⟨797⟩ PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS

▲1. INTRODUCTION AND SCOPE

This chapter describes the minimum standards to be followed for the preparation of compounded sterile preparations (CSPs) for human and animal drugs. Sterile compounding is defined as combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance to create a sterile preparation.

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

Aseptic techniques, processes, and procedures MUST be followed for preparing any sterile medication. Processes and procedures MUST be in place to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, and mix-ups with other products or CSPs.

The use of technologies, techniques, materials, and procedures other than those described in this chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose (e.g., Validation of Alternative Microbiological Methods ⟨1223⟩ and Validation of Compendial Procedures ⟨1225⟩).

Unless otherwise specified in each section, the requirements of this chapter apply to compounding all categories of CSPs.

1.1 Scope

1.1.1 CSPs affected:

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

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

- Implants

1.1.2 Specific practices

Allergenic extracts:

Licensed allergenic extracts are mixed and diluted to prepare prescription sets for administration to patients. A prescription set is a vial or set of vials of premixed licensed allergenic extracts for subcutaneous immunotherapy that have been diluted with an appropriate diluent for an individual patient. Because of certain characteristics of allergenic extracts and allergy practice, preparation of allergenic extract prescription sets is not subject to all of the requirements in this chapter that are applicable to other sterile CSPs. The standards for compounding allergenic extracts, which are described in 21. Compounding Allergenic Extracts, are applicable only when

1. The compounding process involves transfer via sterile needles and syringes of conventionally manufactured sterile allergen products and appropriate conventionally manufactured sterile added substances; and

2. Manipulations are limited to penetrating stoppers on vials with sterile needles and syringes and transferring sterile liquids in sterile syringes to sterile vials.

Blood-derived and other biological materials:

When compounding activities require the manipulation of a patient's blood-derived or other biological material (e.g., autologous serum), the manipulations MUST be clearly separated from other compounding activities and equipment used in CSP preparation activities, and they MUST be controlled by specific standard operating procedures (SOPs) to avoid any cross-contamination. Handling of blood components and other biological materials MUST additionally comply with laws and regulations of the applicable regulatory jurisdiction.

Hazardous drugs:

Handling of sterile hazardous drugs (HDs) MUST additionally comply with Hazardous Drugs—Handling in Healthcare Settings ⟨800⟩.

Repackaging:

Repackaging of a sterile product or preparation from its original container into another container MUST be performed in accordance with the requirements in this chapter.

Sterile radiopharmaceuticals:

Compounding of radiopharmaceuticals is not required to meet the standards of this chapter as they are subject to the requirements in Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging ⟨825⟩.

1.1.3 Personnel and settings affected:

This chapter describes the minimum requirements that apply to all persons who prepare CSPs and all places where CSPs are prepared. This includes but is not limited to pharmacists, technicians, nurses, physicians, veterinarians, dentists, naturopaths, and chiropractors in all places including but not limited to hospitals and other healthcare institutions, medical and surgical patient treatment sites, infusion facilities, pharmacies, and physician or veterinarian practice sites. Any person entering a sterile compounding area, whether preparing a CSP or not, MUST meet the requirements in 3. Personal Hygiene and Garbing.

The compounding facility MUST designate one or more individuals (i.e., the designated person(s)) to be responsible and accountable for the performance and operation of the facility and personnel in the preparation of CSPs and for performing other functions as described in this chapter.

1.2 Administration

For the purposes of this chapter, "administration" means the direct application of a sterile product or preparation to a single patient by injecting, infusing, or otherwise providing a sterile product or preparation in its final form.

Administration of medication is out of the scope of this chapter. Standard precautions such as the Centers for Disease Control and Prevention (CDC) safe injection practices apply to administration. See ⟨800⟩ for additional recommendations for the administration of hazardous drugs.

1.3 Immediate-Use CSPs

When all of the following conditions are met, compounding of CSPs for direct and immediate administration is not subject to the requirements for Category 1, Category 2, or Category 3 CSPs:

1. Aseptic techniques, processes, and procedures are followed, and written SOPs are in place to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, and mix-ups with other conventionally manufactured products or CSPs.

2. Personnel are trained and demonstrate competency in aseptic processes as they relate to assigned tasks and the facility's SOPs.

3. The preparation is performed in accordance with evidence-based information for physical and chemical compatibility of the drugs (e.g., approved labeling, stability and compatibility studies).

4. The preparation involves not more than 3 different sterile products.

5. Any unused starting component from a single-dose container MUST be discarded after preparation is complete. Single-dose containers MUST not be used for more than one patient.

6. Administration begins within 4 h following the start of preparation. If administration has not begun within 4 h following the start of preparation, it MUST be promptly, appropriately, and safely discarded.

7. Unless directly administered by the person who prepared it or administration is witnessed by the preparer, the CSP MUST be labeled with the names and amounts of all active ingredients, the name or initials of the person who prepared the preparation, and the 4-h time period within which administration MUST begin.

Handling of sterile hazardous drugs (HDs) MUST additionally comply with ⟨800⟩.

1.4 Preparation Per Approved Labeling

Compounding does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling or supplemental materials provided by the product's manufacturer.

Preparing a conventionally manufactured sterile product in accordance with the directions in the manufacturer's approved labeling is out of scope of this chapter only if

1. The product is prepared as a single dose for an individual patient; and

2. The approved labeling includes information for the diluent, the resultant strength, the container closure system, and storage time.

See ⟨800⟩ for additional recommendations for the preparation of hazardous drugs.

Proprietary bag and vial systems:

Docking and activation of proprietary bag and vial systems in accordance with the manufacturer's labeling for immediate administration to an individual patient is not considered compounding and MAY be performed outside of an International Organization for Standardization (ISO) Class 5 environment.

Docking of the proprietary bag and vial systems for future activation and administration is considered compounding and MUST be performed in an ISO Class 5 environment in accordance with this chapter, with the exception of 14. Establishing Beyond-Use Dates. Beyond-use dates (BUDs) for proprietary bag and vial systems MUST not be longer than those specified in the manufacturer's labeling.

1.5 CSP Categories

This chapter distinguishes three categories of CSPs: Category 1, Category 2, and Category 3, primarily based on the state of environmental control under which they are compounded, the probability for microbial growth during the time they will be stored, and the time period within which they MUST be used.

Category 1 CSPs are compounded under the least controlled environmental conditions and therefore are assigned a BUD of 12 h or less at controlled room temperature or 24 h or less when refrigerated, if compounded in accordance with all of the applicable requirements for Category 1 CSPs in this chapter.

Category 2 CSPs require more environmental controls and testing than Category 1 CSPs and MAY be assigned a BUD of greater than 12 h at controlled room temperature or more than 24 h if refrigerated, but not exceed the limits established in Table 13 (see 14. Establishing Beyond-Use Dates), if compounded in accordance with all of the applicable requirements for Category 2 CSPs in this chapter.

Category 3 CSPs undergo sterility testing, supplemented by endotoxin testing when applicable, and have more requirements than Category 2 CSPs for personnel qualification, use of sterile garb, use of sporicidal disinfectants, frequency of environmental monitoring, and stability determination. Category 3 CSPs MAY be assigned longer BUDs than those set for Category 2 CSPs but not exceeding the limits in Table 14 (see

14. Establishing Beyond-Use Dates), if compounded in accordance with all applicable requirements for Category 3 CSPs in this chapter (see 14.4 Additional Requirements for Category 3 CSPs).

The requirements that are not specifically described as applicable to Category 1, Category 2, or Category 3, are applicable to the compounding of all CSPs unless the CSP is otherwise described in 1.1 Scope.

Category 1, Category 2, and Category 3 CSPs can be compounded by using only sterile starting ingredients, or by using some or all nonsterile starting ingredients. If all components used to compound are sterile from the start, the sterility of the components MUST be maintained during compounding to produce a CSP.

If one or more of the starting components being used to compound is not sterile, the sterility of the compounded preparation MUST be achieved through a sterilization process (e.g., terminal sterilization in the final sealed container) or sterilizing filtration, and then sterility MUST be maintained if the CSP is subsequently manipulated. When compounding with nonsterile starting components, supplies, or equipment, the quality of the components, the effectiveness of the sterilization step, and bacterial endotoxin mitigation strategies are critical to achieving a sterile preparation that is free from excessive bacterial endotoxins.

2. PERSONNEL TRAINING AND EVALUATION

All personnel who compound or have direct oversight of compounding personnel MUST be initially trained and qualified by demonstrating knowledge and competency in compounding CSPs according to the requirements in this section before being allowed to perform their job functions independently. Designated person(s) are responsible for creating and implementing a training program for personnel and for ensuring that compounders, personnel who have direct oversight of compounders, and personnel who perform restocking or cleaning and disinfection duties are initially trained and qualified by demonstrating knowledge and competency in maintaining the quality of the sterile compounding environment before being allowed to perform their job functions independently. Training and observation MAY be performed by the designated person(s) or an assigned trainer. Personnel who compound or have direct oversight of compounding personnel MUST complete training initially and at least every 12 months in appropriate sterile compounding principles and practices as described below (see 2.1 Demonstrating Knowledge and Competency of Core Skills). Personnel who only perform restocking or cleaning and disinfecting duties outside of the primary engineering control (PEC) MUST complete ongoing training as required by the facility's SOPs. Personnel compounding only immediate-use CSPs MUST complete training as required by the facility's SOPs (see 1.3 Immediate-Use CSPs).

Each compounding facility MUST develop a written training program that describes the required training, the frequency of training, and the process for evaluating the performance of individuals who compound, have direct oversight of compounding personnel, perform in-process checks, final verification, and dispensing of CSPs. This program MUST equip personnel with the appropriate knowledge and train them in the required skills necessary to perform their assigned tasks, and SOPs SHOULD specify the training required for such tasks.

Training and evaluation of personnel MUST be documented (see 20. Documentation).

2.1 Demonstrating Knowledge and Competency of Core Skills

Before beginning to compound CSPs independently or have direct oversight of compounding personnel, personnel MUST complete training and be able to demonstrate knowledge of principles and competency of skills for performing sterile manipulations and achieving and maintaining appropriate environmental conditions as applicable to their assigned job functions. This MUST be completed initially and at least every 12 months in at least the following:

- Hand hygiene
- Garbing
- Cleaning and disinfection
- Calculations, measuring, and mixing
- Aseptic technique
- Achieving and/or maintaining sterility (and apyrogenicity if compounding with nonsterile components)
- Use of equipment
- Documentation of the compounding process (e.g., master formulation and compounding records)
- Principles of high-efficiency particulate air (HEPA)-filtered unidirectional airflow within the ISO Class 5 area
- Proper use of PECs
- Principles of movement of materials and personnel within the compounding area

If the facility has only one person in the compounding operation, that person MUST document that they have obtained training and demonstrated competency, and they MUST comply with the other requirements of this chapter.

2.2 Demonstrating Competency in Garbing and Hand Hygiene

Before beginning to compound Category 1, Category 2, or Category 3 CSPs or have direct oversight of compounding personnel, personnel MUST successfully complete an initial garbing competency evaluation no fewer than 3 separate times. The 3 successful completions MUST be in succession—failure of any of the 3 initial garbing competency evaluations requires repeat testing until personnel successfully complete 3 evaluations in a row. The garbing competency evaluation consists of a visual observation and gloved fingertip and thumb sampling (GFT) of both hands (see Box 1). Each of the 3 initial competency evaluations MUST occur after performing a separate and complete hand hygiene and full garbing procedure. All garbing competencies MUST be completed with gloved fingertip and thumb sampling after garbing (see Box 1) and a documented visual audit while performing hand hygiene and garbing procedures (see 3. Personal Hygiene and Garbing). Gloved fingertip and thumb sampling after garbing, but before applying sterile 70% IPA to gloves, MUST be performed on donned sterile gloves on both hands in a classified area or segregated compounding area (SCA).

Failure is indicated by visual observation of improper hand hygiene and garbing procedures and/or gloved fingertip and thumb sampling results that exceed the action levels in Table 1. Results of the evaluation and corrective actions, in the event of failure, MUST be documented and the documentation maintained to provide a record and long-term assessment of personnel competency. Documentation MUST at a minimum include the name of the person evaluated; evaluation date and time; media and components used including manufacturer, expiration date, and lot number; starting temperature for each interval of incubation; dates of incubation; results and identification of the observer and personnel reading and documenting the results. Microbial identification of the colony-forming units (cfu) is not required for gloved fingertip and thumb sampling.

After the initial garbing competency evaluations, compounding personnel MUST successfully complete the garbing competency (see Table 1) at least one time every 6 months for personnel compounding Category 1 and Category 2 CSPs, and at least one time every 3 months for personnel compounding Category 3 CSPs. Personnel who have direct oversight of compounding personnel, but do not compound, MUST complete a garbing competency evaluation every 12 months. The evaluation SHOULD correspond to the type of garbing activities of the personnel they oversee. Personnel who have direct oversight of compounding personnel MUST not compound unless they successfully complete the garbing competency evaluation at the same intervals required for compounding personnel.

Box 1. Gloved Fingertip and Thumb Sampling Procedures

- Use one sampling media device (e.g., plates, paddles, or slides) per hand, containing general microbial growth agar (e.g., trypticase soy agar [TSA]) supplemented with neutralizing additives (e.g., lecithin and polysorbate 80) as this agar supports both bacterial and fungal growth.
- Label each media device with a personnel identifier, right or left hand, and the date and time of sampling.
- Do not apply sterile 70% isopropyl alcohol (IPA) to gloves immediately before touching the media device because this could cause a false-negative result. Using a separate media device for each hand, collect samples from all gloved fingertips and thumbs from both hands by rolling fingertip pads and thumb pad over the agar surface.
- Incubate the media device at 30°–35° for no less than 48 h and then at 20°–25° for no less than 5 additional days. Samples MUST be incubated in an incubator. Handle and store media devices to avoid contamination and prevent condensate from dropping onto the agar during incubation and affecting the accuracy of the cfu reading (e.g., invert plates).
- Record the number of cfu per hand (left hand, right hand).
- Determine whether the cfu action level is exceeded by counting the total number of cfu from both hands.

2.3 Competency Testing in Aseptic Manipulation

Before beginning to compound Category 1, Category 2, or Category 3 CSPs independently or have direct oversight of compounding personnel, personnel MUST successfully complete an aseptic manipulation competency evaluation. The aseptic manipulation competency evaluation consists of a visual observation, media-fill testing, followed by a gloved fingertip and thumb sampling on both hands, and surface sampling of the direct compounding area to assess aseptic technique and related practices (see Box 2).

For personnel compounding Category 1 and Category 2 CSPs, the aseptic manipulation competency MUST occur initially and at least every 6 months thereafter. For personnel compounding Category 3 CSPs, the aseptic manipulation competency MUST occur initially and at least every 3 months thereafter. Personnel who have direct oversight of compounding personnel MUST complete an aseptic manipulation competency evaluation annually. The evaluation SHOULD correspond to the type of activities of the personnel they oversee but does not require the same quantities. Personnel who have direct oversight of compounding personnel MUST not compound unless they successfully complete the aseptic manipulation competency evaluation that simulates the most difficult and challenging aseptic compounding procedures encountered by the person at the same intervals required for compounding personnel.

When performing a media-fill test, simulate the most difficult and challenging aseptic compounding procedures encountered by the person replacing all the components used in the CSPs with soybean–casein digest media. The simulation MUST capture elements that could potentially affect the sterility of the CSP including but not limited to:

- Factors associated with the length of the process that can pose contamination risk (e.g., operator fatigue, quality of equipment)
- Number of aseptic additions or transfers
- Number, type, and complexity of manipulations
- Number of personnel in the buffer room or SCA

If using commercial sterile microbial growth media, a certificate of analysis (COA) MUST be obtained from the supplier stating that the lot of the growth media will support the growth of microorganisms. Store microbial growth media in accordance with manufacturer instructions and initiate the media-fill test by the expiration date of the media. If preparing sterile microbial growth media in-house for sterile-to-sterile media-fill testing, the growth promotion capability of the media MUST be demonstrated for each batch and documented as described in Sterility Tests ⟨71⟩, Culture Media and Incubation Temperatures, Growth Promotion Test of Aerobes, Anaerobes, and Fungi.

Failure is indicated by visible turbidity or other visual manifestations of growth in the media in one or more container closure unit(s) on or before the end of the incubation period. Microbial identification of the cfu is not required for media-fill testing.

Immediately following the media-fill test, gloved fingertip and thumb sampling MUST be performed on both hands and inside of an ISO Class 5 PEC. If conducting gloved fingertip and thumb sampling in a compounding aseptic isolator (CAI), compounding aseptic containment isolator (CACI), or a

pharmaceutical isolator, samples MUST be taken from the sterile gloves placed over the gloves attached to the restricted-access barrier system (RABS) or pharmaceutical isolator sleeves.

Successful completion of the gloved fingertip and thumb sampling after media-fill testing is defined as ≤3 cfu as a total from both hands. See Table 1 for action levels for gloved fingertip and thumb sampling results. Microbial identification of the cfu is not required for gloved fingertip and thumb sampling.

Surface sampling of the direct compounding area MUST occur in accordance with the requirements in 6.3 Monitoring Surfaces for Viable Particles. A failure in the media fill, gloved fingertip and thumb sampling, or surface sample constitutes an overall failure of the aseptic manipulation competency.

Results of the evaluation and corrective actions MUST be documented and the documentation maintained to provide a record and long-term assessment of personnel competency. Documentation MUST at a minimum include 1) the name of the person evaluated, 2) evaluation date and time, 3) media and components used including their manufacturer or supplier, 4) expiration dates and lot numbers, 5) starting temperature for each interval of incubation, 6) dates of incubation, 7) the results, and 8) the names or other identification of the observer and the person who reads and documents the results.

Box 2. Media-Fill Testing Procedures

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

- If some of the starting components are nonsterile to begin with, dissolve a commercially available nonsterile soybean–casein digest powder in nonbacteriostatic water to make a 3% nonsterile solution. Manipulate it in a manner that simulates nonsterile-to-sterile compounding activities. Prepare at least 1 container as the positive control to demonstrate growth promotion, which is indicated by visible turbidity upon incubation.

- Once the compounding simulation is completed and the final containers are filled with the test media, perform a gloved fingertip and thumb sample on each hand and surface sample of the direct compounding area inside the PEC. Take the samples prior to disinfecting gloves and PEC. Handle and store samples to avoid contamination and prevent condensate from dropping onto the agar during incubation and affecting the accuracy of the cfu reading (e.g., invert containers).

- Incubate the final containers at 20°–25° and 30°–35° for a minimum of 7 days at each temperature band to detect a broad spectrum of microorganisms. The order of the incubation temperatures MUST be described in the facility's SOPs. Final containers MUST be incubated in an incubator.

- Failure is indicated by visible turbidity or other visual manifestations of growth in the media in one or more container closure unit(s) on or before 14 days.

