

〈 797 〉 PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS

INTRODUCTION

This chapter provides procedures and requirements for compounding sterile preparations.

Sterile compounding differs from nonsterile compounding (see [Pharmaceutical Compounding—Nonsterile Preparations](#) 〈 795 〉 and [Good Compounding Practices](#) 〈 1075 〉) primarily by requiring a test for sterility. Sterile compounding also requires cleaner facilities; specific training and testing of personnel in principles and practices of aseptic manipulations; air quality evaluation and maintenance; and sound knowledge of sterilization and solution stability principles and practices. Greater care is required for aqueous injections that are compounded sterile preparations (CSPs)—the most common CSPs used in therapy. Aqueous injections for administration into the vascular and central nervous systems pose the greatest risk of harm to patients if there are issues of nonsterility and large errors in ingredients.

The intent of this chapter is to prevent harm and fatality to patients that could result from microbial contamination (nonsterility), excessive bacterial endotoxins, large content errors in the strength of correct ingredients, and incorrect ingredients in CSPs. The quality control and testing for CSPs in this chapter are appropriate and necessary. The content of this chapter applies to health care institutions, pharmacies, physician practice facilities, and other facilities in which CSPs are prepared, stored, and dispensed. For the purposes of this chapter, CSPs include any of the following:

- a. Preparations prepared according to the manufacturer's labeled instructions and other manipulations when manufacturing sterile products that expose the original contents to potential contamination.
- b. Preparations containing nonsterile ingredients or employing nonsterile components and devices that must be sterilized before administration.
- c. Biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals that possess either of the above two characteristics, and which include, but are not limited to, baths and soaks for live organs and tissues, implants, inhalations, injections, powders for injection, irrigations, metered sprays, and ophthalmic and otic preparations.

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 CSP's in the three risk levels, which are classified according to the potential for microbial, chemical,

and physical contamination. The chapter is divided into the following main sections:

- Responsibilities of all compounding personnel
- The basis for the classification of a CSP into a low-, medium-, and high-risk level, with examples of CSPs and their quality assurance practices in each of these risk levels
- Verification of compounding accuracy and sterilization
- Personnel training and evaluation in aseptic manipulation skills, including representative sterile microbial culture medium transfer and fill challenges
- Environmental quality and control during the processing of CSPs
- Equipment used in the preparation of CSPs
- Verification of automated compounding devices for parenteral nutrition compounding
- Finished preparation release checks and tests
- Storage and beyond-use dating
- Maintaining product quality and control after CSPs leave the compounding facility, including education and training of personnel
- Packing, handling, storage, and transport of CSPs
- Patient or caregiver training
- Patient monitoring and adverse events reporting
- A quality assurance program for CSPs

It is the ultimate responsibility of all personnel who prepare CSPs 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 and fatality to patients who are treated with CSPs.

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 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 health care 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 gloves, goggles, gowns, masks, and hair and shoe covers;
 - c. Use laminar flow clean-air hoods, barrier isolators, and other contamination control devices that are appropriate for the risk level;
 - 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 all ingredients. Before being dispensed, and or administered, the clarity of solutions are visually confirmed; also the identity and amounts of ingredients, procedures to prepare and sterilize CSPs, and specific release criteria are reviewed to assure their accuracy and completeness.
11. Beyond-use dates are assigned based on 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 corresponding to 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 health care 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, such as lipid-based emulsions where administration must be completed within 12 hours of 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 consider the potential additional risks to the integrity of CSPs when assigning beyond-use dates. The pre-administration exposure duration and temperature limits specified in the following low-risk, medium-risk, and high-risk level sections apply in the absence of direct testing results or appropriate information sources that justify different limits for specific CSPs. For a summary of the criteria according to risk levels, please see the *Appendix*.

Low-Risk Level CSPs

CSPs compounded under all of 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 with closed or sealed packaging systems that are performed promptly and attentively.
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 and packages of other sterile products.
4. For a low-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 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 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 contents of ampuls require sterile filtration to remove any glass particles.
2. Manually measuring and mixing no more than three manufactured products 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 air quality (see [Table 1](#)).
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 assure 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 air quality environment, (see [Table 1](#)) 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. The sterile CSPs do not contain broad-spectrum bacteriostatic substances, and they are administered over several days (e.g., an externally worn or implanted infusion device).
5. For a medium-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 30 hours at controlled room temperature (see [General Notices and Requirements](#)), for not more than 7 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 multiple sterile drug products and evacuation of air from those reservoirs before the filled device is dispensed.
3. Filling of reservoirs of injection and infusion devices with volumes of sterile drug solutions that will be administered over several days at ambient temperatures between 25° and 40° .
4. Transfer of volumes from multiple ampuls or vials into a single, final sterile container or product.

