485 away from room air currents that could disrupt the intended airflow patterns. A BSC
486 used to prepare only Category 1 CSPs can be placed in an unclassified area. If used to
487 prepare Category 2 CSPs, the BSC must be located within a restricted access buffer
488 area with an ISO Class 7 or better air quality. If a BSC is used to prepare hazardous
489 drugs, see [\(800\)](#).

490 **RABS:** Can include a CAI or a CACI, and can be used to provide an ISO Class 5
491 environment for preparing CSPs (see [Microbiological Control and Monitoring of Aseptic](#)
492 [Processing Environments \(1116\)](#)). A RABS is different from an isolator (see description
493 of isolators below). In a RABS, glove ports are used to provide physical separation
494 between the surrounding area and the aseptic manipulations. If used to prepare
495 Category 2 CSPs, the area surrounding the RABS must meet ISO Class 7 or better air
496 quality.

497 All transport ports on the RABS must be closed during compounding. When a RABS is
498 used, the recovery time after opening to achieve ISO Class 5 air quality must be
499 documented, and internal procedures must be developed to ensure that adequate
500 recovery time is allowed after opening and closing the RABS, both before and during
501 compounding operations.

502 **Isolator:** Provides isolation from the surrounding area and maintains ISO Class 5 air
503 quality during typical operating conditions. The following standards must be met to
504 qualify as an isolator:

- 505 • High-integrity transfer ports are used to move supplies, ingredients, components,
506 and devices into and out of the isolator.
- 507 • The isolator is decontaminated using a generator that distributes a sporicidal
508 chemical agent throughout the isolator chamber.
- 509 • The isolator maintains constant overpressure of at least 0.05-inch water column.
- 510 • The manufacturer has provided documentation that the isolator will continuously
511 meet ISO Class 5 conditions, including during material transfer.

512 If ISO Class 5 classification is achieved using an isolator that meets the requirements
513 above, the isolator can be located in an ISO Class 8 area and used to prepare Category
514 2 CSPs. In addition, when using an isolator, some functions, such as hand washing, can
515 be done in the ISO Class 8 area. Water sources such as sinks and drains must be
516 located at least 1 meter from the isolator. If the isolator does not meet the requirements
517 above, it is considered a RABS that must be located within at least an ISO Class 7 area
518 to prepare Category 2 CSPs, or within a segregated compounding area to prepare
519 Category 1 CSPs.

520 **Segregated Compounding Areas:** In some situations, a PEC may be located within
521 an unclassified area, without a buffer or ante-area. This type of design is called a
522 segregated compounding area. Category 2 CSPs must never be compounded in
523 segregated compounding areas; only Category 1 CSPs can be compounded in facilities
524 with such designs. It is critical to locate a segregated compounding area away from
525 unsealed windows, doors that connect to the outdoors, and significant traffic flow. A
526 segregated compounding area must not be located adjacent to construction sites,
527 warehouses, food preparation areas, or other environmental control challenges. The
528 impact of activities that will be conducted around or adjacent to the segregated
529 compounding area must be considered carefully when designing such an area, and the
530 perimeter of the segregated compounding area must be defined.

531

ACTIVITIES IN RELATION TO THE PEC

532 The facility where CSPs are prepared must be designed so that activities such as hand
533 hygiene and gowning will not adversely affect the ability of the PEC to function as
534 designed. In facilities with ante-areas and buffer areas, the sink used for hand hygiene
535 must not be placed in the buffer area. The sink should be placed in the ante-area to
536 allow for hand washing before entering the buffer area. In a segregated compounding
537 area, the sink must be located at least 1 meter from the PEC.

538 AIR-EXCHANGE REQUIREMENTS

539 For facilities designed with ante-areas and buffer areas, adequate HEPA-filtered
540 airflow to the buffer and ante-areas is required to maintain the appropriate cleanliness
541 classification during compounding activities. Airflow adequacy is measured in terms of
542 the number of air changes per hour (ACPH). Factors that should be considered when
543 determining appropriate air-exchange requirements for an area include the maximum
544 number of personnel permitted to work in the area, the number of particulates that may
545 be generated from activities and processes in the area, and the effects of temperature.

546 An ISO Class 7 buffer or ante-area supplied with HEPA-filtered air must measure an
547 ACPH of not less than 30, and the ACPH may need to be higher to maintain the
548 classification, depending on the factors previously described. The ACPH of 30 can
549 include recirculated HEPA-filtered air, but at least half (a minimum of 15 ACPH) must be
550 HEPA-filtered fresh air.

551 If an isolator that meets the specifications described above is used to achieve ISO
552 Class 5 air quality, air exchange requirements in the room where the isolator is located
553 can be reduced to 15 ACPH.

554 ESTABLISHING AND MAINTAINING PRESSURE DIFFERENTIALS

555 To prevent the flow of poorer quality air from one area to another area of higher air
556 quality classification, except when a segregated compounding area is used, a minimum
557 differential positive pressure of 0.02-inch water column is required to separate each
558 ISO-classified area. The pressure differential between the ISO Class 7 area and the
559 general pharmacy area must not be less than 0.02-inch water column.

560 A pressure gauge or velocity meter must be used to monitor the pressure differential or
561 airflow between the ante-area and buffer area and between the ante-area and the
562 general environment outside the classified areas. The results must be reviewed and
563 documented on a log at least daily or by a continuous recording device.

564 **4.3 Constructing Areas to Achieve Easily Cleanable Conditions**

565 The surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets in a
566 classified area or in a segregated compounding area must be smooth, impervious, free
567 from cracks and crevices, and non-shedding, thereby promoting cleanability and
568 minimizing spaces in which microorganisms and other contaminants can accumulate.
569 Surfaces must be resistant to damage by disinfectants. Junctures between the ceiling
570 and the walls must be coved or sealed to eliminate cracks and crevices where dirt can
571 accumulate. If ceilings consist of inlaid panels, the panels must be impregnated with a
572 polymer to render them impervious and hydrophobic, and they must be sealed.

573 Walls must be constructed of durable material (e.g., heavy-gauge polymer). Panels
574 must be locked together and sealed. If gypsum board is used, it must be epoxy-coated.
575 Floors must be overlaid with wide sheet vinyl flooring with heat-welded seams and
576 coving to the sidewall. Classified areas and segregated compounding areas must not

577 contain dust-collecting overhangs, such as utility pipes, or ledges, such as windowsills.
578 The exterior lens surface of ceiling light fixtures must be smooth, mounted flush, and
579 sealed. Any other penetrations through the ceiling or walls must be sealed. The buffer
580 area or area inside the perimeter of a segregated compounding area cannot contain
581 water sources (e.g., sinks) or floor drains.

582 Work surfaces must be constructed of smooth, impervious materials, such as stainless
583 steel or molded plastic, so that they can be easily cleaned and disinfected.

584 **4.4 Placement and Movement of Materials**

585 Only furniture, storage shelving, counters, cabinets, supplies, and other materials
586 necessary for performing compounding activities are permitted in buffer or segregated
587 compounding areas. Any objects located in buffer or segregated compounding areas
588 must be smooth, impervious, free from cracks and crevices, non-shedding, and easily
589 cleaned and disinfected. Their number, design, and manner of installation must promote
590 effective cleaning and disinfecting. Certain items are not permitted in buffer areas.
591 These include, but are not limited to, coarse cardboard, external shipping containers,
592 and nonessential paper (e.g., paper towels and tissues).

593 Carts used to transport components or equipment into classified areas must be
594 constructed from stainless steel, nonporous plastic, or sheet metal, with good quality,
595 cleanable casters to promote mobility and ensure ease of disinfection.

596 Certain devices (e.g., computers) and objects (e.g., carts and cabinets) essential to
597 compounding can be located in the segregated compounding area, but must be located
598 at an appropriate distance from the PEC so that they have no detrimental effects on the
599 air quality inside the PEC. The appropriate distance must be determined by considering
600 the surrounding environment and the activities conducted in it.

601 Before being brought into a buffer area or segregated compounding area, objects must
602 be cleaned and disinfected. Equipment and other items used in a buffer area or a
603 segregated compounding area should not be removed except for calibration, servicing,
604 or other activities associated with proper maintenance. If removed, these items must be
605 cleaned and disinfected before they are returned to the buffer area or segregated
606 compounding area.

607 **4.5 Certification and Recertification of Facilities**

608 Before a facility is used to compound either Category 1 or Category 2 CSPs, it must be
609 certified by an independent, qualified individual as meeting its design and air quality
610 specifications (see [Table 3](#)). It is important to place special emphasis on certifying the
611 ISO Class 5 areas. During certification of ISO Class 5 areas, air sampling must be
612 performed inside the PEC and the surrounding ISO-classified areas. Routine staff
613 activity during compounding-related processes must be simulated during certification.

614 Certification of the PEC must include:

- 615 • **Airflow Testing** to determine acceptability of the air velocity and volume, the air
616 exchange rate, and room pressure cascade to ensure that air consistently flows
617 from clean to dirty areas, and that the appropriate quality of air is maintained
618 under typical operating conditions.

- 619
- **HEPA Filter Integrity Testing** using the most penetrating particle size. HEPA filters must be leak tested at the factory and then leak tested again after installation and as part of recertification.
 - **Total Particle Counts Testing** under typical operating conditions by qualified operators using current, state-of-the-art electronic equipment.
 - **Smoke Studies** for each PEC under full operational processing conditions to demonstrate unidirectional airflow and sweeping action over and away from the product(s).
- 626

627 Certification of other ISO-classified areas must include:

- **Airflow Testing** to determine acceptability of the air velocity and volume, the air exchange rate, and room pressure cascade to ensure that air consistently flows from clean to dirty areas and that the appropriate quality of air is maintained under typical operating conditions.
- 631

632 Classified areas must be recertified if there are changes to the area such as redesign, construction, or replacement or relocation of the PEC, or alteration in the configuration of the room that could affect airflow or air quality. Recertification must be done at least every 6 months.

636 All certification and recertification records must be reviewed by supervising personnel or other designated employees to ensure that the controlled environments comply with the proper standards and records must be maintained in accordance with the requirements in *16. Documentation*.

640 **4.6 Design and Construction of Facilities for Compounding with Hazardous Drugs**

641 For design of facilities in which compounding with hazardous drugs will occur, see [\(800\)](#).

643

644

5. ENVIRONMENTAL MONITORING

645 An effective environmental monitoring program provides meaningful information on the quality of the compounding environment and any environmental trends in surrounding areas. In addition, an effective environmental monitoring program will identify potential routes of contamination, allowing for implementation of corrections to prevent CSP contamination. Sterile compounding facilities must develop and implement written environmental monitoring procedures (see *9. SOPs and Master Formulation and Compounding Records*). All environmental sampling and results must be documented, and records must be maintained in accordance with the requirements in *16. Documentation*.

654

5.1 General Monitoring Requirements

655 Sterile compounding facilities must be qualified initially using environmental air and surface sampling as described below to establish a baseline level of environmental quality. After initial qualification, the environment in which sterile compounding activities are performed must be monitored regularly to ensure that the environment remains suitable for sterile compounding.

659

660 Environmental monitoring involves the collection and review of environmental samples
661 from various air and surface locations to detect airborne and surface contaminants.
662 Data from sampling are then used to assess airborne nonviable particulate and
663 microbial contamination risks, potential routes of contamination, and the adequacy of
664 disinfection procedures. Data collected from environmental sampling must be reviewed
665 regularly to detect elevated levels of microbial bioburden, elevated levels of nonviable
666 particulates, or other adverse changes within the environment.

667 Data from air and surface sampling must be reviewed in conjunction with personnel
668 data to assess the state of environmental control and to identify CSP contamination
669 risks. Prompt corrective action in response to any adverse data is essential to maintain
670 the necessary environmental quality for CSP preparation. Data must also be reviewed
671 following corrective actions to confirm that the actions taken have been effective in
672 achieving the required air and surface quality levels (see [Table 3](#) and [Table 5](#)).

673 Routine environmental sampling during compounding operations must be conducted to
674 confirm that the environmental quality in ISO-classified areas is maintained. Sampling
675 also must be performed in any of the following circumstances.

- 676 • As part of the certification of new facilities and equipment
- 677 • As part of recertification, following any servicing of facilities or equipment (see 4.
678 *Buildings and Facilities*)
- 679 • In response to identified problems (e.g., sterility failures; a complaint of patient
680 infection when the CSP is considered to be a potential source of the infection)
- 681 • In response to identified trends (e.g., repeated positive fingertip sampling results
682 or failed media fill simulations; repeated observations of air or surface
683 contamination)

684 The sampling program must include: 1) nonviable airborne particulate sampling; 2)
685 viable airborne particulate sampling; and 3) surface sampling, including but not limited
686 to equipment, work surfaces, and room surfaces.

687 To obtain an environmental sample that is representative of the full operating
688 conditions at the facility, environmental air sampling (both viable and nonviable) must be
689 conducted during periods of typical activity (i.e., when compounding is occurring).
690 However, the sampling program must be designed and conducted in a manner that
691 minimizes the chance that the sampling itself will contribute to contamination of the
692 CSP, the operator, or the environment.

693 The sampling program must be developed based on an understanding of risk factors,
694 including but not limited to criticality of the environment sampled, number and types of
695 activities conducted in the room being monitored, maximum number of personnel that
696 may be working in the room at one time, and how the CSPs will be exposed to the
697 immediate environment during compounding. The sampling program must contain a
698 listing of the sample locations, procedures for collecting samples, frequency of
699 sampling, size of sample (e.g., surface area, volume of air), time of day sampled in
700 relation to activities in the compounding area, and levels that will trigger corrective
701 action. Sampling timing and locations should be carefully selected based on their
702 relationship to the operation performed in the area. Sampling locations, frequencies,
703 and timing must be clearly described in a facility's established Standard Operating

704 Procedure (SOP). It is important to sample locations posing the most contamination risk
705 to the CSP (i.e., the PEC), and sampling locations should be selected that are likely to
706 be representative of the conditions throughout the area.