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Table 1. Action Levels for Gloved Fingertip and Thumb Samplinga

Gloved Fingertip and Thumb Sampling Action Levels

(cfu, total from both hands)

After garbing >0

After media-fill testing >3

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a Action levels are based on the total cfu count from both hands.

Table 2. Initial Training and Competency

Personnel Function Defined by Facility SOPs Required in ⟨797⟩ and Supplemented by Facility SOPs

Training and Competency in Maintaining the Quality of the Sterile Compounding Environment Training and Competency in Sterile Compounding Principles and Practices Garbing Competency (Including GFT) Media Fill with Post-GFT and Surface Sampling

Compounder X X X X

Designated person and personnel with direct oversight of compounding personnel X X X X X

Personnel who restock or clean and disinfect the sterile compounding areaa

X

Personnel who perform in-process checks or final verification of CSPsa

X

Personnel who only compound immediate-use CSPs X

Others (e.g., maintenance personnel, certifiers, contractors, inspectors, surveyors)a

X

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a Personnel who do not compound nor have direct oversight of compounding personnel.

Table 3. Ongoing Training and Competency

Personnel Function Defined by Facility SOPs Required ⟨797⟩ and Supplemented by Facility SOPs

Training and Competency in Sterile Compounding Principles and Practices Garbing Competency

(Including GFT) Media Fill with Post-GFT and Surface Sampling

Compounder At least every 12 months Category 1 and 2 at least every 6 months

Category 3 at least every 3 months Category 1 and 2 at least every 6 months

Category 3 at least every 3 months

Designated person and personnel with direct oversight of compounding personnel At least every 12 months unless compoundinga

At least every 12 months unless compoundinga

At least every 12 months unless compoundinga

Personnel who restock or clean and disinfect the sterile compounding areab

X

Personnel who perform in-process checks or final verification of CSPsb

X

Personnel who only compound immediate-use CSPs X

Others (e.g., maintenance personnel, certifiers, contractors, inspectors, surveyors)b

X

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a If compounding, follow compounder requirements.

b Personnel who do not compound or have direct oversight of compounding personnel.

3. PERSONAL HYGIENE AND GARBING

Personal hygiene and garbing are essential to maintain microbial control of the environment. Most microorganisms detected in cleanrooms are transferred from individuals. Squamous cells are normally shed from the human body at a rate of 106 or more per hour, and those skin particles are covered with microorganisms. Individuals entering a compounding area MUST be properly garbed and MUST maintain proper personal hygiene to minimize the risk of contamination to the environment and/or CSPs.

Individuals that MAY have a higher risk of contaminating the CSP and the environment (e.g., personnel with rashes, recent tattoos, oozing sores, conjunctivitis, or active respiratory infections) MUST report these conditions to the designated person(s). The designated person(s) is responsible for evaluating whether these individuals SHOULD be excluded from working in compounding areas before their conditions have resolved because of the risk of contaminating the CSPs and the environment.

3.1 Personnel Preparation

All personnel entering a compounding area where Category 1, Category 2, or Category 3 CSPs are prepared MUST take appropriate steps to minimize microbial contamination of the environment and of the CSPs, including hand hygiene (see 3.2 Hand Hygiene), garbing (see 3.3 Garbing Requirements), and consideration of needed materials to be brought into the compounding area.

Food (including mints, gum, etc.) and drinks MUST not enter anterooms, buffer rooms, or segregated compounding areas.

Before entering a compounding area, individuals MUST remove any items that are not easily cleanable or are not necessary for compounding. At a minimum, individuals MUST:

- Remove personal outer garments (e.g., bandanas, coats, hats, jackets, sweaters, vests)
- Remove all cosmetics because they shed flakes and particles
- Remove all hand, wrist, and other exposed jewelry, including piercings that could interfere with the effectiveness of garbing (e.g., the fit of gloves, cuffs of sleeves, and eye protection) or otherwise increase the risk of contamination of the CSP. Cover any jewelry that cannot be removed.
- Not wear earbuds or headphones
- Not bring electronic devices that are not necessary for compounding or other required tasks into the compounding area
- Keep nails clean and neatly trimmed to minimize particle shedding and avoid glove punctures. Nail products (e.g., polish, artificial nails, and extenders) MUST not be worn
- Wipe eyeglasses, if worn

The designated person(s) MAY permit accommodations to personnel preparation as long as the quality of the CSP and environment will not be affected. Accommodations MUST be documented.

3.2 Hand Hygiene

Any person entering a compounding area where Category 1, Category 2, or Category 3 CSPs are prepared MUST wash hands and forearms up to the elbows with soap and water before initiating compounding activities. Brushes MUST not be used for hand hygiene. Hand dryers MUST not be used. To minimize the risk of extrinsic contamination, disposable soap containers MUST not be refilled or topped off.

Box 3. Hand Washing Procedures

- Clean underneath fingernails under warm running water using a disposable nail cleaner.
- Wash hands and forearms up to the elbows with soap and water for at least 30 s.
- Dry hands and forearms up to the elbows completely with low-lint disposable towels or wipers.

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The order of hand washing and garbing depends on the placement of the sink (see 4.4 Water Sources). The order of garbing MUST be determined by the facility and documented in the facility's SOPs. Hands MUST be sanitized with alcohol-based hand rub before donning sterile gloves (see Box 4). Sterile gloves MUST be donned in a classified room or SCA.

Box 4. Hand Sanitizing Procedures

- Apply an alcohol-based hand rub to dry skin.
- Apply product to one hand and rub hands together, covering all surfaces of hands and fingers, until hands are dry.
- Allow hands to dry thoroughly before donning sterile gloves.

3.3 Garbing Requirements

Any person entering a compounding area where Category 1, Category 2, or Category 3 CSPs are prepared MUST be properly garbed. Garb MUST be donned and doffed in an order that reduces the risk of contamination. The required garb, manner of storage, and order of garbing MUST be determined by the facility and documented in the facility's SOPs. When preparing Category 2 or Category 3 CSPs, all garb SHOULD be donned in a classified area before entering the buffer room. If hand hygiene is completed outside of a classified area, alcohol-based hand rub MUST be used prior to donning garb. Skin MUST not be exposed inside the ISO Class 5 PEC (e.g., gloves MUST not be donned or doffed inside the ISO Class 5 PEC exposing bare hands). Donning and doffing garb SHOULD not occur in the same area at the same time. The minimum garbing requirements for preparing Category 1 and Category 2 CSPs include the following:

- Low-lint garment with sleeves that fit snugly around the wrists and an enclosed neck (e.g., gown or coverall)
- Low-lint covers for shoes
- Low-lint cover for head that covers the hair and ears, and if applicable, cover for facial hair
- Low-lint face mask
- Sterile powder-free gloves
- If using a RABS (i.e., a CAI or CACI), disposable gloves SHOULD be worn inside the gloves attached to the RABS sleeves. Sterile gloves MUST be worn over the gloves attached to the RABS sleeve

Garb MUST be replaced immediately if it becomes visibly soiled or if its integrity is compromised. Gowns and other garb MUST be stored in a manner that minimizes contamination (e.g., away from sinks to avoid splashing). If compounding Category 1 and Category 2 CSPs, gowns MAY be reused within the same shift by the same person if the gown is maintained in a classified area or adjacent to, or within, the

SCA in a manner that prevents contamination. When personnel exit the compounding area, garb, except for gowns, cannot be reused and MUST be discarded or laundered before reuse. The facility's SOPs MUST describe disinfection procedures for reusing goggles, respirators, and other reusable equipment.

If the facility compounds Category 3 CSPs, additional garbing requirements MUST be continuously met in the buffer room in which Category 3 CSPs are prepared. The following additional garbing requirements MUST be followed in the buffer room where Category 3 CSPs are prepared for all personnel regardless of whether Category 3 CSPs are compounded on a given day:

1. Do not allow any exposed skin in the buffer room (i.e., face and neck MUST be covered).

2. All low-lint outer garb MUST be sterile, including the use of sterile sleeves over gauntlet sleeves when a RABS is used.

3. Disposable garbing items MUST not be reused, and laundered garb MUST not be reused without being laundered and resterilized with a validated cycle.

4. The facility's SOPs MUST describe disinfection procedures for reusing goggles, respirators, and other reusable equipment.

If compounding an HD, appropriate personal protective equipment (PPE) MUST be worn and disposed of in accordance with ⟨800⟩.

Gloves:

Gloves MUST be sterile and powder free. Application of sterile 70% IPA to gloves MUST occur immediately before compounding and regularly throughout the compounding process.

All gloves MUST be inspected for holes, punctures, or tears and MUST be replaced immediately if such defects are detected.

The RABS sleeves and gloves and the pharmaceutical isolator sleeves and gloves SHOULD be changed per the manufacturer's recommendations and as defined in the facility's SOPs.

4. FACILITIES AND ENGINEERING CONTROLS

Sterile compounding facilities MUST be designed, outfitted, and maintained properly to minimize the risk of contamination of CSPs. The required air quality MUST be achieved and maintained through PECs and secondary engineering controls (SECs). The anteroom, buffer room, and SCA MUST be separated from areas not directly related to compounding. The anteroom and buffer room MUST be appropriately controlled to achieve and maintain the required air quality classifications. The design of the facility SHOULD take into account the number of personnel and their movements, and the impact the placement of equipment, supplies, and components could have on the maintenance of air quality. The number of operations being performed, the equipment (e.g., PECs, carts, computers), the personnel in the compounding area (and in adjacent areas), and the complexity of the compounding procedures are critical considerations for maintaining control of environmental conditions in the facility.

4.1 Protection from Airborne Contaminants

Sterile compounding facilities MUST be designed to minimize the risk of airborne contamination of the area in which sterile compounding occurs. Proper design and controls are required to minimize the risk of exposure of CSPs to airborne contaminants.

4.1.1 Air quality standards:

The ISO standards for air quality in controlled environments are provided in Table 4 and referenced throughout this chapter.

Table 4. ISO Classification of Particulate Matter in Room Aira

ISO Class	Particle Count per Cubic Meterb
3	35.2
4	352
5	3520
6	35,200
7	352,000
8	3,520,000

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

b Limits for number of particles ≥0.5 µm measured under dynamic operating conditions.

4.1.2 Design requirements to maintain air quality:

Facilities used for compounding CSPs MUST be designed so that air quality improves with movement through separate operational areas to the PEC. Classified areas in which the air quality is controlled (see Table 4) include anterooms, buffer rooms, and PECs.

- Anterooms providing access only to positive-pressure buffer rooms MUST meet at least ISO Class 8 classification. Anterooms providing access to negative-pressure buffer rooms MUST meet at least ISO Class 7 classification (see ⟨800⟩). Typically, personnel hand hygiene and garbing procedures, staging of components, and other activities that potentially generate higher levels of particulates are performed in the anteroom. Anterooms are also transition areas to ensure that proper air classification and pressure relationships are maintained between classified and unclassified areas.

- A buffer room MUST meet at least ISO Class 7 air quality. Activities in the buffer room MUST be controlled to minimize any effects on air quality in the area where CSPs are prepared.

- Category 1, Category 2, and Category 3 CSPs MUST be compounded in an ISO Class 5 or better PEC. If compounding only Category 1 CSPs, the PEC MAY be placed in an unclassified SCA.

4.2 Facility Design and Environmental Controls

In addition to minimizing airborne contamination, sterile compounding facilities MUST be designed and controlled to provide a well-lighted and comfortable working environment (see Physical Environments That Promote Safe Medication Use ⟨1066⟩). The cleanroom suite SHOULD be maintained at a temperature of 20° or cooler and a relative humidity of 60% or below to minimize the risk of microbial proliferation and to provide comfortable conditions for compounding personnel attired in the required garb. The temperature and humidity MUST be monitored in each room of the cleanroom suite each day that compounding is performed, either manually or by a continuous recording device. The results of the temperature and humidity readings MUST be documented at least once daily or stored in the continuous recording device and MUST be retrievable. The temperature and humidity readings MUST be reviewed as described in the facility's SOPs. Temperature and humidity in the cleanroom suite MUST be controlled through a heating, ventilation, and air conditioning (HVAC) system. Free-standing air conditioners, humidifiers, and dehumidifiers MUST not be used within the classified area or the SCA. Temperature and humidity monitoring devices MUST be verified for accuracy at least every 12 months or as required by the manufacturer.

The designated person(s) is responsible for ensuring that each area related to CSP preparation meets the classified air quality standard appropriate for the activities to be conducted in that area. The designated person(s) MUST also ensure that the ISO Class 5 areas are located, operated, maintained, monitored, and certified to have appropriate air quality.

4.2.1 Types of SECs and design:

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

Cleanroom suite:

The ISO-classified anteroom and buffer room MUST be separated from the surrounding unclassified areas of the facility by fixed walls and doors, and controls MUST be in place to minimize the flow of lower-quality air into the more controlled areas. The classified rooms MUST be equipped with a

pressure-differential monitoring system. Air supplied to the cleanroom suite MUST be introduced through HEPA filters that are located in the ceiling of the buffer room and anteroom.

Air returns in the cleanroom suite MUST be low on the wall unless a visual smoke study demonstrates an absence of stagnant airflow. This smoke study along with environmental monitoring MUST be repeated whenever a change is made to the placement of equipment within the room or any other alteration is performed within the cleanroom suite that affects the quality of the air (e.g., HVAC alterations, change of HEPA filter units).

The anteroom MUST have a line of demarcation to separate the clean side from the dirty side. The anteroom is entered through the dirty side, and the clean side is the area closest to the buffer room. Alternatively, facilities MAY be designed with two separate anterooms—a dirty anteroom and a clean anteroom. The anteroom is entered through the dirty anteroom, and the clean anteroom is the area closest to the buffer room.

It is also critical to control materials (e.g., supplies and equipment) as they move from classified areas of lower quality to those of higher quality (e.g., from an ISO Class 8 anteroom to an ISO Class 7 buffer room to an ISO Class 5 PEC) to minimize the influx of contaminants. Airlocks and interlocking doors MAY be used to facilitate better control of air balance between areas of differing ISO classification (e.g., between the buffer room and anteroom) or between a classified area and an unclassified area (e.g., between the anteroom and a hallway). If a pass-through chamber is used, both doors MUST never be opened at the same time, and doors SHOULD be interlocking.

Due to the interdependence of the various rooms or areas that make up a sterile compounding facility, it is essential to carefully define and control the dynamic interactions permitted between areas and rooms. Consider the placement of door closures, door surfaces, and the movement of the doors, all of which can affect airflow. Seals and sweeps SHOULD not be installed at doors between buffer rooms and anterooms. Access doors SHOULD be hands-free. Tacky mats MUST not be placed within ISO-classified areas. If compounding both sterile and nonsterile preparations (e.g., presterilization procedures), the respective PECs MUST be placed in separate rooms unless those PECs are sufficiently effective that the room can continuously maintain ISO Class 7 classification. If the PECs used for sterile and nonsterile compounding are placed in the same room, they MUST be placed at least 1 m apart, and particle-generating activity MUST not be performed when sterile compounding is in process.

Segregated compounding area (SCA):

A PEC MAY be located within an unclassified area without an anteroom or buffer room. This type of design is called an SCA. Only Category 1 CSPs MAY be compounded in an SCA. The SCA MUST be located away from unsealed windows, doors that connect to the outdoors, and traffic flow, all of which MAY adversely affect the air quality in the PEC. An SCA MUST not be located where environmental control challenges (e.g., restrooms, warehouses, or food preparation areas) could negatively affect the air quality of the PEC within the SCA. The impact of activities (e.g., patient care activities) that will be

conducted around or adjacent to the SCA MUST be considered carefully when designing such an area. The area within 1 m of the PEC SHOULD be dedicated only for sterile compounding (e.g., not storage, hand hygiene, donning and doffing garb, or other highly particle-generating activities such as patient care).

4.2.2 The CSP compounding environment:

The PEC MUST be certified to meet ISO Class 5 or better conditions (see Table 4) during dynamic operating conditions and MUST be designed to minimize the risk of contamination during compounding of CSPs.

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

4.2.3 Types of PECs and placement:

Proper placement of the PEC is critical to ensuring an ISO Class 5 environment for preparing CSPs. Placement of the PEC MUST allow for cleaning around the PEC. See Table 5 for a summary of minimum requirements for the placement of PECs for preparing non-HD CSPs.

Types of PECs and their placement include the following:

Laminar airflow system (LAFS):

An LAFS provides an ISO Class 5 or better environment for sterile compounding. The LAFS provides unidirectional HEPA-filtered airflow that is designed to minimize the risk of contamination of a sterile compounding environment. The unidirectional airflow within the LAFS helps protect the direct compounding area (DCA) from process-generated contamination (e.g., opening wrappings of sterile containers, compounder movement) as well as from outside sources.

Types of LAFS and their placement include the following:

Laminar airflow workbench (LAFW):

An LAFW is a device that provides an ISO Class 5 or better environment for sterile compounding. The LAFW provides either horizontal or vertical unidirectional HEPA-filtered airflow. [NOTE—An LAFW MUST

not be used for preparation of antineoplastic and/or active pharmaceutical ingredient (API) HDs (see ⟨800⟩).]

Integrated vertical laminar flow zone (IVLFZ):

An IVLFZ is a designated ISO Class 5 area serving as the PEC within an ISO Class 7 or cleaner buffer room. In the IVLFZ, unidirectional airflow is created by placing HEPA filters over the entire surface of the worktables and by effective placement of air returns. The unidirectional HEPA-filtered zone MUST be separated from the ISO Class 7 area with a physical barrier to direct the airflow downward over the work area to separate the DCA from potential sources of contamination. Strategic location of air returns in addition to full coverage of HEPA filters above the work surface is required. Both static and dynamic smoke studies verifying a continuous flow of HEPA-filtered air void of turbulence, dead air zones, and refluxing from the HEPA filters to and across the entire work area and to the air returns MUST be documented (e.g., with video). [NOTE—Dynamic airflow smoke pattern tests have shown that it is difficult to achieve this type of design and also achieve and maintain unidirectional airflow under dynamic operating conditions.][NOTE—An IVLFZ MUST not be used for preparation of antineoplastic and/or API HDs (see ⟨800⟩).]

Class II biological safety cabinet (BSC):

A Class II BSC is a ventilated cabinet with an open front and inward and downward unidirectional HEPA-filtered airflow and HEPA-filtered exhaust. The BSC is designed to provide worker protection from exposure to airborne drugs and to provide an ISO Class 5 or better environment for preparing CSPs. [NOTE—The exhaust air from the BSC MUST be externally vented for preparation of antineoplastic and/or API HDs (see ⟨800⟩).]

Placement of LAFS:

The LAFS MUST be located out of traffic patterns and away from room air currents that could disrupt the intended airflow patterns inside the PEC. If used to prepare only Category 1 CSPs, the ISO Class 5 PEC MAY be located in an unclassified SCA. If used to prepare Category 2 or Category 3 CSPs, the LAFS MUST be located within a cleanroom suite with an ISO Class 7 or better buffer room with an ISO Class 8 or better anteroom. A dynamic airflow smoke pattern test MUST be performed in the PEC initially and at least every 6 months to ensure that 1) the LAFS is properly placed into the facility and 2) compounders understand how to utilize the unidirectional airflow to maintain first air in the DCA.

