〈797〉 Pharmaceutical Compounding—Sterile Preparations

INTRODUCTION

The objective of this chapter is to describe conditions and practices to prevent harm, including death, to patients that could result from the following: 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) incorrect types and qualities of ingredients in Compounded Sterile Preparations (CSPs). Nonsterile 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.

To achieve these five objectives, this chapter provides practice and quality standards for CSPs of drugs and nutrients. The standards in this chapter pertain to all pre-administration manipulations and procedures of CSPs, including preparation, storage, and transportation. 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 is the route of administration. The following four specific categories of CSPs are described in this chapter: *Low-Risk Level, Medium-Risk Level,* and *High-Risk Level CSPs;* and *Immediate Use CSPs*. Sterile compounding differs from nonsterile compounding (see *Pharmaceutical Compounding—Nonsterile Preparations* 〈795〉 and *Good Compounding Practices* 〈1075〉) primarily by requiring the maintenance of sterility when compounding exclusively with sterile ingredients and components, i.e., *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., *High-Risk Level CSPs.* Some differences between standards for sterile compounding in this chapter and those for nonsterile compounding in chapter 〈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. International Organization of Standardization (ISO) Classification of Particulate Matter in Room Air [Limits are in particles 0.5 µm and larger per cubic meter (current ISO) and cubic feet (former Federal Standard No. 209E, FS 209E).][*]

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	3520	100
6	Class 1000	35,200	1000
7	Class 10,000	352,000	10,000
8	Class 100,000	3,520,000	100,000

[*] Adapted from former Federal Standard No. 209E, General Services Administration, Washington, DC, 20407 (September 11, 1992) and ISO 4644-1:1999, Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness. For example, 3520 particles of 0.5 µm per m^3 or larger (ISO Class 5) is equivalent to 100 particles per ft^3 (Class 100) (1 m^3 = 35.2 ft^3).

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 both that most sterile compounding is performed by or under the supervision of pharmacists in pharmacies and 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) Biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals that possess any of the characteristics in parts (2) and (3) below and that include the following preparations 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, and suspensions), irrigations for wounds and body cavities, ophthalmic drops and ointments, and tissue implants.

(2) Manufactured sterile products that are prepared either strictly according to the instructions appearing in manufacturers' approved labeling (product package inserts) or that are 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" (see http://www.fda.gov/cder/fdama/difconc.htm). 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 usually refer to chemical stability and not necessarily to microbiological purity or safety.]

(3) The three contamination categories for CSPs described in the section *CSP Microbial Contamination Risk Levels* are assigned primarily according to the potential for microbial contamination during compounding *Low-Risk Level* 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. Therefore *High-Risk Level CSPs* (see the specific criteria described in the *CSP Microbial Contamination Risk Levels* section) must be sterilized before being administered to patients.

ORGANIZATION OF THIS CHAPTER

The sections in this chapter are organized to facilitate practitioners' understanding of the fundamental accuracy and quality practices of CSPs. They provide a foundation for the development and implementation of essential procedures for the safe preparation of CSPs at *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:

- Definitions of chapter terminology
- Responsibility of compounding personnel
- CSP microbial contamination risk levels
- Single-dose and multiple-dose containers
- Hazardous drugs as CSPs
- Radiopharmaceuticals as CSPs
- Verification of compounding accuracy and sterility
- Sterilization methods
- Personnel training and evaluation in aseptic manipulation skills
- Environmental quality and control
- Cleaning and disinfecting the sterile compounding areas
- Personnel cleansing and garbing
- Suggested standard operating procedures
- Environmental monitoring

- Processing
- Verification of automated compounding devices 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
- Packing and transporting CSPs
- Patient or caregiver training
- Patient monitoring and adverse events reporting
- The quality assurance program

All personnel who prepare CSPs are to understand these fundamental practices and precautions, to develop and implement appropriate procedures, and to continually evaluate these procedures and the quality of final CSPs to prevent harm, including death, to patients given CSPs.

DEFINITIONS

Anteroom—An anteroom is an ISO Class 8 (see *Table 1*) or better area where personnel perform hand hygiene and garbing procedures, staging of components, order entry, CSP labeling, and other high-particulate generating activities. 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) that reduces the need for the heating, ventilating and air conditioning (HVAC) control system to respond to large disturbances.[1]

Aseptic Processing (see *Microbiological Evaluation of Cleanrooms* ⟨1116⟩)—Aseptic processing is 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 microbiologic critically controlled conditions.

Beyond-Use Date (see *General Notices and Requirements* and *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩)—For the purpose of this chapter, the beyond-use date is the date or time after which the CSPs shall not be stored or transported. The beyond-use date is determined from the date or time the preparation is compounded.

Biological Safety Cabinet, *Class II* (BSC)—The BSC is a ventilated cabinet for personnel, product, and environmental protection having an open front with inward airflow for personnel

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

protection, downward HEPA filtered laminar airflow for product protection, and HEPA filtered exhausted air for environmental protection.

Buffer Area, Buffer or Core Room, Buffer or Cleanroom Areas, Buffer Room Area, Buffer or Clean Area—This is an ISO Class 7 (see *Table 1*) area where the primary engineering control area (see below) is physically located. Activities that occur in this area include the preparation and staging of components and supplies used when compounding CSPs.

Cleanroom (see *Microbiological Evaluation of Cleanrooms* ⟨1116⟩ and also *Buffer Area*)—A cleanroom is 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 Isolator (CAI)—The CAI is a form of barrier 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 it has first passed through a microbially retentive filter (HEPA minimum).[2]

Critical Area—A critical area is an ISO Class 5 (see *Table 1*) environment.

Critical Sites—Critical sites include sterile ingredients of CSPs and locations on devices and components used to prepare, package, and transfer CSPs that provide opportunity for exposure to contamination.

Disinfectant—A disinfectant is 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 spores. It refers to substances applied to inanimate objects.

Labeling (see *General Notices and Requirements* and www.fda.gov/cder/drugsatfda/glossary.htm)—A term that designates all labels and other written, printed, or graphic matter upon an immediate container of an article or preparation or upon; 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 upon the immediate container.

Media Fill Test (see *Microbiological Evaluation of Cleanrooms* ⟨1116⟩)—A media fill test is 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 (SCDM) is substituted for the actual drug product to simulate admixture compounding.[3] The issues to

[2] *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.
[3] Swarbrick J, Boylan J, *Encyclopedia of Pharmaceutical Technology,* Vol 7.

consider in the development of a media fill test are the following: 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 *Containers for Injections* under *Injections* ⟨1⟩)—A multiple-dose container is a multiple-unit container for articles or preparations intended for parenteral administration only and usually contains antimicrobial preservatives. The beyond-use date 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 compared to adjacent spaces and, therefore, the net flow of air is *into* the room.[1]

Pharmacy Bulk Package (see *Containers for Injections* under *Injections* ⟨1⟩)—The pharmacy bulk package is 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 assure 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—It is 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), and compounding aseptic isolators (CAIs).

Preparation—For the purposes of this chapter, a preparation, or a CSP, 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—For the purposes of this chapter, a product is a commercially manufactured sterile drug or nutrient that has been evaluated for safety and efficacy by the U.S. Food and Drug Administration (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 positive pressure room is one that is at a higher pressure compared to adjacent spaces and, therefore, the net airflow is *out of* the room.[1]

Single-Dose Container (see *General Notices and Requirements* and *Containers for Injections* under *Injections* ⟨1⟩)—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.

Sterilizing Grade Filter—A sterile grade filter is a filter that will remove all microorganisms from a fluid stream, producing a sterile effluent. Such filters typically have a nominal porosity of 0.2 µm.

Sterilization by Filtration—Passage of a fluid or solution through a sterilizing grade filter to produce a sterile effluent.

Terminal Sterilization—Terminal sterilization is 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 (SAL) of usually less than 10^{-6}, i.e., or a probability of less than one in one million of a nonsterile unit.[4]

Unidirectional Flow (see U.S. Food and Drug Administration, Guidance for Industry Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice)—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.

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 beyond-use dates. 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 is 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

[4] U.S. Food and Drug Administration, Guidance for Industry Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice, September 2004 (http://www.fda.gov/cder/guidance/5882fnl.htm).

strength of ingredients, bacterial endotoxins, particulate matter, and pH; labeling accuracy and completeness; beyond-use date 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*) primary engineering devices, and protect personnel and compounding environments from contamination by radioactive, cytotoxic, and chemotoxic drugs (see *Hazardous Drugs as CSPs* section and *Radiopharmaceuticals as CSPs* section);
    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 beyond-use or expiration date has been exceeded.
4. To minimize the generation of bacterial endotoxins, water-containing CSPs that are nonsterile during any phase of the compounding procedure are sterilized within 6 hours after completing the preparation.
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 uses.
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 beyond-use date.
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 (see *Labels and Labeling* in *Preservation, Packaging, Storage, and Labeling* section in the *General Notices and Requirements*) of injections list the names and amounts or concentrations of all ingredients (see *Injections* ⟨ 1 ⟩). Before being dispensed, and/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. Beyond-use dates 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 and administered.