707 Graphic presentation of the results collected over a period of time can be useful in
708 identifying trends, or for indicating that a significant change has occurred, even when
709 the results fall within the specified limits.

710 It is important that personnel be trained in the proper operation of the air sampling
711 equipment used to ensure reproducible sampling. All air sampling devices must be
712 serviced and calibrated at appropriate intervals (i.e., as recommended by the
713 manufacturer).

714 **5.2 Monitoring Air Quality for Nonviable Airborne Particles**

715 Because maintaining appropriate air quality is essential to the overall contamination
716 prevention strategy for sterile compounding, it is imperative that all engineering control
717 equipment function as designed and that the levels of airborne particles remain within
718 acceptable limits during compounding operations (see [Table 3](#)). A monitoring program
719 for nonviable airborne particles must be developed and implemented to measure the
720 performance of the engineering controls that are being used to provide the specified
721 levels of air cleanliness (e.g., in the PEC and ISO Class 7 and 8 areas).

722 AIR SAMPLING TIMING AND LOCATIONS

723 Air sampling sites must be selected in all classified areas. Measurements of air
724 cleanliness must be taken in each PEC, at locations where there is greatest risk to the
725 exposed CSPs, containers, and closures. Measurements of air cleanliness in other
726 classified areas, including the buffer area and ante-area, should be taken at
727 representative locations that reflect the quality of air in the area. When conducting
728 sampling of the PEC, care should be taken to avoid disturbing the unidirectional airflow.

729 Total particle counts of all ISO-classified areas must be conducted during typical
730 operations every 6 months.

731 DATA EVALUATION AND ACTION LEVELS

732 If levels measured during the nonviable air sampling program exceed the criteria in
733 [Table 3](#) for the appropriate ISO classification levels of the area sampled when
734 measured under typical operating conditions, an investigation of the cause must be
735 conducted and corrective action must be taken to prevent future deviations. When
736 nonviable air sampling results for an ISO Class 5 PEC exceed the criteria in [Table 3](#), all
737 compounding activities must cease in that PEC and a corrective action plan must be
738 implemented immediately. When nonviable air sampling results for ISO Class 7 or 8
739 areas exceed the criteria in [Table 3](#), a corrective action plan must be implemented
740 immediately. In such a case, if compounding is continued, the BUDs for any CSPs
741 compounded must not exceed the BUDs for Category 1 CSPs until the area is
742 successfully recertified. Some examples of corrective action include a procedural
743 improvement, such as enhanced disinfection; a process or facility improvement; or
744 HEPA filter replacement or repair. The extent of the investigation should be consistent
745 with the type of excursion, and should include an evaluation of trends.

746 **5.3 Monitoring Air Quality for Viable Airborne Particles**

747 An environmental sampling program for viable airborne particles must be developed
748 and implemented to assess microbiological air quality in all classified areas. The goals
749 of an environmental sampling program are to determine whether contamination is
750 present at unacceptable levels and to assess whether proper personnel practices are
751 being followed and proper environmental conditions maintained.

AIR SAMPLING TIMING AND LOCATIONS

752
753 Air sampling sites must be selected in all classified areas. When conducting sampling
754 of the PEC, care should be taken to avoid disturbing unidirectional airflow. See [Box 5-1](#)
755 for active air sampling procedures. Active air sampling of all ISO-classified areas must
756 be conducted during typical operating conditions at least monthly. Active air sampling is
757 required in each ISO-classified area (e.g., PEC and ISO Class 7 and 8 areas). A
758 general microbiological growth medium that supports the growth of bacteria and fungi,
759 such as trypticase soy agar (TSA) or soybean-casein digest medium, must be used.
760 Samples must be incubated at 20°–25° for 5–7 days and then at 30°–35° for 2–3
761 additional days. A microbiological incubator that is monitored to maintain the required
762 temperature must be used to incubate the samples. The microbiological incubator must
763 be placed in a location outside of a cleanroom or segregated compounding area. All
764 sampling activities must be performed by properly trained individuals.

Box 5-1 Active Air Sampling Procedures for Viable Airborne Monitoring

- Decontaminate sampling equipment according to the manufacturer's instructions and handle aseptically.
- When media are brought into an ISO-classified area, wipe the wrapping with sterile 70% IPA using a low-lint sterile wipe before removing the media from their packaging.
- Examine media used to collect samples for damage or contamination, and handle in an aseptic manner. Discard contaminated or damaged media and conduct an investigation to determine the cause of the damage or contamination. If a damaged sampling device or packaging is identified (e.g., cracks or foreign bodies on the media surface, or discoloration), examine the entire lot of devices from that vendor to determine whether other devices are damaged or contaminated.
- Using an active air sampling device, test at least 1 cubic meter or 1,000 liters of air from each area sampled.
- At the end of the designated sampling, retrieve the medium and cover it to protect it from external contamination. Protect media from physical damage and keep at appropriate temperatures during transport to the incubator.
- Invert the media plates and incubate the medium at 20°–25° for 5–7 days and then at 30°–35° for 2–3 additional days.
- Examine the media plates for growth daily during normal business hours and record the total number of discrete colonies of microorganisms as CFU per cubic meter of air on an environmental sampling form based on sample type, sample location, and sample date.

767 Evaluate counts against the action levels in [Table 4](#), and examine counts in relation to
 768 previous data to identify adverse results or trends. If levels measured during the viable
 769 air sampling program reach or exceed the levels in [Table 4](#), corrective actions must be
 770 taken, including repeat air sampling. If a CFU count is identified below the action levels
 771 in [Table 4](#), primary screening and characterization must be performed (see [Microbial
 772 Characterization, Identification, and Strain Typing \(1113\)](#)). Highly pathogenic
 773 microorganisms (e.g., gram-negative rods, coagulase positive staphylococcus, molds
 774 and yeasts) are potentially fatal to patients receiving CSPs and must be immediately
 775 remedied through cleaning and disinfection, regardless of CFU count. If levels
 776 measured during viable air sampling exceed the levels in [Table 4](#), the genus must be
 777 identified, and when possible, identify the species of any microorganism recovered, with
 778 the assistance of a credentialed microbiology laboratory.

779 **Table 4. Action Levels for Viable Airborne Particle Air Sampling^a**

ISO Class	Air Sampling Action Levels (CFU/m ³) ^b
5	≥1
7	≥10
8	≥100

^a Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice—US Dept of Health and Human Services, Food and Drug Administration, (FDA) September 2004.

^b All action levels must be based on sampling in the vicinity of exposed materials/articles during compounding operations.

780 **5.4 Sampling Surfaces for Contamination**

781 Surface sampling is an important component of the maintenance of a suitably
 782 controlled environment for compounding CSPs, especially because transfer of microbial
 783 contamination from improperly disinfected work surfaces via inadvertent touch contact
 784 by compounding personnel is a potential source of contamination of CSPs. Surface
 785 sampling is useful for evaluating facility and work surface cleaning and disinfecting
 786 procedures, and employee competency in work practices such as cleaning and
 787 disinfection of component/vial surfaces.

788 Surface sampling for microbial contamination must be performed in all ISO-classified
 789 areas. All sampling sites and procedures must be described in the facility's SOP.

790 **SAMPLING TIMING AND LOCATIONS**

791 When conducted, surface sampling must be performed at the conclusion of
 792 compounding activities, but before the area has been cleaned and disinfected. Media
 793 used for surface sampling must be supplemented with additives to neutralize the effects
 794 of any residual disinfecting agents (e.g., TSA with lecithin and polysorbate 80).

795 Multiple locations must be sampled at least monthly within each ISO-classified area,
 796 including the following (see [\(1116\)](#)):

- 797 • The interior of the PEC and equipment contained in it

- 798 • Staging or work areas near the PEC
- 799 • Frequently touched surfaces
- 800 • Pass-through chambers

801 SAMPLING PROCEDURES

802 Contact sampling devices (e.g., plates, paddles, or slides) containing microbial growth
803 media must be used for sampling flat surfaces. Sterile swabs wetted with sterile water
804 can be used when sampling irregular surfaces and difficult-to-reach locations in
805 classified areas, such as crevices, corners, and spaces between surfaces.

806 Surface sampling devices must contain general microbial growth media (e.g., soybean
807 casein digest media) supplemented with neutralizing additives (e.g., lecithin and
808 polysorbate 80). Use a surface sampling device (e.g., plates, paddles, or slides) in the
809 size range of 24- to 36-cm². Contact sampling devices must be certified by the
810 manufacturer to meet growth promotion tests in [Microbial Enumeration Tests \(61\)](#).
811 Contact plates must have a raised convex surface. Plates must be stored according to
812 the manufacturer's recommendation. See [Box 5-2](#) for the procedures for conducting
813 surface sampling with contact sampling devices. Follow the manufacturer's instructions
814 for using sampling swabs.

815 **Box 5-2 Using Devices for Flat Surface Sampling**

- Examine media used to collect samples for damage or contamination and handle in an aseptic manner. Discard contaminated or damaged media and conduct an investigation to determine the cause of the damage or contamination. If a damaged sampling device or packaging is identified (e.g., cracks or foreign bodies on the media surface, or discoloration), examine the entire lot of devices from that vendor to determine whether other devices are damaged or contaminated.
- If using commercially prepared devices, wipe the wrapping with sterile 70% IPA using a low-lint sterile cloth before removing the devices from their packaging.
- Remove the cover from the contact sampling device and 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 wipe to thoroughly clean the sampled area with sterile water and disinfect with sterile 70% IPA.
- After exposure, cover each contact sampling device to protect it from further contamination.
- Invert the plates and incubate the contact sampling devices at 20°–25° for 5–7 days and then at 30°–35° for 2–3 additional days.
- Examine the sampling devices for growth daily during normal business hours, and record the observed count at each time point. At the final time point, record the total number of discrete colonies of microorganisms (CFU/sample) on the environmental sampling record based on sample type, sample location and sample date.

817 If levels measured during surface sampling exceed the criteria in [Table 5](#), an
 818 investigation of the cause must be conducted and corrective action must be taken to
 819 prevent future deviations. When surface sampling results for an ISO Class 5 PEC
 820 exceed the criteria in [Table 5](#), all compounding activities must cease in that PEC. When
 821 surface sampling results for ISO Class 7 or 8 areas exceed the criteria in [Table 5](#), a
 822 corrective action plan must be implemented immediately. In such a case, if
 823 compounding is continued, the BUDs for any CSPs compounded must not exceed the
 824 BUDs for Category 1 CSPs until the surfaces are retested and the results fall below
 825 action levels in [Table 5](#). Some examples of corrective action include a procedural,
 826 facility, or equipment improvement. The extent of the investigation should be consistent
 827 with the type of excursion and should include an evaluation of trends.

828 **Table 5. Action Levels for Surface Sampling**

ISO Class	Work Surfaces Sampled Using Contact Plates (CFU/plate) ^a	Work Surfaces Sampled Using Swabs (CFU/25 cm ² or per sample) ^a	Non-work Surfaces Sampled Using Contact Plates (CFU/plate) ^b	Non-work Surfaces Sampled Using Swabs (CFU/25 cm ² or per sample) ^b
5	>3	>3	N/A ^c	N/A ^c
7	>5	>5	>10	>10
8	>25	>25	>50	>50

^a Work surfaces are those surfaces that are in direct contact with materials used in compounding. These action levels are based on the expectation that materials will be disinfected before introduction to an ISO Class 5 area.

^b Non-work surfaces are those surfaces that do not come into direct contact with materials used in compounding.

^c All surfaces within the ISO Class 5 area are considered work surfaces.

829
830

6. CLEANING AND DISINFECTING COMPOUNDING AREAS

831 Surfaces in compounding areas are a major source of microbial contamination of
 832 CSPs. Therefore, scrupulous attention must be paid to cleaning and disinfection.
 833 Cleaning and disinfecting the surfaces in sterile compounding areas must occur on a
 834 regular basis at the intervals noted in [Table 6](#). Cleaning and disinfection must be
 835 repeated when spills occur; when surfaces, floors, and walls are visibly soiled; and
 836 when microbial contamination is known to have been, or is suspected of having been,
 837 introduced into the compounding areas.

838 If compounding is done less frequently than the cleaning frequencies specified below
 839 (e.g., once a week or once a month), cleaning must occur before each compounding
 840 session begins, instead of according to the frequencies described in [Table 6](#).

841 **Table 6. Minimum Frequency for Cleaning and Disinfecting Surfaces in Classified**
 842 **and Segregated Compounding Areas**

Site	Minimum Frequency
------	-------------------

Site	Minimum Frequency
PEC (except for an isolator)	At the beginning and end of each shift; before each batch; no 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
Isolator (as defined in 4. <i>Buildings and Facilities</i>)	Clean the isolator each time it is opened; decontaminate the isolator once it is closed after each time it has been opened, or after each cleaning cycle, if cleaning occurs without opening
Work surfaces outside the PEC (e.g., buffer area and/or segregated compounding area)	Daily
Floors	Daily
Walls	Monthly
Ceilings	Monthly
Storage shelving	Monthly

843

6.1 Disinfectants

844 Cleaning and disinfection agents must be selected and used with careful consideration
845 of compatibilities, effectiveness, and inappropriate or toxic residues (see *Appendix 2*
846 and [Disinfectants and Antiseptics \(1072\)](#)). The selection and use of disinfectants must
847 be guided by microbicidal activity, inactivation by organic matter, residue, and shelf life.
848 Sporidical agents must be used at least weekly to clean all ISO-classified and
849 segregated compounding areas (see [Disinfectants and Antiseptics \(1072\)](#),
850 [Classification of Disinfectants, Table 2, General Classification of Antiseptics,](#)
851 [Disinfectants, and Sporidical Agents](#)).

852 The frequency, methods, and locations of disinfection agent use must be established
853 in written SOPs, in accordance with the manufacturer's instructions, and followed by
854 environmental services (i.e., custodial) or compounding personnel.