Restricted-access barrier system (RABS):

A RABS is an enclosure that provides HEPA-filtered ISO Class 5 unidirectional air. It allows for the ingress and/or egress of materials through defined openings that have been designed and validated to preclude the transfer of environmental air contamination and are generally not to be opened during compounding operations. RABS include compounding aseptic isolators (CAIs) and compounding aseptic

containment isolators (CACIs). In a CAI or CACI, glove ports are used to provide physical separation between the surrounding area and the aseptic manipulations.

Compounding aseptic isolator:

A CAI is designed for compounding non-HD CSPs. It is designed to maintain an ISO Class 5 environment throughout the compounding and material transfer processes. Air exchange into the CAI from the surrounding environment MUST not occur unless the air has first passed through a HEPA filter. [NOTE—A CAI MUST not be used for preparation of antineoplastic and/or API HDs (see ⟨800⟩).]

Compounding aseptic containment isolator:

A CACI is designed to provide worker protection from exposure to undesirable levels of airborne drug throughout the compounding and material transfer processes and to maintain an ISO Class 5 environment for compounding sterile HD preparations (see ⟨800⟩).

Placement of RABS:

If used to prepare only Category 1 CSPs, the ISO Class 5 environment MAY be achieved by placing the RABS in an unclassified SCA. If used to prepare Category 2 or Category 3 CSPs, the RABS MUST be located within a cleanroom suite with an ISO Class 7 or better buffer room with an ISO Class 8 or better anteroom. For placement of a CACI used for the preparation of antineoplastic and/or API HDs, see ⟨800⟩.

When a RABS is used, the recovery time after opening the transfer chamber to achieve ISO Class 5 air quality MUST be documented (e.g., by the manufacturer), and internal procedures MUST be developed to ensure that adequate recovery time is allowed after opening and closing the RABS, both before and during compounding operations. A dynamic airflow smoke pattern test MUST be performed in the PEC under dynamic operating conditions initially and at least every 6 months to ensure that 1) the RABS is properly integrated into the facility and 2) compounders understand how to utilize the unidirectional airflow to maintain first air in the DCA.

Pharmaceutical isolator:

A pharmaceutical isolator provides isolation from the surrounding area and maintains ISO Class 5 air quality during dynamic operating conditions. [NOTE—A CAI or CACI is not a pharmaceutical isolator.] A pharmaceutical isolator comprises four elements:

1. Controlled workspace
2. Transfer device(s)
3. Access device(s)
4. Integral decontamination system

Placement of pharmaceutical isolators:

A pharmaceutical isolator used to prepare only Category 1 CSPs can be placed in an unclassified SCA. If the pharmaceutical isolator is used to prepare Category 2 or Category 3 CSPs, the pharmaceutical

isolator MUST be placed in an ISO Class 8 or better room. [NOTE—An anteroom is not required when using a pharmaceutical isolator.] A dynamic airflow smoke pattern test MUST be performed in the PEC initially and at least every 6 months to ensure that 1) the pharmaceutical isolator is properly placed in the facility and 2) compounders understand how to utilize the unidirectional airflow to maintain first air in the work zone.

Table 5. Summary of Minimum Requirements for Placement of PECs for Compounding Non-HD CSPsa

PEC Type	Device Type	Placement for Compounding Only Category 1 CSPs	Placement for Compounding Category 2 and 3 CSPs
LAFS	LAFW	Unclassified SCA	ISO Class 7 positive-pressure buffer room with an ISO Class 8 positive-pressure anteroom
	IVLFZ	N/Ab	ISO Class 7 positive-pressure buffer room with an ISO Class 8 positive-pressure anteroom
	BSC	Unclassified SCA	ISO Class 7 positive-pressure buffer room with an ISO Class 8 positive-pressure anteroom
RABS	CAI or CACI	Unclassified SCA	ISO Class 7 positive-pressure buffer room with an ISO Class 8 positive-pressure anteroom
Pharmaceutical isolator	Pharmaceutical isolator	Unclassified SCA	ISO Class 8 positive-pressure room

a For compounding HDs, see ⟨800⟩.

b An IVLFZ MUST not be used in an unclassified area.

If a robotic enclosure is used as the PEC, or placed within the PEC, a dynamic airflow smoke pattern test MUST be performed initially and at least every 6 months thereafter to ensure that 1) it is properly integrated into the facility, 2) there is no turbulence or refluxing at any critical site(s), 3) room air does not enter the PEC where sterile products and/or preparations MAY be exposed, and 4) all processes can be performed without introducing contamination to the DCA(s).

4.2.4 Air exchange requirements:

For cleanroom suites, adequate HEPA-filtered airflow to the buffer room(s) and anteroom(s) is required to maintain the appropriate ISO classification during compounding activities. Airflow is measured in terms of the number of air changes per hour (ACPH). The ACPH MAY need to be higher to maintain the required ISO classification and microbial state of control depending on the following factors:

- Number of personnel permitted to work in the area
- Number of particles that MAY be generated from activities and processes in the area

- Equipment located in the room
- Room pressure

See Table 6 for a summary of ACPH requirements for non-HD sterile compounding areas. Additional ACPH requirements include:

A minimum of 30 total HEPA-filtered ACPH MUST be supplied to ISO Class 7 rooms:

- The total HEPA-filtered air change rate MUST be adequate to maintain ISO Class 7 during dynamic operating conditions considering the factors listed above
- At least 15 ACPH of the total air change rate in a room MUST come from the HVAC through HEPA filters located in the ceiling
- The HEPA-filtered air from the PEC, when added to the HVAC-supplied HEPA-filtered air, MUST increase the total HEPA-filtered ACPH to at least 30 ACPH
- If the PEC is used to meet the minimum total ACPH requirements, the PEC MUST not be turned off except for maintenance
- Rooms where activity levels are high MAY require more HEPA-filtered ACPH to maintain ISO Class 7 air quality under dynamic operating conditions
- The ACPH from HVAC, ACPH contributed from the PEC, and the total ACPH MUST be documented on the certification report

A minimum of 20 total HEPA-filtered ACPH MUST be supplied to ISO Class 8 rooms:

- The total HEPA-filtered air change rate MUST be adequate to maintain ISO Class 8 under dynamic operating conditions considering the factors listed above
- At least 15 ACPH of the total air change rate in a room MUST come from the HVAC through HEPA filters located in the ceiling
- Rooms where activity levels are high MAY require more HEPA-filtered ACPH to maintain ISO Class 8 air quality under dynamic operating conditions
- The total ACPH MUST be documented on the certification report

Table 6. Summary of ACPH Requirements for Non-HD Sterile Compounding Areas

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

_____

4.2.5 Establishing and maintaining pressure differentials:

Continuous differential positive pressure is required to minimize airflow from an area with lower air-quality classification to an area of higher air-quality classification. In a cleanroom suite, a minimum differential positive pressure of 0.020-inch water column is required between adjacent ISO-classified areas (e.g., between the buffer room and anteroom). The pressure differential between the anteroom and the unclassified area MUST not be less than 0.020-inch water column. No pressure differential is required between the SCA and the surrounding area. See ⟨800⟩ for pressure requirements for compounding HD CSPs.

Where pressure differentials are required, a pressure differential monitoring device MUST be used to continuously monitor the pressure differentials. The quantitative results from the pressure monitoring device MUST be reviewed and documented at least daily on the days when compounding is occurring.

4.2.6 Facilities preparing Category 2 or Category 3 CSPs from nonsterile starting components:

Weighing, measuring, or otherwise manipulating components could generate airborne chemical particles (e.g., API or added substances). If preparing Category 2 or Category 3 CSP from nonsterile component(s), presterilization procedures, such as weighing and mixing, MUST be completed in an ISO Class 8 or better environment (e.g., anteroom or buffer room). Presterilization procedures MUST be performed in single-use containment glove bags, containment ventilated enclosures (CVEs), BSCs, or CACIs to minimize the risk of airborne contamination. CVEs, BSCs, or CACIs used for presterilization procedures MUST be certified at least every 6 months.

Presterilization procedures MUST not adversely affect the required air quality of the SEC as demonstrated during certification under dynamic operating conditions. Personnel MUST follow the hygiene and garbing requirements as described in 3. Personal Hygiene and Garbing during presterilization procedures.

4.3 Creating Areas to Achieve Easily Cleanable Conditions

4.3.1 Cleanroom suite:

The surfaces of ceilings, walls, floors, doors, door frames, fixtures, shelving, work surfaces, counters, and cabinets in the classified area MUST be smooth, impervious, free from cracks and crevices, and nonshedding so they can be cleaned and disinfected and to minimize spaces in which microorganisms and other contaminants can accumulate. Surfaces SHOULD be resistant to damage (e.g., rust) by cleaning agents, sporicidal and other types of disinfectants, and tools used to clean. Junctures between the ceiling and the walls and between the walls and the floor MUST be sealed to eliminate cracks and crevices where dirt can accumulate. If ceilings consist of inlaid panels, the panels MUST be caulked around each panel to seal them to the support frame.

Walls MUST be constructed of, or MAY be covered with, durable material (e.g., epoxy painted walls or heavy-gauge polymer) and the integrity of the surface MUST be maintained. Panels MUST be joined together and sealed to each other and the support structure. Floors MUST include coving to the

sidewall, or the juncture between the floor and the wall MUST be caulked. Classified areas SHOULD minimize dust-collecting overhangs, such as utility pipes, and ledges, such as windowsills. If overhangs or ledges are present, they MUST be easily cleanable. The exterior lens surface of ceiling light fixtures MUST be smooth, mounted flush, and sealed. Any other penetrations through the ceiling or walls MUST be sealed.

4.3.2 SCA:

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

4.4 Water Sources

The facility where CSPs are prepared MUST be designed so that activities such as hand hygiene and garbing will not adversely affect the ability of the PEC to function as designed. Sinks SHOULD enable hands-free use. Surfaces of the sink(s) MUST be cleaned and disinfected each day of use, and a sporicidal disinfectant MUST be applied at least monthly (see 7.1 Agents and Supplies for Cleaning, Disinfecting, and Applying Sporicidal Disinfectants).

In facilities with a cleanroom suite, the sink used for hand hygiene MAY be placed either inside or outside of the anteroom. If the sink is located outside of the anteroom, it MUST be located in a clean space to minimize the risk of bringing contaminants into the anteroom. If the sink is located inside the anteroom, it MAY be placed on either the clean side or the dirty side of the anteroom. [NOTE—The order of hand washing and garbing depends on the placement of the sink (see 3.2 Hand Hygiene and 3.3 Garbing Requirements)]. The buffer room MUST not contain plumbed water sources [e.g., sink(s), eyewash(es), shower(s), or floor drain(s)]. The anteroom MUST not contain floor drain(s). If installed, sprinkler systems SHOULD be recessed and covered, and the covers SHOULD be easily cleanable.

In a facility with an SCA design, a hand-washing sink MUST be placed not closer than 1 m to the PEC and MAY be either inside the SCA or in close proximity to the SCA.

4.5 Placement and Movement of Materials

Only furniture, equipment, and other materials necessary for performing compounding activities are permitted in a classified area or SCA, and they SHOULD be low-shedding and easily cleaned and disinfected. Their number, design, location, and manner of installation MUST not impact environmental air quality and MUST promote effective cleaning and disinfecting. No shipping carton(s) or other corrugated or uncoated cardboard are allowed in a classified area or SCA.

Carts used to transport components or equipment into classified areas MUST be constructed from nonporous materials with cleanable casters and wheels to promote mobility and ensure ease of cleaning

and disinfection. In a cleanroom suite, carts MUST not be moved from the dirty side to the clean side of the anteroom unless the entire cart, including casters, is cleaned and disinfected.

Only equipment necessary for performing compounding activities is permitted in the PEC. Proper placement of equipment in a PEC MUST be initially verified by a dynamic airflow smoke pattern test to demonstrate minimal disruption in airflow. The dynamic airflow smoke pattern test MUST be repeated if equipment is placed in a different location. Equipment and other items used in a classified area or SCA SHOULD not be removed except for calibration, servicing, cleaning, or other activities associated with maintenance. If removed, these items MUST be cleaned and wiped with sterile 70% IPA or a suitable disinfectant before they are returned to the classified area or the SCA.

Materials necessary for performing compounding activities that have been exposed in patient care and treatment areas MUST not enter anterooms, buffer rooms, or segregated compounding areas unless thoroughly cleaned and disinfected. The designated person(s) is responsible for addressing other areas of risk in the facility's SOPs. The designated person(s) MAY permit accommodations as long as the quality of the CSP and environment will not be affected. Accommodations MUST be documented.

5. CERTIFICATION AND RECERTIFICATION

Before a compounding area is used to compound either Category 1, Category 2, or Category 3 CSPs, it MUST be independently certified using the requirements in this chapter and when applicable, manufacturer specifications. Certification indicates that the compounding area is meeting its design and air quality specifications (see Table 4).

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

- Airflow testing: Airflow testing is performed to determine acceptability of the air velocity, the room air exchange rate, and the room pressure differential in doorways between adjacent rooms to ensure consistent airflow and that the appropriate quality of air is maintained under dynamic operating conditions. The ACPH from HVAC, ACPH contributed from the PEC, and the total ACPH MUST be documented on the certification report.

- HEPA filter integrity testing: HEPA filters MUST be leak tested at the factory and then leak tested again after installation and as part of recertification.

- Total particle count testing: (See 5.1 Total Airborne Particle Sampling.) Total particle count testing MUST be performed under dynamic operating conditions using calibrated electronic equipment.

- Dynamic airflow smoke pattern test: Smoke pattern tests MUST be performed for each PEC during dynamic operating conditions to demonstrate unidirectional airflow and sweeping action over and away from the preparation(s).

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

All certification and recertification records MUST be reviewed by the designated person(s) to ensure that the classified environments meet the minimum requirements in this chapter. The number of

personnel present in each PEC and SEC during total particle-count tests and dynamic airflow smoke-pattern tests MUST be documented. Records MUST be maintained in accordance with the requirements in 20. Documentation.

A corrective action plan MUST be implemented and documented in response to any out-of-range results. Data collected in response to corrective actions MUST be reviewed to confirm that the actions taken have been effective.

5.1 Total Airborne Particle Sampling

The engineering control equipment function MUST function as designed to ensure that the levels of total airborne particles remain within acceptable limits during compounding (see Table 4). Total airborne particle count testing MUST be conducted in all classified areas during dynamic operating conditions at least every 6 months to measure the performance of the engineering controls that are being used to provide the specified levels of air cleanliness (e.g., in the ISO Class 5 PEC and ISO Class 7 and 8 rooms).

Total airborne particle sampling sites MUST be selected in all classified areas. Measurements of total airborne particles MUST be taken in each PEC at locations where there is greatest risk to the exposed CSPs, containers, and closures. When conducting sampling of the PEC, care SHOULD be taken to avoid disturbing the unidirectional airflow within the PEC. All sampling sites and procedures MUST be described in the facility's SOPs. Measurements of total airborne particles in other classified areas, including the buffer room(s) and anteroom(s), SHOULD be taken at representative locations that reflect the quality of air in the room(s).

Data evaluation and action levels:

If levels measured during the total air sampling program exceed the criteria in Table 4 for the ISO classification of the area sampled, the cause MUST be investigated and corrective action taken and documented. Data collected in response to corrective actions MUST be reviewed to confirm that the actions taken have been effective. Some examples of corrective action include process or facility improvements or HEPA filter replacement or repair. The extent of the investigation SHOULD be consistent with the deviation and SHOULD include an evaluation of trends.

6. MICROBIOLOGICAL AIR AND SURFACE MONITORING

An effective microbiological air and surface monitoring program provides information on the environmental quality of the compounding area. In addition, an effective microbiological air and surface monitoring program identifies environmental quality trends over time, identifies potential routes of contamination, and allows for implementation of corrective actions to minimize the risk of CSP contamination. Sterile compounding facilities MUST develop and implement written procedures for microbiological air and surface monitoring (see 17. SOPs). All microbiological air and surface monitoring procedures, the test results, and the corrective actions MUST be documented, and the records MUST be maintained in accordance with the requirements in 20. Documentation. Data collected in response to corrective actions MUST be reviewed to confirm that the actions taken have been effective.

6.1 General Monitoring Requirements

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

The microbiological air and surface monitoring program involves the collection and evaluation of samples from various air and surface locations to detect airborne and surface contaminants. The data from microbiological airborne and surface sampling are then used to assess risks for contamination, potential routes of contamination, and the adequacy of cleaning and disinfecting agents and procedures. Regular review of the sampling data MUST be performed to detect trends and the results of the review MUST be documented.

In addition, results from microbiological air and surface sampling MUST be reviewed in conjunction with personnel data (i.e., training records, visual observations, competency assessments) to assess the state of control and to identify potential risks of contamination. Corrective action in response to any adverse findings is required to maintain the necessary environmental quality for preparation of CSPs. Data MUST also be reviewed following corrective actions to confirm that the actions taken have been effective in achieving the required microbiological air and surface quality levels (see Table 4, Table 7, and Table 8).

Microbiological air and surface monitoring MUST be performed initially for sterile compounding facilities to establish a baseline level of environmental quality. After initial sampling, the environment in which sterile compounding activities are performed MUST be monitored according to the minimum frequencies described in this section to ensure that the environment remains suitable for sterile compounding.

Evaluating results collected over a period of time can be useful in identifying trends or determining that a significant change has occurred, even when the results fall within the specified levels.

Microbiological air and/or surface monitoring MUST be conducted in all classified areas during dynamic operating conditions to confirm that the required environmental quality is maintained. In addition to the specific sampling frequencies described in this section, sampling MUST be performed in the following circumstances:

- In conjunction with the certification of new facilities and equipment
- After any servicing of facilities or equipment (see 4. Facilities and Engineering Controls)
- In response to identified problems (e.g., positive growth in sterility tests of CSPs)
- In response to identified trends (e.g., repeated positive gloved fingertip and thumb sampling results, failed media fill testing, or repeated observations of air or surface contamination)
- In response to changes that could impact the sterile compounding environment (e.g., change in cleaning agents)

The microbiological air and surface monitoring program MUST be clearly described in the facility's SOPs, which MUST include a diagram of the sampling locations, procedures for collecting samples, frequency

of sampling, size of samples (e.g., surface area, volume of air), time of day of sampling in relation to activities in the compounding area, and action levels that will trigger corrective action.

The times and locations of sampling SHOULD be carefully selected based on their relationship to the activities performed in the area. It is important to obtain samples from locations that pose the highest possible risk of contamination to the CSP and that are likely to be representative of the conditions throughout the area. To obtain air and surface samples that are representative of the typical compounding conditions at the facility, in all PECs and classified rooms, air sampling MUST be conducted during dynamic operating conditions and surface sampling SHOULD be performed at the end of a compounding activity or shift but before the area has been cleaned and disinfected. The monitoring program MUST be designed and conducted in a manner that minimizes the chance that the sampling itself will contribute to contamination of the CSP or the environment.

