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USP General Chapter <797> *Pharmaceutical Compounding – Sterile Preparations*

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This chapter alone is not sufficient for a comprehensive approach to pharmaceutical compounding – sterile preparations. Additional chapters are required for complete implementation; see USP Compounding Compendium or USP-NF.

⟨797⟩ PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS

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1. INTRODUCTION AND SCOPE

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

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 technique must be followed for preparing any sterile medication. 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.

Pursuant to *General Notices, 2.30 Legal Recognition*, assuring compliance with *USP* standards is the responsibility of regulatory bodies. Accreditation or credentialing organizations may adopt and enforce *USP* standards. USP has no role in enforcement.

1.1 Scope

CSPS AFFECTED

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

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

SPECIFIC PRACTICES

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.

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

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

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

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) in order to avoid any cross-contamination. Handling of blood components must additionally comply with jurisdictional standards and guidelines.

Sterile radiopharmaceuticals: Compounding of radiopharmaceuticals is not required to meet the standards of this chapter for Category 1 and Category 2 CSPs and is subject to the requirements in *Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging* ⟨825⟩.

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 physicians' or veterinarians' practice sites. Any person, whether preparing a CSP or not, entering a sterile compounding area 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 medication to a single patient by injecting, infusing, or otherwise providing a sterile medication 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's (CDC's) safe injection practices apply to administration.

1.3 Immediate Use CSPs

Compounding of CSPs for direct and immediate administration to a patient is not subject to the requirements for Category 1 or Category 2 CSPs when all of the following are met:

1. Aseptic processes are followed and written procedures 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. The preparation is performed in accordance with evidence-based information for physical and chemical compatibility of the drugs (e.g., FDA-approved labeling, stability studies).
3. The preparation involves not more than 3 different sterile products.
4. Any unused starting component from a single-dose container must be discarded after preparation for the individual patient is complete. Single-dose containers must not be used for more than 1 patient.
5. Administration begins within 4 hours following the start of preparation. If administration has not begun within 4 hours following the start of preparation, it must be promptly, appropriately, and safely discarded.
6. Unless 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 exact 4-hour time period within which administration must begin.

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 provided by the product's manufacturer and other manufacturer directions consistent with that labeling [21 USC 353a (e)].

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.

PROPRIETARY BAG AND VIAL SYSTEMS

Docking and activation of proprietary bag and vial systems (e.g., addEASE, ADD-Vantage, Mini Bag Plus) 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) 5 environment.

Docking of the proprietary bag and vial systems for *future activation* and administration is considered compounding and must be performed in accordance with this chapter, with the exception of *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 two categories of CSPs, Category 1 and Category 2, primarily based on the conditions under which they are made, the probability for microbial growth, and the time period within which they must be used. Category 1 CSPs are those assigned a BUD of 12 hours or less at controlled room temperature or 24 hours or less when refrigerated if made in accordance with all of the applicable requirements for Category 1 CSPs in this chapter. Category 2 CSPs are those that may be assigned a BUD of greater than 12 hours at controlled room temperature or greater than 24 hours if refrigerated (see *14. Establishing Beyond-Use Dates*) if made in accordance with all of the applicable requirements for Category 2 CSPs in this chapter.

The requirements that are not specifically described as applicable to Category 1 or Category 2, such as training, competency testing, and personal hygiene for personnel, are applicable to the compounding of all CSPs.

CSPs can be compounded either by using only sterile starting ingredients or by using some or all nonsterile starting ingredients. If all of the components used to compound a drug are sterile to begin with, 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 maintained if the CSP is subsequently manipulated. When compounding with nonsterile starting components, supplies, or equipment, the quality of the components and the effectiveness of the sterilization step are critical to achieving a sterile preparation.

2. PERSONNEL TRAINING AND EVALUATION

All personnel involved in the compounding of CSPs must be initially trained and qualified by demonstrating proficiency in compounding CSPs. A designated person must oversee the training of personnel. Training and observation may be performed by the designated person(s) or an assigned trainer. Personnel must complete training every 12 months in appropriate sterile compounding principles and practices.