855

6.2 Cleaning Tools

856 All cleaning tools (e.g., wipes, sponges, and mop heads) must be sterile and low-lint,
857 preferably composed of synthetic microfibers and dedicated for use in buffer or ante-
858 areas or segregated compounding areas. All cleaning tools must be cleaned and re-
859 sterilized after each use. They must be discarded after an appropriate amount of time,
860 to be determined based on the condition of the materials. Disposal must involve
861 collecting them in suitable plastic bags and removing them from classified and
862 segregated compounding areas, with minimal agitation so as not to disperse
863 contaminants into the air.

864

6.3 Cleaning and Disinfecting Floors, Ceilings, Walls, and Shelving

865 Floors in all ISO-classified and segregated compounding areas should be cleaned by
866 mopping with a cleaning and disinfection agent once daily at a time when no aseptic
867 operations are in progress. Mopping should be in the direction of clean to dirty areas.
868 Mopping must be performed by trained personnel using approved agents and
869 procedures, which must be described in written SOPs. In all ISO-classified and
870 segregated compounding areas, the walls, ceilings, and shelving must be cleaned and
871 disinfected monthly.

872 **6.4 Cleaning and Disinfecting Work Surfaces**

873 For both Category 1 and Category 2 CSPs, cleaning and disinfecting work surfaces in
874 the PEC are the most critical steps before preparing CSPs. These surfaces must be
875 cleaned and disinfected more frequently than other surfaces such as walls and ceilings.
876 With the exception of isolators (as defined in 4. *Buildings and Facilities*), all surfaces in
877 the PEC must be cleaned at the beginning and end of each work shift; no longer than
878 30 minutes following the previous surface disinfection when ongoing compounding
879 activities are occurring; when there are spills; and when surface contamination is known
880 or suspected from procedural breaches. Additionally, surfaces in the PEC in direct
881 contact with materials used in compounding must be cleaned before starting each batch
882 of CSPs. When using an isolator, cleaning must be done when the isolator is opened.
883 Decontaminate the isolator once it is closed after each time it has been opened, or after
884 each cleaning cycle, if cleaning occurs without opening. See [Box 6-1](#) for a summary of
885 procedures for cleaning and disinfecting visibly soiled areas in the PEC.

886 **Box 6-1 Procedures for Cleaning and Disinfecting Visibly Soiled Areas in the PEC**

- Remove all items on the surface and remove loose material and residue from spills using a suitable cleaning agent.
- Use sterile water for injection or irrigation and sterile low-lint wipes to remove water-soluble solid residues.
- Wipe the affected area with a disinfectant (e.g., sterile 70% IPA).
- Allow the surface to dry before beginning compounding.

887 Work surfaces in the buffer, ante, and segregated compounding areas must be
888 cleaned and disinfected at least daily, and storage sites for compounding ingredients
889 and supplies must remain free from dust and debris. This must be achieved using a
890 method that does not diminish the ISO Class 7 or 8 air quality.

891 **6.5 Cleaning and Disinfecting Compounding Supplies**

892 No shipping or other external cartons are allowed into the buffer or ante-areas or
893 segregated compounding areas. Before compounding supplies are introduced into
894 buffer areas, they must be wiped with a suitable disinfectant (e.g., sterile 70% IPA) that
895 is delivered from a spray bottle or other suitable delivery method. After the disinfectant
896 is sprayed or wiped on the surface to be disinfected, the disinfectant must be allowed to
897 dry, during which time the item cannot be used.

898 **6.6 Disinfecting Critical Sites**

899 Critical sites (e.g., vial stoppers, ampul necks, and intravenous bag septums) must be
900 disinfected by wiping them with sterile 70% IPA swabs that are commercially available

901 in individual foil-sealed packages (or a comparable method). The IPA must be allowed
902 to dry before piercing stoppers with sterile needles or breaking the necks of ampuls.
903 The sterile 70% IPA swabs used for disinfecting critical sites and devices must not
904 contact any other object before contacting the critical site.

905
906

7. EQUIPMENT AND COMPONENTS

907

7.1 Equipment

908 The equipment used for compounding CSPs must be of appropriate design and
909 adequate size. The equipment also must be of suitable composition such that the
910 surfaces that contact components are not reactive, additive, or sorptive, and therefore,
911 will not affect or alter the purity of the CSP. Equipment in direct contact with the CSP
912 and container–closure system must be sterilized and depyrogenated using methods
913 appropriate for the equipment and container–closure system (see 8. *Sterilization and*
914 *Depyrogenation*, and [Sterilization and Sterility Assurance of Compendial Articles](#)
915 [\(1211\)](#), [Methods of Sterilization](#)).

916 Equipment must be suitably located to facilitate sterile compounding operations. It
917 must be consistently capable of operating properly and within acceptable tolerance
918 limits. Compounding personnel must establish, maintain, and follow written procedures
919 for the calibration, maintenance, and use of the equipment, as well as monitoring it for
920 proper function. Personnel must also maintain results from equipment calibration,
921 annual maintenance reports, and other routine maintenance records in accordance with
922 the requirements in 16. *Documentation*.

923 Automated compounding devices (ACDs) are designed to streamline the labor-
924 intensive processes involved in the compounding of multiple-ingredient preparations
925 (e.g., parenteral nutrition) by automatically delivering the individual ingredients in a
926 predetermined sequence under computerized control. ACDs can improve the accuracy
927 and precision of the compounding process, compared with manual compounding
928 methods.

929 When using ACDs, compounding personnel must conduct an accuracy assessment of
930 the ACD each day it is used to compound CSPs. The volume and weight accuracy of
931 the ACD must be determined, based on manufacturer recommendations, to ensure that
932 the correct quantities of ingredients are delivered to the final container. The precision of
933 the ACD can be monitored based on an assessment of day-to-day variations in its
934 accuracy measures. Compounding personnel must keep a daily record of the accuracy
935 measures and must review the results at least weekly to identify trends over time.

936

7.2 Components

937 Compounding personnel must establish, maintain, and follow written procedures for
938 the selection and inventory control of all CSP components, including all ingredients (i.e.,
939 bulk active pharmaceutical ingredients (APIs) and inactive ingredients), containers, and
940 closures. These written procedures must be followed for all components, from receipt to
941 consumption.

942

COMPONENT SELECTION

943 Compounders must use qualified vendors. A vendor is qualified when there is
944 evidence to support its ability to supply a material that consistently meets all quality
945 specifications. Qualification must include an evaluation of the vendor's reputation and
946 reliability.

947 Ingredients that are the subject of a *USP* or *NF* monograph must be used when
948 available. APIs used in compounding must be manufactured by an FDA-registered
949 facility. Each API must be accompanied by a valid COA that includes the specifications
950 and test results and shows that the API meets the monograph, if one exists, and any
951 additional specifications required to appropriately compound the CSP. Other bulk
952 ingredients should be accompanied by a valid COA that shows that the ingredient
953 meets the monograph, if one exists, and any additional specifications for the ingredient.

954 When ingredients other than APIs cannot be obtained from an FDA-registered facility,
955 compounders must use professional judgment in selecting an acceptable and reliable
956 source. When ingredients are obtained from an unregistered facility, the compounder
957 must establish the identity, strength, purity, and quality of the ingredients obtained from
958 that supplier by reasonable means. These means may include checking each lot of the
959 component when received, or periodically verifying quality by testing a sample of
960 components obtained from that supplier to determine whether the COAs for ingredients
961 sourced from that supplier accurately reflect the characteristics of the ingredients.

962 When components of compendial quality are not obtainable, components of high
963 quality such as those that are chemically pure, analytical reagent grade, or American
964 Chemical Society (ACS)–certified may be used. However, these components should be
965 used cautiously because the standards for analytical reagents or ACS–grade materials
966 do not consider whether the presence of any impurity raises human or animal safety
967 concerns.

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

971 Each lot of commercially available sterile, depyrogenated containers and container–
972 closure systems must be accompanied by a COA or other documentation showing
973 conformance with established specifications.

974 COMPONENT RECEIPT

975 Upon receipt of each lot of a component, a visual inspection must be performed to
976 ensure that the ingredient appears to be what it is represented to be; the lot must also
977 be examined for evidence of deterioration and other aspects of unacceptable quality.
978 Facility personnel must verify the labeling and condition of the component [e.g., whether
979 the outer packaging is damaged and whether temperature-sensing indicators show that
980 the component has been exposed to excessive temperature(s)].

981 Analytical results in the vendor-supplied COA for each lot of incoming ingredient must
982 be inspected against the compounding facility's current specification sheet to ensure
983 that the acceptance criteria are met. If there is a compendial monograph for any
984 ingredient received, facility personnel must verify that the COA for the ingredient
985 demonstrates that the ingredient has met the acceptance criteria of all specified
986 monograph tests for that lot and includes the test results.

987 Any ingredients found to be of unacceptable quality must be promptly rejected, clearly
988 labeled as rejected, and segregated to prevent their use before appropriate disposal.

989 Any other lots of that ingredient from that vendor must be examined to determine
990 whether other lots have the same defect.

991 The date of receipt by the compounding facility must be clearly and indelibly marked
992 on each ingredient package, except for finished dosage forms obtained from FDA-
993 registered manufacturers. For each ingredient, information including receipt date,
994 quantity received, supplier's name, lot number, expiration date, and results of any in-
995 house or third-party testing performed must be recorded. Compounding personnel must
996 keep a written record of each shipment of components received, in accordance with the
997 recordkeeping requirements described in *16. Documentation*.

998 COMPONENT EVALUATION BEFORE USE

999 Before use, all components must be re-inspected. Ingredient packages must be
1000 inspected to detect container breaks, looseness of the cap or closure, and deviation
1001 from the expected appearance, aroma, and texture of the contents that might have
1002 occurred during storage. Sterile container–closures and sterile devices must be visually
1003 inspected to ensure that they are free from defects that could compromise sterility, and
1004 are otherwise suitable for their intended use.

1005 Compounding personnel must ascertain before use that ingredients for CSPs are of
1006 the correct identity and appropriate quality and have been stored under appropriate
1007 conditions. The following information should be used to make this determination:
1008 prescription or medication order, compounding record, master formulation record (if
1009 used), vendor labels and COAs, product labeling, and knowledge of the compounding
1010 facility storage conditions and practices.

1011 If the correct identity, purity, strength, and sterility of ingredients and other components
1012 intended for preparation of CSPs cannot be confirmed (e.g., containers of ingredients
1013 with incomplete labeling, unlabeled syringes, opened ampuls, punctured vial stoppers,
1014 flexible intravenous bags), they must be promptly rejected, clearly labeled as rejected,
1015 and segregated to prevent their use before appropriate disposal.

1016 COMPONENT HANDLING AND STORAGE

1017 All components must be handled and stored in a manner that prevents contamination,
1018 mix-ups, and deterioration. Ingredients must be stored in tightly closed containers under
1019 temperature, humidity, and lighting conditions consistent with those indicated in official
1020 monographs or specified by the suppliers/manufacturer. Moisture-sensitive ingredients
1021 must be stored in tight, well-closed containers.

1022 Packages of ingredients that lack a vendor's expiration date must not be used after 1
1023 year from receipt by the compounding facility, unless appropriate inspection and testing
1024 indicates that the ingredient has retained its purity and quality for use in CSPs.

1025 For information on handling and storage of hazardous drugs, see [\(800\)](#).

1026

1027

8. STERILIZATION AND DEPYROGENATION

1028 Each CSP must be sterile and pyrogen-free before release. When selecting the
1029 sterilization method for each CSP, personnel must take into consideration the nature of
1030 the components, its physical and chemical properties, and the intended container–
1031 closure system. The sterilization method used must sterilize the CSP while maintaining
1032 its physical and chemical stability (i.e., appropriate strength, purity, quality), and the

1033 packaging integrity of the CSP. Utensils and materials in direct contact with the
1034 components, the CSP, and the container–closure system must be sterilized and
1035 depyrogenated using appropriate methods (see [Sterilization of Compendial Articles](#)
1036 [\(1229\)](#)). If sterilization and depyrogenation of container–closure systems is performed
1037 on site, the efficacy of each process must be established and documented, and the
1038 process must be shown to be reproducible. CSPs that are terminally sterilized are
1039 expected to use a process that achieves a sterility assurance level (SAL) of 10^{-6} . An
1040 SAL of 10^{-6} is equivalent to a probability that 1 unit in a million is nonsterile. Generally,
1041 an SAL value cannot be applied to CSPs that are aseptically filled into a sterile
1042 container following sterilization.

1043 The following must be considered when selecting an appropriate sterilization method:

- 1044 • Terminal sterilization (e.g., dry heat, steam, or irradiation) is the preferred
1045 method, unless the specific CSP or container–closure system cannot tolerate
1046 terminal sterilization.
- 1047 • Filtration is not an option if compounding a suspension when the suspended
1048 particles are removed by the filter being used, which could affect the strength of
1049 the CSP.
- 1050 • Dry heat is not an option if a CSP component is labile when exposed to the
1051 temperatures used.
- 1052 • Steam sterilization is not an option if moisture, pressure, or the temperatures
1053 used would degrade the CSP.

1054 A description of the sterilization and depyrogenation process, including the
1055 temperature, pressure (if applicable), duration, and permissible load conditions for each
1056 cycle, must be included in the facility’s written SOPs (see 9. *SOPS and Master*
1057 *Formulation and Compounding Records*.)

1058 In addition, the SOPs must include a schedule and method for establishing and
1059 periodically verifying the effectiveness of the sterilization and depyrogenation methods
1060 selected, as well as the method for maintaining and cleaning the sterilizers and
1061 depyrogenation equipment.