It is important that personnel are trained and competent in air and surface sampling procedures to ensure accurate and reproducible sampling. All impaction air samplers MUST be serviced and calibrated as recommended by the manufacturer.

6.2 Monitoring Air Quality for Viable Airborne Particles

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

6.2.1 Viable air sampling—timing and locations:

Volumetric active air sampling of all classified areas using an impaction air sampler MUST be conducted in each classified area [e.g., ISO Class 5 PEC and ISO Class 7 and 8 room(s)] during dynamic operating conditions. For entities compounding Category 1 and Category 2 CSPs, this MUST be completed at least every 6 months. For entities compounding any Category 3 CSPs, this MUST be completed within 30 days prior to the commencement of any Category 3 compounding and at least monthly thereafter regardless of the frequency of compounding Category 3 CSPs. Air sampling sites MUST be selected in all classified areas.

6.2.2 Viable air sampling procedures:

When conducting sampling of the PEC, care SHOULD be taken to avoid disturbing unidirectional airflow. See Box 5 for active air sampling procedures. A general microbiological growth media that supports the growth of bacteria and fungi MUST be used (e.g., TSA). COAs from the manufacturer MUST verify that the sampling media devices meet the expected growth promotion, pH, and sterilization requirements. Samples MUST be incubated in an incubator at the temperatures listed in Box 5. The incubator temperature MUST be monitored during incubation, either manually or by a continuous recording device, and the results MUST be reviewed and documented as described in the facility's SOPs. The incubator MUST be placed in a location outside of the sterile compounding area.

Box 5. Active Air Sampling Procedures for Viable Airborne Monitoring

1. Follow the manufacturer's instructions for operation of the impaction air sampler, including placement of media device(s).

2. Using the impaction air sampler, test at least 1 cubic meter or 1000 L of air from each location sampled.

3. At the end of each sampling period, retrieve the media device and cover it. Handle and store media devices to avoid contamination and prevent condensate from dropping onto the agar during incubation and affecting the accuracy of the cfu reading (e.g., invert plates).

4. Incubate the media device at 30°–35° for no less than 48 h. Examine for growth. Record the total number of discrete colonies of microorganisms on each media device as cfu per cubic meter of air on an environmental sampling form based on sample type (i.e., viable air), sample location, and sample date.

5. Then incubate the media device at 20°–25° for no less than 5 additional days. Examine for growth. Record the total number of discrete colonies of microorganisms on each media device as cfu per cubic meter of air on an environmental sampling form based on sample type (i.e., viable air), sample location, and sample date.

6. Alternatively, to shorten the overall incubation period, two sampling media devices MAY be collected for each sample location and incubated concurrently.

1. Both media devices could be TSA or one media device could be TSA and the other fungal media (e.g., malt extract agar [MEA] or Sabouraud dextrose agar [SDA]).

2. Incubate each media device in a separate incubator. Incubate one media device at 30°–35° for no less than 48 h, and incubate the other media device at 20°–25° for no less than 5 days. If fungal media are used as one of the samples, incubate the fungal media sample at 20°–25° for no less than 5 days.

3. Count the total number of discrete colonies of microorganisms on each media device, and record these results as cfu per cubic meter of air.

4. Record the results of the sampling on an environmental sampling form based on sample type (i.e., viable air), and include the sample location and sample date.

6.2.3 Viable air sampling data evaluation and action levels:

Evaluate cfu counts against the action levels in Table 7 and examine counts in relation to previous data to identify adverse results or trends. If two sampling media devices are collected at a single location, all recovered growth on each MUST be documented and action levels applied to each sampling media device separately. If levels measured during the viable air monitoring program exceed the levels in Table 7 for the ISO classification levels of the area sampled, the cause MUST be investigated and corrective action MUST be taken. Data collected in response to corrective actions MUST be reviewed to confirm that the actions taken have been effective. The corrective action plan MUST be dependent on the cfu count and the microorganism recovered. Some examples of corrective action include process or facility

improvements, personnel training, cleaning and disinfecting, or HEPA filter repair and/or replacement. The extent of the investigation SHOULD be consistent with the deviation and SHOULD include an evaluation of trends. The corrective action plan MUST be documented and SHOULD include resampling of failed areas to confirm corrective action was successful. If levels measured during viable air sampling exceed the levels in Table 7, an attempt MUST be made to identify any microorganisms recovered to the genus level (see Microbial Characterization, Identification, and Strain Typing ⟨1113⟩) with the assistance of a microbiologist.

Table 7. Action Levels for Viable Airborne Particle Air Sampling

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

6.3 Monitoring Surfaces for Viable Particles

Surface sampling is an important tool used to assist in maintenance of a suitably controlled environment for compounding CSPs. Surface sampling is useful for evaluating facility cleaning and material handling procedures, work surface cleaning and disinfecting procedures, and personnel competency in work practices such as cleaning and disinfecting. All sampling sites and procedures MUST be described in the facility's SOPs.

6.3.1 Surface sampling—timing and locations:

Each classified area, including each room and the interior of each ISO Class 5 PEC and pass-through chambers connecting to classified areas, MUST be sampled for microbial contamination using a risk-based approach. Samples SHOULD be taken from the following classified areas:

- Equipment contained within the PEC
- Staging or work area(s) near the PEC
- Frequently touched surfaces

Surface sampling in the DCA MUST also be conducted in conjunction with media-fill testing to assess aseptic manipulation competency (see 2.3 Competency Testing in Aseptic Manipulation)

When conducted, surface sampling SHOULD be performed at the end of a compounding activity or shift but before the area has been cleaned and disinfected.

For entities compounding Category 1 and Category 2 CSPs, surface sampling of all classified areas, and pass-through chambers connecting to classified areas, MUST be conducted at least monthly (see Microbiological Control and Monitoring of Aseptic Processing Environments ⟨1116⟩).

For entities compounding any Category 3 CSPs, surface sampling of all classified areas, and pass-through chambers connecting to classified areas, MUST be completed prior to assigning a BUD longer than the limits established in Table 13, and at least weekly (see ⟨1116⟩) on a regularly scheduled basis regardless of the frequency of compounding Category 3 CSPs. Additionally, surface sampling MUST be conducted within the PEC used to prepare Category 3 CSPs, at the end of each batch before cleaning and disinfection occurs, unless a self-enclosed robotic device is used. When a self-enclosed robotic device is used as the PEC to prepare Category 3 CSPs, surface sampling MUST be conducted at least once daily at the end of compounding operations, before cleaning and disinfection occurs.

6.3.2 Surface sampling procedures:

See Box 6 for the procedures for surface sampling on flat surfaces. Surface sampling media devices (e.g., plates, paddles, or slides) containing microbial growth media MUST be used for sampling flat surfaces. COAs from the manufacturer MUST verify that the sampling media devices meet the expected growth promotion, pH, and sterilization requirements. Surface sampling media devices MUST contain general microbial growth media (e.g., TSA) supplemented with neutralizing additives (e.g., lecithin and polysorbate 80) to neutralize the effects of any residual disinfecting agents. Surface sampling media devices MUST have a raised convex surface. Sterile swabs wetted with sterile water or a sterile neutralizing buffer MAY be used when sampling irregular surfaces and difficult-to-reach locations such as crevices, corners, and spaces between surfaces. After sampling, the sampled area MUST be thoroughly cleaned and disinfected (see 7. Cleaning, Disinfecting, and Applying Sporicidal Disinfectants and Sterile 70% IPA).

Samples MUST be incubated in an incubator at the temperatures listed in Box 6. The incubator temperature MUST be monitored during incubation, either manually or by a continuous recording device, and the results MUST be reviewed and documented. The incubator MUST be placed in a location outside of the sterile compounding area.

Box 6. Surface Sampling Procedures

1. Remove the cover from the surface sampling media device. Using a rolling motion, firmly press the media surface onto the surface to be sampled. The media device will leave a residue of growth media on the sample site. After sampling, clean and disinfect the sampled area to remove the residue from the surface.

2. Cover each media device. Handle and store media devices to avoid contamination and prevent condensate from dropping onto the agar during incubation and affecting the accuracy of the cfu reading (e.g., invert plates).

3. Incubate media device(s) at 30°–35° for no less than 48 h. Examine for growth. Record the total number of discrete colonies of microorganisms on each media device as cfu per media device on an environmental sampling form based on sample type (i.e., surface), sample location, and sample date.

4. Incubate the media device at 20°–25° for no less than 5 additional days. Examine for growth. Record the total number of discrete colonies of microorganisms on each media device (cfu per sample) on the environmental sampling record based on sample type (i.e., surface), sample location, and sample date.

5. Alternatively, to shorten the overall incubation period, two surface sampling media devices MAY be collected for each sample location and incubated concurrently.

1. Both media devices could be TSA or one media device could be TSA and the other fungal media (e.g., malt extract agar [MEA] or Sabouraud dextrose agar [SDA]). Media MUST be supplemented with neutralizing additives (e.g., lecithin and polysorbate 80).

2. Incubate each media device in a separate incubator. Incubate one media device at 30°–35° for no less than 48 h, and incubate the other media device at 20°–25° for no less than 5 days. If fungal media are used, incubate the fungal media device at 20°–25° for no less than 5 days.

3. Count the total number of discrete colonies of microorganisms on each media device, and record these results as cfu per media device.

4. Record the results of the sampling on an environmental sampling form based on sample type (i.e., surface), and include the sample location and sample date.

6.3.3 Surface sampling data evaluation and action levels:

Evaluate cfu counts against the action levels in Table 8, and examine counts in relation to previous data to identify adverse results or trends. If two sampling media devices are collected at a single location, all recovered growth on each MUST be documented and action levels applied to each sampling media device separately. If levels measured during surface sampling exceed the levels in Table 8 for the ISO classification levels of the area sampled, the cause MUST be investigated and corrective action MUST be taken. Data collected in response to corrective actions MUST be reviewed to confirm that the actions taken have been effective. The corrective action plan MUST be dependent on the cfu count and the microorganism recovered. Some examples of corrective action include process or facility improvements, personnel training, cleaning and disinfecting, or HEPA filter replacement and/or repair. The extent of the investigation SHOULD be consistent with the deviation and SHOULD include an evaluation of trends. The corrective action plan MUST be documented. If levels measured during surface sampling exceed the levels in Table 8, an attempt MUST be made to identify any microorganism recovered to the genus level (see ⟨1113⟩) with the assistance of a microbiologist.

Table 8. Action Levels for Surface Sampling

ISO Class	Surface Sampling Action Levels (cfu/media device)
5	>3

7 >5

8 >50

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7. CLEANING, DISINFECTING, AND APPLYING SPORICIDAL DISINFECTANTS AND STERILE 70% IPA

Surfaces in classified areas used to prepare Category 1, Category 2, and Category 3 CSPs MUST be:

- Cleaned
- Disinfected
- Sporicidal disinfectants applied

according to the frequencies described in Table 10 for each CSP category.

Additionally, in a PEC, sterile 70% IPA MUST be applied after cleaning and disinfecting, or after the application of a one-step disinfectant cleaner or sporicidal disinfectant, to remove any residue. Sterile 70% IPA MUST also be applied immediately before initiating compounding. During the compounding process sterile 70% IPA MUST be applied to the horizontal work surface, including any removable work trays, of the PEC at least every 30 min if the compounding process takes 30 min or less. If the compounding process takes more than 30 min, compounding MUST not be disrupted, and the work surface of the PEC MUST be disinfected immediately after compounding.

These activities are important because surfaces in classified areas and SCAs are a potential source of microbial contamination of CSPs.

The process of cleaning involves removing organic and inorganic materials from surfaces, usually with a manual or mechanical process and a cleaning agent. The process of disinfecting involves destruction of microorganisms, usually with a chemical agent. The process of applying a sporicidal disinfectant involves the destruction of bacterial and fungal spores. See Table 9 for a summary of the purposes of the cleaning, disinfectant, and sporicidal disinfectants.

Table 9. Purpose of Cleaning, Disinfecting, and Sporicidal Disinfectants

Type of Agent Purpose

Cleaning An agent, usually containing a surfactant, used for the removal of substances (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.

Disinfectant A chemical or physical agent used on inanimate surfaces and objects to destroy fungi, viruses, and bacteria.

Sporicidal A chemical or physical agent that destroys bacterial and fungal spores when used at a sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.

Surfaces MUST be cleaned prior to being disinfected with an EPA-registered disinfectant (or equivalent for entities outside the US) unless an EPA-registered (or equivalent for entities outside the US) one-step disinfectant cleaner is used to accomplish both the cleaning and disinfection in one step. A sporicidal disinfectant MUST also be applied. Some EPA-registered (or equivalent) one-step disinfectant cleaners MAY have sporicidal properties. Cleaning and disinfecting surfaces and applying a sporicidal disinfectant MUST occur at the minimum frequencies specified in Table 10.

All cleaning and disinfecting activities MUST be performed by trained and appropriately garbed personnel using facility-approved agents and procedures, which MUST be described in written SOPs. Personnel MUST be trained if there are any changes in the cleaning and disinfecting procedures. Cleaning MUST be performed in the direction of clean to dirty areas. The same floor mop MAY be used in both the buffer and anteroom, but only in that order. Mops used in areas where HDs are compounded MUST be dedicated for use only in those areas.

The frequency, method(s), and location(s) of cleaning, disinfecting, and applying sporicidal disinfectants MUST be established in written SOPs, in accordance with the manufacturer's instructions and MUST be followed by all cleaning personnel. The manufacturer's directions or published data for the minimum contact time MUST be followed for each of the cleaning, disinfecting, and sporicidal disinfectants used. When sterile 70% IPA is used, it MUST be allowed to dry. All cleaning, disinfecting, and application of sporicidal disinfectants MUST be documented according to the facility's SOPs.

Table 10. Minimum Frequency for Cleaning and Disinfecting Surfaces and Applying Sporicidal Disinfectants in Classified Areas and in the SCAa

Site Cleaning Disinfectingb

Applying

Sporicidal Disinfectant

PEC(s) and equipment inside the PEC(s) • Equipment and all interior surfaces of the PEC daily on days when compounding occurs and when surface contamination is known or suspected • Equipment and all interior surfaces of the PEC daily on days when compounding occurs and when surface contamination is known or suspected • Monthly for entities compounding Category 1 and/or Category 2 CSPs

• Weekly for entities compounding Category 3 CSPs

Removable work tray of the PEC, when applicable • Work surface of the tray daily on days when compounding occurs

• All surfaces and the area underneath the work tray monthly • Work surface of the tray on days when compounding occurs

• All surfaces and the area underneath the work tray monthly • Work surfaces of the tray monthly

• All surfaces and the area underneath the work tray monthly

Pass-through chambers • Daily on days when compounding occurs • Daily on days when compounding occurs • Monthly for entities compounding Category 1 and/or Category 2 CSPs

• Weekly for entities compounding Category 3 CSPs

Work surface(s) outside the PEC • Daily on days when compounding occurs • Daily on days when compounding occurs

Floor(s) • Daily on days when compounding occurs • Daily on days when compounding occurs

Wall(s), door(s), and door frame(s) • Monthly • Monthly • Monthly

Ceiling(s)c

Storage shelving and bin(s)

Equipment outside the PEC(s)

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a Cleaning of sinks is described in 4.4 Water Sources.

b Many disinfectants registered by the EPA are one-step cleaning and disinfecting agents, which means that the disinfectant has been formulated to be effective in the presence of light-to-moderate soiling without a separate cleaning step.

c Ceilings of the SCA are required to be cleaned, disinfected, and applied with sporicidal disinfectant only when visibly soiled and when surface contamination is known or suspected.

7.1 Agents and Supplies for Cleaning, Disinfecting, and Applying Sporicidal Disinfectants

7.1.1 Agents:

Cleaning and disinfecting agents MUST be selected and used with careful consideration of compatibilities, effectiveness, and user safety. Considerations when selecting and using disinfectants include their antimicrobial activity, inactivation by organic matter, residue, shelf life, preparation requirements of the agent, and suitability for surfaces being disinfected. After the disinfectant or sporicidal disinfectant is applied to the surface, the agent MUST be allowed to dwell for the minimum contact time specified by the manufacturer.

Cleaning, disinfecting and sporicidal agents used within the PEC MUST be sterile. When diluting concentrated cleaning and disinfecting agents for use in the PEC, sterile water MUST be used. In classified areas outside of the PEC, sterile cleaning and disinfecting agents SHOULD be used. When diluting concentrated cleaning and disinfecting agents for use outside of the PEC, sterile water SHOULD be used.

7.1.2 Supplies:

All cleaning and disinfecting supplies (e.g., wipers, sponges, pads, and mop heads) with the exception of tool handles and holders MUST be low lint. In addition, cleaning and disinfecting supplies used in the PEC MUST be sterile with the exception of tool handles and holders, which MUST be cleaned and disinfected prior to use in a PEC.

Wipers, sponges, pads, and mop heads SHOULD be disposable. If disposable cleaning supplies are used, they MUST be discarded after each cleaning activity. Reusable cleaning tools MUST be made of cleanable materials (e.g., handles SHOULD not be made of wood or any other porous material) and MUST be cleaned and disinfected before and after each use. Reusable cleaning tools MUST be dedicated for use in the classified areas or SCA and MUST not be removed from these areas except for disposal. They MUST be discarded as determined based on the condition of the tools. Cleaning supplies used in the classified areas and SCAs MUST be disposed of in a manner that minimizes the potential for dispersing contaminants into the air (e.g., with minimal agitation, away from work surfaces).

Once opened, sterile cleaning and disinfecting agents and supplies (e.g., closed containers of sterile wipers) and sterile 70% IPA MAY be reused for a time period specified as by the manufacturer and/or described in the facility written SOPs.

7.2 Procedures for Cleaning, Disinfecting, and Applying Sporicidal Disinfectants and Sterile 70% IPA in the PEC

Clean, disinfect, and apply a sporicidal disinfectant to equipment and all interior surfaces in the PEC at the minimum frequencies specified in Table 10. See Box 7 and Box 8 for procedures for cleaning, disinfecting, and applying a sporicidal disinfectant in the PEC.

Box 7. Procedures for Cleaning and Disinfecting the PEC

- If necessary, remove visible particles, debris, or residue with an appropriate solution (e.g., Sterile Water for Injection or Sterile Water for Irrigation) using sterile, low-lint wipers.
- Using a sterile low-lint wiper, apply a sterile cleaning agent followed by a sterile EPA-registered disinfectant or apply a sterile EPA-registered (or equivalent for entities outside the US) one-step disinfectant cleaner to equipment and all interior surfaces of the PEC.
- Ensure the contact time specified by the manufacturer is achieved.
- Using a sterile low-lint wiper, apply sterile 70% IPA to equipment and all interior surfaces in the PEC.
- Allow the surface to dry completely before beginning compounding.