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 appropriate risk level—low, medium, or high—is assigned according to the corresponding probability of contaminating a CSP with (1) microbial contamination (microbial organisms, spores, and endotoxins) and (2) chemical and physical contamination (foreign chemicals and 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-risk, medium-risk, and high-risk 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 to consider the potential additional risks to the integrity of CSPs when assigning beyond-use dates. The pre-administration duration and temperature limits specified in the following low-risk, medium-risk, and high-risk level sections 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 no more than three commercially manufactured sterile products and entries into one container package (e.g., bag, vial) of sterile product to make the CSP.
3. Manipulations are limited to aseptically opening ampuls, penetrating sterile 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 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 at –20° or colder.

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 (3) manufactured products including an infusion or diluent solution to compound drug admixtures and nutritional solutions.

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 and goggles.
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.

Example of a Media-Fill Test Procedure—This, or an equivalent test, is performed at least annually by each person authorized to compound in a low-risk level 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. Within an ISO Class 5 (see *Table 1*) air quality environment, three sets of four 5-mL aliquots of sterile Soybean–Casein Digest Medium 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 as described in the *Personnel Training and Evaluation in Aseptic Manipulation Skills* section.

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 at –20° or colder.

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.

Example of a Media-Fill Test Procedure—This, or an equivalent test, is performed at least annually under conditions that closely simulate the most challenging or stressful conditions encountered during compounding. This test is completed without interruption 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 as described in the *Personnel Training and Evaluation in Aseptic Manipulation Skills* section.

High-Risk Level CSPs

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

High-Risk Conditions—

1. Nonsterile ingredients, including manufactured products for routes of administration other than those listed under *c.* in the *Introduction* are incorporated or a nonsterile device is employed before terminal sterilization.
2. 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 are exposed to air quality worse than ISO Class 5 (see *Table 1*) for more than 1 hour (see *Immediate Use CSPs* section).
3. Before sterilization, nonsterile procedures such as weighing and mixing are conducted in air quality worse than ISO Class 7 (see *Table 1*), compounding personnel are improperly garbed and gloved (see *Personnel Cleansing and Garbing*); or water-containing preparations are stored for more than 6 hours.
4. 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⟩).
5. For a sterilized high-risk 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 at –20° or colder.

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 CSP solutions subjected to terminal sterilization are passed through a filter with a nominal porosity not larger than 1.2 µm 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 0.22-µm porosity filter entirely within an ISO Class 5 (see *Table 1*) or superior air quality environment.

Examples of High-Risk Compounding—

1. Dissolving nonsterile bulk drug and nutrient powders to make solutions, which 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* section).
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.

Example of a Media-Fill Test Procedure CSPs Sterilized by Filtration—This, or an equivalent test, is performed under conditions that closely simulate the most challenging or stressful conditions encountered when compounding high-risk level CSPs. [NOTE—Sterility tests for autoclaved CSPs are not required unless they are prepared in batches of more than 25 units. This test is completed without interruption 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-µm porosity 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 25° to 35°. Inspect for microbial growth over 14 days as described in the *Personnel Training and Evaluation in Aseptic Manipulation Skills* section.

IMMEDIATE USE CSPs

For the purpose of emergency or immediate patient care, CSPs are exempted from the requirements described in this chapter for *Low-Risk Level, Medium-Risk Level,* and *High-Risk Level CSPs* when all of the following criteria are met:

1. Only simple aseptic measuring and transfer manipulations are performed with not more than three (3) sterile nonhazardous commercial drug and diagnostic radiopharmaceutical drug products, including an infusion or diluent solution.
2. Unless required for the preparation, the preparation procedure occurs continuously without delays or interruptions and does not exceed 1 hour.
3. At no point during preparation and prior to administration are critical surfaces and ingredients of the CSP directly exposed to contact contamination such as human touch, cosmetic flakes or particulates, blood, human body substances (excretions and secretions e.g., nasal and oral), and nonsterile inanimate sources.
4. Administration begins not later than one (1) hour following the start of preparing the CSP.
5. When the CSP is not administered by the person who prepared it, or its administration is not witnessed by the person who prepared it, the CSP shall bear a label listing patient identification information such as name and identification number(s), the names and amounts of all ingredients, the name or initials of the person who prepared the CSP, and the exact 1-hour beyond-use time and date.
6. If administration has not begun within one (1) hour following the start of preparing the CSP, the CSP is promptly and safely discarded. *Immediate Use CSPs* shall not be stored for later use.

CSPs containing three (3) or fewer commercial sterile drug products that are stored in excess of one (1) hour before beginning to be administered must comply with the *Low-Risk Level* standards; CSPs containing more than three (3) commercial sterile drug products and those requiring complex manipulations and/or preparation methods must comply with the *Medium-Risk Level* standards; and CSPs prepared from nonsterile ingredients or components must comply with the *High-Risk Level* standards in this chapter. Because of known safety risks of hazardous drugs to healthcare workers and other nonpatients who may be exposed to them, hazardous

drugs such as cancer chemotherapy drugs and all those on the National Institute for Occupational Safety and Health list (NIOSH)[5] shall not be prepared as *Immediate Use CSPs*. Hazardous drugs must be prepared using suitable ISO Class 5 (see *Table 1*) environment containment equipment and/or devices in a manner fully compliant with the standards in this chapter including the *Hazardous Drugs as CSPs* section. Personnel who prepare and administer *Immediate Use CSPs* are responsible for recognizing the potential harm to patients that may result when such CSPs are microbially contaminated and administered over long durations. Compounding in worse than ISO Class 5 (see *Table 1*) conditions increases the likelihood of microbial contamination, and administration durations exceeding a few hours increase the potential for clinically significant microbial colonization; thus, for patient harm.

SINGLE-DOSE AND MULTIPLE-DOSE CONTAINERS

Opened or needle-punctured single-dose containers such as ampuls, 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* section), 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 contain antimicrobial preservatives. The beyond-use date 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 preparations (CSPs) 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 (see "Sample list of drugs that should be handled as hazardous" in Appendix A of NIOSH Publication No. 2004-165: *Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings* at http://www.cdc.gov/niosh/docs/2004-165/) can result in (1) acute effects, such as skin rashes; (2) chronic effects, including adverse reproductive events; and (3) possibly cancer.

Hazardous drugs shall only be prepared for administration under conditions that protect the healthcare workers and other personnel in the preparation and administration area. Hazardous drugs shall be stored separately from other inventory in a manner to prevent contamination and

[5] NIOSH, see Appendix A at http://www.cdc.gov/niosh/docs/2004-165/.

personnel exposure. Such storage is preferably within a containment area such as a negative pressure room. The storage area must have sufficient general exhaust ventilation, at least 12 air exchanges per hour (ACPH)[6] to dilute and remove any airborne contaminants. Hazardous drugs shall be handled with caution using appropriate chemotherapy gloves during distribution, receiving, stocking, inventorying, preparing 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 Class II or III biological safety cabinet (BSC), or a compounding aseptic isolator (CAI) that meets or exceeds the standards for CAI in this chapter. When other primary engineering controls, e.g., closed-system vial-transfer devices (CSTD) are used, this shall be within the BSC or CAI to provide backup containment and ISO Class 5 (see *Table 1*) environment. The ISO Class 5 (see *Table 1*) BSC or CAI shall be placed in an ISO Class 7 (see *Table 1*) room that is physically separated, i.e., a different room, from other preparation areas, and optimally has no less than 0.01-inch water column negative pressure[1] to adjacent positive pressure ISO Class 7 (see *Table 1*), or better, anterooms, thus providing inward airflow to contain any airborne drug. If a compounding isolator that meets the requirements of this chapter is used outside of a cleanroom, the room must maintain a minimum negative pressure of 0.01 inch water column and have a minimum of 12 air changes per hour (ACPH). Note that an anteroom leading to a positive pressure room may be ISO Class 8 (see *Table 1*) but an anteroom leading to a negative pressure room shall meet at least ISO Class 7 (see *Table 1*) criteria so that air drawn into the negative pressure environment is of the same ISO Class 7 (see *Table 1*) quality. A pressure indicator shall be installed that can be readily monitored for correct room pressurization. The BSC and CAI optimally shall be 100% vented to the outside air through HEPA filtration (see the Ventilated cabinet section at http://www.cdc.gov/niosh/docs/2004-165/). In facilities that prepare a very low volume of hazardous drugs (e.g., less than 5 preparations/week), the use of two tiers of containment, e.g., CSTD within a BSC or CAI that are located in a non-negative pressure room is acceptable. In addition, containment of the finished hazardous product shall be maintained throughout the administration/disposal phase utilizing needleless or closed administration systems.

Appropriate personnel protective equipment (PPE) shall be worn when compounding in a BSC or CAI, and when using CSTD devices. Appropriate PPE may include gowns, face masks, eye protection, hair covers, shoe covers or dedicated shoes, double gloving, and complying with manufacturers' recommendations when using CAI (http://www.cdc.gov/niosh/docs/2004-165/).

[6] 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.

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 must 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 must 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 BSC or CAI; (3) correct use of CSTD devices; (4) containment, clean-up, 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.] Ongoing quality assurance shall be an integral part of hazardous drug preparation. In order to assure containment, especially in operations preparing large volumes of hazardous drugs, environmental sampling to detect uncontained hazardous drugs needs to be performed routinely: e.g., initially as a benchmark and at least every 6 months. This sampling shall include surface wipe sampling of the working area of BSC and CAI, counter tops where finished preparations are placed, areas adjacent to BSC and CAI, 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/cm^2 has 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, and improving engineering controls.