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 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 air quality environment (see [Table 1](#)). 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 ingredients, components, devices, and mixtures are exposed to air quality inferior to ISO Class 5 (see [Table 1](#)). This includes storage in environments inferior to ISO Class 5 of opened or partially used packages of manufactured sterile products that lack antimicrobial preservatives.
3. Nonsterile preparations are exposed for at least 6 hours before being sterilized.
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 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 steam sterilization are passed through a filter with a nominal porosity not larger than $1.2\ \mu\text{m}$ preceding or during filling into their final containers. Sterilization of high-risk level CSPs by filtration is conducted entirely with an ISO Class 5 or superior air quality environment (see [Table 1](#)).

Examples of High-Risk Compounding—

1. Dissolving nonsterile bulk drug and nutrient powders to make solutions, which will be terminally sterilized.
2. Sterile ingredients, components, devices, and mixtures are exposed to air quality inferior to ISO Class 5 (see [Table 1](#)). This includes storage in environments inferior to ISO Class 5 of opened or partially used packages of manufactured sterile products that lack antimicrobial preservatives.
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 semi-annually by each person authorized to compound high-risk level CSPs.

Example of a Media-Fill Test Procedure—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. 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% 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 controls, and they generate exponential microbial growth, 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 into 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.

VERIFICATION OF COMPOUNDING ACCURACY AND STERILIZATION

The compounding procedures and sterilization methods for CSPs correspond to correctly designed and verified written documentation in the compounding facility. Verification requires planned testing designed to demonstrate effectiveness of all procedures critical to the 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. To ensure that the identities and concentrations of ingredients are accurate, and in the absence of reliable observations and data to confirm and extrapolate those parameters, samples of CSPs are assayed.

Sterilization Methods

The licensed health care 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—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 2 hours to achieve sterility and depyrogenation (see *Dry-Heat Sterilization* under [Sterilization and Sterility Assurance of Compendial Articles](#) { 1211 }). 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 BY FILTRATION

Commercially available sterile filters must be approved for human-use applications in sterilizing pharmaceutical fluids. Both filters that must be sterilized before processing CSPs and those filters that are commercially available, disposable, sterile, and pyrogen-free have a nominal porosity of 0.2 µm, which includes 0.22-µm porosity. They should be certified by the manufacturer to retain at least 10⁷ microorganisms of a strain of *Brevundimonas (Pseudomonas) diminuta* on each cm² of upstream filter surface under conditions similar to those in which the CSPs will be sterilized. In emergency situations when sterile 0.2-µm porosity membranes are not available, filters of the same composition and 0.45-µm nominal porosity may be used. Sterilizing filters with 0.2-µm and 0.45-µm nominal porosities will not remove bacterial endotoxins and viruses by physical retention.

The supervising health care professional 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 that the filters will achieve sterility and maintain prefiltration pharmaceutical quality of the specific CSP. The filter dimensions and material 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.

When filter devices are assembled from separate nonsterile components by compounding personnel, such devices shall be identified to be sterile and ascertained to be effective under relevant conditions before they are used to sterilize CSPs. For example, sterility can be identified using biological indicators (see [Biological Indicators](#) { 1035 }). Filter units used to sterilize CSPs can also be subjected to the manufacturer's recommended integrity test, such as the bubble point test.

When commercially available sterile disposable filter devices are used, the compounding personnel may accept the written certification from suppliers that the filters retain at least 10^7 cfu, of *Brevundimonas (Pseudomonas) diminuta* on each cm^2 of filter surface. 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 may cause undetectable damage to filter integrity and shrinkage of microorganisms to sizes smaller than filter porosity.

Sterile, commercially available sterilizing filter devices for use on handheld syringes may be checked by feeling for greater resistance on the plunger when filtering air after an aqueous fluid has been filtered.

STEAM STERILIZATION

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, it is necessary that all materials 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.

Items that are not directly exposed 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 $1.2\ \mu\text{m}$ 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 〉](#)).

PERSONNEL TRAINING AND EVALUATION IN ASEPTIC MANIPULATION SKILLS

Personnel who prepare CSPs must be provided with appropriate training from expert personnel, audio–video instructional sources, and professional publications in the theoretical principles and practical skills of aseptic manipulations 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 semi-annually 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 re-instructed and re-evaluated by expert compounding personnel to assure 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 validation,¹ (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 incubated at 25° to 35° for 14 days. Failure is indicated by visible turbidity in the medium on or before 14 days.

Example of a Media-Fill Test Procedure—Perform the test as directed in the section *Quality Assurance of Low-Risk Level CSPs*.

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 is explained in this section. In addition, operations using nonsterile components require the use of a method of preparation designed to produce a sterile product.

Critical Site Exposure

The degree of exposure of the product during processing will be affected by the length of

time of exposure, the size of the critical site exposed, and the nature of the critical site.