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Box 8. Procedures for Applying a Sporicidal Disinfectant in the PEC

- If necessary, remove visible particles, debris, or residue with an appropriate solution (e.g., Sterile Water for Injection or Sterile Water for Irrigation) using sterile, low-lint wipers.
- After cleaning and disinfecting (see Box 7), apply the sterile sporicidal disinfectant using a sterile low-lint wiper to all surfaces and the area underneath the work tray; if the sporicidal disinfectant is a

sterile EPA-registered (or equivalent for entities outside the US) one-step disinfectant sporicidal cleaner, separate cleaning and disinfecting steps are not required.

- Ensure the contact time specified by the manufacturer is achieved.
- Using a sterile low-lint wiper, apply sterile 70% IPA to all interior surfaces, including underneath the work tray.
- Allow the surface to dry completely before beginning compounding.

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8. INTRODUCING ITEMS INTO THE SEC AND PEC

8.1 Introducing Items into the SEC

Before any item is introduced into the clean side of anteroom(s), placed into pass-through chamber(s), or brought into the SCA, providing that packaging integrity will not be compromised, it MUST be wiped with a sporicidal disinfectant, EPA-registered disinfectant, or sterile 70% IPA using low-lint wipers by personnel wearing gloves. If an EPA-registered disinfectant or sporicidal disinfectant is used, the agent MUST be allowed to dwell for the minimum contact time specified by the manufacturer. If sterile 70% IPA is used, it MUST be allowed to dry. The wiping procedure SHOULD not compromise the packaging integrity or render the product label unreadable.

8.2 Introducing Items into the PEC

Just before any item is introduced into the PEC, it MUST be wiped with sterile 70% IPA using sterile low-lint wipers and allowed to dry before use. When sterile items are received in sealed containers designed to keep them sterile until opening, the sterile items MAY be removed from the covering as the supplies are introduced into the ISO Class 5 PEC without the need to wipe the individual sterile supply items with sterile 70% IPA. The wiping procedure MUST not render the product label unreadable.

8.3 Use of Sterile 70% IPA on Critical Sites within the PEC

Critical sites (e.g., vial stoppers, ampule necks, and intravenous bag septums) MUST be wiped with sterile 70% IPA in the PEC to provide both chemical and mechanical actions to remove contaminants. The sterile 70% IPA MUST be allowed to dry before personnel enter or puncture stoppers and septums or break the necks of ampules.

9. EQUIPMENT, SUPPLIES, AND COMPONENTS

9.1 Equipment

PECs are described in 4.2.3 Types of PECs and placement. Other equipment used in compounding CSPs (e.g., automated compounding devices [ACDs] and balances) SHOULD be of suitable composition such that the surfaces that contact components are not reactive or sorptive. Equipment that MUST be brought into classified areas MUST be wiped with a sporicidal disinfectant, EPA-registered disinfectant, or sterile 70% IPA using low-lint wipers.

Equipment MUST be placed in a manner that facilitates sterile compounding operations. The equipment MUST be capable of operating properly and within required performance parameters. Compounding personnel MUST follow established SOPs for the calibration, maintenance, cleaning, and use of the equipment based on the manufacturer's recommendations. Personnel MUST maintain records from equipment calibration, verification, and maintenance in accordance with the requirements in 20. Documentation.

ACDs and other similar equipment are designed to assist in the compounding of preparations by delivering specific volumes of solution(s) automatically under computerized control.

Before using ACDs or other similar equipment, compounding personnel MUST conduct an accuracy assessment before the first use and again each day the equipment is used to compound CSPs. The precision of the equipment can be monitored based on an assessment of day-to-day variations in its accuracy measures. Compounding personnel MUST maintain a daily record of the accuracy measurements on the days the equipment is in use. Corrective actions MUST be implemented if accuracy measurements are outside the manufacturer's specification.

Weighing, measuring, or otherwise manipulating components that could generate airborne chemical particles (e.g., active pharmaceutical ingredients [APIs], added substances, conventionally manufactured products) MUST be evaluated to determine if these activities MUST be performed in a PEC or other closed system processing device (e.g., single use containment glove bag) to reduce the potential exposure to personnel or contamination of the facility or CSPs (See 4.2.6 Facilities preparing Category 2 or Category 3 CSPs from nonsterile starting component(s)). The process evaluation MUST be carried out in accordance with the facility's SOPs and the assessment MUST be documented.

9.2 Supplies

Supplies (e.g., beakers, utensils, needles, syringes, filters, and tubing sets) SHOULD be of suitable composition such that the surfaces that contact components are not reactive or sorptive. Supplies in direct contact with the CSP MUST be sterile and depyrogenated.

9.3 Components

Compounding personnel MUST follow the facility's SOPs, which MUST address the selection, receipt, evaluation, handling, storage, and documentation of all CSP components, including all ingredients and container closures.

9.3.1 Component selection:

Conventionally manufactured sterile products SHOULD be used when available and appropriate for the intended CSP.

When APIs are used:

- MUST comply with the criteria in the USP–NF monograph, if one exists
- MUST have a COA that includes the specifications (e.g., compendial requirements for quality) and that test results for the component show that the API meets expected quality

- In the United States, MUST be manufactured by an FDA-registered facility
- Outside of the United States, MUST comply with the laws and regulations of the applicable regulatory jurisdiction

For all components other than APIs:

- MUST comply with the criteria in the USP–NF monograph, if one exists
- MUST be accompanied by documentation (e.g., COA, labeling) that includes the specifications and test results and shows that the component meets the specifications
- In the US, SHOULD be manufactured by an FDA-registered facility

o If a component cannot be obtained from an FDA-registered facility, the designated person(s) MUST select an acceptable and reliable source (see Good Distribution Practices for Bulk Pharmaceutical Excipients ⟨1197⟩). The compounding facility MUST establish the identity, strength, purity, and quality of the ingredients obtained from that supplier by reasonable means. Reasonable means MAY include but are not limited to visual inspections, evaluation of a COA supplied by the manufacturer, and/or verification by analytically testing a sample to determine conformance with the COA or other specifications.

- Outside of the US, MUST comply with the laws and regulations of the applicable regulatory jurisdiction

When CSPs are used as components, see 16. Use of CSPs as Components. All APIs and other components used MUST be evaluated for suitability for use in sterile drug preparation. Components labeled with “not for pharmaceutical use”, “not for injectable use”, “not for human use” or an equivalent statement MUST not be used to compound for these purposes.

Each lot of commercially available sterile, depyrogenated containers and container closure systems MUST be accompanied by a COA or other documentation showing conformance with established specifications (i.e., sterility and depyrogenation requirements). If sterilization and depyrogenation of supplies or container closure systems are performed on site, the efficacy of each process MUST be established and documented (see Sterilization of Compendial Articles ⟨1229⟩).

9.3.2 Component receipt:

Upon receipt of each lot of a component, the external packaging MUST be examined for evidence of deterioration and other aspects of unacceptable quality. Facility personnel MUST verify the labeling and condition of the component [e.g., whether the outer packaging is damaged and whether temperature-sensing indicators show that the component has been exposed to excessive temperature(s)].

Any component found to be of unacceptable quality MUST be promptly rejected, clearly labeled as rejected, and segregated from active stock to prevent use before appropriate disposal. Any other lots of that component from that vendor MUST be examined to determine whether other lots have the same defect.

The date of receipt by the compounding facility MUST be clearly marked on each API or added substance package that lacks a vendor expiration date. Packages of components (i.e., API and added substances) that lack a vendor's expiration date MUST be assigned a conservative expiration date, not to exceed 1 year after receipt by the compounding facility.

9.3.3 Component evaluation before use:

Compounding personnel MUST ascertain before use that components for CSPs are of the correct identity, appropriate quality, within expiry date and have been stored under appropriate conditions. The following information SHOULD be used to make this determination: prescription or medication order, compounding record (CR), master formulation record (if used), vendor label(s), COA(s) of API(s) and other component(s), product labeling of any conventionally manufactured sterile products, labeling of CSP(s), and documentation of the compounding facility's storage conditions and practices.

All components MUST be reinspected before use. All packages MUST be reinspected to detect container breaks, looseness of the cap or closure, and deviation from the expected appearance, aroma, and/or texture of the contents that might have occurred during storage. Sterile container closures MUST be visually reinspected to ensure that they are free from defects that could compromise sterility and that they are otherwise suitable for their intended use.

Any component found to be of unacceptable quality MUST be promptly rejected, clearly labeled as rejected, and segregated from active stock to prevent use before appropriate disposal. Any other lots of that component from that vendor MUST be examined to determine whether other lots have the same defect.

9.3.4 Component handling and storage:

All components MUST be handled and stored in a manner that prevents contamination, mix-ups, and deterioration.

Components MUST be stored in closed containers under temperature, humidity, and lighting conditions consistent with those indicated in official monographs or specified by the suppliers and/or manufacturers.

Personnel MUST monitor temperature in the area(s) where components are stored either manually at least once daily on days that the facility is open or by a continuous temperature recording device to determine whether the temperature remains within the appropriate range. The results of the temperature readings MUST be documented on a temperature log or stored in the continuous recording device and MUST be retrievable. All monitoring equipment MUST be calibrated or verified for accuracy as recommended by the manufacturer or every 12 months if not specified by the manufacturer.

10. STERILIZATION AND DEPYROGENATION

When selecting the sterilization method for CSPs prepared from one or more nonsterile starting components or using nonsterile supplies or devices, personnel MUST take into consideration the nature of the component(s), their physical and chemical properties, and the intended container closure system.

The sterilization method used MUST sterilize the CSP without degrading its physical and chemical stability (e.g., affecting its strength, purity, or quality) or the packaging integrity. (See also the ⟨1229⟩ series of chapters.)

The following MUST be considered when selecting an appropriate sterilization method:

- Terminal sterilization (e.g., steam, dry heat, or irradiation) is the preferred method unless the specific CSP or container closure system cannot tolerate terminal sterilization
- Steam sterilization is not an option if moisture, pressure, or the temperatures used would degrade the CSP or if there is insufficient moisture to sterilize the CSP within the final, sealed, container closure system
- Filtration MAY not be an option for some compounded preparations, for example preparations with suspended drug particles or emulsions with a significant droplet size.

CSPs that are terminally sterilized (e.g., steam, dry heat, or irradiation) MUST use a process intended to achieve a probability of a nonsterile unit (PNSU) of 10−6. [NOTE—This is also called the sterility assurance level (SAL).] A PNSU of 10−6 is equivalent to a probability that 1 unit in a million is nonsterile. A PNSU value cannot be applied to CSPs that are aseptically filled into a sterile container following sterilization by filtration because sterilization by filtration is not terminal sterilization.

Injectable compounded preparations that contain nonsterile components or that come into contact with nonsterile devices (e.g., containers, tubing) during any phase of the compounding procedure MUST be sterilized within 6 h after completing the preparation to minimize the generation of bacterial endotoxins in CSPs.

A description of the terminal sterilization and depyrogenation process, including the temperature, pressure (if applicable), duration, permissible load conditions for each cycle, and the use of biological indicators and endotoxin challenge vials (ECVs) MUST be included in the facility's SOPs.

SOPs MUST include training and competency of personnel on all sterilization methods and equipment used by the facility. In addition, the SOPs MUST include a schedule and method for establishing and verifying the effectiveness of the terminal sterilization and depyrogenation methods selected, as well as the methods for maintaining and cleaning the sterilizing and depyrogenation equipment.

10.1 Depyrogenation

See Dry Heat Depyrogenation ⟨1228.1⟩. Dry heat depyrogenation MUST be used to render glassware, metal, and other thermostable containers and components pyrogen free. Depyrogenation processes typically operate at a range of temperatures, from approximately 170°–400°, depending on the exposure time (e.g., a cycle might hold the items at 250° for 30 min to achieve sterility and depyrogenation). The duration of the exposure period MUST include sufficient time for the items to reach the depyrogenation temperature. The items MUST remain at the depyrogenation temperature for the duration of the depyrogenation period.

The effectiveness of the dry heat depyrogenation cycle MUST be established initially and verified annually using ECVs to demonstrate that the cycle is capable of achieving a ≥3-log reduction in

endotoxins (see Bacterial Endotoxins Test ⟨85⟩). The effectiveness of the depyrogenation cycle MUST be re-established if there are changes to the depyrogenation cycle described in SOPs (e.g., changes in load conditions, duration, or temperature). This verification MUST be documented.

Items that are not thermostable MUST be depyrogenated by multiple rinses with sterile, nonpyrogenic water (e.g., Sterile Water for Injection or Sterile Water for Irrigation) and then thoroughly drained or dried immediately before use in compounding See Depyrogenation by Rinsing ⟨1228.4⟩.

10.2 Sterilization by Filtration

See Sterilizing Filtration of Liquids ⟨1229.4⟩. Sterilizing filters MUST be sterile, depyrogenated, have a nominal pore size of 0.22 µm or smaller, and be appropriate for pharmaceutical use. Sterilizing filters with labeling that states “for laboratory use only” or a similar statement MUST not be used for compounding CSPs. Sterilizing filters MUST be certified by the manufacturer to retain at least 107 microorganisms of a strain of Brevundimonas diminuta per square centimeter of upstream filter surface area under conditions similar to those in which the CSPs will be filtered (i.e., pressure, flow rate, and volume filtered).

The designated person(s) MUST ensure—from available published information, from supplier documentation, or through direct challenge (e.g., filtering the CSP)—that the filters 1) are chemically and physically compatible with all ingredients in the CSP (e.g., water-miscible alcohols MAY damage filter integrity); 2) are chemically stable at the pressure and temperature conditions that will be used; and 3) have enough capacity to filter the required volumes. The filter dimensions and the CSP to be sterilized by filtration SHOULD permit the sterilization process to be completed without the need for replacement of the filter during the process. Filter units used to sterilize CSPs MUST be subjected to the manufacturers’ recommended integrity testing, such as a post-use bubble point test. If multiple filters are required for the compounding process, each of the filters MUST pass a filter-integrity test.

When CSPs are known to contain excessive particulate matter, a prefiltration step MUST be performed using a filter of larger nominal pore size (e.g., 1.2 µm) or a separate filter of larger nominal pore size SHOULD be placed upstream of (i.e., prior to) the sterilizing filter to remove gross particulate contaminants before the CSP is passed through the sterilizing-grade filter. Excessive particulate matter requiring a prefiltration step could potentially be a signal of an inappropriate formulation, and therefore the formulation and the process SHOULD be assessed and modified if necessary. CSPs that were prepared using a filter that failed integrity tests MUST be discarded or, after investigating the cause of the failure and selection of an appropriate filter, refiltered for sterilization not more than one additional time.

10.3 Sterilization by Steam Heat

Temperatures used to achieve sterilization by steam heat are lower than those used to achieve depyrogenation. The process of thermal sterilization using saturated steam under pressure (i.e., autoclaving) is the preferred method for terminal sterilization of aqueous CSPs in their final, sealed container closure system (see Steam Sterilization by Direct Contact ⟨1229.1⟩). Steam sterilization is not an option if moisture, pressure, or the temperatures used would degrade the CSP.

To achieve sterility when steam sterilization is used, all materials MUST be directly exposed to steam under adequate pressure for the length of time necessary, as determined by use of appropriate

biological indicators, to render the items sterile (e.g., 20−60 min at 121° saturated steam under a pressure of 15 psi, depending on the volume or size of the CSP being sterilized). The duration of the exposure period MUST include sufficient time for the entire contents of the CSP and other items to reach the sterilizing temperature. The CSP and other items MUST remain at the sterilizing temperature for the duration of the sterilization period.

CSPs MUST be placed in the autoclave to allow steam to reach the CSPs without entrapment of air. Flat, stainless-steel trays with low sides or ventilated bottoms will permit steam contact. When preparing items that MUST be wrapped for steam sterilization, wrap them in low-lint protective fabric or paper or seal in envelopes that will permit steam penetration and are designed to minimize the risk of post-sterilization microbial contamination. For CSPs, immediately before filling containers that will be steam sterilized, solutions MUST be passed through a filter with a nominal pore size of not larger than 1.2 µm for removal of particulate matter.

Sealed containers MUST be able to generate steam internally. Stoppered and crimped empty vials MUST contain a small amount of sterile water to generate steam.

The effectiveness of steam sterilization MUST be verified and documented with each sterilization run or load by using appropriate biological indicators, such as spores of Geobacillus stearothermophilus (ATCC 12980, ATCC 7953, or equivalent; see Biological Indicators for Sterilization ⟨1229.5⟩), and other confirmation methods such as physicochemical indicators (see Physicochemical Integrators and Indicators for Sterilization ⟨1229.9⟩).

The steam supplied MUST be generated using water per the manufacturer's recommendation. A calibrated data recorder or chart MUST be used to monitor each cycle and to examine for cycle irregularities (e.g., deviations in temperature or pressure). The date, run, and load numbers of the steam sterilizer used to sterilize a CSP MUST be documented in the CR.

10.4 Sterilization by Dry Heat

Dry heat MAY be used for those items that cannot be sterilized by steam or other means when the moisture would damage the material or the wrapping material is impermeable (see Dry Heat Sterilization ⟨1229.8⟩). Sterilization by dry heat requires higher temperatures and longer exposure times than sterilization by steam. The duration of the exposure period MUST include sufficient time for the entire contents of CSPs and other items to reach the sterilizing temperature. The CSP and other items MUST remain at the sterilizing temperature for the duration of the sterilization period. Immediately before filling ampules and vials that will be sterilized by dry heat, CSP solutions MUST be passed through a filter with a nominal pore size of not larger than 1.2 µm for removal of particulate matter.

Dry heat sterilization is usually performed in an oven designed for sterilization at 160° or higher. If lower temperatures are used, they MUST be shown to achieve effective sterilization (see ⟨1229.8⟩, Validation of Dry Heat Sterilization, Biological Indicators).

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

The effectiveness of the dry heat sterilization method MUST be verified and documented with each sterilization run or load using appropriate biological indicators such as spores of Bacillus atrophaeus (ATCC 9372; see ⟨1229.5⟩) and other confirmation methods (e.g., temperature-sensing devices). The date, run, and load numbers of the dry heat oven used to sterilize a CSP MUST be documented in the CR.

11. MASTER FORMULATION AND COMPOUNDING RECORDS

11.1 Creating Master Formulation Records

A master formulation record (MFR) is a detailed record of procedures that describes how the CSP is to be prepared. An MFR MUST be created for all CSPs prepared from nonsterile ingredient(s) or CSPs prepared for more than one patient. Any changes or alterations to the MFR MUST be approved and documented according to the facility's SOPs. Box 9 lists the information that MUST be included in an MFR.