1062 The following sections provide general guidance on specific sterilization methods.

1063 **8.1 Sterilization by Filtration**

1064 See [Sterilizing Filtration of Liquids \(1229.4\)](#). Commercially available sterile filters must
1065 be certified by the manufacturer as suitable for pharmaceutical use when used to
1066 sterilize CSPs. Sterilizing filters must be sterile and pyrogen-free and have a nominal
1067 pore size of 0.2 or 0.22 μm . They must be certified by the manufacturer to retain at least
1068 10^7 microorganisms of a strain of *Brevundimonas diminuta* per square centimeter of
1069 upstream filter surface area under conditions similar to those in which the CSPs will be
1070 filtered (i.e., pressure, flow rate, and volume filtered).

1071 The person responsible for selecting the sterilization method must ascertain from
1072 appropriate information sources that the sterilizing-grade membrane filter selected is
1073 chemically and physically compatible with the specific formulation of the CSP. For
1074 example, CSPs containing water-miscible alcohols may cause undetectable damage to
1075 filter integrity and shrinkage of microorganisms to sizes smaller than the filter’s nominal
1076 pore size.

1077 The responsible person must ensure, directly or from appropriate documentation from
1078 the supplier, that the filters 1) are chemically and physically stable at the pressure and
1079 temperature conditions that will be used; 2) have enough capacity to filter the required
1080 volumes; and 3) will yield a sterile filtrate while maintaining pre-filtration pharmaceutical
1081 quality, including strength of ingredients of the specific CSP. The filter dimensions and
1082 the preparation to be sterilized by filtration should permit the sterilization process to be
1083 completed without the need for replacement of the filter during the process. When CSPs
1084 are known to contain excessive particulate matter, to maximize the efficiency of the final
1085 sterilizing filtration, a pre-filtration step should be performed using a filter of larger
1086 nominal pore size, or a separate filter of larger nominal pore size should be placed
1087 upstream of (i.e., prior to) the sterilizing filter to remove gross particulate contaminants
1088 before the CSP is passed through the sterilizing grade filter. Excessive particulate
1089 matter requiring a prefiltration step also could be a signal of an inappropriate
1090 formulation, and therefore the formulation and the process should be assessed to
1091 ensure that they are appropriate; if necessary, they should be modified. Filter units used
1092 to sterilize CSPs must be subjected to the manufacturers' recommended post-use
1093 integrity test, such as a bubble point test.

1094 **8.2 Sterilization by Steam Heat**

1095 See [Steam Sterilization by Direct Contact \(1229.1\)](#). The process of thermal
1096 sterilization using saturated steam under pressure (i.e., autoclaving) is the preferred
1097 method for terminal sterilization of aqueous preparations in their final, sealed container-
1098 closure system. Steam heat sterilization is not an option if moisture, pressure, or the
1099 temperatures used would degrade the CSP. Steam heat sterilization is also used to
1100 sterilize many components (e.g., elastomeric closures) and some types of equipment.
1101 To achieve sterility, all materials must be directly exposed to steam under adequate
1102 pressure for the length of time necessary, as determined by use of appropriate
1103 biological indicators, to render the items sterile (i.e., kill any microorganisms, including
1104 bacterial spores that might be present). This is usually between 20 and 60 minutes at
1105 121° saturated steam under a pressure of 15 psi. The duration of the exposure period
1106 must include sufficient time for the CSP or other items to reach the sterilizing
1107 temperature. The CSP and other items must remain at the sterilizing temperature for the
1108 duration of the sterilization period. The sterilization cycle should be designed to achieve
1109 a SAL of 10⁻⁶.

1110 CSPs must be placed in suitable trays to allow steam to reach the CSPs without
1111 entrapment of air. Flat, stainless steel trays with low sides or ventilated bottoms will
1112 permit steam contact. When preparing plastic, glass, and metal devices or other items
1113 for steam sterilization, the items must be wrapped in low-lint protective fabric or paper or
1114 sealed in envelopes that will permit steam penetration and prevent post sterilization
1115 microbial contamination. Immediately before filling ampuls and vials that will be steam
1116 sterilized, solutions must be passed through a filter having a nominal pore size of not
1117 larger than 1.2 µm for removal of particulate matter.

1118 Sealed containers must be able to generate steam internally. Stoppered and crimped
1119 empty vials must contain a small amount of moisture to generate steam. Deep
1120 containers, such as beakers and graduated cylinders, should be placed on their sides to
1121 prevent air entrapment, or should have a small amount of water placed in them when
1122 steam sterilized. Porous materials and those items with occluded pathways (e.g.,

1123 tubing) should only be sterilized by steam if the autoclave chamber has suitable cycles
1124 for dry goods, such as a pre-vacuum process to remove air before steam is sent into the
1125 chamber. Elastomeric closures and many other dry goods will need a drying cycle after
1126 steam exposure to remove condensed or absorbed moisture.

1127 The effectiveness of steam sterilization must be established and verified with each
1128 sterilization run or load by using appropriate biological indicators, such as spores of
1129 *Geobacillus stearothermophilus*, ATCC 12980, ATCC 7953 or equivalent (see [Biological](#)
1130 [Indicators for Sterilization \(1035\)](#)), and other confirmation methods such as
1131 physicochemical indicators and integrators (see [Sterilization—Chemical and](#)
1132 [Physicochemical Indicators and Integrators \(1209\)](#)).

1133 The steam supplied must be free of contaminants and generated using clean water.
1134 The seals on the doors of autoclave chambers should be examined visually every day
1135 they are used for cracks or other damage, and the seal surfaces should be kept clean.
1136 A data recorder or chart must be used to monitor each cycle and to examine for cycle
1137 irregularities (e.g., deviations in temperature or pressure).

1138 Because the temperatures used to achieve sterilization by steam heat are lower than
1139 those used to achieve depyrogenation, materials in direct contact with the CSP (e.g.,
1140 the container–closure system) must first undergo a depyrogenation process (e.g., dry
1141 heat or rinsing with pyrogen-free water) before being sterilized using steam heat, unless
1142 the materials used are certified to be pyrogen-free (see [Depyrogenation \(1228\)](#)).

1143 **8.3 Sterilization by Dry Heat**

1144 See [Dry Heat Sterilization \(1229.8\)](#). Dry heat can be used only for those items that
1145 cannot be sterilized by steam or other means, when either the moisture would damage
1146 the material or the wrapping material is impermeable. Sterilization by dry heat requires
1147 higher temperatures and longer exposure times than sterilization by steam. The
1148 duration of the exposure period must include sufficient time for the CSP or other items
1149 to reach the sterilizing temperature. The CSP and other items must remain at the
1150 sterilizing temperature for the duration of the sterilization period.

1151 Dry heat sterilization is usually done in an oven designed for sterilization at a
1152 temperature of 160° or higher, although sterilization processes at lower temperatures
1153 have been developed and validated. If lower temperatures are used, they must be
1154 shown to achieve effective sterilization (see [Dry Heat Sterilization \(1229.8\)](#), [Validation](#)
1155 [of Dry Heat Sterilization, Biological Indicators](#)).

1156 Heated air must be evenly distributed throughout the chamber, which is typically done
1157 by an air blower. The oven must be equipped with temperature controls and a timer.
1158 During sterilization, sufficient space must be left between materials to allow for good
1159 circulation of the hot air. A data recorder or chart must be used to monitor each cycle
1160 and the data must be reviewed to identify cycle irregularities (e.g., deviations in
1161 temperature or exposure time).

1162 The effectiveness of the dry heat sterilization method must be established and verified
1163 with each sterilization run or load using appropriate biological indicators such as spores
1164 of *Bacillus atrophaeus*, ATCC 9372, (see [\(1035\)](#)) and other confirmation methods (e.g.,
1165 temperature-sensing devices).

1166 Because the temperatures used to achieve sterilization by dry heat are lower than
1167 those used to achieve depyrogenation, materials in direct contact with the CSP (e.g.,

1168 the container–closure system) must first undergo a depyrogenation process (e.g., dry
1169 heat or rinsing with pyrogen-free water) before being sterilized using dry heat, unless
1170 the materials used are certified to be pyrogen-free (see [\(1228\)](#)).

1171 **8.4 Depyrogenation by Dry Heat**

1172 See [\(1228\)](#). Dry heat depyrogenation must be used to render glassware and other
1173 thermostable containers pyrogen-free. Depyrogenation processes typically operate at a
1174 range of temperatures from approximately 170° up to about 400°, depending on the
1175 exposure time. For example, a typical cycle would hold the items at 250° for 30 minutes.
1176 The duration of the exposure period must include sufficient time for the items to reach
1177 the depyrogenation temperature. The items must remain at the depyrogenation
1178 temperature for the duration of the depyrogenation period.

1179 The effectiveness of the dry heat depyrogenation cycle must be established and
1180 verified annually using endotoxin challenge vials (ECVs) to demonstrate that the cycle is
1181 capable of achieving a ≥ 3 -log reduction in endotoxins (see [Bacterial Endotoxins Test](#)
1182 [\(85\)](#)).

1183 **9. SOPS AND MASTER FORMULATION AND COMPOUNDING RECORDS**

1185 Every compounding facility must establish and follow written SOPs for sterile
1186 compounding. The SOPs must ensure that the entire compounding operation is well
1187 designed, functions as designed, and will yield CSPs that are safe for administration to
1188 patients. The compounding process for CSPs must be described in SOPs.

1189 A Master Formulation Record is required when CSPs are prepared in a batch for
1190 multiple patients or when CSPs are prepared from nonsterile ingredients. A Master
1191 Formulation Record documents the ingredients, specific procedures, equipment to be
1192 used, and testing required for each CSP. A Compounding Record is required for every
1193 CSP prepared and requires documentation by all individuals involved in the actual
1194 preparation of the CSP.

1195 **9.1 Creating and Following SOPs**

1196 Facilities preparing CSPs must develop SOPs on all aspects of the compounding
1197 operation. All personnel who conduct or oversee compounding activities must be trained
1198 in the SOPs and are responsible for ensuring that they are followed. All compounding
1199 personnel must:

- 1200 • Be able to immediately recognize potential problems, deviations, or errors
1201 associated with preparing a CSP (e.g., related to equipment, facilities,
1202 materials, personnel, compounding process, or testing) that could potentially
1203 result in contamination or other adverse impact on CSP quality
- 1204 • Report any problems, deviations, or errors to the compounding supervisor or
1205 designee, who must take corrective actions

1206 Compounding supervisors must ensure that SOPs are appropriate and are fully
1207 implemented, which includes ensuring that staff demonstrate consistency and
1208 competency in performing every procedure that relates to their job function.

1209 Compounding supervisors must also ensure that appropriate follow-up occurs if
1210 problems, deviations, or errors are identified.

1211 **9.2 Creating Master Formulation Records**

1212 A Master Formulation Record must be created for CSPs prepared in a batch for
1213 multiple patients or for CSPs prepared from nonsterile ingredients. Any changes or
1214 alterations to the Master Formulation Record must be performed only by authorized
1215 personnel and must be documented. [Box 9-1](#) lists the information that must be included
1216 in a Master Formulation Record.

1217 **Box 9-1 Master Formulation Record**

A Master Formulation Record must include at least the following information:

- Name, strength, and dosage form of the CSP
- Physical description of the final preparation
- Identities and amounts of all ingredients and appropriate container–closure systems
- Complete instructions for preparing the CSP, including equipment, supplies, and a description of the compounding steps
- BUD and storage requirements
- Quality control procedures (e.g., pH, filter integrity, and visual inspection)
- Sterilization method, if applicable (e.g., filter, steam, or dry heat)
- Any other information needed to describe the operation and ensure its repeatability (e.g., adjusting pH and tonicity and temperature)

1218 **9.3 Creating Compounding Records**

1219 A Compounding Record must be created by the compounder preparing the CSP to
1220 document the compounding process. The Compounding Record or inventory control
1221 system must permit traceability of all ingredients. The Master Formulation Record (when
1222 used) can be used as the basis for preparing the Compounding Record. For example, a
1223 copy of the Master Formulation Record can be made that contains spaces for recording
1224 the information needed to complete the Compounding Record. It is critical that the
1225 Compounding Record document in detail any deviations from the process outlined in
1226 the Master Formulation Record and any problems or errors experienced during the
1227 compounding of the CSP. [Box 9-2](#) lists the information that must be included in a
1228 Compounding Record.

1229 Each Compounding Record must be reviewed and approved before the CSP is
1230 released (signature or initials and date).

1231 **Box 9-2 Compounding Records**

Compounding Records must include at least the following information:

- Name, strength, and dosage form of the CSP
- Master Formulation Record reference for the preparation, when used
- Date and time of preparation of the CSP
- Assigned internal identification number (e.g., prescription or lot number)
- Signature or initials of individuals involved in each step (e.g., technician or pharmacist)
- Name, vendor or manufacturer, lot number, and expiration date of each ingredient and container–closure system
- Weight or measurement of each ingredient
- Documentation of the calculations made to determine and verify quantities and/or concentrations of components, if appropriate
- Documentation of quality control procedures in accordance with the SOP (e.g., filter integrity, pH, and visual inspection)
- Any deviations from the Master Formulation Record, if used, and any problems or errors experienced during the compounding of the CSP
- Total quantity compounded
- Assigned BUD
- Duplicate container label if prepared in a batch

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10. RELEASE TESTING

1234 At the completion of compounding, before release and dispensing, the CSP must be
1235 inspected as described below to determine whether the physical appearance of the
1236 CSP is as it should be and to confirm that the CSP and its labeling match the
1237 prescription or medication order.

1238 The physical inspection described in *10.1 Physical Inspection of CSP* must be
1239 performed on all CSPs before they are released. In addition, sterility and bacterial
1240 endotoxin testing must be performed in some cases (see *12. Establishing Beyond-Use*
1241 *Dates and In-Use Times*), as described in *10.2 Sterility Testing* and *10.3 Bacterial*
1242 *Endotoxins Testing*. All checks and inspections, and any other tests or checks
1243 necessary to ensure the quality of the CSP (e.g., assays), must be included in the
1244 facility's SOP (see *9. SOPS and Master Formulation and Compounding Records*).
1245 Additional quality assurance and quality control activities are discussed in *13. Quality*
1246 *Assurance and Quality Control*.