A critical site is any opening providing a direct pathway between a sterile product and the environment or any surface coming in direct contact with the product and the environment. The risk of such a site picking up contamination from the environment increases with time of exposure. Therefore, the processing plan and the intent of the operator should give due consideration to organization, efficiency, and speed in order to keep such exposure time to a minimum. For example, an ampul should not be opened unnecessarily in advance of use.

The size of the critical site affects the risk of contamination entering the product: the greater the exposed area, the greater the risk. An open 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 vial or bottle is much greater than during the momentary exposure of a needle tip.

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 an alcohol pad, more readily than does the smooth glass surface of the neck of an ampul. Therefore, the surface disinfection can be expected to be more effective for an ampul.

Once the ampul is open, the critical site of exposure is greatly increased, creating a pathway with the potential for introduction of glass, fiber, and dust into the fluid contained in the ampul.

The prevention or elimination of airborne particles must be given high priority. Airborne contaminants 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 can be removed from the vicinity of critical sites.

Clean Rooms and Barrier Isolators

In general, sterile product preparation facilities utilize laminar airflow workbenches (LAFWs) to provide an adequate critical site environment. A discussion of the necessary facilities and proper procedures for preparing sterile products using LAFWs in clean rooms is presented below. The use of alternative systems in clean rooms that have been verified to achieve the same or better level of environmental quality as that achieved by properly operated LAFWs may also be utilized. An emerging alternative technology utilizes barrier isolator systems to minimize the extent of personnel contact and interaction, to separate the external environment from the critical site, and to provide an ISO Class 5 environment (see [Table 1](#)) for preparing CSPs. A well-designed positive pressure barrier isolator, supported by

adequate procedures for its maintenance, monitoring, and control, may offer an acceptable alternative to the use of conventional LAFWs in clean rooms for aseptic processing. An example of the arrangement of a clean-room floor plan for low- and medium-risk level CSPs is illustrated in [Figure 1](#). The second drawing in [Figure 1](#) depicts an appropriate multicompartment clean-room floor plan for high-risk level CSPs.

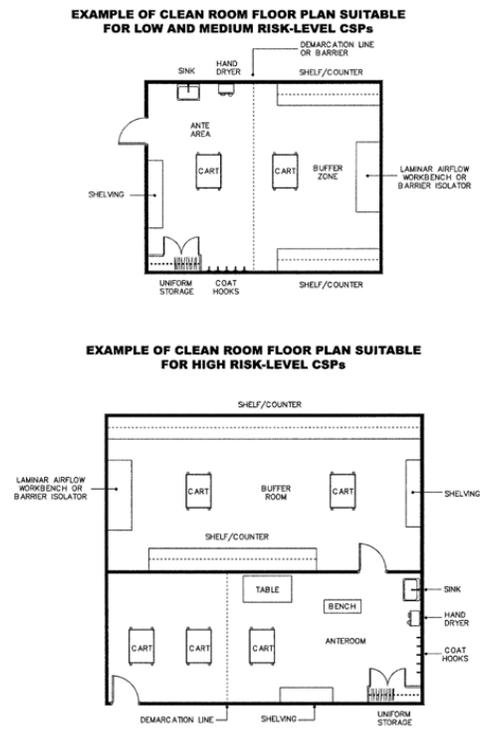


Fig. 1

Environmental Controls

Engineering controls reduce the potential for airborne contamination in workspaces by limiting the amount and size of contaminants in the CSP processing environment. Primary engineering controls are used and generally include horizontal flow clean benches, vertical flow clean benches, biological safety cabinets, and barrier isolators. Primary environmental control must provide at least ISO Class 5 quality of air (see [Table 1](#)) to which sterile ingredients and components of CSPs are directly exposed. Secondary engineering controls generally provide a buffer zone or buffer room as a core for the location of the workbenches or isolators.

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, FS209E).]^{*}

Class Name	Particle Size

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 the Federal Standard No. 209E, General Services Administration, Washington, DC, 20407 (September 11, 1992) and ISO [4644-1:1999 Clean rooms and associated controlled environments—Part 1: Classification of air cleanliness. For example, 3520 particles of 0.5 µm per m³ or larger (ISO Class 5) is equivalent to 100 particles per ft³ (Class 100) (1 m³ = 34.314 ft.³).

Airflow through high-efficiency particulate air (HEPA) filters is unidirectional or columnar, and because of the pore size of the filter the “first air” at the face of the filter is, for the purposes of aseptic compounding, free from airborne particulate contamination. Barrier isolators provide a suitable environment by restricting any ambient air from the work chamber. These systems are not as sensitive to external environments as the HEPA-filtered unidirectional airflow units.

Several aspects of barrier isolation and filtered unidirectional airflow in work environment must be understood and practiced in the compounding process. Policies and procedures for maintaining and working in the prescribed conditions for aseptic processing must be prepared, updated, maintained, and implemented and are determined by the scope and risk levels of the activities undertaken in the SP compounding operation.