Each compounding facility must develop a written training program that describes the required training, the frequency of training, and the process for evaluating the performance of individuals involved in preparing CSPs. This program should

equip personnel with the appropriate knowledge and train them in the required skills necessary to perform their assigned tasks. Training and evaluation of personnel must be documented.

2.1 Demonstrating Proficiency in Core Competencies

Before beginning to prepare CSPs independently, all compounding personnel must complete training and be able to demonstrate knowledge of principles and proficiency of skills for performing sterile manipulations and achieving and maintaining appropriate environmental conditions. Competency must be demonstrated 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
- 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 primary engineering controls (PECs)
- Principles of movement of materials and personnel within the compounding area

All compounding personnel must complete written or electronic testing every 12 months. Any other personnel handling CSPs and/or accessing the compounding area must complete training and demonstrate competency in maintaining the quality of the environment in which they are performing their assigned task. The designated person(s) must ensure that any person who enters the sterile compounding area maintains the quality of the environment.

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

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

Initial gloved fingertip and thumb sampling evaluates a compounder's competency in correctly performing hand hygiene and garbing (see *Box 2-1*). Before being allowed to independently compound, all compounders must successfully complete an initial competency evaluation, including visual observation and gloved fingertip and thumb sampling on both hands, no fewer than 3 separate times. Each fingertip and thumb evaluation must occur after performing a separate and complete hand hygiene and full garbing procedure. After the initial competency evaluation, compounding personnel must successfully complete gloved fingertip and thumb sampling at least every 6 months after completing the media-fill test (see *2.3 Competency Testing in Aseptic Manipulation*).

Initial gloved fingertip and thumb sampling must be performed on donned sterile gloves in a classified area or segregated compounding area (SCA). Subsequent gloved fingertip and thumb sampling must be performed on donned sterile gloves 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) sleeves.

Successful completion of initial gloved fingertip and thumb sampling is defined as zero colony-forming units (cfu). Successful completion of subsequent gloved fingertip and thumb sampling after media-fill testing is defined as ≤3 cfu (total from both hands). Action levels for gloved fingertip and thumb sampling results are shown in *Table 1*.

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/time, media and components used including manufacturer, expiration date and lot number, starting temperature for each interval of incubation, dates of incubation, the results, and the identification of the observer and the person who reads and documents the results.

Box 2-1. Gloved Fingertip and Thumb Sampling Procedures

- Use one sampling device per hand (e.g., plates, paddles, or slides) containing general microbial growth agar [e.g., trypticase soy agar (TSA)] supplemented with neutralizing additives (e.g., lecithin and polysorbate 80) as this agar supports both bacterial and fungal growth.
- Label each sampling device with a personnel identifier, whether it was from the 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 sampling device because this could cause a false-negative result.
- Using a separate sampling device for each hand, collect samples from all gloved fingers and thumbs from both hands by rolling finger pads and thumb pad over the agar surface.
- Incubate the sampling device at a temperature of 30°–35° for no less than 48 hours and then at 20°–25° for no less than 5 additional days. Store media devices during incubation to prevent condensate from dropping onto the agar 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.

Table 1. Action Levels for Gloved Fingertip and Thumb Sampling[a]

Gloved Fingertip and Thumb Sampling	Action Levels (total number of cfu from both hands)
Initial sampling after garbing	>0
Subsequent sampling after media-fill testing (every 6 months)	>3

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

2.3 Competency Testing in Aseptic Manipulation

All compounding personnel must perform media-fill testing to assess their sterile technique and related practices (see *Box 2-2*) initially and every 6 months thereafter. Gloved fingertip and thumb sampling must be performed inside of an ISO Class 5 PEC following media-fill tests to evaluate the ability of the compounder to demonstrate acceptable aseptic processing.

When performing a media-fill test, simulate the most difficult and challenging compounding procedures and processing conditions encountered by the person replacing all the components used in the CSPs with soybean–casein digest media.

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 before 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.

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/time, media and components used including manufacturer, expiration date and lot number, starting temperature for each interval of incubation, dates of incubation, the results, and the identification of the observer and the person who reads and documents the results.