1247 10.1 Physical Inspection of CSP

1248 After compounding, and as a condition of release, each individual CSP unit must be
1249 inspected to identify any apparent physical defect. Each individual injectable CSP unit
1250 must be inspected against a lighted white background and a black background for
1251 evidence of visible particulates or other foreign matter, or discoloration. Some CSPs
1252 also must be visually checked for certain characteristics (e.g., emulsions must be
1253 checked for phase separation). Pre-release inspection also must include a visual
1254 inspection of container–closure integrity (e.g., checking for leakage, cracks in the

1255 container, or improper seals). CSPs with observed defects must be immediately
1256 discarded, or marked and segregated from acceptable units in a manner that prevents
1257 them from being released or dispensed.

1258 When a CSP will not be released or dispensed promptly after preparation, a pre-
1259 release inspection must be conducted immediately before it is released or dispensed to
1260 make sure that the CSP does not exhibit any defects, such as precipitation, cloudiness,
1261 or leakage, which may develop during storage. A CSP with such defects must be
1262 immediately discarded, or marked and segregated from acceptable units in a manner
1263 that prevents it from being released or dispensed.

1264 **10.2 Sterility Testing**

1265 Category 1 CSP BUDs apply regardless of whether sterility testing is conducted (see
1266 [Table 7](#)). If a Category 2 CSP is assigned a BUD that requires sterility testing (see
1267 [Table 8](#)), the testing must be performed in a manner consistent with [\(71\)](#), with the
1268 exception, in some cases, of the batch sizes specified in [Sterility Tests \(71\), Table 3.](#)
1269 [Minimum Number of Articles to be Tested in Relation to the Number of Articles in the](#)
1270 [Batch](#). If the number of units of CSPs to be prepared in a single batch is less than the
1271 number of units needed for testing, additional units may be required to be compounded
1272 to be able to conduct sterility testing. For batch sizes of 1–39 units, each sterility test
1273 must be performed using a number of units equal to 10% of the batch size, rounded up
1274 to the next whole number. For batch sizes of 40 or more units, the sample sizes
1275 specified in [Sterility Tests \(71\), Table 3](#) must be used.

1276 When the CSP formulation permits, the Membrane Filtration method is the method of
1277 choice for sterility testing. The preferred alternative is the Direct Inoculation of the
1278 Culture Medium method; both methods are described in [\(71\)](#).

1279 If sterility testing will be conducted, ideally the results should be obtained before
1280 dispensing to patient(s). If it is anticipated that there will be situations in which there
1281 may be an urgent need to dispense a CSP before the results of the sterility testing are
1282 known, a written procedure (SOP) must be developed and followed; this SOP must
1283 describe how these situations will be handled. In addition, this SOP must require
1284 frequent observation of the incubating test specimen and must require immediate recall
1285 of the dispensed CSP (if possible) or immediate notification of the patient's prescriber, if
1286 any evidence of microbial growth is found during the test.

1287 Positive sterility test results must prompt a rapid and systematic investigation into the
1288 causes of the sterility failure, including identification of the contaminating organism (at
1289 least to the genus level) and any aspects of the facility, process, or personnel that may
1290 have contributed to the sterility failure. The source of the contamination, if identified,
1291 must be corrected, and the facility should determine whether the conditions causing the
1292 sterility failure affect other CSPs. The investigation and resulting corrective actions
1293 must be documented.

1294 **10.3 Bacterial Endotoxins Testing**

1295 All Category 2 CSPs made from one or more nonsterile ingredients, except those for
1296 inhalation and topical ophthalmic administration, must be tested to ensure that they do
1297 not contain excessive bacterial endotoxins (see [\(85\)](#) and [Pyrogen Test \(151\)](#)). A CSP
1298 does not need to be tested for bacterial endotoxins if the COA for the nonsterile
1299 ingredient lists the endotoxins burden, or if the compounding facility has predetermined

1300 the endotoxins burden of the nonsterile ingredient and found it acceptable, and the
1301 material is stored under cool and dry conditions.
1302 In the absence of a bacterial endotoxins limit in an official monograph or other CSP
1303 formula source, the CSP must not exceed the endotoxins limit calculated as described
1304 in [\(85\)](#) for the appropriate route of administration.

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11. LABELING

1307 CSPs must be labeled with adequate, legible identifying information to prevent errors
1308 during storage, dispensing, and use. The term labeling designates all labels and other
1309 written, printed, or graphic matter on an article's immediate container or on, or in, any
1310 package or wrapper in which it is enclosed, except any outer shipping container. The
1311 term label designates that part of the labeling on the immediate container. See [Labeling](#)
1312 [\(7\), Labels and Labeling for Products and Other Categories, Compounded](#)
1313 [Preparations](#).

1314 The label must, at a minimum, display prominently and understandably the following
1315 information:

- 1316 • Assigned internal identification number (e.g., prescription or lot number)
- 1317 • Brand and/or generic name(s), or active ingredient(s) and amounts or
1318 concentrations
- 1319 • Dosage form
- 1320 • Total amount, if it is not obvious from the container
- 1321 • Storage conditions
- 1322 • BUD and when appropriate, an in-use time (see *12. Establishing Beyond-Use*
1323 *Dates and In-Use Times*)
- 1324 • Whether it is a single-dose or multiple-dose container
- 1325 • Indication that the preparation is compounded

1326 The labeling must, at a minimum, display prominently and understandably the
1327 following information:

- 1328 1. Patient name, or for animal drugs, owner's name and species of patient
- 1329 2. Route of administration, if known
- 1330 3. Any special handling instructions
- 1331 4. Any warning statements that are applicable
- 1332 5. Name, address, and contact information of the compounder if the CSP is to be
1333 sent outside of the facility in which it was compounded

1334 Labeling operations must be controlled to prevent labeling errors and CSP mix-ups. A
1335 final check must be conducted to verify that the correct and complete label has been
1336 affixed to the finished CSP. All labels must also comply with applicable state laws and
1337 regulations.

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12. ESTABLISHING BEYOND-USE DATES AND IN-USE TIMES

1340 Each CSP label must state the date beyond which the preparation cannot be used and
1341 must be discarded. A CSP may also be labeled with an in-use time within which it must
1342 be used after it has been opened or punctured. A number of critical parameters must be
1343 considered before establishing these dates. It is also important to understand the
1344 various terms that are used in discussion of these dates.

1345 **12.1 Terminology**

1346 A number of terms are used to describe the time period during which a drug is
1347 considered to retain its desired characteristics so that it can be safely administered to a
1348 patient to achieve the desired therapeutic effect.

1349 The expiration date identifies the time during which a conventionally manufactured
1350 drug product may be expected to maintain its labeled identity, strength, quality, and
1351 purity, provided it is kept under the labeled storage conditions. The expiration date limits
1352 the time during which a conventionally manufactured product may be dispensed or
1353 used. Expiration dates are determined based on product-specific studies that evaluate
1354 the specific formulation of a drug product in the specific container in which it is to be
1355 stored and under the conditions to which it could be exposed. Temperature, humidity,
1356 and light are some of the factors that can affect whether and how much a product
1357 degrades over time. An expiration date is determined by taking representative samples
1358 from batches and placing them in storage under controlled conditions and then testing
1359 them at scheduled intervals to determine whether they meet specifications throughout
1360 their labeled shelf lives. When an expiration date is stated only in terms of the month
1361 and the year, it is a representation that the intended expiration date is the last day of the
1362 stated month.

1363 A BUD is included on the label of each CSP to indicate the date or date and hour after
1364 which the CSP must not be used, because its required quality characteristics (e.g.,
1365 sterility, strength, purity) cannot be ensured. The term expiration date is not appropriate
1366 for CSPs, because the types of full stability studies conducted by manufacturers to
1367 establish expiration dates for conventionally manufactured products are not typically
1368 performed for CSPs. BUDs for CSPs are calculated in terms of hours or days.

1369 An in-use time refers to the time before which a conventionally manufactured product
1370 or a CSP must be used after it has been opened or needle punctured (e.g., after a
1371 container closure of a vial has been penetrated).

1372 **12.2 Critical Parameters to Be Considered in Establishing a BUD**

1373 Time is a critical factor in establishing a BUD. The more time that passes between the
1374 compounding of a CSP and its administration to a patient, the greater the risk of harm to
1375 the patient if the stability or sterility of the CSP has been compromised. With respect to
1376 sterility, this is especially the case if microbial contamination is present from the outset.
1377 BUDs for CSPs should be established conservatively to ensure that the drug maintains
1378 its required characteristics until administration to reduce the risk to patients of receiving
1379 a contaminated or degraded preparation. Both sterility and stability considerations must
1380 be taken into account when establishing a BUD.

1382 Microbial contamination of a CSP poses a significant risk to patients, and if the CSP is
1383 contaminated during preparation, the risk increases the longer the time the CSP is
1384 stored before administration.

1385 When establishing a BUD for a CSP, it is critical that compounding personnel carefully
1386 consider all of the possible ways that the sterility of the CSP could be compromised
1387 over time. The following factors related to sterility must be carefully considered:

- 1388 • Whether the CSP will be tested for sterility, and the results will be known, before
1389 the CSP is released or dispensed
- 1390 • Whether the CSP will be terminally sterilized in its final container (provided the
1391 drug and its container–closure can withstand the terminal sterilization process)
1392 (see 8. *Sterilization and Depyrogenation*)
- 1393 • Whether the CSP contains a preservative, or is inherently susceptible to
1394 microbial survival or growth, if contaminated
- 1395 • Whether the container–closure system and sealing method will ensure the
1396 integrity of the CSP until administration to the patient

1397 STABILITY CONSIDERATIONS

1398 Over time, active ingredient(s) in a CSP may degrade, reducing the strength of the
1399 preparation and/or producing harmful impurities. Additionally, the container–closure
1400 system may degrade, which can lead to several potential deleterious effects, such as: 1)
1401 reducing the integrity of the CSP; 2) leaching of harmful chemicals into the preparation
1402 from the container–closure system; and/or 3) absorption of the active ingredient onto
1403 the container, thereby reducing potency. When establishing a BUD for a CSP, it is
1404 critical that compounding personnel carefully consider all of the possible ways that the
1405 physical or chemical characteristics of the CSP could change over time. The following
1406 issues must be carefully considered:

- 1407 • The chemical and physical stability properties of the drug and/or its formulation
1408 (i.e., if the drug and its formulation are known to degrade over time and/or
1409 under certain storage conditions)
- 1410 • The compatibility of the container–closure system with the finished preparation
1411 (e.g., consider leachables, interactions, and storage conditions of the
1412 components)

1413 In addition:

- 1414 • If the CSP includes components from conventionally manufactured product(s),
1415 the BUD of the CSP must not exceed the shortest remaining expiration date of
1416 any of the starting components.
- 1417 • If the CSP includes components from other compounded preparations, the BUD
1418 of the final CSP must not exceed the shortest remaining BUD of any of the
1419 starting CSP components.

1420 12.3 Establishing a BUD for a CSP

1421 BUDs for CSPs must be established in accordance with [Table 7](#) for Category 1 CSPs
1422 and [Table 8](#) for Category 2 CSPs. The BUDs specified in the tables indicate the hours
1423 or days after the CSP is prepared and beyond which the CSP cannot be used. The BUD
1424 is determined from the time the CSP is compounded. One day is equivalent to 24 hours.
1425 The BUDs in [Table 7](#) and [Table 8](#) for CSPs are based on the risk of microbial
1426 contamination, not the physical or chemical stability of the CSP, and involve the
1427 following assumptions:

- 1428 1. The CSP and its components can remain chemically and physically stable for the
1429 BUD period
- 1430 2. None of the factors identified in *12.2 Critical Parameters to Be Considered in*
1431 *Establishing a BUD*, would require a shorter BUD

1432 If there is any indication, based on the factors described in *12.2. Critical Parameters to*
1433 *be Considered in Establishing a BUD*, that the particular CSP formulation will not remain
1434 chemically or physically stable for the specified period, a shorter BUD must be assigned
1435 based on the time period during which the CSP is expected to remain chemically and
1436 physically stable.
1437 [Table 8](#) establishes the longest permitted BUDs for Category 2 CSPs, based the
1438 following variables:

1439 METHOD OF ACHIEVING STERILITY

1440 Because terminal sterilization using a verified method provides reasonable assurance
1441 that a CSP will be sterile, [Table 8](#) allows longer BUDs for CSPs that are terminally
1442 sterilized and not sterility tested than for aseptically prepared CSPs that are not sterility
1443 tested. Not all CSPs can be terminally sterilized, and if the CSP is aseptically prepared
1444 (e.g., using only sterile products or sterilized by filtration), the shorter BUDs in [Table 8](#)
1445 for aseptically prepared CSPs that are not sterility tested must not be exceeded.

1446 STARTING COMPONENTS

1447 An aseptically prepared CSP compounded from one or more nonsterile starting
1448 component has a higher risk of microbial contamination than an aseptically prepared
1449 CSP compounded only from sterile starting components. [Table 8](#) allows for longer
1450 BUDs for CSPs aseptically prepared from only sterile starting components.

1451 WHETHER THE CSP WILL BE STERILITY TESTED AND THE RESULTS KNOWN BEFORE THE DRUG IS 1452 RELEASED OR DISPENSED

1453 Sterility testing (see *10.2 Sterility Testing*) before releasing or dispensing a CSP can
1454 provide additional assurance of the absence of contamination. When the results of
1455 sterility testing are known before dispensing, a longer BUD is permitted in [Table 8](#). If
1456 sterility testing is not performed, a shorter BUD is required in [Table 8](#).