In general, the CSP work environment is designed to have the cleanest work surfaces (horizontal or vertical clean benches, biological safety cabinets, or isolators) located in a buffer area, which is preceded by an anteroom that provides a clean area for donning personnel barriers, such as hair covers, gloves, gowns, or full clean-room attire. The class limit of the buffer or core room has to be demonstrably better than that of ambient air to reduce the risk of contaminants being blown, dragged, or otherwise introduced into the filtered unidirectional airflow environment. For example, strong air currents from opened doors, personnel traffic, or air streams from the heating, ventilating, and air-conditioning systems can easily disrupt the unidirectional, columnar airflow in the open-faced workbenches. The operators may also introduce disruptions in flow by their own movements and by the placement of objects onto the work surface.

Buffer or clean-room areas in which LAFWs are located are to provide at least ISO Class 8 air quality (see [Table 1](#)). Measuring, weighing, mixing, and other manipulations of nonsterile

in-process CSPs are also performed in air quality of at least ISO Class 8 (see [Table 1](#)). Appropriate air conditioning and humidity controls must be in place for the buffer area.

Tasks carried out within the buffer area should be limited to those for which a controlled environment is necessary. Only the furniture, equipment, supplies, and other goods required for the tasks to be performed may be brought into this room, and they should be nonpermeable, nonshedding, and resistant to disinfectants. Whenever such items are brought into the room, they should first be cleaned and sanitized. Whenever possible, equipment and other items used in the buffer area should not be taken from the room except for calibration, servicing, or other activity 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 sanitizing 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 of 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 should contain no sinks or floor drains. Work surfaces should be constructed of smooth, impervious materials, such as stainless steel or molded plastic, so that they are readily cleanable and sanitizable. Carts should be of stainless steel wire 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 sanitizable. Their number, design, and manner of installation should promote effective cleaning and sanitizing.

CSP Environment

The contamination reduction conditions and procedures in this section include LAFWs being located within buffer or clean-room areas that maintain at least an ISO Class 8 (see [Table 1](#)). It is preferred, but not necessary, to locate barrier isolators within such a buffer air quality area. The frequency and amount of personnel access to buffer air quality areas is restricted to minimize contaminants, while allowing delivery of essential materials for CSPs. Food,

drinks, and materials exposed in patient care and treatment areas must never be introduced into areas where components and ingredients for CSPs are present.

In an area near, but physically isolated from the buffer room area—the anteroom area—supplies, such as needles, syringes, ampuls, bags, vials of parenteral fluids, and packages of transfer tubing sets for large-volume fluids are uncartoned and disinfected.

Hand sanitizing and gowning activities also occur in the anteroom area adjacent to the buffer area. Faucet handles are designed to be hands-free. Before processing CSPs, hands are resanitized after donning all appropriate garb, except for gloves. A demarcation line or barrier identifies the separation of the buffer area from the anteroom area. Compounding personnel must be capable of accessing the buffer area without use of their hands. Anteroom areas adjacent to buffer areas are intended to minimize the introduction of contaminants into buffer areas.

Cleaning and Sanitizing the Workspaces

The cleaning, sanitizing, and organizing of the direct and contiguous compounding areas (DCCA) is the responsibility of trained operators (pharmacists and technicians) following written procedures and is performed at the beginning of each shift. 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 sanitizing agent² that is left on for a time sufficient to exert its antimicrobial effect.

Work surfaces near the DCCA in the buffer or clean area are cleaned in a similar manner, including counter tops and supply carts. Storage shelving is emptied of all supplies and then cleaned and sanitized at least weekly, using approved agents.

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 sanitizing 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 sanitization 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, supplies and equipment removed from shipping cartons are wiped with a sanitizing agent, such as sterile 70% isopropyl alcohol (IPA)³, which is checked periodically for contamination. Alternatively, if supplies are planned to be received in sealed pouches, the pouches can be removed as the supplies are introduced into the buffer or clean area without the need to sanitize the individual supply items. No shipping or other external cartons may be taken into the buffer or clean area. Cleaning and sanitizing of the anteroom area is performed at least weekly by trained and supervised custodial personnel, in accordance with written procedures. However, floors are cleaned and sanitized daily, always proceeding from the buffer or clean area to the anteroom area. Storage shelving is emptied of all supplies and cleaned and sanitized at planned intervals, preferably monthly.

These cleaning and sanitizing procedures apply to both low-risk and high-risk operations.

Personnel Cleansing and Gowning

Personnel are critical keys to the maintenance of asepsis when carrying out their assigned responsibilities. They must be thoroughly trained in aseptic techniques and be highly motivated to maintain these standards each time they prepare a sterile product.