Box 2-2. Media-Fill Testing Procedures

- If all of the starting components are sterile to begin with, manipulate them in a manner that simulates sterile-to-sterile compounding activities, and transfer the sterile soybean–casein digest media into the same types of container–closure systems commonly used at the facility. Do not further dilute the media unless specified by the manufacturer.
- If some of the starting components are nonsterile to begin with, use a nonsterile soybean–casein digest powder to make a solution. Dissolve nonsterile commercially available soybean–casein digest medium 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, incubate them in an incubator for 7 days at 20°–25° followed by 7 days at 30°–35° to detect a broad spectrum of microorganisms.
- Failure is indicated by visible turbidity or other visual manifestations of growth in the media in one or more container–closure unit(s) on or before 14 days.

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 10^6 or more per hour, and those skin particles are covered with microorganisms.[1, 2] 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 infection) must report these conditions to the designated person(s).

[1] Agalloco J, Akers JE. Aseptic processing: a vision of the future. *Pharm Technol*. 2005; Aseptic Processing supplement, s16.
[2] Eaton T. Microbial risk assessment for aseptically prepared products. *Am Pharm Rev*. 2005;8(5):46–51.

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 CSP and the environment.

3.1 Personnel Preparation

Individuals entering a compounding area must take appropriate steps to minimize microbial contamination of the environment and the CSPs, including hand hygiene (*3.2 Hand Hygiene*), garbing (*3.3 Garbing Requirements*), and consideration of needed materials to be brought into the compounding area. Before entering a compounding area, individuals must remove any items that are not easily cleanable or that 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 as long as the quality of the CSP and environment will not be affected.

3.2 Hand Hygiene

Personnel must wash hands and forearms up to the elbows with soap and water before initiating compounding activities *Box 3-1*). Brushes must not be used for hand hygiene. Hand dryers must not be used. A closed system of soap (i.e., non-refillable container) to minimize the risk of extrinsic contamination must be readily available or in close proximity to the sink.

Box 3-1. Hand Washing Procedures

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

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 SOP. Hands must be sanitized with alcohol-based hand rub before donning sterile gloves (see *Box 3-2*). Sterile gloves must be donned in a classified room or SCA.

Box 3-2. Hand Sanitizing Procedures

- Apply an alcohol-based hand rub to dry skin following the manufacturer's instructions for the volume of product to use.
- 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 must be properly garbed in accordance with the facility's SOPs. Garb must be donned and doffed in an order that reduces the risk of contamination. The order of garbing must be determined by the facility and documented in the facility's SOP. Sterile gloves must be donned in a classified room or SCA. 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 ante-room or the SCA at the same time. The minimum garbing requirements include:

- Low-lint garment with sleeves that fit snugly around the wrists and that is enclosed at the neck (e.g., gowns or coveralls)
- Low-lint, disposable covers for shoes
- Low-lint, disposable covers for head that cover the hair and ears, and if applicable, disposable cover for facial hair
- Face mask
- Sterile powder-free gloves
- If using a RABS, such as a CAI or CACI, disposable gloves (e.g., cotton, nonsterile, sterile) should be worn inside gloves attached to the RABS sleeves. Sterile gloves must be worn over 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). When personnel exit

the compounding area, garb except for gowns cannot be reused and must be discarded. Gowns may be re-used within the same shift if the gown is maintained in a classified area or inside the perimeter of an SCA.

If compounding a 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 regularly throughout the compounding process and whenever nonsterile surfaces (e.g., vials, counter tops, chairs, or carts) are touched.

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 gauntlet sleeves and gloves should be changed per the manufacturer's recommendations and as defined in the facility's SOP.

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 ante-room, buffer room, and SCA must be separated from areas not directly related to compounding. The ante-room 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 equipment, supplies, and components to maintain and facilitate 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.

AIR QUALITY STANDARDS

The ISO standards for air quality in controlled environments are provided in *Table 2* and referenced throughout this chapter.

Table 2. ISO Classification of Particulate Matter in Room Air[a]

ISO Class	Particle Count[b] /m³
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.

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 2*) include ante-rooms, buffer rooms, and PECs.