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. The NIOSH Publication No. 2004-165 at www.cdc.gov/niosh/docs/2004-165/ and the references under the heading, Sterile Hazardous Preparations at http://www.ashp.org/SterileCpd/ are recommended sources for education and training in principles and practices of safety with hazardous drugs.

RADIOPHARMACEUTICALS AS CSPs

Compounding of radiopharmaceuticals for positron emission tomography (PET) shall be performed as specified in the general test chapter *Radiopharmaceuticals for Positron Emission*

Tomography—Compounding ⟨ 823 ⟩ . In the case of PET compounding, chapter ⟨ 823 ⟩ supersedes this chapter.

For the purposes of this chapter, the following shall be designated *Low-Risk Level CSPs*: (1) radiopharmaceutical dosage units with volumes of 15 mL and less and expiration times of 18 hours and shorter, such as those prepared from eluates from technetium-99m/molybdenum 99 generator systems; and (2) commercially manufactured cyclotron radiopharmaceuticals that contain preservatives and bear expiration times of 72 hours or shorter. These radiopharmaceuticals shall be compounded using appropriately shielded vials and syringes in a properly functioning and certified vertical LAFW, Class II Type B2 BSC, or other suitable containment device (e.g., CAI) 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 manufacturer's 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 system 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 or doses of radioactivity shall be avoided.

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 CSPs, and standard nonpathogenic bacterial cultures may be added to nondispensable specimens of high-risk CSPs before terminal sterilization for subsequent evaluation by sterility testing. Packaged and labeled CSPs are visually inspected for physical integrity and expected appearance, including final fill amount. The accuracy of identities, concentrations, amounts, and purities of ingredients in CSPs is 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 (e.g., in the case of unlabeled syringes, opened ampuls, punctured stoppers of vials and bags, or 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 are 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 expected 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- and medium-risk CSPs.

3. Personnel ascertain from appropriate information sources that the sterile microporous membrane filter used to sterilize CSP solutions, either during compounding or administration, is chemically and physically compatible with the CSP.

Sterilization of High-Risk Level CSPs by Filtration

Commercially available sterile filters must be approved for human-use applications in sterilizing pharmaceutical fluids. Sterile filters used to sterilize CSPs shall be pyrogen-free and have a nominal porosity of 0.2 µm or 0.22 µm. They should be certified by the manufacturer to retain at least 10^7 microorganisms of a strain of *Brevundimonas (Pseudomonas) diminuta* on each cm^2 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* section).

The compounding supervisor must ensure, directly or from appropriate documentation, that the filters are chemically and physically stable at the pressure and temperature conditions to be used and have enough capacity to filter volumes, and that the filters 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 must 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 or larger porosity 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 must also be subjected to the manufacturer's recommended integrity test, such as the bubble point test.

Compounding personnel must 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, for example, water-miscible alcohols, may cause undetectable damage to filter integrity and shrinkage of microorganisms to sizes smaller than filter porosity.

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 one 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 must 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 porosity not larger than 1.2 µm for removal of particulate matter. Sealed containers must be able to generate steam internally; thus, stoppered and crimped empty vials must contain a small amount of moisture to generate steam.

The description of steam sterilization conditions and duration for specific CSPs is included in written documentation in the compounding facility. The effectiveness of steam sterilization is verified using appropriate biological indicators (see *Biological Indicators* ⟨1035⟩) or other confirmation methods (see *Sterilization and Sterility Assurance of Compendial Articles* ⟨1211⟩ or *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 should 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 sterilization by steam. Dry heat should only be used for those materials that cannot be sterilized by steam, when the moisture would either damage or be impermeable to the materials. During sterilization sufficient space should be left between materials to allow for good circulation of the hot air. The effectiveness of dry heat sterilization shall be verified using appropriate biological indicators (see *Biological Indicators* ⟨1035⟩) and temperature sensing devices.

PERSONNEL TRAINING AND EVALUATION IN ASEPTIC MANIPULATION SKILLS

Personnel who prepare CSPs must be trained conscientiously and skillfully by expert personnel, 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, must be immediately reinstructed and re-evaluated by expert compounding personnel to ensure correction of all aseptic practice deficiencies.

Media-Fill Challenge Testing—The skill of personnel to aseptically prepare CSPs may be evaluated using sterile fluid bacterial culture media-fill verification,[7] (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.

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 within a range of 20° to 35° for 14 days. Failure is indicated by visible turbidity in the medium on or before 14 days.

ENVIRONMENTAL QUALITY AND CONTROL

Achieving and maintaining sterility and overall freedom from contamination of a pharmaceutical product is dependent upon 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 upon 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 product.

Exposure of Critical Sites

Critical sites include ingredients of CSPs and locations on devices and components used to prepare, package, and transfer CSPs that provide opportunity for exposure to contamination. The risk of critical sites becoming contaminated increases with the duration of exposure, the potency and concentration of the contaminants, and the spatial area of the critical sites. Critical sites for low-, medium-, and high-risk level CSPs must not be exposed to air quality worse than ISO Class 5 (see *Table 1*).

The size of the critical site affects the risk of contamination entering the product: the greater the exposed area, the greater the risk. For example, an open ampul, vial, or bottle exposes to contamination a critical site of much larger area than the tip of a 26-gauge needle. Therefore, the risk of contamination when entering an open ampul, vial, or bottle is much greater than during the momentary exposure of a needle tip.

[7] FDA Guideline on Guidance for Industry Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice, September 2004 (http://www.fda.gov/cder/guidance/5882fnl.htm).

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 70% isopropyl alcohol (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.

The prevention or elimination of physical contact contamination and airborne particles must be given high priority. Airborne contaminants, especially those generated by sterile compounding personnel, are much more likely to reach critical sites than contaminants that are adhering to the floor or other surfaces below the work level. Further, particles that are relatively large or of high density settle from the airspace more quickly, and thus they must be precluded from ISO Class 5 (see *Table 1*) environments in which critical sites are exposed.

ISO Class 5 Air Sources, Cleanrooms, Buffer Zones, and Anterooms

The most common sources of ISO Class 5 (see *Table 1*) air quality for exposure of critical sites are horizontal and vertical LAFWs and CAIs. A cleanroom (see *Microbiological Evaluation of Cleanrooms and Other Controlled Environments* ⟨1116⟩) is a compounding environment that is supplied with high-efficiency particulate air (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 zone is an area that provides at least ISO Class 7 (see *Table 1*) air quality. An anteroom or ante-area provides at least ISO Class 8 air quality. *Figure 1* illustrates placement of LAFWs in cleanrooms used for low-risk and medium-risk level (top) and high-risk level (bottom) sterile compounding. The floor plans depicted in *Figure 1* are suggestions only, not restrictive or prescriptive requirements. Placement of devices (e.g., computers and printers) and objects (e.g., carts and cabinets) that are not essential to compounding in buffer zones and cleanrooms is dictated by their effect on the required environmental quality of air atmospheres and surfaces, which must be verified by monitoring (see the *Environmental Monitoring* section). 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.