Box 9. Master Formulation Records

An MFR MUST include at least the following information:

- Name, strength or activity, and dosage form of the CSP
- Identities and amounts of all ingredients; if applicable, relevant characteristics of components (e.g., particle size, salt form, purity grade, solubility)
- Type and size of container closure system(s)
- Complete instructions for preparing the CSP, including equipment, supplies, a description of the compounding steps, and any special precautions
- Physical description of the final CSP
- BUD and storage requirements
- Reference source to support the stability of the CSP
- Quality control (QC) procedures (e.g., pH testing, filter integrity testing)
- Other information as needed to describe the compounding process and ensure repeatability (e.g., adjusting pH and tonicity; sterilization method, such as steam, dry heat, irradiation, or filter)

11.2 Creating Compounding Records

A CR documents the compounding of each CSP. A CR MUST be created for all Category 1, Category 2, and Category 3 CSPs. A CR MUST also be created for immediate-use CSPs prepared for more than one patient. The CR MUST be created to document the compounding process. A prescription or medication order or label MAY serve as the CR. If an ACD, workflow management system, or other similar equipment is used, the required information in the CR MAY be stored electronically as long as it is

retrievable and contains the required information (see Box 10). An MFR can serve as the basis for preparing the CR. For example, a copy of the MFR can be made that contains spaces for recording the information needed to complete the CR. Box 10 lists the information that MUST be included in a CR.

Box 10. Compounding Records

CRs MUST include at least the following information:

- Name, strength or activity, and dosage form of the CSP
- Date and time of preparation of the CSP
- Assigned internal identification number (e.g., prescription, order, or lot number)
- A method to identify the individuals involved in the compounding process and individuals verifying the final CSP
- Name of each component
- Vendor, lot number, and expiration date for each component for CSPs prepared for more than one patient and for CSPs prepared from nonsterile ingredient(s)
- Weight or volume of each component
- Strength or activity of each component
- Total quantity compounded
- Final yield (e.g., quantity, containers, number of units)
- Assigned BUD and storage requirements
- Results of QC procedures (e.g., visual inspection, filter integrity testing, pH testing)

If applicable, the CR MUST also include:

- MFR reference for the CSP
- Calculations made to determine and verify quantities and/or concentrations of components

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12. RELEASE INSPECTIONS AND TESTING

All release testing procedures (e.g., visual inspections and testing) MUST be included in the facility's documentation (see 11. Master Formulation and Compounding Records and 17. SOPs). Any out-of-specification results MUST be investigated, and a corrective action plan MUST be implemented and documented as part of the quality assurance (QA) and QC program (see 18. Quality Assurance and Quality Control).

12.1 Visual Inspection

At the completion of compounding, before release and dispensing, the CSP MUST be visually inspected to determine whether the physical appearance of the CSP is as expected (e.g., free of inappropriate visible particulates or other foreign matter, discoloration, or other defects). The CSP label MUST be visually inspected to confirm that the CSP and its labeling match the prescription or medication order. The inspection also MUST include a visual inspection of container closure integrity (e.g., checking for leakage, cracks in the container, or improper seals). Any CSP found to be of unacceptable quality (e.g., observed defects) MUST be promptly rejected, clearly labeled as rejected, and segregated from active stock to prevent use before appropriate disposal.

When a CSP will not be released or dispensed on the day of preparation, a visual inspection MUST be conducted immediately before it is released or dispensed to make sure that the CSP does not exhibit any defects such as precipitation, cloudiness, or leakage, which could develop during storage. Any CSP found to be of unacceptable quality (e.g., observed defects) MUST be promptly rejected, clearly labeled as rejected, and segregated from active stock to prevent use before appropriate disposal. Defects that indicate sterility or stability problems MUST be investigated to determine the cause according to the facility's SOPs (see 18. Quality Assurance and Quality Control).

12.2 Sterility Testing

Sterility testing is not required for Category 1 CSPs (see Table 12). For Category 2 CSPs assigned a BUD that requires sterility testing (see Table 13) and all Category 3 CSPs, the testing MUST be performed according to ⟨71⟩ or a validated alternative method (see ⟨1223⟩) that is noninferior to ⟨71⟩ testing.

If sterility testing is performed, the minimum quantity of each container to be tested for each media is specified in ⟨71⟩, Table 2, and the number of containers required to be tested in relation to the batch size is specified in ⟨71⟩, Table 3, except as described below. The maximum batch size for all CSPs requiring sterility testing MUST be limited to 250 final yield units.

If the number of CSPs to be compounded in a single batch is less than the number of CSPs needed for testing as specified in ⟨71⟩, Table 3, additional units MUST be compounded to perform sterility testing as follows:

- If 1–39 CSPs are compounded in a single batch, the sterility testing MUST be performed on a number of units equal to 10% of the number of CSPs prepared, rounded up to the next whole number. For example:
  - If 1 CSP is compounded, 10% of 1 rounded up to the next whole number would indicate that 1 additional CSP MUST be prepared for sterility testing
  - If 39 CSPs are compounded, 10% of 39 rounded up to the next whole number would indicate that 4 additional CSPs MUST be prepared for sterility testing
- If more than 40 CSPs are prepared in a single batch, the sample sizes specified in ⟨71⟩, Table 3 MUST be used.

If sterility testing is performed according to ⟨71⟩, the Method Suitability Test from that chapter MUST be performed to ensure that contamination can be recovered. If performing sterility testing according to ⟨71⟩, the Membrane Filtration method from that chapter is the method of choice when the CSP formulation permits. The preferred alternative is the ⟨71⟩, Test for Sterility of the Product to Be

Examined, Direct Inoculation of the Culture Medium method. If an alternative method is used for sterility testing, the method MUST be validated (see ⟨1223⟩) and demonstrated to be suitable for that CSP formulation.

Sterility tests resulting in failures MUST prompt an investigation into the possible causes and MUST include identification of the microorganism, as well as an evaluation of the sterility testing procedure, compounding facility, process, and/or personnel that MAY have contributed to the failure. The source(s) of the contamination, if identified, MUST be corrected, and the facility MUST determine whether the conditions causing the sterility failure affect other CSPs. The investigation and resulting corrective actions MUST be documented.

12.3 Bacterial Endotoxins Testing

Category 1 injectable CSPs do not require testing for bacterial endotoxins. Category 2 injectable CSPs compounded from one or more nonsterile component(s) and assigned a BUD that requires sterility testing (see Table 13) and Category 3 injectable CSPs compounded from one or more nonsterile component(s) MUST be tested to ensure that they do not contain excessive bacterial endotoxins (see ⟨85⟩). Category 2 injectable CSPs compounded from one or more nonsterile component(s) and assigned a BUD that does not require sterility testing SHOULD be tested for bacterial endotoxins. In the absence of a bacterial endotoxin limit in an official USP–NF monograph or other CSP formula source, the CSP MUST not exceed the endotoxin limit calculated as described in ⟨85⟩ for the appropriate route of administration for humans. CSPs for nonhuman species MUST not exceed the endotoxin limit calculated as described in ⟨85⟩ based on the largest recommended dose and weight (or average weight for more than a single animal) of the target animal species unless a different limit is scientifically supported. CSPs administered epidurally SHOULD have the same endotoxin limit as that of intrathecally administered CSPs. See also Guidelines on the Endotoxins Test ⟨1085⟩.

13. LABELING

Category 1, Category 2, and Category 3 CSPs MUST be labeled with appropriate, legible identifying information to prevent errors during storage, dispensing, and use. The term labeling designates all labels and other written, printed, or graphic matter on the immediate container or on or inside any package or wrapper in which it is enclosed, except any outer shipping container. The term label designates that part of the labeling that is on the immediate container. See Labeling ⟨7⟩.

All labeling MUST be in compliance with laws and regulations of the applicable regulatory jurisdiction.

The label on each immediate container of the CSP MUST, at a minimum, display prominently and legibly the following information:

- Assigned internal identification number (e.g., barcode, prescription, order, or lot number)
- Active ingredient(s) and their amount(s), activity(ies), or concentration(s)
- Storage conditions if other than controlled room temperature
- BUD
- Dosage form

- Total amount or volume if it is not obvious from the container
- If it is a single-dose container, a statement stating such when space permits
- If it is a multiple-dose container, a statement stating such

The labeling on the CSP MUST display the following information, as applicable:

- Route(s) of administration
- Special handling instructions
- Warning statements
- Compounding facility name and contact information if the CSP is to be sent outside of the facility or healthcare system in which it was compounded

The labeling on the CSP SHOULD indicate that the preparation is compounded.

Labeling procedures MUST be followed as described in the facility's SOPs to prevent labeling errors and CSP mix-ups. The label of the CSP MUST be verified to ensure that it conforms with the

1. Prescription or medication order;
2. MFR, if required (see 11.1 Creating Master Formulation Records); and
3. CR, if required (see 11.2 Creating Compounding Records)

14. ESTABLISHING BEYOND-USE DATES

14.1 Terminology

Each CSP label MUST state the date, or the hour and date, beyond which the preparation MUST not be used and MUST be discarded (i.e., the BUD). The BUD is determined from the date and time that preparation of the CSP is initiated. The BUD is not intended to limit the time during which the CSP is administered (e.g., infused).

BUDs and expiration dates are not the same. An expiration date identifies the time during which a conventionally manufactured product, API, or added substance can be expected to meet the requirements of a USP–NF monograph, if one exists, or maintain expected quality provided it is kept under the specified storage conditions. The expiration date limits the time during which a conventionally manufactured product, API, or added substance MAY be dispensed or used (see ⟨7⟩, Labels and Labeling for Products in Other Categories, Expiration Date and Beyond-Use Date). Expiration dates are assigned by manufacturers based on analytical and performance testing of the sterility, chemical and physical stability, and packaging integrity of the product. Expiration dates are specific to a particular formulation in its container and at stated exposure conditions of illumination and temperature. See Table 11 for a summary of terms.

Table 11. Summary of Terms

Term	Definition	Applicability

BUD Either the date, or hour and date, after which a CSP MUST not be used. The BUD is determined from the date and time that preparation of the CSP is initiated Applies to all CSPs

Expiration date The time during which a product can be expected to meet the requirements of the USP–NF monograph, if one exists, or maintain expected quality provided it is kept under the specified storage conditions. Applies to all conventionally manufactured products, APIs, and added substances

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14.2 Parameters to Consider in Establishing a BUD

BUDs for CSPs SHOULD be established conservatively to ensure that the drug maintains its required characteristics (i.e., stability and sterility) until its BUD.

When establishing a BUD for a CSP, compounders MUST consider parameters that MAY affect quality, including but not limited to:

- Chemical and physical stability properties of the drug and/or its formulation
- Materials of composition of the container closure system and compatibility of the container closure system with the final preparation (e.g., leachables, interactions, adsorption, and storage conditions)

The BUDs for CSPs are based primarily on factors that affect the achievement and maintenance of sterility, which include but are not limited to the following:

- Conditions of the environment in which the CSP is prepared
- Aseptic processing and sterilization method
- Starting components (e.g., sterile or nonsterile ingredients)
- Whether or not sterility testing is performed
- Storage conditions (e.g., packaging and temperature)

14.2.1 Terminal sterilization methods and aseptic processing:

A CSP MAY be prepared by the following methods (see 10. Sterilization and Depyrogenation):

- Terminal sterilization, which includes compounding with sterile and/or nonsterile starting ingredient(s) and subsequent sterilization with a process intended to achieve a PNSU of 10−6 (e.g., steam, dry heat, irradiation).
- Aseptic processing, which includes 1) compounding with only sterile starting ingredient(s) or 2) compounding with nonsterile ingredient(s) followed by sterilization by filtration. [NOTE—Sterilization by filtration is not a form of terminal sterilization.]

Terminal sterilization is the preferred method of sterilization, unless the specific CSP or container closure system cannot tolerate terminal sterilization. Table 13 allows for longer BUDs for terminally

sterilized CSPs than for aseptically processed CSPs because terminal sterilization using a verified method provides reasonable assurance that a CSP will be sterile.

14.2.2 Starting components:

The use of one or more nonsterile starting component(s) is a risk factor to be considered when preparing a CSP. A longer BUD is permitted for CSPs that are aseptically processed from conventionally manufactured sterile starting component(s) than from one or more nonsterile starting component(s).

14.2.3 Sterility testing:

Sterility testing (see 12.2 Sterility Testing) of a CSP can provide additional assurance of the absence of contamination, although passing a sterility test does not guarantee that all units of a batch of CSPs are sterile because contamination MAY not be uniformly distributed throughout the batch. A longer BUD is permitted if sterility testing results are within acceptable limits. The maximum batch size for all CSPs requiring sterility testing MUST be limited to 250 final yield units.

14.2.4 Storage conditions:

Storage in colder conditions (i.e., in a refrigerator or freezer [see Packaging and Storage Requirements ⟨659⟩]) has been shown to slow the growth of most microorganisms. However, the chemical and physical stability of the CSP and its components MUST be considered when storing in colder conditions (e.g., some formulations MAY precipitate when stored in a refrigerator or freezer). A longer BUD is permitted in Table 12 and Table 13 for CSPs stored in colder conditions than for CSPs stored at controlled room temperature.

If the CSP will be stored in a frozen state, the container closure system MUST be able to withstand the physical stress (i.e., without breaking or cracking) during storage in a freezer. The CSP MUST be thawed in appropriate conditions to avoid compromising the physical and chemical stability of the preparation and its components (e.g., do not heat in a microwave). Once the CSP is thawed, the CSP MUST not be refrozen.

CSPs MAY be stored under different storage conditions before they are used (e.g., CSPs MAY first be frozen, then thawed in the refrigerator, and finally kept at controlled room temperature before administration). The storage time of a CSP MUST not exceed the original BUD placed on the CSP for its labeled storage condition, and BUDs MUST not be additive. For example, an aseptically processed CSP prepared from one or more nonsterile starting component(s) cannot be stored for 45 days in a freezer, then 4 days refrigerated, and then 24 h at controlled room temperature for a total of 50 days. Once a CSP has been stored under a condition that would require a shorter BUD (e.g., controlled room temperature), the CSP MUST be used within the time frame for that storage condition (in the previous example, 24 h).

14.3 Establishing a BUD for a CSP

BUDs for CSPs MUST be established in accordance with Table 12 for Category 1 CSPs, Table 13 for Category 2 CSPs and Table 14 for Category 3 CSPs. One day is equivalent to 24 h.

The BUD limits in these tables are based on the risk of microbial contamination or not achieving and maintaining sterility despite implementation of the requirements in this chapter. The CSP formulation

MUST remain chemically and physically stable, and its packaging MUST maintain its integrity for the duration of the BUD.

A shorter BUD MUST be assigned when the stability of the CSP or its components is less than the hours or days stated in the applicable table below. Additionally:

- The BUD MUST not exceed the shortest remaining expiration date of any of the commercially available starting components.

- For CSPs prepared from one or more compounded components, the BUD SHOULD generally not exceed the shortest BUD of any of the individual compounded components. However, there MAY be acceptable instances when the BUD of the final CSP exceeds the BUD assigned to compounded components (e.g., pH-altering solutions). If the assigned BUD of the final CSP exceeds the BUD of the compounded components, the physical, chemical, and microbiological quality of the final CSP MUST not be negatively impacted.

Table 12 establishes the longest permitted BUDs for Category 1 CSPs. Category 1 CSPs MAY be prepared in an SCA or cleanroom suite (see 4.2 Facility Design and Environmental Controls).

Table 12. BUD Limits for Category 1 CSPsa

Storage Conditions

Controlled Room Temperature

(20°–25°) Refrigerator

(2°–8°)

≤12 h ≤24 h

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a A shorter BUD MUST be assigned when the physical and chemical stability of the CSP is less than the BUD limit stated in the table.

Table 13 establishes the longest permitted BUDs for Category 2 CSPs. Category 2 CSPs MUST be prepared in a cleanroom suite (see 4.2 Facility Design and Environmental Controls).

Table 13. BUD Limits for Category 2 CSPsa

Preparation Characteristics Storage Conditions

Compounding Method Sterility Testing Performed and Passed Controlled Room Temperature

(20°–25°) Refrigerator

(2°–8°) Freezer

(−25° to −10°)

Aseptically

processed CSPs No Prepared from one or more nonsterile starting component(s): 1 day

Prepared from one or more nonsterile starting component(s): 4 days Prepared from one or more nonsterile starting component(s): 45 days

Prepared from only sterile starting components:

4 days Prepared from only sterile starting components:

10 days Prepared from only sterile starting components:

45 days

Yes 30 days 45 days 60 days

Terminally sterilized CSPs No 14 days 28 days 45 days

Yes 45 days 60 days 90 days

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a A shorter BUD MUST be assigned when the physical and chemical stability of the CSP is less than the BUD limit stated in the table.

14.4 Additional Requirements for Category 3 CSPs

14.4.1 Assigning Category 3 BUDs:

Increasing the storage time of a CSP introduces additional risk for chemical degradation, physical incompatibilities, the compromising of the container closure system, and microbial proliferation. To address these risks and maintain a higher state of environmental control, additional requirements MUST be met when assigning BUDs for Category 3 CSPs in accordance with Table 14. Category 3 CSPs MUST not be assigned a BUD longer than the limits in Table 14.

14.4.2 Facility and Personnel Requirements for Category 3 CSPs:

In addition to the requirements in this section, other facility and personnel requirements related to compounding Category 3 CSPs are addressed throughout the chapter.

- Category 3 personnel competency requirements apply to personnel who participate in or oversee the compounding of Category 3 CSPs (see 2.2 Demonstrating Competency in Garbing and Hand Hygiene and 2.3 Competency Testing in Aseptic Manipulation).

- Category 3 garbing requirements apply to all personnel entering the buffer room where Category 3 CSPs are compounded and apply at all times regardless of whether Category 3 CSPs are being compounded on a given day (see 3.3 Garbing Requirements).

- Increased environmental monitoring requirements apply to all classified areas where Category 3 CSPs are compounded and apply at all times regardless of whether Category 3 CSPs are being compounded on a given day (see 6.2 Monitoring Air Quality for Viable Airborne Particles and 6.3 Monitoring Surfaces for Viable Particles).

- The frequency of application of sporicidal disinfectants applies to all classified areas where Category 3 CSPs are compounded and applies at all times regardless of whether Category 3 CSPs are being compounded on a given day (see Table 10).

14.4.3 Stability Requirements for Category 3 CSPs:

The BUD assigned to a Category 3 CSP MUST be supported by stability data obtained using a stability-indicating analytical method that is able to distinguish the active ingredient from its degradants and impurities (e.g., by forced degradation studies) and quantify the amount of the active ingredient.

- The Category 3 CSP MUST be prepared according to the exact formulation (API and other ingredients of identical grade and procedures) from which the stability data are derived.

- The Category 3 CSP MUST be packaged and stored in a container closure of the same materials of composition as that used in the study.

- The analytical method MUST be validated based on characteristics such as those described in ⟨1225⟩.

- The compounding facility MUST have documentation of the stability study, including a description of the methodology (e.g., number of samples taken, storage conditions), validation of the method, the stability-indicating analytical method, and all of the results of the study.