- Ante-rooms providing access to positive pressure buffer rooms must meet at least ISO Class 8 classification. Ante-rooms 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 ante-room. Ante-rooms 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 and Category 2 CSPs must be prepared 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 below 60% to minimize the risk for microbial proliferation and 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 humidifiers/dehumidifiers and air conditioners must not be used within the classified area or within the perimeter of 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.

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 ante-room 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. Air supplied to the cleanroom suite must be introduced through HEPA filters that are located in the ceiling of the buffer and ante-rooms.

Air returns in the cleanroom suite must be low on the wall unless a visual smoke study demonstrates an absence of stagnant airflow where particulate will accumulate. This smoke study along with environmental monitoring must be repeated whenever a change to the placement of equipment within the room is made 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 classified rooms must be equipped with a pressure-differential monitoring system. The ante-room must have a line of demarcation to separate the clean side from the dirty side. Alternatively, facilities may be designed with two separate ante-rooms, a clean ante-room and a dirty ante-room. The ante-room is entered through the dirty side/room, and the clean side/room is the area closest to the buffer room. Required garb must be donned prior to entering the clean side/room of the ante-room (see *3. Personal Hygiene and Garbing*).

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., ISO Class 8 ante-room to ISO Class 7 buffer room to 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 ante-room), or between a classified area and an unclassified area (e.g., between the ante-room and an unclassified area such as a hallway). If a pass-through 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 and ante-rooms. Access doors should be hands-free. Tacky mats must not be placed within ISO-classified areas.

Segregated compounding area (SCA): A PEC may be located within an unclassified area, without an ante-room or buffer room. This type of design is called an SCA. Only Category 1 CSPs can 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. A visible perimeter must establish the boundaries of the SCA.

THE CSP COMPOUNDING ENVIRONMENT

The PEC must be certified to meet ISO Class 5 or better conditions (see *Table 2*) during dynamic operating conditions and must be designed to prevent 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.

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 3* 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 prevent 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: Examples of LAFS include LAFWs, integrated vertical laminar flow zones (IVLFZs), and biological safety cabinets (BSCs).

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 work tables and 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—A 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 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 ante-room. 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 that generally are not to be opened during compounding operations.

Types of RABS: Examples of RABS include CAIs and 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 (CAI): 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 (CACI): 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 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 ante-room. 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 CSPs, the pharmaceutical isolator must be placed in an ISO Class 8 or better room. [NOTE—An ante-room 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 into the facility and 2) compounders understand how to utilize the unidirectional airflow to maintain first air in the work zone. For placement of a pharmaceutical isolator used for the preparation of HDs, see ⟨800⟩.

Table 3. Summary of Minimum Requirements for Placement of PEC for Compounding Non-HD CSPs[a]

PEC Type	Device Type	Placement for Compounding Category 1 CSPs	Placement for Compounding Category 2 CSPs
	LAFW	Unclassified SCA	ISO Class 7 positive pressure buffer room with an ISO Class 8 positive pressure ante-room
	IVLFZ	N/A[b]	ISO Class 7 positive pressure buffer room with an ISO Class 8 positive pressure ante-room
LAFS	BSC	Unclassified SCA	ISO Class 7 positive pressure buffer room with an ISO Class 8 positive pressure ante-room
RABS	CAI or CACI	Unclassified SCA	ISO Class 7 positive pressure buffer room with an ISO Class 8 positive pressure ante-room
Pharmaceutical isolator	Pharmaceutical isolator	Unclassified SCA	ISO Class 8 positive pressure room

[a] For compounding HDs, refer to ⟨800⟩.
[b] An IVLFZ must not be used in an unclassified area.

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

AIR EXCHANGE REQUIREMENTS

For cleanroom suites, adequate HEPA-filtered airflow to the buffer room(s) and ante-room(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 particulates that may be generated from activities and processes in the area
- the equipment located in the room
- the room pressure
- the effects of temperature

See *Table 4* for a summary of ACPH requirements for non-HD sterile compounding areas.

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, increases 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 4. 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

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 each ISO classified area (e.g., between the buffer room and ante-room). The pressure differential between the ante-room 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.