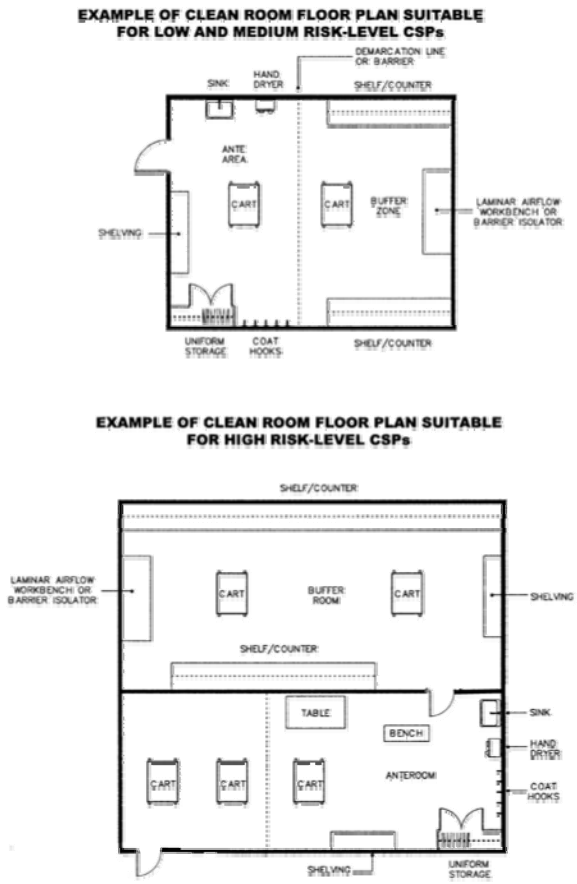

Figure 1

Facility Design and Environmental Controls

Compounding facilities are physically designed and environmentally controlled to minimize airborne contamination contacting critical sites. Primary engineering controls typically include, but are not limited to, LAFWs, BSCs, and CAIs, which provide an ISO Class 5 (see *Table 1*) environment for the exposure of critical sites. Primary engineering controls must 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 cleanrooms and anterooms generally provide a buffer zone or buffer room as a core for the location of the primary engineering control. Buffer zones or cleanrooms 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 anterooms and ante-areas. Airborne contamination control is achieved in the primary engineering control through the use of HEPA filters. The airflow in the primary engineering control is typically 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 should 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 should be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions.[7] The principles of HEPA filtered unidirectional airflow in the work environment must 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 primary engineering control area must 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 (primary engineering controls) located in a buffer area. The buffer area should maintain at least ISO Class 7 (see *Table 1*) conditions for 0.5-µm and larger particles under dynamic operating conditions. The room should 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 should 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 inches water column is required. For cleanrooms or buffer zones not physically separated from the anteroom, the principle of displacement airflow should be employed. This concept utilizes a low pressure differential, high airflow principle. Using displacement airflow typically requires an air velocity of 40 feet per minute (fpm) or more from the buffer room across the line of demarcation into the ante-area. The displacement concept is not applied to high risk compounding applications.[8] The primary engineering control should be placed within a buffer room in such a manner as to avoid conditions that could adversely affect its 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 primary engineering control should 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 air changes per hour (ACPH). Adequate HEPA filtered airflow supplied to the cleanroom and anteroom is required to maintain cleanliness classification during operational activity through the number of air changes per hour. Factors that should be considered when determining air-change requirements include number of personnel working in the room, compounding processes that generate particulates, as well as temperature effects. An ISO Class 7 (see *Table 1*) cleanroom supplied with HEPA filtered air shall receive an ACPH of not less than 30. The primary engineering control is a good augmentation to generating air changes in the air supply of a room but cannot be the

[8] 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.

sole source of HEPA filtered air. If the room has an ISO Class 5 (see *Table 1*) recirculating device, a minimum of 15 ACPH through the room supply HEPA filters is adequate providing the combined ACPH is not less than 30. More air changes may be required based on the number of personnel and processes. HEPA filtered supply air is introduced at the ceiling with low-wall mounted returns, creating a general top-down dilution of room 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.[9] Activities and tasks carried out within the buffer area should 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 should be brought into the room. They should be nonpermeable, nonshedding, cleanable, and resistant to disinfectants. Whenever such items are brought into the room, they should first be cleaned and disinfected. Whenever possible, equipment and other items used in the buffer area should not be taken out of the room 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 should 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 should be resistant to damage by disinfectant agents. Junctures of ceilings to walls should be coved or caulked to avoid cracks and crevices where dirt can accumulate. If ceilings consist of inlaid panels, the panels should be impregnated with a polymer to render them impervious and hydrophobic, and they should 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, or 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 should be sealed. The buffer area shall not contain sources of water (sinks) or floor drains. Work surfaces should 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 should be smooth, impervious, free from cracks and crevices, nonshedding, cleanable, and disinfectable. Their number, design, and manner of installation should promote effective cleaning and disinfection. Placement of devices (e.g., computers and printers) and objects (e.g., carts and cabinets) that are not essential to compounding in buffer zones and cleanrooms is dictated by

[9] 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.

their effect on the required environmental quality of air atmospheres and surfaces, which must be verified by monitoring.

Placement of Primary Engineering Controls Within ISO Class 7 Buffer Areas

Primary engineering controls (LAFWs, BSCs, and CAIs) are located within a restricted access ISO Class 7 (see *Table 1*) buffer area within a cleanroom with the exception below (see *Figure 1*). Only authorized personnel and materials required for compounding and cleaning are permitted in the buffer area. Presterilization procedures for high-risk level CSPs, such as weighing and mixing, shall be completed in an ISO Class 8 (see *Table 1*) or better environment.

CAIs must be placed in an ISO Class 7 (see *Table 1*) cleanroom *unless* they meet all of the following conditions: The isolator must 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 must maintain ISO Class 5 (see *Table 1*) levels during compounding operations. It is incumbent on the compounding personnel to obtain documentation from the manufacturer that the CAI will meet this standard when located in worse than ISO Class 7 (see *Table 1*) environments.

Additional Personnel Requirements

Food, drinks, and materials exposed in patient-care and treatment areas, must not enter anterooms, ante-areas, and buffer 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 a donor's white-blood cells), the manipulations must be clearly separated from routine paths and equipment used in CSP preparation activities, and they must be controlled by specific standard operating procedures 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., 70% IPA) when possible in an anteroom-type 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 anteroom or 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 anteroom, or ante-area, from the buffer area. Adequate provision for performing antiseptic hand cleansing utilizing 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 Sterile Compounding Areas

The cleaning and disinfecting practices and frequencies in this section apply to direct and contiguous compounding areas (DCCAs), which include ISO Class 5 (see *Table 1*) compounding areas for exposure of critical sites as well as buffer rooms, anterooms, and ante-areas (see *Table 2*). Trained compounding personnel are responsible for developing and practicing written procedures for cleaning and disinfecting the DCCAs. These procedures shall be conducted at the beginning of each work shift and when there are spills or environmental quality breaches. Before compounding is performed, all items are removed from the DCCA and all surfaces are cleaned of loose material and residue from spills, followed by an application of a residue-free disinfecting agent (e.g., IPA), that is left on for a time sufficient to exert its antimicrobial effect. Work surfaces in the ISO Class 7 (see *Table 1*) buffer areas and ISO Class 8 (see *Table 1*) anterooms or ante-areas are cleaned and disinfected at least daily, and dust and debris are 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›).

Table 2. Minimum Frequency of Cleaning and Disinfecting Sterile Compounding Areas

Site	Minimum Frequency
ISO Class 5 (see *Table 1*) Primary Engineering Control (e.g., LAFW, BSC, CAI)	At the beginning of each shift
Counters and easily cleanable work surfaces	Daily
Floors	Daily
Walls	Monthly
Ceilings	Monthly
Storage shelving	Monthly

Floors in the buffer or clean area are cleaned by mopping once daily when no aseptic operations are in progress. Mopping may be performed by trained and supervised custodial personnel using approved agents described in the written procedures. Only approved cleaning and disinfecting agents are used with careful consideration of compatibilities, effectiveness, and inappropriate or toxic residues. Their schedules of use and methods of application are in accord with written procedures. All cleaning tools, such as wipers, sponges, and mops, are nonshedding and dedicated to use in the buffer or clean area. Floor mops may be used in both the buffer or clean area and anteroom area, but only in that order. Most wipers are discarded after one use. If cleaning tools are reused, their cleanliness is maintained by thorough rinsing and disinfecting

after use and by storing in a clean environment between uses. Trash is collected in suitable plastic bags and removed with minimal agitation.

In the anteroom area, walls, ceilings, and shelving shall be cleaned monthly. Supplies and equipment removed from shipping cartons are wiped with a disinfecting agent, such as IPA. The IPA shall be delivered from a wash or spray bottle, the discharge opening of which must not contact any objects or materials before contacting the surfaces to be disinfected. Wiping with small IPA swabs that are commercially available in individual foil-sealed packages is preferred for disinfecting stoppers on bags and vials before they are pierced with sterile needles and for necks of ampuls before they are broken. The surface of IPA swabs for disinfecting stoppers must not contact any other object before contacting the stoppers. After IPA is sprayed or wiped on a surface to be disinfected, allow the IPA to remain for at least 30 seconds before the surface is contacted to prepare CSPs. Alternatively, if supplies are received in sealed pouches, the pouches can be removed as the supplies are introduced into the buffer or clean area without the need to disinfect the individual supply items. No shipping or other external cartons may be taken into the buffer or clean area.

Cleaning and disinfecting of counters and other easily cleanable surfaces of the anteroom area is performed at least daily by trained and supervised custodial personnel, in accordance with written procedures. However, floors are cleaned and disinfected daily, always proceeding from the buffer or clean area to the anteroom area. Storage shelving, emptied of all supplies, walls, and ceilings are cleaned and disinfected at planned intervals, monthly if not more frequently.

Personnel Cleansing and Garbing

The careful cleansing of hands and arms, and correct donning of personal protective equipment (PPE) by compounding personnel, constitute the first major step in preventing microbial contamination in CSPs. Personnel must also be thoroughly competent and highly motivated to perform flawless aseptic manipulations with ingredients, devices, and components of CSPs. Squamous cells are normally shed from the human body at a rate of 10^6 or more per hour, and those skin particles are laden with microorganisms.[10,11] When persons are afflicted with rashes, sunburn, weeping sores, conjunctivitis, active respiratory infection, as well as when they wear sheddable 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 afflictions as mentioned above shall be excluded from working in ISO Class 5 and ISO Class 7 (see *Table 1*) compounding areas until their condition is remedied. Personnel wearing cosmetics that may shed and could contact critical

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

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

sites shall not be permitted to prepare CSPs until the cosmetics are sufficiently removed from the skin.

Before entering the clean area, compounding personnel must remove the following: 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 body jewelry that can interfere with the effectiveness of PPE (e.g., fit of gloves and cuffs of sleeves, or visible body piercing above the neck). The wearing of artificial nails or extenders is prohibited while working in the sterile compounding environment. Natural nails must also be kept neat and trimmed. Personnel must don the following PPE and perform hand hygiene in an order that proceeds from the dirtiest to cleanest activities. 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 mask/eye shield. Eye shields are optional unless working with irritants like germicidal disinfecting agents.