If the Category 3 CSP is an injection (Particulate Matter in Injections ⟨788⟩) or if it is an ophthalmic solution (Particulate Matter in Ophthalmic Solutions ⟨789⟩), particulate-matter testing is conducted once per formulation with acceptable results.

Once for each formulation and for each container closure system in which it will be packaged, the container closure system used is evaluated for and conforms to container closure integrity to the end of the BUD (see Package Integrity Evaluation—Sterile Products ⟨1207⟩).

14.4.4 Release testing for Category 3 CSPs

- Each time the Category 3 CSP is prepared, it is sterility tested and meets the requirements of ⟨71⟩ or a validated alternative method (see Table 14) that is noninferior to ⟨71⟩ testing.

- Each time the Category 3 CSP is prepared, it is tested for endotoxins for acceptable results, if endotoxin testing is required under 12.3 Bacterial Endotoxins Testing.

Table 14 establishes the longest permitted BUDs for Category 3 CSPs. If all of the conditions described for Category 3 CSPs in this chapter are not met, the applicable BUD in Table 13 MUST not be exceeded.

Table 14: BUD Limits for Category 3 CSPsa

Preparation Characteristics Storage Conditions

Compounding Method Controlled Room Temperature

(20°–25°) Refrigerator

(2°–8°) Freezer

(−25° to −10°)

Aseptically processed, sterility tested, and passing all applicable tests for Category 3 CSPs 60 days 90 days 120 days

Terminally sterilized, sterility tested, and passing all applicable tests for Category 3 CSPs 90 days 120 days 180 days

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a A shorter BUD MUST be assigned when the physical and chemical stability of the CSP is less than the BUD limit stated in the table.

14.5 Multiple-Dose CSPs

A compounded multiple-dose container is designed to contain more than one dose, intended to be entered or penetrated multiple times, and usually contains a preservative. A preservative is intended to inhibit the growth of microorganisms and minimize the risk of contamination. The use of preservatives MUST be appropriate for the CSP formulation and the route of administration. For example, the preservative MUST not be inactivated by any ingredients in the CSP, and some preservatives are not always appropriate for the patient (e.g., neonates) or route of administration (e.g., intrathecal or ophthalmic injection). The use of preservatives, however, MUST not be considered a substitute for aseptic technique.

A multiple-dose CSP MUST be prepared as a Category 2 or Category 3 CSP. An aqueous multiple-dose CSP MUST additionally pass antimicrobial effectiveness testing in accordance with Antimicrobial Effectiveness Testing ⟨51⟩. The compounder MAY rely on antimicrobial effectiveness testing 1) conducted (or contracted for) once for each formulation in the particular container closure system in which it will be packaged or 2) results from an FDA-registered facility or published in peer-reviewed literature sources, provided that the CSP formulation (including any preservative) and container closure system are exactly the same as those tested, unless a bracketing study is performed. Antimicrobial effectiveness testing MAY be performed on a low concentration and a high concentration of the active ingredient in the formulation to establish preservative effectiveness across various strengths of the same formulation (e.g., bracketing). The concentration of all other ingredients (including preservatives) MUST be the same throughout the bracketing study.

After a multiple-dose CSP container is initially entered or punctured, the multiple-dose container MUST not be used for longer than the assigned BUD or 28 days if supported by antimicrobial effectiveness testing results (see ⟨51⟩) on the CSP, whichever is shorter.

The container closure system used to package the multiple-dose CSP MUST be evaluated for and conform to container closure integrity (see ⟨1207⟩). The container closure integrity test needs to be conducted only once on each formulation and on fill volume in the particular container closure system in which the multiple-dose CSP will be packaged.

Multiple-dose, nonpreserved, aqueous topical, and topical ophthalmic, CSPs:

The beyond-use date of a multiple-dose, aqueous, nonpreserved CSP intended for topical, including topical ophthalmic, administration MAY be assigned in accordance with 14.5 Multiple-Dose CSPs. However, unpreserved aqueous, topical, including topical ophthalmic, formulations, are at high risk of microbial proliferation if contaminated during preparation or use.

To minimize the risk of patient harm, the requirement for passing antimicrobial effectiveness testing in accordance with ⟨51⟩ is not required only if the preparation is:

- Prepared as a Category 2 or Category 3 CSP
- For use by a single patient
- Labeled (in the label or labeling) to indicate that once opened, it MUST be discarded after 24 h when stored at controlled room temperature and/or that once opened, it MUST be discarded after 72 h when stored under refrigeration

15. USE OF CONVENTIONALLY MANUFACTURED PRODUCTS AS COMPONENTS

This section addresses the time within which an entered or punctured conventionally manufactured product MUST be used.

15.1 Use of Conventionally Manufactured Single-Dose Containers

A conventionally manufactured single-dose container is a container closure system that holds a sterile product for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. If a single-dose vial is entered or punctured only in an ISO Class 5 or cleaner air, it MAY be used up to 12 h after initial entry or puncture as long as the labeled storage requirements during that 12-h period are maintained. Opened single-dose ampules MUST not be stored for any time period.

15.2 Use of Conventionally Manufactured Multiple-Dose Containers

A conventionally manufactured product in a multiple-dose container is intended to contain more than one dose of a drug product (see ⟨659⟩, General Definitions, Injection Packaging Systems). Once initially entering or puncturing the multiple-dose container, the multiple-dose container MUST not be used for more than 28 days (see ⟨51⟩) unless otherwise specified by the manufacturer on the labeling.

15.3 Use of Conventionally Manufactured Pharmacy Bulk Packages

A conventionally manufactured pharmacy bulk package is a container of a sterile product for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the sterile preparation of admixtures for infusion or, through a sterile transfer device, for the filling of empty sterile containers. The pharmacy bulk package MUST be used according to the manufacturer's labeling (see ⟨659⟩, General Definitions, Injection Packaging Systems). The pharmacy bulk package MUST be entered or punctured only in an ISO Class 5 PEC.

16. USE OF CSPs AS COMPONENTS

This section addresses the use of CSPs (e.g., multiple-dose CSPs, single-dose CSPs, and compounded stock solutions) as components to prepare final CSPs.

When a CSP is used as a component, care MUST be taken to minimize the risk of contamination of both the starting component CSP and the final CSP(s).

- Component CSP: The component CSP MUST be assigned a BUD consistent with 14. Establishing Beyond-Use Dates and MUST be stored under conditions for its assigned BUD when not in use.

- Final CSP: The final CSP MUST be assigned a BUD consistent with 14. Establishing Beyond-Use Dates.

16.1 Use of Compounded Multiple-Dose CSPs

A multiple-dose CSP is designed to contain more than one dose of sterile preparation, intended to be entered or punctured multiple times, and usually contains a preservative. Multiple-dose CSPs are required to meet the criteria for antimicrobial effectiveness testing (see ⟨51⟩) and the requirements in 14.5 Multiple-Dose CSPs. Multiple-dose CSPs MUST be stored under the conditions upon which its BUD is based (e.g., refrigerator or controlled room temperature). After a multiple-dose CSP is initially entered or punctured, the multiple-dose CSP MUST not be used for longer than the assigned BUD or 28 days, whichever is shorter. This time limit for entering or puncturing is not intended to restrict the BUD of the final CSP. See 14. Establishing Beyond-Use Dates

16.2 Use of Compounded Single-Dose CSPs and CSP Stock Solutions

When a compounded single-dose CSP or CSP stock solution is used as a component to compound additional CSPs, the original compounded single-dose CSP or CSP stock solution MUST be entered or punctured in ISO Class 5 or cleaner air and MUST be stored under the conditions upon which its BUD is based (e.g., refrigerator or controlled room temperature). The component CSP MAY be used for sterile compounding for up to 12 h or its assigned BUD, whichever is shorter, and any remainder MUST be discarded. This time limit for entering or puncturing is not intended to restrict the BUD of the final CSP. See 14. Establishing Beyond-Use Dates.

17. SOPs

Facilities that prepare CSPs MUST develop SOPs for the compounding process and other support activities. SOPs MUST include the types of CSPs that are prepared (i.e., Category 1, Category 2, Category 3). A designated person(s) MUST ensure that SOPs are appropriate and are implemented, which includes ensuring that personnel demonstrate competency in performing every procedure that relates to their

job function. A designated person(s) MUST follow up to ensure that corrective actions are taken if problems, deviations, failures, or errors are identified. The corrective action MUST be documented.

All personnel who perform or oversee compounding or support activities MUST be trained in the SOPs. All compounding personnel MUST be trained to:

- Recognize potential problems, deviations, failures, or errors associated with preparing a CSP (e.g., those related to equipment, facilities, materials, personnel, the compounding process, or testing) that could potentially result in contamination or other adverse impact on CSP quality
- Report any problems, deviations, failures, or errors to the designated person(s)

SOPs MUST be reviewed initially and at least every 12 months by the designated person(s) to ensure that they reflect current practices, and the review MUST be documented. Any changes or alterations to an SOP MUST be made only by a designated person(s) and MUST be documented. Revisions to SOPs MUST be communicated to all personnel involved in these processes and procedures, and personnel SHOULD document acknowledgment of the communication.

18. QUALITY ASSURANCE AND QUALITY CONTROL

QA is a system of procedures, activities, and oversight that ensures that the compounding process consistently meets quality standards. QC is the sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the CSP. See Quality Assurance in Pharmaceutical Compounding ⟨1163⟩.

A facility's QA and QC programs MUST be formally established and documented in the facility's SOPs that ensure that all aspects of the preparation of CSPs are conducted in accordance with the requirements in this chapter (⟨797⟩) and the laws and regulations of the applicable regulatory jurisdiction. Designated person(s) MUST ensure that the facility has formal, written QA and QC programs that establish a system of:

1. Adherence to procedures
2. Prevention and detection of errors and other quality problems
3. Evaluation of complaints and adverse events
4. Appropriate investigations and corrective actions

The facility's SOPs MUST describe the roles, duties, and training of the personnel responsible for each aspect of the QA program. Designated person(s) responsible for the QA program MUST have the training, experience, responsibility, and authority to perform these duties. The overall QA and QC program MUST be reviewed at least once every 12 months by the designated person(s). The results of the review MUST be documented, and appropriate action MUST be taken if needed.

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

If a CSP is dispensed or administered before the results of release testing are known, the facility MUST have procedures in place to:

- Immediately notify the prescriber of a failure of specifications with the potential to cause patient harm (e.g., sterility, strength, purity, bacterial endotoxin, or other quality attributes)
- Recall any unused dispensed CSPs and quarantine any stock remaining in the pharmacy
- Investigate if other lots are affected and recall if necessary

An SOP for recall of out-of-specification dispensed CSPs MUST contain:

- Procedures to determine the severity of the problem and the urgency for implementation and completion of the recall
- Procedures to determine the distribution of any affected CSP, including the date and quantity of distribution
- Procedures to identify patients who have received the CSP
- Procedures for disposal and documentation of the recalled CSP
- Procedures to investigate and document the reason for failure

The sterile compounding facility MUST document the implementation of the recall procedures. The recall MUST be reported to appropriate regulatory bodies as required by laws and regulations of the applicable regulatory jurisdiction.

18.2 Complaint Handling

Compounding facilities MUST develop and implement SOPs for handling complaints. Complaints MAY include but are not limited to concerns or reports on the quality, labeling, or possible adverse reactions related to a specific CSP.

A designated person(s) MUST review all complaints to determine whether the complaint indicates a potential quality problem with the CSP. If it does, a thorough investigation into the cause of the problem MUST be initiated and completed. The investigation MUST consider whether the quality problem extends to other CSPs. Corrective action, if necessary, MUST be implemented for all potentially affected CSPs.

Consider whether to initiate a recall of potentially affected CSPs and whether to cease sterile compounding processes until all underlying problems have been identified and corrected.

A readily retrievable written or electronic record of each complaint MUST be kept by the facility, regardless of the source of the complaint (e.g., email, telephone, or mail). The record MUST contain the name of the complainant or other unique identifier, the date the complaint was received, the nature of the complaint, and the response to the complaint. In addition, to the extent that the information is known, the following SHOULD be recorded: the name and strength of the CSP and the assigned internal identification number (e.g., prescription, order, or lot number).

The record MUST also include the findings of any investigation and any follow-up. Records of complaints MUST be easily retrievable for review and evaluation for possible trends and MUST be retained in accordance with the record-keeping requirements in 20. Documentation. A CSP that is returned in

connection with a complaint MUST be quarantined until it is destroyed after completion of the investigation and in accordance with laws and regulations of the applicable regulatory jurisdiction.

18.3 Adverse Event Reporting

Adverse events potentially associated with the quality of CSPs MUST be reported in accordance with the facility's SOPs and all laws and regulations of the applicable regulatory jurisdiction. If the investigation into an adverse event reveals a quality problem with a CSP that is likely to affect other patients, those patients and prescribers potentially affected MUST be informed.

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

Processes and techniques for handling, storing, packaging, and transporting CSPs MUST be outlined in the facility's SOPs. Personnel who will be handling, storing, packaging, and transporting CSPs within the facility MUST be trained in accordance with the relevant SOPs, and the training MUST be documented.

19.1 Handling and Storing CSPs

CSPs MUST be handled in a manner that maintains CSP quality and packaging integrity. To help ensure that CSP quality is maintained during storage at the compounding facility, personnel MUST monitor conditions in the storage areas. A controlled temperature area (see ⟨659⟩) MUST be established and monitored to ensure that the temperature remains within the appropriate range for the CSP. The temperature MUST be monitored each day, either manually or by a continuous recording device. The results of the temperature readings MUST be documented in a temperature log per facility SOPs or stored in the continuous temperature recording device and MUST be retrievable. Temperature monitoring devices MUST be verified for accuracy at least every 12 months or as required by the manufacturer.

The compounding facility MUST detect and minimize temperature excursions that are outside the temperature limits within the controlled temperature areas. When it is known that a CSP has been exposed to temperatures either below or above the storage temperature limits for the CSP, a designated person(s) MUST determine (e.g., by consulting literature or analytical testing) whether the CSP is expected to retain its integrity or quality. If this cannot be determined, it MUST be discarded.

19.2 Packaging of CSPs

Packaging materials SHOULD protect CSPs from damage, leakage, contamination, degradation, and adsorption while preventing inadvertent exposure to transport personnel. The facility MUST select appropriate shipping containers and packaging materials based on the product specifications, information from vendors, and the mode of transport.

Alternative modes of transport and/or special packaging (e.g., tamper-evident closures) MAY be needed to protect the quality of CSPs. If the CSP is sensitive to light, light-resistant packaging materials MUST be used. In some cases, the CSP MUST be packaged in a special container (e.g., a cooler) to protect it from temperature fluctuations.

19.3 Shipping and Transporting CSPs

Compounding personnel MUST select modes of transport that are expected to deliver properly packed CSPs in an undamaged, sterile, and stable condition. Inappropriate transport can adversely affect the

quality of CSPs. For example, preparation-specific considerations SHOULD be given to physical shaking that might occur during pneumatic tube transport or undue exposure to heat, cold, or light. When shipping or transporting CSPs that require special handling (e.g., CSPs with stability concerns), personnel MUST include specific handling instructions on the exterior of the container.

20. DOCUMENTATION

All facilities where CSPs are prepared MUST have and maintain written or electronic documentation to demonstrate compliance with the requirements in this chapter. This documentation MUST include, but is not limited to, the following:

- Personnel training, competency assessments, and qualification records including corrective actions for any failures
- Certification reports, including corrective actions for any failures
- Environmental air and surface monitoring procedures and results
- Equipment records (e.g., calibration, verification, and maintenance reports)
- Receipt of components
- SOPs, MFRs (if required), and CRs (if required)
- Release inspection and testing records
- Information related to complaints and adverse events including corrective actions taken
- Results of investigations and corrective actions

Documentation MUST comply with all laws and regulations of the applicable regulatory jurisdiction. Records MUST be legible and stored in a manner that prevents their deterioration and/or loss. All required documentation for a particular CSP (e.g., MFR, CR, and release inspection and testing results) MUST be readily retrievable for at least 2 years after preparation or as required by laws and regulations of the applicable regulatory jurisdiction or accrediting organization(s), whichever is longer.

21. COMPOUNDING ALLERGENIC EXTRACTS

Licensed allergenic extracts are mixed and diluted into prescription sets for an individual patient, even though these allergenic extract combinations are not specified in the approved licenses for the licensed biological products (e.g., Biological License Applications [BLA]).

Allergenic extract prescription sets MUST follow standards at least as stringent as those in this section as follows:

21.1 Personnel Qualifications for Compounding Allergenic Extract Prescription Sets

- A designated person(s) with training and expertise in allergen immunotherapy is responsible for ensuring that personnel who will be preparing allergenic extract prescription sets are trained, evaluated, and supervised.

- Before beginning to independently prepare allergenic extracts, all compounding personnel MUST complete training and be able to demonstrate knowledge of principles and skills for sterile compounding.

- Annual personnel training and competency MUST be documented. Personnel MUST demonstrate knowledge and competency in these procedures by passing written or electronic testing before they can be allowed to compound allergenic extract prescription sets.

- Before being allowed to independently compound, all compounders MUST successfully complete gloved fingertip and thumb sampling on both hands (see Box 1 and Table 1) no fewer than 3 separate times. Each fingertip and thumb evaluation MUST occur after performing separate and complete hand hygiene and garbing procedures. After the initial competency evaluation, compounding personnel MUST successfully complete gloved fingertip and thumb sampling on both hands at least every 12 months thereafter.

- Compounding personnel MUST have their sterile technique and related practices evaluated at least every 12 months as demonstrated by successful completion of a media-fill test (see Box 2). If compounding outside of a PEC, the post-media-fill surface sample is not required.

- Personnel who fail competency evaluations MUST successfully pass reevaluations in the deficient area(s) before they can resume compounding of allergenic extract prescription sets. The designated person(s) MUST identify the cause of failure and determine appropriate retraining requirements.

- Personnel who have not compounded an allergenic extract prescription set in more than 6 months MUST be evaluated in all core competencies before resuming compounding duties.

21.2 Personnel Hygiene and Garbing for Compounding Allergenic Extract Prescription Sets

- Before beginning compounding of allergenic extract prescription sets, personnel MUST perform hand hygiene (see Box 3) and garbing procedures according to the facility's SOPs.

- The minimum garb requirements include:

o A low-lint garment with sleeves that fit snugly around the wrists and an enclosed neck (e.g., gowns)

o A low-lint, disposable head cover that covers the hair and ears and, if applicable, a disposable cover for facial hair

o Face mask

o Sterile powder-free gloves

- Throughout the compounding process, personnel MUST apply sterile 70% IPA onto all surfaces of the gloves and allow them to dry thoroughly.