Prior to entering the buffer or clean area, operators should remove outer lab jackets or the like, makeup, and jewelry and should thoroughly scrub hands and arms to the elbow. After drying hands and arms they should properly don clean, nonshedding uniform components, including hair covers, shoe covers, knee-length coats or coveralls, and appropriate protective gloves, in that order. The coats should fit snugly at the wrists and be zipped or snapped closed in the front. Shoe covers should be donned so that feet then touch the floor only on the clean side of the bench or other demarcation. Face masks should be donned just before beginning activities in the DCCA to minimize airborne contaminants from coughing, sneezing, and talking.

When preparing CSPs in a vertical flow LAFW with a transparent shield between the face of the operator and sterile components, or when using an isolator, wearing a face mask is optional, but head and facial hair must be covered.

Appropriate powder-free protective gloves are sterile or, if nonsterile, are sanitized with an appropriate antimicrobial cleaner such as 70% alcohol before use. Protective gloves are put on as the last uniform component. When nonsterile gloves, chosen for their chemically protective composition, are used, they are disinfected with sterile 70% isopropyl alcohol or an antimicrobial agent that is allowed to evaporate before beginning compounding procedures. Sterile and sanitized gloves do not remain sterile and clean during compounding activities because they come in contact with nonsterile surfaces and air. Therefore, compounding personnel must be trained to avoid touching sterile surfaces of packages, transfer devices,

and components within ISO Class 5 or superior environments (see [Table 1](#)). During protracted compounding activities, personnel should intermittently resanitize their gloves with sterile 70% isopropyl alcohol.

Proper scrubbing and gowning immediately prior to entry into the buffer or clean area is required of all personnel, without exception. Should the operator find it necessary to leave the room, the coat may be carefully removed at the entrance and hung inside out for redonning upon re-entry, but only during the same shift. However, hair covers, masks, shoe covers, and gloves should be discarded and new ones donned prior to re-entry.

For high-risk operations, it is especially critical to minimize the risk of contamination on lab coats, coveralls, and other garb to be worn in the buffer or clean area. Preferably, fresh clean garb should be donned upon each entry into the buffer or clean area to avoid liberating contaminants from previously worn garb. Alternatively, garb that has been worn may be removed with the intention of regarbing for re-entry into the buffer or clean area and stored during the interim under proper control and protection in the anteroom area. Garb worn or taken outside the confines of the anteroom area cannot be worn in the buffer or clean area.

Dispersion of particles from body surfaces, such as from skin rashes, sunburn, or cosmetics, increases the risk of contamination of critical sites and must be appropriately controlled or minimized. If severe, the operator must be excluded from the buffer or clean area until the condition is remedied, especially for high-risk operations.

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 sterile IPA, while being transferred to a clean, sanitized 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 sanitized 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. An air dryer or disposable nonshedding towels are used to dry hands and arms after washing.
10. Personnel entering the buffer or clean area, after scrubbing, should don attire as described under *Personnel Cleansing and Gowning*.
11. No chewing gum, 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 sanitized with sterile 70% isopropyl alcohol, or other effective antimicrobial agents, using a nonlinting wipe.
13. When LAFWs or barrier isolators are used as the ISO Class 5 air quality environment (see [Table 1](#)), 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 sanitizing 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 behind an exposed critical site in a horizontal position or above in the vertical laminar flow workbench.
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 sanitized with adequate frequency with an approved disinfectant.
19. All rubber stoppers of vials and bottles and the neck of ampuls are sanitized 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

In addition to the evaluation and verification of personnel aseptic techniques and of the adequacy of compounding processes and procedures (see *Personnel Training and Evaluation in Aseptic Manipulation Skills* section), assessment and verification of the adequacy of the sterile compounding environment is essential, especially for preparing high-risk preparations. Evaluation of environmental quality is performed by measuring both the total number of particles and the number of viable microorganisms in the controlled air

environments of the compounding area.

Certification that each LAFW and barrier isolator is functioning properly and meets the air quality requirement of ISO Class 5 (refer to *Clean Rooms and Barrier Isolators* and [Table 1](#) in the *Environmental Quality and Control* section) is performed by a qualified operator(s) using current, state-of-the-art electronic air sampling at least every six months and whenever the LAFW or barrier isolator is relocated. Similarly, the air quality of the buffer or clean area and anteroom area is evaluated by a qualified operator(s) for conformance to ISO Class 7 and ISO Class 8 requirements, as appropriate, at least every six months and when renovations occur. These records are maintained and reviewed by the supervising pharmacist or other designated employee.

Evaluation of airborne microorganisms in the controlled air environments (LAFW, barrier isolators, buffer or clean area, and anteroom area) is performed by properly trained individuals using suitable electric air samplers or by exposing sterile nutrient agar plates for a suitable time frame. For either approach, the air sampling is performed at locations judged by compounding personnel to be the most prone to contamination during compounding activities: this includes zones of air backwash turbulence within LAFWs and other areas where air backwash turbulence may enter the compounding area. Such evaluations are performed as a regular and ongoing process at least monthly for sterile compounding areas used for low- and medium-risk preparations and at least weekly for areas used for high-risk preparations.