After donning dedicated shoes or shoe covers, head and facial hair covers, and face masks, perform a hand hygiene procedure by removing debris from underneath fingernails using a nail cleaner under running warm water followed by vigorous hand washing. Wash hands and arms to the elbows for at least 30 seconds with either a plain (nonantimicrobial) soap, or antimicrobial soap, and water while in the anteroom/ante-area. The use of antimicrobial scrub brushes is not recommended as they can cause skin irritation and skin damage. Hands and forearms will be completely dried using either a lint-free disposable towels or an electronic hand dryer. After completion of hand washing, don nonshedding disposable gowns with sleeves that fit snugly around the wrists.

Once inside the clean area, prior to donning sterile, powder-free gloves, antiseptic hand cleansing must be performed using an alcohol-based surgical hand scrub with persistent activity[12] (e.g., alcohol-based preparations containing either 0.5% or 1.0% chlorhexidine gluconate) following manufacturers' recommendations. Allow hands 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 gloves may be accomplished by applying 70% IPA to all contact surface areas of the gloves and letting the gloves dry thoroughly. Only use gloves that have been tested for compatibility with alcohol disinfection by the manufacturer. Routine application of 70% IPA should occur throughout the compounding day and whenever nonsterile surfaces (e.g. vials, counter tops, chairs, and carts) are touched. Gloved hands shall also be routinely inspected for holes,

[12] *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/.

punctures, or tears and replaced immediately if detected, along with performing antiseptic hand cleansing as indicated above. Compounding personnel must be trained and evaluated in the avoidance of touching critical sites with contaminated gloves.

When compounding personnel must temporarily exit the ISO Class 7 (see *Table 1*) environment during a work shift, the exterior gown, if not visibly soiled, may be removed and retained in the ISO Class 8 (see *Table 1*) anteroom/ante-area, to be re-donned during that same work shift only. However, shoe covers, hair and facial hair covers, face mask/eye shield, and gloves must be replaced with new ones before re-entering the ISO Class 7 (see *Table 1*) clean environment along with performing proper hand hygiene.

During high-risk compounding activities that precede terminal sterilization, such as weighing and mixing, 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 8 (see *Table 1*) must re-garb PPE along with washing their hands properly, performing antiseptic hand cleansing with a waterless alcohol-based surgical scrub, and donning sterile gloves upon re-entering the ISO Class 7 (see *Table 1*) clean area. When CAIs[2] 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.

SUGGESTED STANDARD OPERATING PROCEDURES

The pharmacy should have written, properly approved standard operating procedures (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 or clean area is restricted to qualified personnel with specific responsibilities or assigned tasks in the area.
2. All cartoned supplies are decontaminated in the anteroom area by removing them from shipping cartons and wiping or spraying with a disinfecting agent, such as IPA, while being transferred to a clean, disinfected cart or other conveyance for introduction into the buffer or clean area. Individual pouched supplies need not be wiped because the pouches can be removed as these supplies are introduced into the buffer or clean area.
3. Supplies required frequently or otherwise needed close at hand but not necessarily needed for the scheduled operations of the shift are decontaminated and stored on the shelving in the anteroom area.

4. Carts used to bring supplies from the storeroom cannot be rolled beyond the demarcation line in the anteroom area, and carts used in the buffer or clean 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 prepared and brought into the buffer or clean 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 or clean area, but avoid excessive accumulation of supplies.
6. Objects that shed particles cannot be brought into the buffer or clean area, including pencils, cardboard cartons, paper towels, and cotton items. Only nonshedding paper-related products (boxes, work records, and so forth) can be brought into the buffer or clean area.
7. Traffic flow in and out of the buffer or clean area must be minimized.
8. Personnel preparing to enter the buffer or clean area must remove all jewelry from hands and arms.
9. Personnel entering the buffer or clean area must first scrub hands and arms with soap, including using a scrub brush on the fingers and nails.
10. Personnel entering the buffer or clean area must scrub and should don attire as described in the *Personnel Cleansing and Garbing* section.
11. No chewing gum, drinks, candy, or food items may be brought into the buffer or clean area or anteroom area.
12. At the beginning of each compounding activity session, and after liquids are spilled, the surfaces of the direct compounding environment are first cleaned with *Purified Water* to remove water soluble residues. Immediately thereafter, the same surfaces are disinfected with IPA or other effective antimicrobial agents, using a nonlinting wipe.
13. When LAFWs or CAIs are used as the ISO Class 5 (see *Table 1*) air quality environment, their blowers must be operated continuously during compounding activity, including during interruptions of less than 8 hours. When the blower is turned off and before other personnel enter to perform compounding activities, only one person can enter the contiguous buffer area for the purposes of turning on the blower (for at least 30 minutes) and of disinfecting the work surfaces.
14. Traffic in the area of the DCCA is minimized and controlled. The DCCA is shielded from all less clean air currents that are of higher velocity than the clean laminar airflow.
15. Supplies to be utilized in the DCCA for the planned procedures are accumulated and then decontaminated by wiping or spraying the outer surface with IPA or removing the outer wrap at the edge of the DCCA as the item is introduced into the aseptic work area.

16. After proper introduction into the DCCA 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 in a horizontal position or above in the vertical LAFW.
17. All supply items are arranged in the DCCA so as to reduce clutter and to provide maximum efficiency and order for the flow of work.
18. 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.
19. All rubber stoppers of vials and bottles and the necks of ampuls are disinfected with IPA prior to the introduction of a needle or spike for the removal of product.
20. After the preparation of every admixture, the contents of the container are thoroughly mixed and then inspected for the presence of particulate matter, evidence of incompatibility, or other defects.
21. After procedures are completed, used syringes, bottles, vials, and other supplies are removed, but with a minimum of exit and re-entry into the DCCA to minimize the risk of introducing contamination into the aseptic workspace.

ENVIRONMENTAL MONITORING

Assessment and verification of the adequacy of the aseptic compounding environment is essential. Environmental monitoring programs are designed to promptly identify potential sources of contamination, allowing for implementation of corrective actions in order to minimize the possibility of CSP contamination. This program provides information, which demonstrates that the engineering controls, disinfecting procedures, and employee work practices create an environment within the compounding area that consistently maintains acceptably low microbial levels. The compounding area includes the ISO Class 5 (see *Table 1*) primary engineering controls. ISO Class 7 (see *Table 1*) buffer room (cleanroom) and ISO Class 8 (see *Table 1*) anteroom or ante-area. The value of an environmental monitoring program lies in the consistent, quantitative assessment of environmental conditions in these areas over time.

Sampling Plan

The evaluation of environmental quality is performed by measuring the number of airborne viable particles (microorganisms) in the ISO classified air environments within the compounding area and the total number of particles (nonviable and viable). The environmental quality of the ISO classified areas as it pertains to microbial bioburden is evaluated by assessing the number of viable and nonviable particles in the air.

An environmental sampling plan shall be developed for monitoring airborne viable particles. Selected sampling sites should include multiple locations within each ISO Class 5 (see *Table 1*) environment and in the ISO Class 7 and 8 (see *Table 1*) areas. The plan should include location, method of sampling, volume of air sampled, frequency of sampling, time of day as related to activity in the compounding area, and action levels.

Monitoring of the data generated by the program can detect changes in the microbial bioburden; such changes may be allowed for indication of changes in the state-of-control within the environment. It is recommended that compounding personnel refer to *Microbiological Evaluation of Cleanrooms and Other Controlled Environments* ⟨1116⟩ and the *CDC Guidelines for Environmental Infection Control in Healthcare Facilities–2003*[7,13] for more information.

Although ⟨1116⟩ is an informational chapter and not applicable to controlled environments for use by licensed pharmacies, it can provide valuable information in helping compounding sites establish a robust environmental monitoring program. Changes in the microbial bioburden found during monitoring can allow for detection and resolution of problems in the system before loss of control of the environment.

Growth Media

A general microbiological growth medium such as Soybean–Casein Digest Medium (also known as trypticase soy broth or agar (TSA) should be used to support the growth of bacteria. Malt extract agar (MEA) or some other media that supports the growth of fungi should also be used. 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).

Air Sampling

Evaluation of airborne microorganisms in the controlled air environments (LAFWs, CAIs, BSCs, buffer or clean areas, and anterooms/areas) is performed by properly trained individuals using suitable electric air samplers. Impaction is the preferred method of active air sampling.

Use of settling plates for qualitative air sampling cannot be relied upon and shall not be used solely to determine the quality of air in the controlled environment. The settling of particles by gravity onto culture plates is highly dependent on the particle size and is strongly influenced by air movement. Given the unpredictable and uncontrollable nature of ambient particle movement, pharmacists or technicians cannot directly relate the number of colony-forming units (cfu) on a settling plate to the concentrations of the corresponding particles in the sampled environment.

Samples collected by gravity on settling plates are not suitable substitutes for volumetric air samples and should not be used to determine the relative air concentrations of different microorganisms because of the method's collection bias.

[13] CDC Guideline for Environmental Infection Control in Health-Care Facilities, 2003 (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5210a1.htm).

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 should include zones of air backwash turbulence within laminar airflow workbench and other areas where air backwash turbulence may enter the compounding area (doorways, in and around ISO Class 5 (see *Table 1*) engineering controls and environments).

The instructions in the manufacturer's user manual for verification and use of these electric air samplers that actively collect volumes of air for evaluation must be followed. A sufficient volume of air should be tested per location in order to maximize sensitivity. These air sampling devices need to be serviced and calibrated as recommended by the manufacturer. Consideration should be given to the overall effect the chosen sampling method will have on the unidirectional airflow within a compounding environment.