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

Weighing, measuring, or otherwise manipulating components could generate airborne chemical particles (e.g., API, added substances). If preparing a Category 2 CSP from nonsterile component(s), presterilization procedures, such as weighing and mixing, must be completed in no worse than an ISO Class 8 environment (e.g., ante-room, buffer room). Presterilization procedures must be performed in single-use containment glove bags, containment ventilated enclosure (CVE) , BSC, or CACI to minimize the risk of airborne contamination. CVE, BSC, or CACI 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

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 non-shedding 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 by cleaning agents, disinfectants, sporicidal agents, 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.

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 by cleaning agents, disinfectants, sporicidal agents, 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 sink(s) must be cleaned and disinfected at least daily and a sporicidal agent must be applied at least monthly (see *7.1 Cleaning, Disinfecting,*

and Sporicidal Agents). If compounding is not performed daily, cleaning and disinfecting of the sink must be completed before initiating compounding.

In facilities with a cleanroom suite, the sink used for hand hygiene may be placed either inside or outside of the ante-room. If the sink is located outside of the ante-room, it must be located in a clean space to minimize the risk of bringing in contaminants into the ante-room. If the sink is located inside the ante-room, it may be placed on either the clean side or the dirty side of the ante-room. [NOTE—The order of hand washing and garbing depends on the placement of the sink (see *3.2 Hand Hygiene*).] The buffer room must not contain plumbed water sources [e.g., sink(s), eyewash(es), shower(s), or floor drain(s)]. The ante-room 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, the sink must be accessible but located at least 1 meter away from the PEC. The sink must not be located inside the perimeter of 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 ante-room 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 an 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 inside the perimeter of the SCA.

5. CERTIFICATION AND RECERTIFICATION

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

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 and volume, the 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

It is imperative that all engineering control equipment function as designed and that the levels of total airborne particles remain within acceptable limits during compounding (see *Table 2*). A monitoring program for total airborne particles must be developed and implemented 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 count testing must be conducted in all classified areas during dynamic operating conditions at least every 6 months.

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 SOP. Measurements of total airborne particles in other classified areas, including the buffer room(s) and ante-room(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 2* 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 2*, *Table 5*, and *Table 6*).

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 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 must 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 in the proper operation of the air and surface sampling equipment to ensure accurate and reproducible sampling. All active air sampling devices 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.

VIABLE AIR SAMPLING—TIMING AND LOCATIONS

Volumetric active air sampling of all classified areas using an impaction device 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 at least every 6 months. Air sampling sites must be selected in all classified areas.

SAMPLING PROCEDURES

When conducting sampling of the PEC, care should be taken to avoid disturbing unidirectional airflow. See *Box 6-1* 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 media meets the expected growth promotion, pH, and sterilization requirements. Samples must be incubated in an incubator at temperatures that will promote growth of bacteria and fungi. 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 6-1. Active Air Sampling Procedures for Viable Airborne Monitoring

- Follow the manufacturer's instructions for operation of the active air sampling device, including placement of media.
- Using the sampling device, test at least 1 cubic meter or 1000 liters of air from each location sampled.
- At the end of the sampling, retrieve the media devices and cover them.
- Invert the media and incubate at 30°–35° for no less than 48 hours. Examine for growth. Record the total number of discrete colonies of microorganisms on each 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.
- Then incubate the inverted media at 20°–25° for no less than 5 additional days. Examine the media devices 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.
- Alternatively, to shorten the overall incubation period, two samples may be collected for each sample location and incubated concurrently.
  - Both samples could be TSA or one sample could be TSA and the other fungal media (e.g., malt extract agar (MEA) or sabouraud dextrose agar (SDA)).
  - Incubate each sample in a separate incubator. Incubate one sample at 30°–35° for no less than 48 hours, and incubate the other sample 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.
  - Count the total number of discrete colonies of microorganisms on each sample, and record these results as cfu per cubic meter of air.
  - 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.