1457 If a sterility test is performed and there is an urgent need to dispense the CSP before
1458 sterility test results become available, a CSP can be dispensed to a patient before the
1459 end of the sterility testing period if:

- 1460 • The prescriber specifically requests dispensing before completion of the sterility
1461 test, and the request is documented

- The patient and the prescriber are notified of any microbial growth during the sterility testing. The species of microbial contaminant is reported to the prescriber to ensure appropriate medical therapy following exposure to a contaminated CSP

PRESENCE OF A PRESERVATIVE

Although a preservative must not be considered a substitute for good aseptic practices, preservatives can be added to multiple-dose CSPs because they may inhibit the growth of microorganisms for short periods of time. If a CSP contains a preservative whose effectiveness for the length of the BUD has been verified based on antimicrobial effectiveness testing (see [Antimicrobial Effectiveness Testing \(51\)](#)), the BUD in [Table 8](#) for a CSP containing a preservative can be assigned. Shorter BUDs are required for preservative-free CSPs, as compared to CSPs that contain a verified preservative. The particular CSP formulation must pass antimicrobial effectiveness testing in accordance with [\(51\)](#) at the completion of the sterility test (if conducted) or at the time of preparation (if sterility testing is not performed). The test must be completed and the results obtained on the specific formulation before any of the CSP is released or dispensed. The test needs to be conducted only once on each formulation in the particular container–closure system in which it will be stored or released/dispensed.

STORAGE CONDITIONS

The specified conditions under which a CSP will be stored are important in determining an appropriate BUD. Storage in a refrigerator or in a freezer (see [Packaging and Storage Requirements \(659\)](#)) has been shown to slow the growth of microorganisms. Therefore, [Tables 7](#) and [8](#) allow for longer BUDs for CSPs stored in colder conditions than when stored at controlled room temperature.

Storage under frozen conditions places the container–closure under physical stress, and the degree of stress may depend on the formulation and other factors. Therefore, if a Category 2 CSP is to be stored in a freezer, the integrity of the CSP in the particular container–closure system in which it will be stored must have been demonstrated for 45 days at frozen storage. A container–closure integrity test needs to be conducted only once on each formulation and fill volume in the particular container–closure system in which it will be stored or released/dispensed. Once the CSP is thawed, the CSP must not be re-frozen.

It must be recognized that CSPs may be stored under different storage conditions before they are used (e.g., they may first be frozen, and then thawed in the refrigerator, and finally kept at controlled room temperature before administration). The storage time of a CSP must not exceed the original BUD placed on the CSP for its labeled storage conditions, and BUDs are not additive. For example, a CSP cannot be stored for 4 days at controlled room temperature, then 7 days refrigerated, and then 45 days in a freezer, for a total of 56 days. Once a CSP is stored under a condition that would require a shorter BUD (i.e., controlled room temperature), the CSP must be used within the shorter timeframe for that storage condition (in this example, 4 days).

Table 7. BUDs for Category 1 CSPs^a

	Storage Conditions
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Storage Conditions		
	Controlled Room Temperature (20°–25°)	Refrigerator (2°–8°)
BUD	≤12 hours	≤24 hours

^a The BUDs specified in the table indicate the hours after the Category 1 CSP is prepared beyond which the CSP cannot be used. The BUD is determined from the time the CSP is compounded.

Table 8. BUDs for Category 2 CSPs^a

Preparation Characteristics				Storage Conditions				
Method of Achieving Sterility	Sterility Testing Performed	Preservative Added		Controlled Room Temperature (20°–25°)	Refrigerator (2°–8°)	Freezer (–25° to –10°) ^b		
BUD	Aseptically prepared CSPs	No	No	Prepared from one or more nonsterile starting component	Prepared from one or more nonsterile starting component	Prepared from one or more nonsterile starting component		
				4 days	7 days	45 days		
		Yes	No	No	Prepared from only sterile starting components	Prepared from only sterile starting components	Prepared from only sterile starting components	
					6 days	9 days	45 days	
			Yes	No	Yes ^c	28 days	42 days	45 days
						28 days	42 days	45 days
Terminally Sterilized CSPs	No	No	14 days	28 days	45 days			
			28 days	42 days	45 days			
	Yes	No	Yes ^c	28 days	42 days	45 days		
				42 days	42 days	45 days		

^a The BUDs specified in the table indicate the days after the Category 2 CSP is prepared beyond which the CSP cannot be used. The BUD is determined from the time the CSP is compounded. One day is equivalent to 24 hours.

^b The integrity of the container–closure system with the particular CSP in it must have been demonstrated for 45 days at frozen storage. The container–closure integrity test needs to be conducted only once on each formulation in the particular container–closure system in which it will be stored or released/dispensed.

^c The particular CSP formulation must pass antimicrobial effectiveness testing in accordance with (51) at the time of preparation. The test must be completed and the results obtained on the specific formulation before any of the CSP is dispensed. The test needs to be conducted only once on each formulation in the

Preparation Characteristics			Storage Conditions		
Method of Achieving Sterility	Sterility Testing Performed	Preservative Added	Controlled Room Temperature (20°–25°)	Refrigerator (2°–8°)	Freezer (–25° to –10°) ^b

particular container–closure system in which it will be stored or released/dispensed.

^d The particular CSP formulation must pass antimicrobial effectiveness testing in accordance with (51) at the completion of sterility test (i.e., 14 days after preparation). The test must be completed and the results obtained on the specific formulation before any of the CSP is dispensed. The test needs to be conducted only once on each formulation in the particular container–closure system in which it will be stored or released/dispensed.

1505 **12.4 Establishing In-Use Times**

1506 The in-use time is the time before which a conventionally manufactured product or a

1507 CSP must be used after it has been opened or needle-punctured. The in-use time

1508 assigned cannot exceed the expiration date of the conventionally manufactured product

1509 or the BUD of a CSP. The in-use time may be dependent on the type of product or CSP

1510 and the environment where the manipulations occur (e.g., ISO Class 5, or worse than

1511 ISO Class 5). [Table 9](#) specifies the in-use times for conventionally manufactured

1512 products and CSPs that are opened, stored, and used for sterile compounding in ISO

1513 Class 5 or better air quality. [Table 10](#) specifies the in-use times for conventionally

1514 manufactured products and CSPs that are opened and/or stored in worse than ISO

1515 Class 5 air quality.

1516 **Table 9. In-Use Times for Conventionally Manufactured Products and CSPs**

1517 **Opened, Stored, and Used for Sterile Compounding in ISO Class 5 or Better Air**

1518 **Quality**

Components	In-Use Time
Conventionally Manufactured Sterile Product	
Ampuls	Use <i>immediately</i> after opening and passing through a sterile particulate filter
Pharmacy Bulk Package	As specified by the manufacturer
Single-dose container (e.g., bag, bottle, syringe, or vial)	6 hours
Multiple-dose container	28 days, unless otherwise specified by the manufacturer
CSP	
Compounded single-dose container	6 hours
Compounded stock solutions	6 hours
Compounded multiple-dose container ^a	28 days, unless otherwise specified by the original compounder

^a The particular CSP formulation must pass antimicrobial effectiveness testing in accordance with (51) at

Components	In-Use Time
Conventionally Manufactured Sterile Product	
the completion of the sterility test (if conducted) or at the time of preparation (if sterility testing is not performed). The test must be completed and the results obtained on the specific formulation before any of the CSP is released or dispensed. The test needs to be conducted only once on each formulation in the particular container–closure system in which it will be stored or released/dispensed.	

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Table 10. In-Use Times for Conventionally Manufactured Products and CSPs Opened and/or Stored in Worse than ISO Class 5 Air^a

Components	In-Use Time
Conventionally Manufactured Sterile Product	
Ampuls	Use <i>immediately</i> after opening and passing through a sterile particulate filter
Pharmacy Bulk Package	Not applicable. Contents of pharmacy bulk packages must be used only in an ISO Class 5 or better environment.
Single-dose container (e.g., bag, bottle, syringe, vial)	Use for a single patient within the time specified by the manufacturer, or by the end of the case or procedure, whichever comes first. Discard remainder.
Multiple-dose container	28 days, unless otherwise specified by the manufacturer
CSP	
Compounded single-dose container	Use for a single patient immediately. Discard remainder.
Compounded multiple-dose container ^b	28 days, unless otherwise specified by the original compounder
^a Compounding or repackaging must not occur in worse than ISO Class 5 air. ^b The particular CSP formulation must pass antimicrobial effectiveness testing in accordance with (51) at the completion of the sterility test (if conducted) or at the time of preparation (if sterility testing is not performed). The test must be completed and the results obtained on the specific formulation before any of the CSP is released or dispensed. The test needs to be conducted only once on each formulation in the particular container–closure system in which it will be stored or released/dispensed.	

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13. QUALITY ASSURANCE AND QUALITY CONTROL

1523 A quality assurance (QA) and quality control (QC) program is necessary to ensure that
1524 consistently high-quality CSPs are prepared. QA is a set of written processes that, at a
1525 minimum, verifies, monitors, and reviews the adequacy of the compounding process.
1526 QC is the observation of techniques and activities that demonstrate that requirements
1527 are met.

1528 Each facility must have a formal, written QA and QC program that establishes a
1529 system of adherence to procedures, prevention and detection of errors and other quality
1530 problems, and appropriate corrective actions when needed. A facility's QA program
1531 must be formally established and documented in SOPs that ensure that all aspects of

1532 the preparation of CSPs are conducted in accordance with this chapter and applicable
1533 federal, state, and local laws and regulations.

1534 The QA program must, at a minimum, address the following functions:

- 1535 • Personnel qualifications and training:
 - 1536 ○ Periodically review personnel files for each employee to determine
 - 1537 whether personnel continue to meet basic qualifications, are obtaining
 - 1538 required training, and are getting qualified and requalified in
 - 1539 accordance with the specified frequencies (e.g., gloved fingertip/thumb
 - 1540 sampling)
 - 1541 ○ Assess staff performance, including aseptic techniques, cleanroom
 - 1542 behavior, and other critical activities (e.g., media-fill testing)
- 1543 • Component selection and handling:
 - 1544 ○ Carefully select, and ensure ongoing qualification of suppliers and
 - 1545 service providers (e.g., chemical vendors and external testing
 - 1546 laboratories)
 - 1547 ○ Select ingredients that are the subject of a *USP* or *NF* monograph and
 - 1548 that are manufactured at an FDA-registered facility, when available
 - 1549 ○ Inspect incoming components against their COAs to ensure that they
 - 1550 meet their specifications
 - 1551 ○ Quarantine, properly dispose of, and investigate components that do
 - 1552 not meet their specifications
- 1553 • Design and maintenance of the building, facility, and equipment:
 - 1554 ○ Review the adequacy of the design of the building, facility, and
 - 1555 equipment; when changes are made, assess their effects to make sure
 - 1556 they do not adversely affect the operation (e.g., certification)
 - 1557 ○ Ensure that facilities and equipment used in compounding are installed,
 - 1558 operated, and maintained properly per appropriate and pre-established
 - 1559 specifications
 - 1560 ○ Detect adverse trends in environmental monitoring data to take
 - 1561 preventive action and corrective action
- 1562 • Compounding process:
 - 1563 ○ Approve Master Formulation Records (when used), or any changes to
 - 1564 them, before they are implemented
 - 1565 ○ Review Compounding Records for accuracy, completeness, and
 - 1566 conformance to established specifications
 - 1567 ○ Review final labeling against prescription or medication orders
 - 1568 ○ Ensure that all errors, process problems, or deviations from procedures
 - 1569 are documented
 - 1570 ○ Investigate any error, deviation, out-of-specification result, or complaint,
 - 1571 and implement, oversee, and document appropriate corrective action to
 - 1572 prevent recurrence
- 1573 • Final CSP release:
 - 1574 ○ Assess the final CSP before release (e.g., physical inspection, sterility
 - 1575 testing, and analytical testing)

- 1576 ○ Review internal or external testing programs (if used) for conformance
1577 with applicable standards (e.g., sterility testing and endotoxin testing)
1578 • Documentation:
1579 ○ Establish SOPs and assess conformance to SOPs
1580 ○ Establish and assess conformance with document control and records
1581 management procedures
1582 ○ Establish, maintain, and follow written procedures for handling all
1583 written and oral complaints regarding a CSP

1584 The roles and duties of personnel responsible for each aspect of the QA program must
1585 be described in the SOPs. Designated personnel responsible for the QA program must
1586 have adequate training, experience, responsibility, and authority to perform these
1587 duties.

1588 The overall QA program must be assessed annually.

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14. CSP STORAGE, HANDLING, PACKAGING, AND TRANSPORT

1591 Appropriate processes or techniques for storing, handling, packaging, and transporting
1592 CSPs must be in place and must also be outlined in SOPs. Personnel who will be
1593 storing, handling, packaging, and transporting CSPs within the facility must be properly
1594 trained in accordance with the relevant SOPs.

1595

14.1 Storing CSPs within the Compounding Facility

1596 To help ensure that CSP quality is retained while the CSP is stored at the
1597 compounding facility, compounding personnel must monitor conditions in the drug
1598 storage areas. A controlled temperature area must be checked at least once daily to
1599 determine whether the temperature remains within the appropriate range, and the
1600 results must be documented on a temperature log. If the compounding facility uses a
1601 continuous temperature recording device, compounding personnel must verify at least
1602 once daily that the recording device is functioning properly. In addition, the
1603 compounding facility must adhere to appropriate procedures for all controlled
1604 temperature areas to ensure that such spaces are not subject to prolonged temperature
1605 fluctuations (e.g., by leaving a refrigerator door open too long).

1606 When it is known that a CSP has been exposed to temperatures that exceed storage
1607 temperature limits, (i.e., temperatures warmer than the warmest labeled limit or
1608 temperatures exceeding 40° for more than 4 hours), the CSP should be discarded.

1609

14.2 Handling of CSPs

1610 CSPs must be handled properly while in the compounding facility to maintain CSP
1611 quality and packaging integrity. For example, techniques should be in place to prevent
1612 the depression of syringe plungers or dislodging of syringe tips. Additionally,
1613 disconnection of system components (e.g., where CSPs are dispensed with
1614 administration sets attached to them) must be prevented throughout the BUD or until
1615 administration of the CSP.