Collection Methods—There are a number of different manufacturers of electric air sampling equipment. It is important that compounding personnel refer to the manufacturers' recommended procedures when using the equipment to perform active air sampling procedures. It is recommended that compounding personnel also refer to *Methodology and Instrumentation for Quantitation of Viable Airborne Microorganisms* under *Microbiological Evaluation of Cleanrooms and Other Controlled Environments* ⟨ 1116 ⟩, which can provide more information on the use of active air samplers and the volume of air that should be sampled to detect environmental bioburden excursions.

Sampling Frequency—Active electronic air sampling that is designed not to interrupt airflow while sampling shall be performed and the results evaluated at least monthly for low- and medium-risk level compounding operations and at least weekly for high-risk level compounding operations. More frequent sampling will provide earlier detection of loss of environmental control.

Surface Sampling

Surface sampling is recommended but not required. Surface sampling can be an important component of the microbial environmental monitoring program in controlled environments. It is also useful to evaluate cleaning procedures and employee work practices. Surface sampling should only be performed when no compounding activity is occurring on or near the surface to be tested. For these reasons, sampling is often performed at the end of a shift or the end of the work day. Surface sampling may be performed in all ISO classified areas and can be accomplished using contact plates and/or swabs. Sample areas should be defined on the sample plan or form. The sample size usually ranges from 24 to 30 cm^2. Contact plates are filled with general growth medium and neutralizing agents such as lecithin and polysorbate 80. Swabs should contain a transport medium and are most appropriate for irregular surfaces.

Collection Methods—To sample using a contact plate, gently touch the area with the agar surface and roll the plate across the surface to be sampled. The contact plates should be incubated as stated in the subsection *Sampling Plate Incubation Period.* The contact plate will

leave a media residue behind. Therefore, immediately after sampling with the contact plate the sampled area should be thoroughly cleaned and disinfected prior to resuming compounding.

To sample an area with a swab, rub the swab in a twisting motion across the surface within a defined surface area template. After collection of the sample, the swab is placed in an appropriate media containing a neutralizer, processed by appropriate means, and plated to the desired nutrient agar. Results should be reported as cfu per surface area.

Sampling Frequency—Surface sampling should be performed when no other activities are occurring in critical areas and the results evaluated at least monthly for low- and medium-risk level compounding operations and at least weekly for high-risk level compounding operations. More frequent sampling will provide earlier detection of loss of environmental control.

Glove Fingertips Sampling

Personnel monitoring is required because direct touch contamination is the most likely source of introducing microorganisms into CSPs. Contact agar plates are used to sample gloved fingertips after compounding CSPs immediately after exiting the ISO Class 5 (see *Table 1*) environment. Glove fingertip sampling must occur outside of the ISO Class 5 (see *Table 1*) environment. Do not disinfect gloves with IPA immediately prior to sampling. Disinfecting gloves immediately before sampling will provide false negative results. The minimum sampling schedule is provided in *Table 3.* Plates filled with nutrient agar with neutralizing agents added are used when sampling personnel fingertips. Personnel should “touch” the agar with the fingertips of both hands in a manner to create a slight impression in the agar. The gloves must be discarded and hand hygiene performed after performing this procedure.

When a finger plate result for personnel monitoring after proper incubation exceeds the action limit, a review of hand hygiene and garbing procedures as well as glove and surface disinfection procedures and work practices should occur.

Air and Surface Sampling Frequencies

The sampling frequency table *(Table 3)* details the required sampling intervals for each of the respective CSP risk level compounding areas. If two or more risk levels of compounding (e.g., medium- and high-risk level) activity should occur in a pharmacy, then the more stringent frequency of sampling must be performed routinely. If compounding occurs in multiple locations within an institution (e.g., main pharmacy and satellites), environmental monitoring is required for each individual compounding area.

Table 3. Environmental Monitoring Sampling Schedule

	Low-Risk Level CSPs	Medium-Risk Level CSPs	High-Risk Level CSPs
Required air sampling	Once a month	Once a month	Weekly
Required glove fingertips[a]	Weekly	Weekly	Daily

	Low-Risk Level CSPs	Medium-Risk Level CSPs	High-Risk Level CSPs
Recommended ISO surface sampling	Weekly	Weekly	Daily
[a] At least one individual or 10% of the compounding personnel, whichever is larger, to be sampled.			

Sampling Plate Incubation Period

At the end of the designated sampling or exposure period for all environmental monitoring activities (air, surface, or personnel), the plates are recovered, covers secured, inverted and incubated at a temperature and for a time period conducive to multiplication of microorganisms. Trypticase soy broth or agar (TSA) should be incubated at between 33° and 37° for 2 days. Malt extract agar (MEA) or other suitable fungal media should be incubated at between 26° and 30° for 7 days.

Action Limits, Documentation, and Data Evaluation

The greatest value of viable microbial monitoring in the air and on surfaces of the aseptic environment are realized when normal baseline cfu counts are determined over a period of time. Environmental monitoring data shall be collected and trended as a means of evaluating the overall control of the compounding environment.

The number of discrete colonies of microorganisms are counted and reported as 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.

Action levels shall be determined based on baseline data gathered. *Table 4* should only be used as a guideline or as interim levels until baseline data has been gathered. Determining the baseline cfu counts permits identification of an increasing trend of microbial cfu. An increasing trend in cfu counts should prompt a re-evaluation of the adequacy of cleaning procedures, operational procedures, personnel work practices, and air filtration efficiency within the aseptic compounding location. When action levels are exceeded, an investigation into the source of the contamination shall be conducted. Sources could include heating, ventilating, and air conditioning (HVAC) systems, damaged HEPA filters, and changes in personnel garbing habits or working practices. Eliminate the source of the problem, clean the affected area, and then resample.

Table 4. Action Levels (Counts) of Microbial Colony-Forming Units (cfu) per Cubic Meter of Air or Contact Plate[a]

ISO Class of Sampled Location	Sampled Sources and Their Action Levels (Counts) of Microbial cfu		
	Active Air[b] (required)	Glove Fingertip (required)	Inanimate Surfaces (recommended)

5	**> 3**	**> 3**	**> 3**
7	> 20	not required	> 20
8	> 100	not required	> 100

[a] The cfu action levels are adapted from those in *Microbiological Evaluation of Cleanrooms and Other Controlled Environments* ⟨1116⟩.
[b] At least one cubic meter, m^3, or 1000 liters, L, of air must be sampled.

Nonviable Particle Facility Environmental Monitoring Program

A program to monitor nonviable particles differs from that of 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, e.g., ISO Class 5, ISO Class 7, or ISO Class 8 (see *Table 1*).

Engineering Control Performance Verification

Primary (e.g., LAFWs, BSCs, and CAIs) and secondary (e.g., buffer and ante rooms/areas) engineering controls are essential components of the overall contamination control strategy for aseptic compounding. As such, it is imperative that they perform as designed and the resulting levels of contamination are within acceptable limits. Certification procedures such as those outlined in the CETA Certification Guide for Sterile Compounding Facilities (CAG-003-2005) should be performed by a qualified individual no less than every 6 months and whenever the device or room is relocated, altered, or major service to the facility is performed.

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

- Not more than 3,520 particles 0.5 µm size and larger per cubic meter of air (ISO Class 5, see *Table 1*) for any LAFW, BSC, and CAI;
- Not more than 352,000 particles of 0.5 µm size and larger per cubic meter of air (ISO Class 7, see *Table 1*) for any buffer room;
- Not more than 3,520,000 particles of 0.5 µm size and larger per cubic meter of air (ISO Class 8, see *Table 1*) for any anteroom/area.

All certification records shall be maintained and reviewed by the supervising pharmacist or other designated employee to ensure that the controlled environments comply with the proper air cleanliness, room pressures, and air changes per hours. (Refer to Cleanrooms, CAIs, and *Table 1* in the *Environmental Quality and Control* section.)

Pressure Differential Monitoring

A pressure gauge or velocity meter shall be installed to monitor the pressure differential or airflow between the cleanroom and anteroom and the anteroom and the general pharmacy area. The results should be reviewed and documented on a daily basis in a log. The pressure between the ISO Class 7 (see *Table 1*) and general pharmacy area should not be less than 5 Pa (0.02-inch water column, w.c.). Facilities used to compound low-risk CSPs utilizing directional airflow should maintain a minimum velocity of 0.2 m/s (40 fpm).

PROCESSING

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 must be developed for each site. This program equips the 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 must successfully complete specialized training in aseptic techniques and aseptic area practices prior to preparing CSPs (see *Personnel Training and Evaluation in Aseptic Manipulation Skills* section).

Components

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

STERILE INGREDIENTS AND COMPONENTS

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 COMPONENTS

If any nonsterile components, including containers, devices, 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 must 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, must be stored in tightly closed containers under temperature, humidity, and lighting conditions that are either

indicated in official monographs or approved by suppliers; also the date of receipt in the compounding facility must 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 one 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, and 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. The bulk drug substance or excipient 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, controlled procedures for use of the equipment and specified time frames for these activities are established and followed. Routine maintenance and time intervals are also outlined in these written procedures. 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 FOR PARENTERAL NUTRITION COMPOUNDING

Automated compounding devices (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, the ACDs can improve the accuracy and precision of the compounding process compared to the traditional, manual compounding methods. Pharmacists should consult the general information chapter *Validation of*

Compendial Methods ⟨ 1225 ⟩ for verification parameters to be considered when evaluating an ACD.