DATA EVALUATION AND ACTION LEVELS

Evaluate cfu counts against the action levels in *Table 5*, and examine counts in relation to previous data to identify adverse results or trends. If two devices of media are collected at a single location, all recovered growth on each must be documented and action levels applied to each media device. If levels measured during the viable air monitoring program exceed the levels in *Table 5* 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 viable air sampling exceed the levels in *Table 5*, 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 5. Action Levels for Viable Airborne Particle Air Sampling[a]

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

Table 5. Action Levels for Viable Airborne Particle Air Sampling[a] *(continued)*

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

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

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 of component and/or vial surfaces. All sampling sites and procedures must be described in the facility's SOP.

SURFACE SAMPLING: TIMING AND LOCATIONS

Surface sampling of all classified areas and pass-through chambers connecting to classified areas for microbial contamination must be conducted at least monthly (see *Microbiological Control and Monitoring of Aseptic Processing Environments* ⟨1116⟩). Each classified area must be sampled, including the following:

- The interior of the PEC and the equipment contained in it
- Staging or work area(s) near the PEC
- Frequently touched surfaces

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

SAMPLING PROCEDURES

See *Box 6-2* for the procedures for surface sampling on flat surfaces. Surface sampling devices (e.g., plates, paddles, or slides) containing microbial growth media must be used for sampling flat surfaces. COAs from the manufacturer must verify that the devices meet the expected growth promotion, pH, and sterilization requirements. Surface sampling devices must contain general microbial growth media (e.g., TSA) supplemented with neutralizing additives (e.g., lecithin and polysorbate 80) to neutralize the effects of any residual disinfecting agents. Surface sampling 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 Agents in Compounding Areas*).

Samples must be incubated in a calibrated incubator at temperatures that will promote growth of bacteria and fungi. 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 6-2. Surface Sampling Procedures

- Remove the cover from the surface sampling device. Using a rolling motion, firmly press the media surface onto the surface to be sampled. The surface sampling device will leave a residue of growth media on the sample site. After sampling, remove the residue from the surface using sterile 70% IPA.
- Cover each surface sampling device. Store media devices during incubation to prevent condensate from dropping onto the agar and affecting the accuracy of the cfu reading (e.g., invert plates).
- Incubate the surface sampling devices at 30°–35° for no less than 48 hours. Examine for growth. Record the total number of discrete colonies of microorganisms on each device as cfu per sample on an environmental sampling form based on sample type (i.e., surface), sample location, and sample date.
- Incubate the surface sampling device at 20°–25° for no less than 5 additional days. Examine the device for growth. Record the total number of discrete colonies of microorganisms on each media device (cfu per sample) on the environmental sampling record based on sample type (i.e., surface), sample location, and sample date.
- Alternatively, to shorten the overall incubation period, two samples may be collected for each sample location and incubated concurrently.
  - Both samples could be TSA or one sample could be TSA and the other fungal media (e.g., MEA or SDA).
  - Incubate each sample in a separate incubator. Incubate one sample at 30°–35° for no less than 48 hours, and incubate the other sample 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.
  - Count the total number of discrete colonies of microorganisms on each sample, and record these results as cfu per sample.
  - 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.

DATA EVALUATION AND ACTION LEVELS

Evaluate cfu counts against the action levels in *Table 6*, and examine counts in relation to previous data to identify adverse results or trends. If two devices were collected at a single location, all recovered growth on each must be documented and action levels are applied to each device of media. If levels measured during surface sampling exceed the levels in *Table 6* 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 6*, an attempt must be made to identify any microorganism recovered to the genus level (see ⟨1113⟩) with the assistance of a microbiologist.

Table 6. Action Levels for Surface Sampling

ISO Class	Surface Sampling Action Levels (cfu/device or swab)
5	>3
7	>5
8	>50

7. CLEANING, DISINFECTING, AND APPLYING SPORICIDAL AGENTS IN COMPOUNDING AREAS

Cleaning, disinfecting, and applying a sporicidal agent are important because surfaces in classified areas and SCA 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.

Surfaces must be cleaned prior to being disinfected unless an Environmental Protection Agency (EPA)-registered (or equivalent) one-step disinfectant cleaner is used to accomplish both the cleaning and disinfection in one step. A sporicidal agent must be applied to destroy bacterial and fungal spores. Some EPA-registered (or equivalent) one-step disinfectant cleaners may have sporicidal properties. After cleaning and disinfecting or the application of a one-step disinfectant cleaner, or the application of a sporicidal agent in a PEC, apply sterile 70% IPA to remove any residue. See *Table 7* for a summary of the purposes of the cleaning, disinfectant, and sporicidal agents.