For electric air samplers that actively collect volumes of air for evaluation, the instructions for verification and use of these devices must be followed. When using the passive exposure of sterile nutrient agar settling plates, the covers are removed and the media is exposed for a period usually lasting 1 hour or longer to collect viable microorganisms as they fall from the environment. At the end of the designated exposure period, the plates are recovered and incubated at a temperature and for a time period conducive to multiplication of microorganisms on the nutrient agar—usually at 30° to 35° for a minimum of 48 hours. The number of discrete colonies of microorganisms are then counted and reported as colony forming units (cfu). This provides a measurement of the level of microbial contamination in the air within the tested environment.

The greatest value of viable microorganism monitored in the air of the compounding environment is realized when normal baseline cfu counts are determined over a period of time. Determining the baseline cfu counts permits identification of a trend toward increasing microbial cfu counts. A sufficiently increasing trend in cfu counts over time must prompt a re-evaluation of the adequacy of cleaning procedures, operational procedures, and air filtration

efficiency within the sterile compounding location. Action may be warranted when an increasing trend to 50% above the baseline for areas used for high- and medium-risk preparations or to 100% above baseline for areas used for low-risk preparations is found.

A written plan and schedule for the environmental monitoring procedures for airborne microorganisms must be established and followed. The plan must be adequate to evaluate the various controlled air environment areas (LAFW, barrier isolator, buffer or clean area, and anteroom area) of the sterile compounding facility. All compounding personnel are trained in and educated about the importance of this environmental monitoring process. For sterile compounding areas used for low- and medium-risk preparations, a minimum of monthly evaluation is appropriate. For sterile compounding areas used for high-risk preparations, at least weekly evaluation is appropriate.

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).

Aseptic Technique

Critical operations are carried out by appropriately trained and qualified personnel in a DCCA using proper aseptic techniques described in a written procedure (see *Suggested Standard Operating Procedures*). Aseptic technique is equally applicable to the preparation of sterile sensitizing and chemotoxic agents. However, it is essential to recognize that additional precautions must be utilized to protect the personnel and the compounding environment from the potential adverse effects of these chemotoxic products. The minimum requirements for this process include the following: working and verified vertical laminar airflow work bench, barrier isolator, or other environmental containment and control device with biohazard control capabilities; the protective capabilities of gowns, masks, bouffants, and gloves; sprayback and spill control techniques and equipment; the use specialized compounding devices and equipment; and proper disposal.

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 compounded at a high-risk level. 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, 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 are

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 is 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 health care 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 Procedures](#) < 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 for administration by injection into the vascular and central nervous systems 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 >). 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 in 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 products are individually inspected just prior to leaving the storage area. Those products 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 product unit, where possible, should be inspected against lighted white or black background or both for evidence of visible particulates or other foreign matter. Pre-release inspection also includes container–closure integrity and any other apparent visual defect. Products with observed defects should be immediately discarded or marked and segregated from acceptable products in a manner that prevents their administration. When products 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 for administration by injection into the vascular and central nervous systems 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.

In such a case, a written procedure requiring daily observation of the media and requiring an immediate recall if there is any evidence of microbial growth must be available. In addition, the patient and the physician of the patient to whom a potentially contaminated CSP was administered is 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 for administration by injection into the vascular and central nervous systems 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 >). 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 m² 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.

To inhibit microbial growth from undetected contamination, finished CSPs that will not be immediately dispensed and administered must be refrigerated at 2° to 8°, unless their chemical and physical stability are known to be adversely affected by cold temperatures. When CSPs are filled into patient-worn infusion devices that are likely to attain temperatures exceeding 30° for more than 24 hours, the chemical and physical stability at such temperatures and durations must be confirmed from either appropriate literature sources or direct testing.

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 one 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

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 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 are 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 health care 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. Semi-quantitative 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.

If multiple-dose parenteral medication vials (MDVs) are used, refrigerate the MDVs after they are opened unless otherwise specified by the manufacturer. Discard the MDVs when empty, when suspected or visible contamination occurs, or when the manufacturer's stated expiration date is reached, provided the manufacturer's storage conditions have been adhered to. Expiration dating not specifically referenced in the package insert should not exceed 30 days once the vial has been opened.