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,* which represents a typical additive volume (e.g., 40 mL for small-volume range of 1 to 100 mL; or 300 mL for large-volume range of 100 to 1000 mL), is programmed into the ACD and delivered to the appropriate volumetric container. The pharmacist then consults *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. The pharmacist consults *Weights and Balances* ⟨ 41 ⟩ for acceptable tolerances of the weights used. In addition, the same volume of *Sterile Water for Injection* used to assess volumetric accuracy is then weighed on the balance used in conjunction with the ACD. For example, if 40 mL of water was used in the volumetric assessment, its corresponding weight should be about 40 g (assuming the relative density of water is 1.0). In addition, during the use of the ACD, certain additives, such as potassium chloride (corrected for density differences) can also be tested in the same manner as 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 must 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 percent and not more than 105.0 percent of the labeled amount of $C_6H_{12}O_6 \cdot H_2O$. The hospital or institutional chemistry laboratories have to 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, potassium chloride, and so forth. 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, the pharmacist must keep a daily

record of the above-described accuracy assessments and review the results over time. This review must 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

All high-risk level CSPs that are prepared in groups of more than 25 identical individual single-dose packages (such as ampuls, bags, syringes, and vials), or in multiple-dose vials for administration to multiple patients, or are exposed longer than 12 hours at 2° to 8° and longer than 6 hours at warmer than 8° before they are sterilized are tested to ensure that they are sterile (see *Sterility Tests* ⟨ 71 ⟩) and do not contain excessive bacterial endotoxins (see *Bacterial Endotoxins Test* ⟨ 85 ⟩).

Inspection of Solution Dosage Forms and Review of Compounding Procedures

All CSPs that are intended to be solutions must 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 CSPs 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 must 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 must 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, confirm accuracy of measurements 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 automated compounding devices, which measure by weight using the quotient of the programmed volume divided by the density or specific gravity, must 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 must be included in the standard operating procedures 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 (such as ampuls, bags, syringes, vials), or in multiple-dose vials for administration to multiple patients, or exposed longer than 12 hours at 2° to 8° and longer than 6 hours at warmer than 8° before they are sterilized must be tested to ensure that they are sterile (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 (such as ampuls, bags, syringes, vials), or in multiple-dose vials for administration to multiple patients, or exposed longer than 12 hours at 2° to 8° and longer than 6 hours at warmer than 8° before they are sterilized must 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 must not exceed the amount of USP Endotoxin Units (EU per hour per kg of body weight or m^2 of body surface area) specified in the above chapter for the appropriate route of administration.

Identity and Strength Verification of Ingredients

Compounding facilities must 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 beyond-use date; 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 to 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 must be assayed by methods that are specific for the active ingredients.

STORAGE AND BEYOND-USE DATING

Beyond-use dates for compounded preparations are usually assigned based on professional experience, which should include careful interpretation of appropriate information sources for the same or similar formulations (see *Stability Criteria and Beyond-Use Dating* in the general test chapter *Pharmaceutical Compounding—Nonsterile Preparations* ⟨ 795 ⟩). Beyond-use dates 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 must 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, but not exceeding 40° (see *General Notices and Requirements*) for more than 4 hours, such CSPs should be discarded, unless appropriate documentation or direct assay data confirms their continued stability.

Determining Beyond-Use Dates

Beyond-use dates and expiration dates are not the same (see *General Notices and Requirements*). Expiration dates for the chemical and 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 beyond-use dates based on chemical and physical stability parameters. Beyond-use dates for CSPs that are prepared strictly in accordance with manufacturers' product labeling must be those specified in that labeling, or from appropriate literature sources or direct testing. Beyond-use dates for CSPs that lack justification from either appropriate literature sources or by direct testing evidence must be assigned as described in the section *Stability Criteria and Beyond-Use Dating* in the general test chapter *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩.

In addition, the pharmacist 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, pharmacists 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, tables, and so forth would result in theoretical beyond-use dates. 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 CSP's characteristics (such as composition, concentration of ingredients, fill volume, or 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 must be considered when assigning beyond-use dates. 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 beyond-use dates, the pharmacy should have written policies and procedures governing the determination of the beyond-use dates for all compounded products. When attempting to predict a theoretical beyond-use date, a compounded or an admixed product 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 product. Product-specific, experimentally determined stability data evaluation protocols are preferable to published stability information. Pharmacists should consult the general information chapter under *Pharmaceutical Stability* ⟨1150⟩ for the appropriate stability parameters to be considered when initiating or evaluating a product-specific stability study.

Compounding personnel who assign beyond-use dates to CSPs when lacking direct chemical assay results must critically interpret and evaluate the most appropriate available information sources to decide a conservative and safe beyond-use date. The standard operating procedures manual of the compounding facility and each specific CSP formula record must describe the general basis used to assign the beyond-use date and storage conditions.

When manufactured multiple-dose vials (MDVs; see *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 an 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 beyond-use date 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.

Proprietary Bag and Vial Systems

Sterility storage and stability beyond-use times for attached and activated (activated is defined as allowing contact of the previously separate diluent and drug contents) container pairs of drug products for intravascular administration, such as ADD-Vantage® and Mini Bag Plus® are as indicated by the manufacturers. 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, pharmacists must monitor the drug storage areas within the pharmacy. Controlled temperature areas in compounding facilities include the following: controlled room temperature, 15° to 30° with mean kinetic temperature 25°; cold temperature, 2° to 8°; freezing temperature, –10° and colder (see *General Notices)* if needed to achieve freezing; and microbial culture media at the media-specific temperature range. A controlled temperature area should be monitored at least once daily and the results documented on a temperature log. Additionally, pharmacy personnel should 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 Bureau of Standards calibrated thermometer that has adequate accuracy and sensitivity

for the intended purpose and should be properly calibrated at suitable intervals. If the pharmacy uses a continuous temperature recording device, pharmacy personnel should verify at least once daily that the recording device itself is functioning properly.

The temperature sensing mechanisms should be suitably placed in the controlled temperature storage space to reflect accurately its true temperature. In addition, the pharmacy should 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 pharmacy departments for maintaining quality and control of CSPs that are dispensed and administered within their parent healthcare organizations.[14]

Compounding personnel shall ensure proper storage and security of CSPs prepared by or dispensed from the compounding facility, until either their beyond-use dates 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 assuring 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. While 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,

[14] Accrediting organizations require that sterile drug and nutrient compounding be controlled by the pharmacy departments of its accredited institutions.

appropriate written policies and procedures are 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 must be addressed in written procedures. 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 (for example, where CSPs are dispensed with administration sets attached to them) must be prevented throughout the beyond-use date 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 has to 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, have to be addressed on a product-specific basis. Alternate transport modes or special packaging measures might be needed for the proper assurance of quality of these CSPs. The use of tamper-proof closures and seals on CSP ports can add an additional measure of security to ensure product integrity regardless of 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 pharmacy or other 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 must be properly trained to deliver

the CSP to the appropriate storage location. Outdated and unused CSPs must be returned to the pharmacy or other compounding facility for disposition.

Written procedures have to 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 pharmacy personnel. Inspections must confirm compliance with appropriate storage conditions, separation of drugs and food, proper use of multiple-dose containers, and the avoidance of using single-dose products as multiple-dose containers. CSPs, as well as all other drug products, must 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 must be confirmed from either relevant and reliable sources or direct testing.

Redispensed CSPs

The pharmacy or other compounding facility must 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 CSP was maintained under continuous refrigeration and protected from light, if required; and no evidence of tampering or any readying for use outside the pharmacy exists. Assignment of new storage times and beyond-use dates 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 CSP must not be redispensed if there is not adequate assurance that product quality and packaging integrity (including the connections of devices, where applicable) were continuously maintained between the time the CSP left and the time that it was returned. Additionally, CSPs must not be redispensed if redispensing cannot be supported by the originally assigned beyond-use time.

Education and Training

The assurance of CSP quality and packaging integrity is highly dependent upon the proper adherence of all personnel to the pertinent written procedures. The compounding personnel must 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-event and incident reporting programs.

PACKING AND TRANSPORTING CSPS

The following sections, *Packing CSPs for Transit* and *Transit of CSPs,* 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 standard operating procedures 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 must 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 CSPs 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 must 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 must periodically review the

delivery performance of couriers to ascertain that CSPs are being efficiently and properly transported.

Storage in Locations Outside CSP Facilities

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

1. Labels and accessory labeling for CSPs include clearly readable beyond-use dates, 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 upon the patient or caregiver for the storage, handling, and administration of CSPs. The instructional objectives for the training program includes 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 CSP is prescribed, goals of therapy, expected therapeutic outcome, and potential side effects of the CSP.
2. Inspect all drug products, 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 and related supplies and equipment in the home, including all special requirements related to same.
4. Visually inspect all drug products, 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 pharmacy, 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's training program are formally assessed. The patient or caregiver is expected to demonstrate to appropriate healthcare personnel their mastery of their 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 must 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 must 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 standard operating procedures manuals of compounding facilities must 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 must 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 Food and Drug Administration (FDA) and United States Pharmacopeia (USP).