Table 7. Purpose of Cleaning, Disinfecting, and Sporicidal Agents

Type of Agent	Purpose
Cleaning agent	An agent used for the removal of residues (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.
Disinfectant	A chemical or physical agent used on inanimate surfaces and objects to destroy fungi, viruses, and bacteria.
Sporicidal agent	A chemical or physical agent that destroys bacterial and fungal spores when used at a sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.

Cleaning and disinfecting surfaces and applying a sporicidal agent must occur at the minimum frequencies specified in *Table 8* or, if compounding is not performed daily, cleaning and disinfecting must be completed before initiating compounding.

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 frequency, method(s), and location(s) of cleaning, disinfecting, and sporicidal agent use 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 the cleaning, disinfecting, and sporicidal agents used. When sterile 70% IPA is used, it must be allowed to dry. All cleaning, disinfecting, and application of sporicidal agents must be documented according to facility SOPs.

Table 8. Minimum Frequency for Cleaning and Disinfecting Surfaces and Applying Sporicidal Agents in Classified Areas and within the Perimeter of the SCA[a]

Site	Cleaning	Disinfecting	Applying Sporicidal
PEC(s) and equipment inside the PEC(s)	Equipment and all interior surfaces of the PEC daily and when surface contamination is known or suspected.	• Equipment and all interior surfaces of the PEC daily and when surface contamination is known or suspected. • Apply sterile 70% IPA to the horizontal work surface at least every 30 minutes if the compounding process takes 30 minutes or less. If the compounding process takes more than 30 minutes, compounding must not be disrupted and the work surface of the PEC must be disinfected immediately after compounding.	Monthly
Removable work tray of the PEC	• Work surface of the tray daily • All surfaces and the area underneath the work tray monthly	• Work surface of the tray daily • All surfaces and the area underneath the work tray monthly	• Work surface of the tray monthly • All surfaces and the area underneath the work tray monthly
Pass-through(s)	Daily	Daily[b]	Monthly
Work surface(s) outside the PEC	Daily	Daily[b]	Monthly
Floor(s)	Daily	Daily[b]	Monthly
Wall(s), door(s), and door frame(s)	Monthly	Monthly[b]	Monthly
Ceiling(s)[c]	Monthly	Monthly[b]	Monthly
Storage shelving and bins	Monthly	Monthly[b]	Monthly
Equipment outside the PEC(s)	Monthly	Monthly[b]	Monthly

[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 agent only when visibly soiled and when surface contamination is known or suspected.

7.1 Cleaning, Disinfecting, and Sporicidal 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 agent is applied to the surface, the agent must be allowed to dwell for the minimum contact time specified by the manufacturer.

7.2 Cleaning Supplies

All cleaning supplies (e.g., wipers, sponges, and mop heads) with the exception of tool handles and holders must be low-lint. Wipers, 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., no wooden handles) 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. Dispose of cleaning supplies used in the classified areas and SCAs in a manner that minimizes the potential for dispersing contaminants into the air (e.g., with minimal agitation, away from work surfaces).

7.3 Cleaning, Disinfecting, and Applying Sporicidal Agents in the PEC

Clean, disinfect, and apply a sporicidal agent to equipment and all interior surfaces in the PEC at the minimum frequencies specified in *Table 8*. See *Box 7-1* and *Box 7-2* for procedures for cleaning, disinfecting, and applying a sporicidal agent in the PEC.

Box 7-1. Procedures for Cleaning and Disinfecting the PEC

- 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 low-lint wiper, apply a cleaning agent, followed by a disinfecting agent, or apply an EPA-registered (or equivalent) 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 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.

Box 7-2. Procedures for Applying a Sporicidal Agent in the PEC

- 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 (*Box 7-1*), apply the sporicidal agent using a low-lint wiper to all surfaces and the area underneath the work tray. If the sporicidal agent is an EPA-registered (or equivalent) 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 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.