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 storage areas in the pharmacy (refrigerators, 2° to 8°; freezers, -20° to -10°; and incubators, 30° to 35°; etc.) 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 an NBS 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 PRODUCT QUALITY AND CONTROL AFTER THE CSP LEAVES THE PHARMACY

Sterile Preparations for Institutional Use

This section pertains to the responsibilities of the pharmacy for maintaining product quality and control after the CSP leaves the pharmacy for distribution and use within the organized health care system to which the pharmacy belongs. The pharmacy is responsible for the quality of all CSPs prepared by or dispensed from the pharmacy, throughout the life cycle of the CSP, regardless of where the CSP exists physically within the organized health care system. In fulfilling this general responsibility, the pharmacy 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 pharmacy personnel assigned to these functions. The pharmacy should assist in the education and training of nonpharmacy 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 pharmacy. Where nonpharmacy personnel are assigned tasks involving any of these responsibilities, the policies and procedures encompassing those tasks should be developed by the pharmacy in consultation with other institutional departments as appropriate. Activities or concerns that should be addressed as the pharmacy fulfills these responsibilities are as follows.

PACKAGING, HANDLING, AND TRANSPORT

Inappropriate processes or techniques involved with packaging, handling, and transport can adversely affect product quality and package integrity. While pharmacy 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 nonpharmacy personnel who are not under the direct administrative control of the pharmacy. Under these circumstances, appropriate written policies and procedures are established by the pharmacy with the involvement of other departments or services whose personnel are responsible for carrying out those CSP-related functions for which the pharmacy has a direct interest. The performance of the nonpharmacy personnel is monitored for compliance to established policies and procedures.

The critical requirements that are unique to CSPs and that are necessary to ensure product 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 life cycle of the product. Foam padding or inserts are particularly useful where CSPs are transported by pneumatic tube systems. Regardless of the methods used, the pharmacy 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 pharmacy.

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. 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. Appropriate cushioning for pneumatic tube transport should be selected and evaluated to ensure that the products so conveyed can withstand the stresses induced by the system. Pneumatic transport of nonevaluated packaging alternatives should be avoided. Additional references should be consulted as necessary for further information on handling chemotoxic and other hazardous drugs.

USE AND STORAGE

The pharmacy 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 for disposal or possible reuse.

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.

ADMINISTRATION

Procedures essential for generally ensuring product 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 products, 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 drug products into the reservoirs of implantable or portable infusion pumps.

REDISPENSED CSPS

The pharmacy must have the sole authority for determining whether a CSP not administered as originally intended can be used for an alternate patient or under alternate conditions. All CSPs that are not used as originally intended must be returned to the pharmacy for appropriate disposition, which may include redispensing, but only if adequate continuing quality can be fully ensured. The following may provide such assurance: the CSP was maintained under continuous refrigeration and protected from light, if required; no evidence of tampering or any readying for use outside the pharmacy exists; and there is sufficient time remaining until the originally assigned beyond-use time and date will be reached. 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 to the pharmacy. 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 pharmacy 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 on *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 health care 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 health care 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) Program⁴ 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.⁵

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.

APPENDIX

CRITERIA	LOW-RISK LEVEL	MEDIUM-RISK LEVEL	HIGH-F
Compounding Conditions	<ul style="list-style-type: none"> • Compounded entirely under ISO Class 5 (Class 100) conditions • Compounding involves only transfer, measuring, and mixing manipulations with closed or sealed packaging systems that are performed promptly and attentively • 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 and packages of other sterile products 	<ul style="list-style-type: none"> • All conditions listed under low-risk level • 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 conditions • Compounding process includes complex aseptic manipulations other than the single-volume transfer 	<ul style="list-style-type: none"> • Non ingr inco non: emp term steri • Ster com devi mixt expc qual ISO 100) • Non prep expc mori befo steri • Non prep term but : for b endi • It is

		<ul style="list-style-type: none"> • Compounding process requires unusually long duration • The sterile CSPs do not contain broad-spectrum bacteriostatic agents, and are administered over several days 	the (and stre ingre their com spec unoj ope of bi
QA Program	<ul style="list-style-type: none"> • Formalized in writing • Describes specific monitoring and evaluation activities • Reporting and evaluation of results • Identification of follow-up activities when thresholds are exceeded • Delineation of individual responsibilities for each aspect of the program 	See low-risk level.	See low-ris
QA Practices	<ul style="list-style-type: none"> • Routine disinfection and quality testing of direct compounding environment • Visual confirmation of personnel processes regarding gowning, etc. • Review of orders and packages of ingredients to assure correct identity and amounts of ingredients • Visual inspection of CSP • Media-fill test procedure performed at least annually for each person 	See low-risk level.	See low-ris
Outcome Monitoring	Yes	Yes	Yes