21.3 Facilities for Compounding Allergenic Extract Prescription Sets

- The compounding process MUST occur in an ISO Class 5 PEC or in a dedicated allergenic extract compounding area (AECA). The PEC or AECA used to compound allergenic extract prescription sets

MUST be located away from unsealed windows, doors that connect to the outdoors, and traffic flow, all of which MAY adversely affect the air quality. Neither a PEC nor an AECA MAY be located where environmental control challenges (e.g., restrooms, warehouses, or food preparation areas) could negatively affect the air quality. The PEC or the work surfaces in the AECA MUST be located at least 1 m away from a sink. The impact of activities that will be conducted around or adjacent to the PEC or AECA MUST be considered carefully when designing such an area.

- If used, the PEC MUST be certified at least every 6 months (see 5. Certification and Recertification).

- If used, a visible perimeter MUST define the AECA.

o Access to the AECA during compounding MUST be restricted to authorized personnel.

o During compounding activities, no other activity is permitted in the AECA.

o The surfaces of walls, floors, fixtures, shelving, counters, and cabinets in the AECA MUST be cleanable.

o Carpet is not allowed in the AECA.

o Surfaces SHOULD be resistant to damage by cleaning and disinfecting agents.

o The surfaces in the AECA upon which the allergenic extract prescription sets are prepared MUST be smooth, impervious, free from cracks and crevices, and non-shedding to allow for easy cleaning and disinfecting.

o Dust-collecting overhangs such as utility pipes, ledges, and windowsills SHOULD be minimized. If overhangs or ledges are present, they MUST be easily cleanable.

o The AECA MUST be designed and controlled to provide a well-lighted working environment, with temperature and humidity controls for the comfort of compounding personnel wearing the required garb.

21.4 Cleaning and Disinfecting for Compounding Allergenic Extract Prescription Sets

- In a PEC, all interior surfaces of the PEC MUST be cleaned and disinfected each day of use before compounding begins and when surface contamination is known or suspected. Apply sterile 70% IPA to the horizontal work surface between each prescription set.

- In an AECA, all work surfaces in the AECA where direct compounding is occurring MUST be cleaned and disinfected each day of use before compounding begins and when surface contamination is known or suspected. Apply sterile 70% IPA to the horizontal work surface between each prescription set.

o If present, walls, doors, and door frames within the perimeter of the AECA MUST be cleaned and disinfected monthly and when surface contamination is known or suspected.

o Ceilings within the perimeter of the AECA MUST be cleaned and disinfected when visibly soiled and when surface contamination is known or suspected.

- Vial stoppers on packages of conventionally manufactured sterile ingredients MUST be wiped with sterile 70% IPA to ensure that the critical sites are wet and allowed to dry before they are used to compound allergenic extract prescription sets.

21.5 Establishing BUDs for Allergenic Extract Prescription Sets

- The BUD for the prescription set MUST be no later than the earliest expiration date of any allergenic extract or any diluent that is part of the prescription set, and the BUD MUST not exceed 1 year from the date the prescription set is mixed or diluted.

21.6 Labeling for Allergenic Extract Prescription Sets

- The label of each vial of an allergenic extract prescription set MUST display the following prominently and understandably:

o Patient name

o Type and fractional dilution of each vial, with a corresponding vial number

o BUD

o Storage conditions

21.7 Shipping and Transporting Allergenic Extract Prescription Sets

- If shipping or transporting allergenic extract prescription sets, compounding personnel MUST select modes of transport that are expected to deliver properly packed prescription sets in an undamaged, sterile, and stable condition. Inappropriate transport can adversely affect the quality of allergenic extract prescription sets.

- When shipping or transporting allergenic extract prescription sets that require special handling, personnel MUST include specific handling instructions on the exterior of the container.

21.8 Documentation for Compounding Allergenic Extract Prescription Sets

- All facilities where allergenic extract prescription sets are prepared MUST have and maintain written or electronic documentation to include, but not limited to, the following:

o SOPs describing all aspects of the compounding process

o Personnel training records, competency assessments, and qualification records including corrective actions for any failures

o Certification reports of the PEC, if used, including corrective actions for any failures

o Temperature logs for refrigerator(s)

o CRs for individual allergenic extract prescription sets (see Box 10)

o Information related to complaints and adverse events including corrective actions taken

o Investigations and corrective actions

GLOSSARY

ACD:Automated compounding device.

ACPH:Air changes per hour.

Active pharmaceutical ingredient (API):Any substance or mixture of substances intended to be used in the compounding of a preparation, thereby becoming the active ingredient in that preparation and furnishing pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans and animals or affecting the structure and function of the body. Also referred to as Bulk drug substance. A conventionally manufactured drug product is not an API but is typically manufactured from an API(s).

Added substance:An ingredient that is necessary to compound a preparation but is not intended or expected to cause a pharmacologic response if administered alone in the amount or concentration contained in a single dose of the compounded preparation. The term is used synonymously with the terms inactive ingredient, excipient, and pharmaceutical ingredient.

Administration:The direct application of a sterile product or preparation to a single patient by injecting, infusing, or otherwise providing a sterile product or preparation in its final form.

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

Alcohol-based hand rub:An alcohol-containing preparation (liquid, gel, or foam) designed for application to the hands of healthcare personnel to inactivate microorganisms and/or temporarily suppress their growth. Such preparations MAY contain one or more types of alcohol, other active ingredients, excipients, and humectants.

Allergenic extract:A biological substance used for the diagnosis and/or treatment of allergic diseases such as allergic rhinitis, allergic sinusitis, allergic conjunctivitis, bee venom allergy, and food allergy.

Allergenic extract compounding area (AECA):A designated space, area, or room that is not required to be classified, with a visible perimeter that is suitable for preparation of allergenic extract prescription sets.

Allergenic extract prescription set:Combinations of licensed allergenic extracts that would be mixed and diluted to provide subcutaneous immunotherapy to an individual patient, even though these allergenic extract combinations are not specified in the approved BLAs for the licensed biological products.

Anteroom:An ISO Class 8 or cleaner room with fixed walls and doors where personnel hand hygiene, garbing procedures, and other activities that generate high particulate levels MAY be performed. The anteroom is the transition room between the unclassified area of the facility and the buffer room.

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

Aseptic technique:A set of methods used to keep objects and areas free of microorganisms and thereby minimize infection risk to the patient. It is accomplished through practices that maintain the microbe count at an irreducible minimum.

Assigned trainer:One or more individuals assigned by the designated person(s) to be responsible and accountable for directly providing the training, observation, and/or evaluation of personnel for the preparation of CSPs.

Batch:More than one CSP prepared as described in the MFR in a single, discrete process, and expected to have uniform character and quality, within specified limits.

Beyond-use date (BUD):The date, or hour and the date, after which a CSP MUST not be used, stored, or transported. The date is determined from the date and time the preparation is compounded.

Biological safety cabinet (BSC):A ventilated cabinet that MAY be used for compounding. These cabinets are divided into three general classes (Class I, Class II, and Class III). Class II BSCs are further divided into types (Type A1, Type A2, Type B1, Type B2, and Type C1).

Biological safety cabinet (BSC), Class II:A ventilated cabinet with an open front and inward and downward unidirectional HEPA-filtered airflow and HEPA-filtered exhaust. A BSC used to prepare a CSP MUST be capable of providing an ISO Class 5 or better environment for preparation of the CSPs.

BLA:Biological license application.

Blood components:Any therapeutic constituent of blood separated by physical or mechanical means (e.g., white cells, red cells, platelets, plasma, serum). It is not intended to include plasma-derived products (e.g., albumin, coagulation factors, immunoglobulins) manufactured under an approved BLA or equivalent.

BMBL:Biosafety in Microbiological and Biomedical Laboratories.

Buffer room:An ISO Class 7 or cleaner room with fixed walls and doors where PEC(s) that generate and maintain an ISO Class 5 environment are physically located. The buffer room MAY only be accessed through the anteroom or another buffer room.

Bulk drug substance:See the entry for Active pharmaceutical ingredient.

Category 1 CSP:A CSP that is assigned a BUD of 12 h or less at controlled room temperature or 24 h or less refrigerated that is compounded in accordance with all applicable requirements for Category 1 CSPs in this chapter.

Category 2 CSP:A CSP that MAY be assigned a BUD of greater than 12 h at controlled room temperature or greater than 24 h refrigerated that is compounded in accordance with all applicable requirements for Category 2 CSPs in this chapter.

Category 3 CSP:A CSP that MAY be assigned a BUD exceeding the limits in Table 13 for Category 2 CSPs and is compounded in accordance with all applicable requirements for Category 3 CSPs in this chapter.

CDC:Centers for Disease Control and Prevention.

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

CFU:Colony-forming units.

Classified area:An area that maintains an air quality classification based on the ISO standards required in this chapter (see also the definition for ISO class).

Cleaning:The process of removing substances (e.g., organic and inorganic material) from objects and surfaces, normally accomplished by manually or mechanically using water with detergents or enzymatic products.

Cleaning agent:An agent, usually containing a surfactant, used for the removal of substances (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.

Cleanroom suite:A classified area that consists of both an anteroom and buffer room.

Component:Any ingredient used in the compounding of a preparation, including any active ingredient, added substance, or conventionally manufactured product.

Compounded sterile preparation (CSP):A preparation intended to be sterile that is created by combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance.

Compounded stock solution:A sterile mixture of components that is used to compound additional CSPs.

Compounding:The process of combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance to create a sterile preparation.

Compounding area:The area where compounding is occurring (i.e., a cleanroom suite, inside the perimeter of the SCA, or AECA).

Compounding aseptic containment isolator (CACI):A type of RABS that uses HEPA filtration to provide an ISO Class 5 unidirectional air environment designed for the compounding of sterile HDs.

Compounding aseptic isolator (CAI):A type of RABS that uses HEPA filtration to provide an ISO Class 5 unidirectional air environment designed for compounding of sterile non-HDs.

Compounding record (CR):Documents the compounding of each CSP.

Container closure system:Packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection.

Containment glove bag:A single-use disposable glove bag that is capable of containing airborne chemical particles.

Containment ventilated enclosure (CVE):A non-ISO classified full or partial enclosure that uses ventilation principles to capture, contain, and remove airborne contaminants through HEPA filtration and prevent their release into the work environment.

Conventionally manufactured product:A pharmaceutical dosage form, usually the subject of an application approved by the applicable national regulatory agency, that is manufactured under current good manufacturing practice conditions.

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

Designated person(s):One or more individuals assigned to be responsible and accountable for the performance and operation of the facility and personnel as related to the preparation of CSPs.

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

Disinfectant:A chemical or physical agent used on inanimate surfaces and objects to destroy fungi, viruses, and bacteria. Sporicidal disinfectants are considered a special class of disinfectants that also are effective against bacterial and fungal spores.

Dynamic airflow smoke pattern test:A PEC test in which a visible source of smoke, which is neutrally buoyant, is used to observe air patterns within the unidirectional space (i.e., the DCA) under dynamic operating conditions (see the entry for Dynamic operating conditions). This test is not appropriate for ISO Class 7 or ISO Class 8 cleanrooms that do not have unidirectional airflow (see the entry for Visual smoke study).

Dynamic operating conditions:Conditions in the compounding area in which operating personnel are present and simulating or performing compounding. The conditions SHOULD reflect the largest number of personnel and highest complexity of compounding expected during routine operations as determined by the designated person(s).

ECV:Endotoxin challenge vial.

EPA:US Environmental Protection Agency.

Excipient:See the entry for Added substance.

FDA:US Food and Drug Administration.

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

Final yield:The total number of containers actually prepared at the end of the compounding process prior to release testing.

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

Formulation:The specific qualitative and quantitative composition of the final CSP.

Garb:Items such as gloves, garments (e.g., gowns), shoe covers, head and facial hair covers, masks, and other items designed to reduce particle-shedding from personnel and minimize the risk of contamination of CSP(s).

GFT:Gloved fingertip and thumb sampling.

Hazardous drug (HD):Any drug identified by at least one of the following six criteria: carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity in humans, organ toxicity at low dose in humans or animals, genotoxicity, or new drugs that mimic existing HDs in structure or toxicity.

High-efficiency particulate air (HEPA) filtration:Being, using, or containing a filter designed to remove 99.97% of airborne particles measuring 0.3-micron or greater in diameter passing through it.

HVAC:Heating, ventilation, and air conditioning.

Integrated vertical laminar flow zone (IVLFZ):A designated ISO Class 5 area serving as the PEC within an ISO Class 7 or cleaner buffer room. In the IVLFZ, unidirectional airflow is created by placing HEPA filters over the entire surface of the worktables and by effective placement of air returns.

IPA:Isopropyl alcohol.

ISO:International Organization for Standardization.

ISO class:An air-quality classification from the International Organization for Standardization.

Label:The part of the labeling on the immediate container.

Labeling:All labels and other written, printed, or graphic matter on the immediate container or on or inside any packaging system or wrapper in which the article is enclosed, except any outer shipping container.

Laminar airflow system (LAFS):A device or zone within a buffer room that provides an ISO Class 5 or better air quality environment for sterile compounding. The system provides a unidirectional HEPA-filtered airflow.

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

Line of demarcation:A visible line on the floor that separates the clean and dirty sides of the anteroom.

Low-lint wiper:A wiper exhibiting few, if any, fibers or other contamination, visible without magnification, which is separate from, or easily removed from, the wiper material in a dry condition.

Master formulation record (MFR):A detailed record of procedures that describes how the CSP is to be prepared.

MEA:Malt extract agar.

Media-fill test:A simulation used to qualify processes and personnel engaged in sterile compounding to ensure that the processes and personnel are able to prepare CSPs without contamination.

Monograph:A quality documentary standard within USP–NF that articulates the quality expectations for a medicine including for its identity, strength, purity, and performance. It also describes the tests to validate that a medicine and its ingredients meet these criteria.

Multiple-dose container:A container of sterile product for parenteral administration (e.g., injection or infusion) that is designed to contain more than one dose of the sterile product. A multiple-dose container is usually required to meet the antimicrobial effectiveness testing criteria. See ⟨659⟩, Injection Packaging Systems, Multiple-dose container.

One-step disinfectant cleaner:A product with an EPA-registered (or equivalent) claim that it can clean and disinfect a nonporous surface in the presence of light to moderate organic soiling without a separate cleaning step.

Oversight:The review, monitoring, and supervision of actions taken by personnel, bearing responsibility for those actions, and being available for consultation if and when needed even if not physically present.

Pass-through chamber:An enclosure with sealed doors on both sides that SHOULD be interlocked. The pass-through chamber is positioned between two spaces for the purpose of minimizing particulate transfer while moving materials from one space to another.

Perimeter:A visible demarcation (such as a door, walls, or visible marking on the floor) that defines the SCA or AECA.

Pharmaceutical isolator:An enclosure that provides HEPA-filtered ISO Class 5 unidirectional air operated at a continuously higher pressure than its surrounding environment and is decontaminated using an automated system. It uses only decontaminated interfaces or rapid transfer ports for materials transfer. [NOTE—A CAI or CACI is not a pharmaceutical isolator.]

Pharmacy bulk package:A conventionally manufactured sterile product for parenteral use that contains many single doses intended for use in a pharmacy admixture program. A pharmacy bulk package MAY either be used to prepare admixtures for infusion or, through a sterile transfer device, for filling sterile containers. See ⟨659⟩, Injection Packaging Systems, Pharmacy bulk package.

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

PPE:Personal protective equipment.

Preservative:A substance added to inhibit microbial growth.

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

Probability of a nonsterile unit (PNSU):The probability of an item being nonsterile after it has been exposed to a verified sterilization process. A PNSU value can only be applied to terminal sterilization. [NOTE—This is also called the sterility assurance level (SAL).]

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

Quality assurance (QA):A system of procedures, activities, and oversight that ensures that the compounding process consistently meets quality standards.

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

Reconstitution:The process of adding a diluent to a conventionally manufactured product to prepare a sterile solution or suspension.

Release inspection and testing:Visual inspection and testing performed to ensure that a preparation meets appropriate quality characteristics.

Repackaging:The act of removing a sterile product or preparation from its original primary container and placing it into another primary container, usually of smaller size without further manipulation.

Restricted-access barrier system (RABS):An enclosure that provides HEPA-filtered ISO Class 5 unidirectional air that allows for the ingress and/or egress of materials through defined openings that have been designed and validated to preclude the transfer of contamination, and that generally are not to be opened during operations. Examples of RABS include CAIs and CACIs.

SDA:Sabouraud dextrose agar.

Secondary engineering control (SEC):The area where the PEC is placed (e.g., a cleanroom suite or an SCA). It incorporates specific design and operational parameters required to minimize the risk of contamination within the compounding area.

Segregated compounding area (SCA):A designated space, area, or room that is not required to be classified and is defined with a visible perimeter. The SCA MUST contain a PEC and is suitable for preparation of Category 1 CSPs only.

Single-dose containers:A container of sterile product for parenteral administration (e.g., injection or infusion) that is designed for use with a single patient as a single injection/infusion. A single-dose container usually does not contain a preservative. See ⟨659⟩, Injection Packaging Systems, Single-dose container.

SOP:Standard operating procedure.

Specification:The tests, analytical methods, and acceptance criteria to which any component, CSP, container closure system, equipment, or other material used in compounding CSPs MUST conform to be considered acceptable for its intended use.

Sporicidal disinfectant:A chemical or physical agent that destroys bacterial and fungal spores when used in sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.

Stability:The extent to which a product or preparation retains physical and chemical properties and characteristics within specified limits throughout its expiration or BUD.

Sterility:The absence of viable microorganisms.

Sterility assurance level (SAL):See the entry for Probability of a nonsterile unit (PNSU).

Sterilization by filtration:Passage of a gas or liquid through a sterilizing-grade membrane to yield filtrates that are sterile.

Sterilizing-grade filter:Filter membranes that are documented to retain 100% of a culture of 107 microorganisms of a strain of Brevundimonas diminuta per square centimeters of membrane surface under a pressure of not less than 30 psi. Such filter membranes are nominally 0.22- or 0.2-µm pore size.

Terminal sterilization:The application of a lethal process (e.g., steam, dry heat, irradiation) to sealed containers for the purpose of achieving a predetermined PNSU of greater than 10−6 or a probability of less than one in one million of a nonsterile unit.

TSA:Trypticase soy agar.

Unclassified space:A space not required to meet any air cleanliness classification based on the ISO.

Unidirectional airflow:Air within a PEC moving in a single direction in a uniform manner and at sufficient velocity to sweep particles away from the DCA.

Verify:To confirm that a method, process, system, or equipment will perform as expected under the conditions of actual use.

Visual smoke study:A test, used in ISO Class 7 and ISO Class 8 rooms that do not have unidirectional airflow, in which a visible source of smoke, which is neutrally buoyant, is used to verify an absence of stagnant airflow. This test does not need to be performed under dynamic operating conditions and is not appropriate for PECs (see the entry for Dynamic airflow smoke pattern test).

Workflow management system:Technology comprised of hardware and/or software that allows for automation to assist in the verification of components of, and preparation of, CSPs and to document components and processes.▲ (Official 1-Nov-2023)

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Auxiliary Information -

Please check for your question in the FAQs before contacting USP.