1616

14.3 Packaging of CSPs

1617 Compounding personnel must select and use packaging materials that will maintain
1618 the physical integrity, sterility, and stability of the CSPs. Packaging materials must
1619 protect CSPs from damage, leakage, contamination, degradation, and adsorption, while
1620 simultaneously protecting transport personnel from harm. The facility must have written
1621 SOPs that describe appropriate shipping containers and insulating and stuffing
1622 materials based on the product specifications, information from vendors, and knowledge
1623 of the mode of transport. For example, when CSPs are transported within the facility
1624 through pneumatic tube systems, foam padding or inserts may be useful for preventing
1625 breakage and spills. Compounding personnel must continuously monitor the
1626 effectiveness and reliability of the packaging materials.

1627 Alternative modes of transport and/or special packaging may be needed to protect the
1628 quality of CSPs. The use of tamper-evident closures and seals on CSP ports can
1629 provide an additional measure of security that can help ensure product integrity,
1630 regardless of the transport method used. If the CSP is sensitive to light, light-resistant
1631 packaging materials must be used. In some cases, the CSP should be packaged in a
1632 special container (e.g., a cooler) to protect it from temperature fluctuations.

1633 **14.4 Transporting CSPs**

1634 Compounding personnel must select modes of transport that are expected to deliver
1635 properly packed CSPs in an undamaged, sterile, and stable condition. Inappropriate
1636 handling and transport can adversely affect the quality of CSPs in general, particularly
1637 certain CSPs with unique stability concerns. For example, the physical shaking that
1638 might occur during pneumatic tube transport, or undue exposure to heat or light, must
1639 be considered and addressed on a preparation-specific basis. Compounding personnel
1640 must include specific handling instructions on the exteriors of containers that are used
1641 to transport CSPs.

1642 **14.5 Handling of Hazardous Drugs**

1643 For information on the storage, packaging, handling, and transport of hazardous drugs,
1644 see [\(800\)](#).

1645 **15. COMPLAINT HANDLING AND ADVERSE EVENT REPORTING**

1647 Compounding facilities must provide patients and other CSP recipients with a way to
1648 submit questions and report any concerns or complaints they may have regarding a
1649 CSP. SOPs must be developed, implemented, and followed for the receipt,
1650 acknowledgment, and handling of all complaints about the quality and labeling of, or
1651 possible adverse reactions to, a specific CSP.

1652 **15.1 Complaint Handling**

1653 A qualified individual must review all complaints to determine whether the complaint
1654 indicates a potential quality problem with the CSP. If so, a thorough investigation into
1655 the cause of the problem must be initiated and completed promptly. The investigation
1656 must consider whether the quality problem extends to other batches of the same CSP,
1657 or to other CSPs that could have been affected. Corrective action, if necessary, must be
1658 implemented immediately for all potentially affected CSPs. When warranted, consider
1659 whether to initiate a recall of potentially affected CSPs and whether to cease sterile

1660 compounding operations until all underlying problems have been identified and
1661 corrected.

1662 A written record of each complaint must be kept, regardless of the source (e.g., e-mail,
1663 telephone, mail). The record must contain the name of the complainant, the date the
1664 complaint was received, the nature of the complaint, and the response to the complaint.
1665 In addition, to the extent that the information is known, the following should be recorded:
1666 the name and strength of the CSP, the prescription or medication order number, and the
1667 lot number, if one is assigned. The record must also include the findings of any
1668 investigation and any follow-up. Complaint records must be easily retrievable for review
1669 and evaluation for possible trends and must be retained in accordance with the
1670 recordkeeping requirements in *16. Documentation*. A CSP that is returned in connection
1671 with a complaint must be quarantined until it is destroyed after completion of the
1672 investigation and in accordance with applicable federal, state, and local laws and
1673 regulations.

1674 **15.2 Adverse Event Reporting**

1675 Reports of potential adverse events involving a CSP must be reviewed promptly and
1676 thoroughly by compounding personnel. The reports must be handled in accordance with
1677 the procedures for handling complaints as described in section *15.1 Complaint*
1678 *Handling*, as well as the record retention requirements described in *16. Documentation*.
1679 Relevant healthcare professionals and patients must be informed as appropriate. If
1680 required, adverse events must be reported in accordance with applicable state and local
1681 laws and regulations. In addition, serious or unexpected adverse events associated with
1682 a CSP should be reported to the FDA through the MedWatch program for human drugs
1683 and Form FDA 1932a for animal drugs.

1684 **16. DOCUMENTATION**

1686 All facilities where CSPs are prepared must have and maintain written documentation
1687 to demonstrate compliance with this chapter, including all SOPs, Master Formulation
1688 Records (when used), Compounding Records, laboratory and equipment records,
1689 prescriptions or medication orders, and all information related to complaints.

1690 All records must be legible and stored in a manner that prevents their deterioration
1691 and/or loss. Records can be kept electronically. Records must be maintained either at
1692 the facility or at another location that is readily accessible within a reasonable period of
1693 time.

1694 All records specific to the compounding of a particular CSP (e.g., Master Formulation
1695 Record, Compounding Record, and testing results) must be kept for at least 3 years
1696 after the BUD of the CSP, or as required by state laws and regulations, whichever is
1697 longer. Facility design and initial qualification records must be kept as long as the facility
1698 is in operation. All other records must be kept for at least 3 years, or as required by
1699 state laws and regulations, whichever is longer. Examples include records related to
1700 personnel training and qualification, equipment maintenance and calibration, receipt of
1701 components, environmental monitoring, complaints, and quality assurance.

1702 Recordkeeping must also comply with all applicable federal laws and regulations.

1703
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17. RADIOPHARMACEUTICALS AS CSPS

1705 Radiopharmaceuticals are associated with risks of radiation exposure to healthcare
1706 practitioners and unintentional radiation exposure to patients. Compounding of
1707 radiopharmaceuticals must comply with applicable federal, state, and local laws and
1708 regulations such as those from the Nuclear Regulatory Commission (NRC), FDA, and
1709 State Boards of Pharmacy.

1710 Unless done in strict conformance with the manufacturer's package insert, any further
1711 use or handling and manipulation of conventionally manufactured radiopharmaceutical
1712 product is considered compounding and must follow the standards in this chapter and
1713 applicable federal, state, and local laws and regulations. Radiation exposures must be
1714 kept as low as reasonably achievable (the ALARA principle). Therefore, appropriate
1715 shielding must be used to help minimize radiation exposure. Additional equipment
1716 needed for radiation control when compounding may include, but is not limited to:

- 1717 • Radiation detectors
- 1718 • Static and handheld monitors
- 1719 • Handheld monitors
- 1720 • Lead (or other appropriate) shielding
- 1721 • Shielded waste cans
- 1722 • Non-shedding absorbent mats
- 1723 • L-Blocks
- 1724 • Tongs
- 1725 • Syringe, vial, and elution shields
- 1726 • Syringe re-cappers
- 1727 • Final unit dose containment shielding
- 1728 • Dose calibrators
- 1729 • Dippers and dipper lifts

1730 Radioisotope generator systems (e.g., Tc-99m/Mo-99, Rb-82/Sr-82, Ga-68/Ge-68)
1731 must be stored and eluted (operated) under conditions recommended by the
1732 manufacturer and applicable state and federal regulations. The generators must be
1733 eluted in an ISO Class 8 or cleaner air environment that allows special generator
1734 shielding, airflow requirements, and the use of lifting devices (e.g., cranes and/or
1735 wenchers) due to the weight of the generator and shielding. Radioisotope generators
1736 producing radioisotopes with a half-life of 15 minutes or less (e.g., Rb-82/Sr-82) can be
1737 eluted in accordance with the manufacturer's instructions at the point of care (e.g., at
1738 the bedside or in the patient care area). Visual inspection of radiopharmaceutical CSPs
1739 containing high concentrations of radioactivity (e.g., for color and absence of particulate
1740 material) must be performed in accordance with ALARA principles to limit acute and
1741 chronic radiation exposure of the inspecting personnel.

1742 All compounding personnel must be properly gowned and garbed as described in 3.
1743 *Personal Hygiene and Personal Protective Equipment*. However, personnel
1744 compounding radiopharmaceuticals are permitted to use personal radiation dosimeters.
1745 Personal radiation dosimeters can be film, thermoluminescent, or electronic. Whole-
1746 body badge radiation dosimeters must be worn underneath the gown, whereas

1747 ring/wrist badges that measure the dose at the extremities must be worn under gloves.
1748 If personnel are going from a cleanroom to a patient care area, all PPE must be
1749 changed before leaving one area and entering the other.

1750 When compounding activities require the manipulation of a patient's blood-derived or
1751 other biological material (e.g., radiolabeling of white blood cells), the manipulation must
1752 be performed in a separate, dedicated ISO Class 7 area that contains a PEC. All blood
1753 manipulations in the radiolabeling process, except for the centrifuge steps, must be
1754 performed inside the dedicated PEC. Dedicated equipment must be used for all blood
1755 manipulations. Strict SOPs must be developed and implemented to minimize the risk of
1756 patient-to-patient cross-contamination.

1757 Some radiopharmaceutical preparations (e.g., volatile or gaseous preparations such
1758 as iodine or xenon) may require pressurization configurations that are different from
1759 those described in 4. *Buildings and Facilities*. In these cases, the facility must comply
1760 with applicable federal, state, and local laws and regulations.

1761 Nonradioactive compounds may be compounded in the same compounding area in
1762 which radioactive compounds have been prepared, provided the following takes place:

- 1763 • The ISO Class 5 area is decontaminated and monitored for radioactivity above
1764 background levels.
- 1765 • The dose calibrator is left inside the PEC.
- 1766 • The PEC is operated in accordance with all the standards in this chapter when
1767 nonradioactive CSPs are being prepared.

1768 GLOSSARY

1769 **Airlock:** A space with interlocked doors, constructed to maintain air pressure control
1770 when items move between two adjoining areas (generally with different air cleanliness
1771 standards). The intent of an airlock is to prevent ingress of particulate matter and
1772 microbial contamination from a lesser-controlled area.

1773 **Ante-area:** An ISO Class 8 or cleaner area where personnel hand hygiene and
1774 garbing procedures and other activities that generate high particulate levels are
1775 performed. The ante-area is the transition area between the unclassified area of the
1776 facility and the buffer area. [NOTE—The ante-area is sometimes referred to as an ante-
1777 room when solid doors and walls are present.]

1778 **Aseptic processing or preparation:** A process by which separate, sterile
1779 components (e.g., drugs, containers, or closures) are brought together under conditions
1780 that maintain their sterility. The components can either be purchased as sterile or, when
1781 starting with nonsterile components, can be separately sterilized prior to combining
1782 (e.g., by membrane filtration, autoclave).

1783 **Batch:** More than one unit of CSP prepared in a single process and intended to have
1784 uniform characteristics and quality, within specified limits.

1785 **Beyond-use date (BUD):** The date or time after which a CSP cannot be used and
1786 must be discarded. The date or time is determined from the date or time when the
1787 preparation was compounded.

1788 **Biological safety cabinet (BSC):** A ventilated cabinet with unidirectional HEPA-
1789 filtered airflow and HEPA-filtered exhaust to protect the worker from hazardous drugs. A
1790 BSC used to prepare a CSP must be capable of providing an ISO Class 5 environment
1791 for preparation of the CSP.

1792 **Buffer area:** An ISO Class 7 (or ISO Class 8 if using an isolator) or cleaner area
1793 where the PEC that generates and maintains an ISO Class 5 environment is physically
1794 located.

1795 **Category 1 CSP:** A CSP assigned a BUD of 12 hours or less at controlled room
1796 temperature or 24 hours or less refrigerated.

1797 **Category 2 CSP:** A CSP assigned a BUD of greater than 12 hours at controlled room
1798 temperature or greater than 24 hours refrigerated that is compounded in accordance
1799 with all applicable standards for Category 2 CSPs in this chapter.

1800 **Certificate of analysis (COA):** A report from the supplier of a component, container,
1801 or closure that accompanies the supplier's material and contains the specifications and
1802 results of all analyses and a description of the material.

1803 **Classified space:** A space that maintains an air cleanliness classification based on
1804 the International Organization for Standardization (see also definition for ISO Class).

1805 **Cleanroom:** An ISO-classified room in which the concentration of airborne particles is
1806 controlled to meet a specified airborne-particulate cleanliness class to prevent particle
1807 and microbial contamination of CSPs.

1808 **Compounded sterile preparation (CSP):** A preparation intended to be sterile that is
1809 created by combining, diluting, pooling, or otherwise altering a drug product or bulk drug
1810 substance. A product produced by reconstituting a conventionally manufactured product
1811 for an individual patient strictly in accordance with the directions contained in the
1812 approved labeling provided by the product manufacturer is not considered a CSP for the
1813 purposes of this chapter.

1814 **Compounding aseptic containment isolator (CACI):** A type of RABS that uses
1815 HEPA filtration to provide an ISO Class 5 clean air environment designed for the
1816 compounding of sterile hazardous drugs.

1817 **Compounding aseptic isolator (CAI):** A type of RABS that uses HEPA filtration to
1818 provide an ISO Class 5 clean air environment designed for compounding of sterile non-
1819 hazardous drugs.

1820 **Compounded stock solution:** A compounded solution to be used in the preparation
1821 of multiple units of a finished CSP.

1822 **Container-closure system:** The sum of packaging components that together
1823 contain and protect the dosage form. This includes primary packaging components and
1824 secondary packaging components, if the latter are intended to provide additional
1825 protection.

1826 **Conventionally manufactured product:** A pharmaceutical dosage form, usually the
1827 subject of an FDA-approved application, and manufactured under current good

1828 manufacturing practice conditions. Conventionally manufactured products are not
1829 compounded preparations.