<p>Reports/Documents</p>	<ul style="list-style-type: none"> • Written policies and procedures • Adverse event reporting • Complaint procedures • Periodic review of quality control documents 	<p>See low-risk level.</p>	<p>See low-ris</p>
<p>Patient and Caregiver Training</p>	<ul style="list-style-type: none"> • Formalized program that includes <ul style="list-style-type: none"> ○ Understanding of the therapy provided ○ Handling and storage of the CSP ○ Appropriate administration techniques ○ Use and maintenance of any infusion device involved ○ Use of printed material ○ Appropriate follow-up 	<p>See low-risk level.</p>	<p>See low-ris</p>
<p>Maintaining Product Quality and Control once the CSP leaves the Pharmacy (both institutional based and NICPs)</p>	<ul style="list-style-type: none"> • Packaging, handling, and transport <ul style="list-style-type: none"> ○ Written policies and procedures including the packaging, handling, and transport of chemotoxic/hazardous CSPs • Use and storage <ul style="list-style-type: none"> ○ Written policies and procedures • Administration <ul style="list-style-type: none"> ○ Written policies and procedures dealing with such issues as handwashing, aseptic technique, site care, 	<p>See low-risk level.</p>	<p>See low-ris</p>

	<p>etc.</p> <ul style="list-style-type: none"> • Education/Training <ul style="list-style-type: none"> ○ Written policies and procedures dealing with proper education of patients and caregivers ensuring all of the above 				
Storage and Beyond-Use Dating	<ul style="list-style-type: none"> • Specific labeling requirements • Specific beyond-use dating policies, procedures, and requirements • Policies regarding storage 	See low-risk level.	See low-ris		
Storage Conditions and Beyond-Use Dating for completed CSP	In the absence of sterility testing, storage periods (before administration) exceed the following:				
	<p>Room temperature 2°–8° ≤–20°</p>	<p>≤48 hours ≤14 days ≤45 days</p>	<p>Room temperature 2°–8° ≤–20°</p>	<p>≤30 hours ≤7 days ≤45 days</p>	<p>Room temperature 2°–8° ≤–20°</p>
Finished Product-Release Checks and Tests	<ul style="list-style-type: none"> • Written policies and procedures that address <ul style="list-style-type: none"> ○ Physical inspections ○ Compounding accuracy checks 	See low-risk level.	See low-ris		
Finished Product-Release Checks and Tests	<ul style="list-style-type: none"> • Written policies and procedures that address <ul style="list-style-type: none"> ○ Sterility testing ○ Pyrogen testing ○ Potency testing 	See low-risk level.	See low-ris		
CSP Work Environment	<ul style="list-style-type: none"> • Appropriate solid surfaces • Limited (but necessary) furniture, fixtures, etc. • Anteroom area 	See low-risk level.	See low-ris		

	<ul style="list-style-type: none"> • Buffer zone 		
Equipment	<ul style="list-style-type: none"> • Written policies and procedures that address calibration, routine maintenance, personnel training 	See low-risk level.	See low-ris
Components	<ul style="list-style-type: none"> • Written policies and procedures that address Sterile components 	See low-risk level.	Sterile and component the comper if available <ul style="list-style-type: none"> • Writ and that
Processing: Aseptic Technique	<ul style="list-style-type: none"> • Written policies and procedures that address specific training and performance evaluation • Critical operations are carried out in a Direct Compounding Common Area (DCCA) 	See low-risk level.	See low-ris
Environmental Control	<ul style="list-style-type: none"> • Policies and procedures that address <ul style="list-style-type: none"> ○ Cleaning and sanitizing the workspaces (DCCA) ○ Personnel and gowning ○ Standard operating procedures 	See low-risk level.	See low-ris
Verification Procedures <ul style="list-style-type: none"> • Sterility Testing 	Not required	Not required	Yes, recom
Verification Procedures <ul style="list-style-type: none"> • Environmental 	<ul style="list-style-type: none"> • Certification of LAFW and barrier isolates every six (6) months 	See low-risk level.	See low-ris

Monitoring	<ul style="list-style-type: none"> • Certification of the buffer room/zone and anteroom/zone every six (6) months • Bacterial monitoring using an appropriate manner at least monthly 		
Verification Procedures <ul style="list-style-type: none"> • Personnel Training and Education 	Initially and annually thereafter <ul style="list-style-type: none"> • Didactic review • Written testing • Media-fill testing 	See low-risk level.	See low-ris

¹ FDA Guideline on Sterile Drug Products Produced by Aseptic Processing, June 1987, pp. 20-27; PDA Technical Monograph No. 2, Validation of Aseptic Filling for Solution Drug Products, 1980.

² Approved by the pharmacist in charge.

³ NOTE—70% isopropyl alcohol (IPA) may harbor resistant microbial spores. Therefore, IPA used in aseptic areas should always be filtered through a 0.2-µm hydrophobic filter to render it sterile.

⁴ 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.

⁵ 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.

Auxiliary Information—Staff Liaison : [Claudia C. Okeke, Ph.D., Scientific Fellow](#)

Expert Committee : (SCC05) Sterile Compounding 05

USP31–NF26 Page 319

Pharmacopeial Forum : Volume No. 32(3) Page 852

Phone Number : 1-301-816-8243