THE QUALITY ASSURANCE PROGRAM

A provider of CSPs must have in place a formal Quality Assurance (QA) Program[15] 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.[16]

Characteristics of a QA plan include the following:

1. Formalization in writing;
2. Consideration of all aspects of the preparation and dispensing of products as described in this chapter, including environmental testing, validation results, etc.;
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. Appropriate evaluation of environmental monitoring might include, for example, the trending of an indicator such as settling plate counts. In general, the selection of indicators and the effectiveness of the overall QA plan is reassessed on an annual basis.

[15] Other accepted terms that describe activities aimed at assessing and improving the quality of care rendered include Continuous Quality Improvement, Quality Assessment and Improvement, and Total Quality Management.
[16] 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.

ACRONYMS

ACD	automated compounding devices
ACPH	air changes per hour
ALARA	as low as reasonably achievable
ASHRAE	American Society of Heating, Refrigerating and Air-Conditioning Engineers
BSC	biological safety cabinet
CAI	compounding aseptic isolator
CDC	Centers for Disease Control and Prevention
CETA	Controlled Environment Testing Association
cfu	colony-forming units
CSPs	compounded sterile preparations
CSTD	closed-system vial-transfer devices
DCCA	direct and contiguous compounding areas
EU	Endotoxin Unit
FDA	Food and Drug Administration
FPM	feet per minute
HEPA	high efficiency particulate air
HICPAC	Healthcare Infection Control Practices Advisory Committee
HPLC	high performance liquid chromatography
HVAC	heating, ventilation, and air conditioning
IPA	isopropyl alcohol
LAFW	laminar airflow workbenches
MDVs	multiple-dose vials
MEA	malt extract agar
MMWR	Morbidity and Mortality Weekly Report
NBS	National Bureau of Standards
NIOSH	National Institute for Occupational Safety and Health
PET	positron emission tomography
PPE	personal protective equipment
QA	quality assurance
SAL	sterility assurance level
SCC	Sterile Compounding Expert Committee
SCDM	Soybean–Casein Digest Medium
SOP	standard operating procedures
SVI	sterile vial for injection
TLC	thin-layer chromatography
TSA	trypticase soybroth or agar
USP	United States Pharmacopeia

APPENDIX

Principle Competencies, Conditions, Practices, and Quality Assurances That Are Required (▸ "shall" or "must") and Recommended (• "should" or "is advised") 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 the full text and all official USP terminology, content, and conditions therein.

⟨ 797 ⟩ Section	Competencies, Conditions, and Practices
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 at which facility the standards 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.
DEFINITIONS	▸ Several that are important to ⟨ 797 ⟩.
Pharmacy Bulk Package	▸ One penetration of the closure with sterile devices in ISO Class 5 or cleaner air to obtain multiple single doses. ▸ Labeled "Pharmacy Bulk Package—Not for Direct Infusion." ▸ Beyond-use time after initial entry is that stated by the manufacturer.
RESPONSIBILITY OF COMPOUNDING PERSONNEL	▸ Practices and quality assurance procedures 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.

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	▸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 −20° or colder. ▸Media-fill test at least annually by compounding personnel.
Medium-Risk Level CSPs	▸Aseptic manipulations within an ISO Class 5 environment using prolonged and complex mixing and transfer, or more than three sterile products and entries into any container, or 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 −20° 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 1 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 −20° or colder. ▸Media-fill test at least semiannually by compounding personnel.
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

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	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 CAIs) for concurrent personnel protection and exposure of critical sites are in a separate ISO Class 7 room with at least 0.01-inch water column negative pressure. ▸ Segregated drug storage is in a room with at least 12 air changes per hour (ACPH). ▸ CAIs that mainain ISO Class 5 environment within the compounding chamber when located in air quality worse than ISO Class 7 must be located in rooms with a minimum of 0.01-inch water column negative pressure and 12 air changes per hour (ACPH). ▸ Annual documentation of full training of personnel regarding storage, handling, and disposal of hazardous drugs. • Total external exhaust of primary engineering controls. • Negative pressure in drug storage rooms. • 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. ▸ 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.
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.
Sterilization Methods	▸ Verify methods achieve sterility while

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	maintaining appropriate strength, purity, quality, and packaging integrity. ▸Prove sterility of high risk level batches of more than 25 units by USP chapter 〈71〉 or superior sterility testing. • Prove effectiveness for high risk level of 25 units or less by USP chapter 〈71〉, equivalent, or superior sterility testing.
Sterilization of High-Risk Level CSPs by Filtration	▸Nominal 0.2-µm porosity 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 porosity filter into final containers to remove particulates before sterilization.
PERSONNEL TRAINING AND EVALUATION IN ASEPTIC MANIPULATION SKILLS	▸Pass didactic and media-fill testing initially, followed by annually.
ENVIRONMENTAL QUALITY AND CONTROL Exposure of Critical Sites	▸ISO Class 5 or better air. ▸Preclude direct contact (e.g., touch and secretions) contamination.
Facility Design and Environmental Controls	▸Primary engineering controls provide unidirectional (i.e., laminar) HEPA air at a velocity sufficient to prevent airborne particles from contacting critical sites. ▸Cleanrooms for nonhazardous and nonradioactive CSPs are supplied with HEPA that enters from ceilings with return vents low on walls, and provide not less than 30 air changes per hour. ▸Buffer rooms or zones 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 anterooms or ante-areas is at least 40 feet per

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	minute. • Surfaces and essential furniture in buffer rooms or zones and cleanrooms are nonporous, smooth, nonshedding, impermeable, cleanable, and resistant to disinfectants.
Placement of Primary Control within ISO Class 7 Buffer Areas	▸Primary engineering controls for nonhazardous and nonradioactive CSPs are located in cleanrooms, 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. ▸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 anterooms or ante-areas. ▸Antiseptic hand cleansing and sterile gloves in buffer areas or rooms.
Cleaning and Disinfecting the Sterile Compounding Areas	▸Trained personnel write detailed procedures including cleansers, disinfectants, and nonshedding wipe and mop materials. ▸Work surfaces in ISO Class 7 and 8 areas cleaned at least daily. ▸Floors in ISO Class 7 and 8 areas cleaned daily when no compounding occurs. ▸IPA (70% isopropyl alcohol) remains on surfaces to be disinfected for at least 30 seconds before such are used to prepare CSPs. ▸Emptied shelving, walls, and ceilings in anterooms and ante-areas cleaned at least monthly.
Personnel Cleansing and Garbing	▸Personnel with rashes, sunburn, weeping sores, conjunctivitis, active respiratory infection, and sheddable cosmetics are prohibited from preparing CSPs. ▸Compounding personnel 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

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	anteroom or ante-area: shoes or shoe covers, head and facial hair covers, face mask, fingernail cleansing, hand and forearm washing and drying; nonshedding gown. ▸ Order of cleansing and gloving in buffer room or area: hand cleansing with a persistently active alcohol-based product containing 0.5% to 1.0% chlorhexidine gluconate, allow hands to dry; sterile gloves. ▸ Routinely disinfect gloves with 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.
STANDARD OPERATING PROCEDURES	▸ All facilities are required to have these, and they must include at least the items enumerated in this section.
ENVIRONMENTAL MONITORING Sampling Plan	▸ Plan includes locations, methods, air volumes, frequency, and time of day sampling occurs in ISO Class 5, 7, and 8 controlled environments.
Growth Media	• Typical media to support bacterial and fungal growth in contact samples.
Air Sampling	▸ At least monthly by active electronic air sampling in controlled ISO Class 5, 7, and 8 areas for preparing Low- and Medium-risk level CSPs, and at least weekly in those areas where High-risk level CSPs are prepared. • Improve environmental controls and aseptic personnel practices when $\geq$3, $\geq$20, and $\geq$100 microbial cfu per m^3 air are detected in, respectively, ISO Class 5, 7, and 8 controlled environments.
Surface Sampling	• Surfaces in primary engineering controls using sterile contact agar plates or swabs. • At least monthly in ISO Class 5, 7, and 8 areas for preparing Low- and Medium-risk level CSPs, and at least weekly in those areas where High-risk

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	level CSPs are prepared. • Improve cleaning, disinfecting, and personnel aseptic practices when ≥3, ≥5, and ≥100 microbial cfu per 24 to 30 cm^2 area are detected in, respectively, ISO Class 5, 7, and 8 controlled environments.
Personnel Monitoring	▸Fingertips of gloves of at least one member or 10% of compounding personnel, whichever is greater, using sterile agar plates weekly when compounding Low- and Medium-risk level CSPs, and daily when compounding High-risk level CSPs. • Improve cleaning, disinfecting, and personnel aseptic practices when ≥3 microbial cfu are detected per sample.
Total Particle Counts	▸Active electronic air sampling in ISO Class 5, 7, and 8 controlled areas at least every 6 months, and when primary engineering controls are relocated and physical structures are changed in cleanrooms, buffer rooms or zones, and anterooms or ante-areas.
Pressure Differential Monitoring	• Pressure differential between ISO Class 7 cleanrooms and surrounding uncontrolled environment is not less than 0.02-inch water column.
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.

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	▸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 or shorter 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.

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