1830 **Critical site:** A location that includes any component or fluid pathway surfaces (e.g.,
1831 vial septa, injection ports, and beakers) or openings (e.g., opened ampuls and needle
1832 hubs) that are exposed and at risk of direct contact with air (e.g., ambient room or
1833 HEPA filtered), moisture (e.g., oral and mucosal secretions), or touch contamination.

1834 **Direct compounding area:** A critical area within the ISO Class 5 PEC where critical
1835 sites are exposed to unidirectional HEPA-filtered air, also known as first air.

1836 **Disinfectant:** A chemical agent used on inanimate surfaces and objects to destroy
1837 fungi, viruses, and bacteria, but not necessarily their spores.

1838 **Expiration date:** Date placed on a conventionally manufactured product to limit the
1839 time during which it can be used.

1840 **Filter integrity test:** A test (e.g., bubble point test) of the integrity of a sterilizing
1841 grade filter performed after the filtration process to detect whether the integrity of the
1842 filter has been compromised.

1843 **First air:** The air exiting the HEPA filter in a unidirectional air stream.

1844 **Hazardous drug:** Any drug identified by at least one of the following six criteria:
1845 carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity in humans,
1846 organ toxicity at low dose in humans or animals, genotoxicity, or new drugs that mimic
1847 existing hazardous drugs in structure or toxicity.

1848 **In-use time:** The time before which a conventionally manufactured product or a CSP
1849 must be used after it has been opened or needle punctured (e.g., after a container
1850 closure of a vial has been penetrated).

1851 **ISO Class:** An air quality classification from the International Organization for
1852 Standardization.

1853 **Isolator:** An enclosure that provides HEPA-filtered ISO Class 5 unidirectional air
1854 operated at a continuously higher pressure than its surrounding environment and is
1855 decontaminated using an automated system. It uses only decontaminated interfaces or
1856 rapid transfer ports for materials transfer.

1857 **Label:** A display of written, printed, or graphic matter on the immediate container of
1858 any article.

1859 **Labeling:** All labels and other written, printed, or graphic matter that are 1) on any
1860 article or any of its containers or wrappers, or 2) accompanying such an article.

1861 **Laminar airflow system (LAFS):** A device or zone within a buffer area that provides
1862 an ISO Class 5 or better environment for sterile compounding. The system provides a
1863 unidirectional HEPA-filtered airflow.

1864 **Laminar airflow workbench (LAFW):** A device that is a type of LAFS that provides
1865 an ISO Class 5 or better environment for sterile compounding. The device provides a
1866 unidirectional HEPA-filtered airflow.

1867 **Media fill test:** A simulation used to qualify processes and personnel engaged in
1868 sterile compounding to ensure that the processes and personnel are able to produce
1869 sterile CSPs without microbial contamination.

1870 **Microbial contamination:** The presence of microorganisms in, or on, an item.

1871 **Multiple-dose container:** A container of sterile medication for parenteral
1872 administration (e.g., injection or infusion) that is designed to contain more than one
1873 dose of the medication. A multiple-dose container is usually required to meet the
1874 antimicrobial effectiveness testing criteria. See [Container Content for Injections \(697\)](#),
1875 [Determination of Volume of Injection in Containers, Multi-Dose Containers](#).

1876 **Pass-through:** An enclosure with seals on interlocking doors that are positioned
1877 between two spaces for the purpose of minimizing particulate transfer while moving
1878 materials from one space to another.

1879 **Pharmacy bulk package:** A conventionally manufactured sterile product for
1880 parenteral use that contains many single doses intended for use in a pharmacy
1881 admixture program. A pharmacy bulk package may either be used to prepare
1882 admixtures for infusion or, through a sterile transfer device, for the filling of empty sterile
1883 syringes.

1884 **Positive-pressure room:** A room that is maintained at higher pressure than the
1885 adjacent spaces, and therefore the net airflow is out of the room.

1886 **Primary engineering control (PEC):** A device or zone that provides an ISO Class 5
1887 environment for sterile compounding.

1888 **Preservative:** A substance added to inhibit microbial growth or to prevent
1889 decomposition or undesirable chemical changes.

1890 **Pyrogen:** A substance that induces a febrile reaction in a patient.

1891 **Pyrogen-free:** A substance lacking sufficient endotoxins or other fever-inducing
1892 contamination to induce a febrile or pyrogenic response.

1893 **Quality assurance (QA):** A system of procedures, activities, and oversight that
1894 ensures that operational and quality standards are consistently met.

1895 **Quality control (QC):** The sampling, testing, and documentation of results that, taken
1896 together, ensure that specifications have been met before release of the preparation.

1897 **Reconstitution:** The process of adding a diluent to a powdered medication to
1898 prepare a sterile solution or suspension.

1899 **Release testing:** Testing performed to ensure that a preparation meets appropriate
1900 quality characteristics.

1901 **Repackaging:** The act of removing a conventionally manufactured sterile product
1902 from its original primary container and placing it into another primary container, usually
1903 of smaller size.

1904 **Responsible person:** The individual accountable for an activity.

- 1905 **Restricted access barrier system (RABS):** An enclosure that provides HEPA-
1906 filtered ISO Class 5 unidirectional air that allows for the ingress and/or egress of
1907 materials through defined openings that have been designed and validated to preclude
1908 the transfer of contamination, and that generally are not to be opened during operations.
1909 Examples of RABS include CAIs and CACIs.
- 1910 **Segregated compounding area:** A designated, unclassified space, area, or room
1911 that contains a PEC and is suitable for preparation of Category 1 CSPs only.
- 1912 **Single-dose containers:** A container of sterile medication for parenteral
1913 administration (e.g., injection or infusion) that is designed for use with a single patient as
1914 a single injection/infusion. A single-dose container usually does not contain a
1915 preservative.
- 1916 **Specification:** The tests, analytical methods, and acceptance criteria to which a drug
1917 substance, drug product, CSP, component, container–closure system, equipment, or
1918 other material used in drug preparation must conform to be considered acceptable for
1919 its intended use.
- 1920 **Stability:** The extent to which a CSP retains physical and chemical properties and
1921 characteristics within specified limits throughout its BUD.
- 1922 **Sterility:** The freedom from viable microorganisms.
- 1923 **Sterility testing:** A documented and established laboratory procedure for detecting
1924 viable microbial contamination in a sample or preparation.
- 1925 **Sterilizing-grade membranes:** Filter membranes that are documented to retain
1926 100% of a culture of 10^7 microorganisms of a strain of *Brevundimonas diminuta* per cm^2
1927 of membrane surface under a pressure of not less than 30 psi. Such filter membranes
1928 are nominally 0.22- μm or 0.2- μm pore size.
- 1929 **Sterilization by filtration:** Passage of a gas or liquid through a sterilizing-grade
1930 membrane to consistently yield filtrates that are sterile.
- 1931 **Terminal sterilization:** The application of a lethal process (e.g., dry heat, steam,
1932 irradiation) to sealed containers for the purpose of achieving a predetermined SAL of
1933 greater than 10^{-6} or a probability of less than one in one million of a nonsterile unit.
- 1934 **Unclassified space:** A space not required to meet any air cleanliness classification
1935 based on the International Organization for Standardization (ISO).
- 1936 **Unidirectional airflow:** Air within a PEC moving in a single direction in a uniform
1937 manner and at sufficient speed to reproducibly sweep particles away from the direct
1938 compounding area or testing area.
- 1939 **Verification:** Confirmation that a method, process, or system will perform as
1940 expected under the conditions of actual use.

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APPENDICES

1943

Appendix 1. Acronyms

ACD	Automated compounding device
ACPH	Air changes per hour
ALARA	As low as reasonably achievable
API	Active pharmaceutical ingredient
BSC	Biological safety cabinet
BUD	Beyond-use date
CACI	Compounding aseptic containment isolator
CAI	Compounding aseptic isolator
CFU	Colony-forming units
COA	Certificate of analysis
CSP	Compounded sterile preparation
ECV	Endotoxin challenge vial
FDA	Food and Drug Administration
HEPA	High-efficiency particulate air
HVAC	Heating, ventilation, and air conditioning
IPA	Isopropyl alcohol
ISO	International Organization for Standardization
LAFS	Laminar airflow system
LAFW	Laminar airflow workbench
NRC	Nuclear Regulatory Commission
PEC	Primary engineering control
PPE	Personal protective equipment
QA	Quality assurance
QC	Quality control
RABS	Restricted access barrier system
SAL	Sterility assurance level
SOP	Standard operating procedure
TSA	Trypticase soy agar

Appendix 2. Common Disinfectants Used in Health Care for Inanimate Surfaces and Noncritical Devices, and Their Microbial Activity and Properties^a

Chemical Category of Disinfectant
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		Isopropyl Alcohol	Accelerated Hydrogen Peroxide	Quaternary Ammonium (e.g., dodecyl dimethyl ammonium chloride)	Phenolics	Chlorine (e.g., sodium hypochlorite)	Iodophors (e.g., povidone-iodine)
Concentration Used		60%–95%	0.5% ^b	0.4%–1.6% aq	0.4%–1.6% aq	100–5000 ppm	30–50 ppm
Microbial Inactivation ^c	Bacteria	+	+	+	+	+	+
	Lipophilic viruses	+	+	+	+	+	+
	Hydrophilic viruses	±	+	±	±	+	±
	M. tuberculosis	+	+	±	+	+	±
	Mycotic agents (fungi)	+	+	+	+	+	±
	Bacterial spores	–	–	–	–	+	–
Important Chemical and Physical Properties	Shelf life >1 week	+	+	+	+	+	+
	Corrosive or deleterious effects	±	–	–	–	±	±
	Non-evaporable residue	–	–	+	+	–	+
	Inactivated by organic matter	+	±	+	±	+	+
	Skin irritant	±	–	+	+	+	±
	Eye irritant	+	–	+	+	+	+
	Respiratory irritant	–	–	–	–	+	–
	Systemic toxicity	+	–	+	+	+	+

Key to abbreviation and symbols: aq = diluted with water; ppm = parts per million; + = yes; – = no; ± = variable results.

Chemical Category of Disinfectant							
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^a Modified from World Health Organization, Laboratory Bio Safety Manual 1983 and Rutala WA. Antisepsis, disinfection and sterilization in the hospital and related institutions. *Man Clin Microbiol.* Washington D.C.: American Society for Microbiology;1995, 227–245.

^b Accelerated hydrogen peroxide is a new generation of hydrogen peroxide-based germicides in which the potency and performance of the active ingredient have been enhanced and accelerated through the use of appropriate acids and detergents.

^c Inactivation of the most common microorganisms (i.e., bacteria) occurs with a contact time of ≤1 minute; inactivation of spores requires longer contact times (e.g., 5–10 minutes for 5,000 ppm chlorine solution against *C. difficile* spores). Perez J, Springthorpe VS, Sattar SA. Activity of selected oxidizing microbicides against the spores of *Clostridium difficile*: relevance to environmental control. *Am J Infect Con.* 2005;33(6):320–325.

1948 ▲ **USP40**

1949 SWS WORKFLOW VALIDATION

1950

XML Attribute	XML Value	SWS Attribute	SWS Value	Notes
corres-id	*missing*			XML inconsistent with SWS
corres-id	*missing*			XML inconsistent with SWS
corres-id	*missing*			XML inconsistent with SWS
corres-id	*missing*			XML inconsistent with SWS
corres-id	*missing*			XML inconsistent with SWS
corres-id	*missing*			XML inconsistent with SWS
corres-id	*missing*			XML inconsistent with SWS

1951 ¹ U.S. Food and Drug Administration, Guidance for Industry, *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*, September 2004.

1953 ² Guidelines for Environmental Infection Control in Health-Care Facilities, Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC), MMWR, vol. 52, no. RR-10, June 6, 2003, figure 3, pg. 12-

1956 ³ NSF/ANSI 49.

1957 ⁴ ISO 14644 4:2001 Cleanrooms and associated controlled environments—Design, construction, and start-up, *Case Postale 56*, CH-1211 Geneve 20, Switzerland, tel. +41 22 749 01 11.

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⁵ By definition (IEST RP CC 001.4), HEPA filters are a minimum of 99.97% efficient when tested using 0.3 µm thermally generated particles and a photometer or rated at their most penetrating particle size using a particle counter.

⁶ Sample procedures are detailed in CETA Applications Guide CAG 002 2006 section 2.09.

⁷ Controlled Environment Testing Association, 1500 Sunday Drive, Ste. 102, Raleigh, NC 27607; www.CETAinternational.org.

⁸ Agalloco J, Akers JE. Aseptic Processing: A Vision of the Future. *Pharmaceutical Technology*, 2005. Aseptic Processing supplement, s16.

⁹ Eaton T. Microbial Risk Assessment for Aseptically Prepared Products. *Am Pharm Rev.* 2005; 8 (5, Sep/Oct): 46–51.

¹⁰ *Guideline for Hand Hygiene in Health care Settings*, MMWR, October 25, 2002, vol. 51, No. RR-16 available on the Internet at <http://www.cdc.gov/handhygiene/>.

¹¹ The use of additional resources, such as the Accreditation Manual for Home Care from the Joint Commission on Accreditation of Healthcare Organizations, may prove helpful in the development of a QA plan.

¹² See *American Society of Heating, Refrigerating and Air Conditioning Engineers, Inc. (ASHRAE), Laboratory Design Guide*.

¹³ *CETA Applications Guide for the Use of Compounding Isolators in Compounding Sterile Preparations in Healthcare Facilities*, CAG 001 2005, Controlled Environment Testing Association (CETA), November 8, 2005.

¹ Centers for Disease Control and Prevention and the Safe Injection Practices Coalition, One & Only Campaign, http://www.oneandonlycampaign.org/safe_injection_practices. [▲] USP40

² Agalloco J, Akers JE. Aseptic processing: a vision of the future. *Pharm Technol.* 2005; Aseptic Processing supplement, s16. [▲] USP40

³ Eaton T. Microbial risk assessment for aseptically prepared products. *Am Pharm Rev.* 2005;8(5):46–51. [▲] USP40