8. INTRODUCING ITEMS INTO THE SEC AND PEC

8.1 Introducing Items into the Cleanroom Suite and SCAs

Before any item is introduced into the clean side of ante-room(s), placed into pass-through(s), or brought inside the perimeter SCA and when packaging integrity will not be compromised, it must be wiped with a sporicidal agent, EPA-registered disinfectant, or sterile 70% IPA using low-lint wipers by personnel wearing gloves. If an EPA-registered disinfectant or sporicidal agent 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 must not 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 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 entering or puncturing stoppers/septums or breaking the necks of ampules.

9. EQUIPMENT, SUPPLIES, AND COMPONENTS

9.1 Equipment

PECs are described in *4.2 Facility Design and Environmental Controls, 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 agent, 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.

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 facility SOPs, which must address the selection, receipt, evaluation, handling, storage, and documentation of all CSP components, including all ingredients, containers, and closures.

COMPONENT SELECTION

Conventionally manufactured sterile products should be used when available and appropriate for the intended CSP.
APIs:

- Must comply with the criteria in the *USP–NF* monograph, if one exists
- Must have a COA that includes the specifications and test results and shows that the API meets the specifications
- Must be obtained from an FDA-registered facility

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
- Should be obtained from an FDA-registered facility
    - If it 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 is 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.

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⟩).

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 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.

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, master formulation record (if used), vendor labels, COAs of API(s) and other component(s), product labeling of conventionally manufactured sterile products, labeling of CSPs, and documentation of the compounding facility storage conditions and practices.

All components must be re-inspected before use. All packages must be re-inspected to detect container breaks, looseness of the cap or closure, and deviation from the expected appearance, aroma, and texture of the contents that might have occurred during storage. Sterile container–closures must be visually re-inspected to ensure that they are free from defects that could compromise sterility and 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 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.

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 manufacturer.

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, and quality) or the packaging integrity. See also the ⟨1229⟩ family of chapters.

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

- Terminal sterilization (e.g., dry heat, steam, 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 is not an option when compounding a suspension if the suspended drug particles are removed by the filter being used.

CSPs that are terminally sterilized (e.g., dry heat, steam, 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 hours 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° up to about 400°, depending on the exposure time (e.g., a cycle might hold the items at 250° for 30 minutes 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, temperature). This verification must be documented.

Items that are not thermostable must be depyrogenated by rinsing with sterile, non-pyrogenic water (e.g., *Sterile Water for Injection*, *Sterile Water for Irrigation*) and then thoroughly drained or dried immediately before use in compounding.

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 include labeling for pharmaceutical use. Sterilizing filters with labeling that states "for laboratory use only" or an equivalent statement must not be used for compounding CSPs. Sterilizing filters must be certified by the manufacturer to retain at least 10^7 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, if necessary, modified. 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 no 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., between 20 and 60 minutes 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 for steam sterilization that must be wrapped, wrap them in low-lint protective fabric or paper or sealed in envelopes that will permit steam penetration and that are designed to prevent post-sterilization microbial contamination. For CSPs, immediately before filling ampules and vials 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. Deep containers, such as beakers and graduated cylinders, must be inverted or placed on their sides at a downward-sloping angle to minimize air entrapment and to facilitate condensate drainage, or must have a small amount of sterile water placed in them before steam sterilization. Porous materials and those items with occluded pathways (e.g., tubing) must only be sterilized by steam if the autoclave chamber has suitable cycles for dry goods, such as a pre-vacuum process to remove air before steam is sent into the chamber. Elastomeric closures and many other dry goods will need a drying cycle after steam exposure to remove condensed or absorbed moisture.

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 and integrators (see *Physicochemical Integrators and Indicators for Sterilization* ⟨1229.9⟩).

The steam supplied must be free of contaminants and 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 compounding record.

10.4 Sterilization by Dry Heat

Dry heat may be used for those items that cannot be sterilized by steam or other means, when either 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.

Dry heat sterilization is usually performed in an oven designed for sterilization at a temperature of 160° or higher. If lower temperatures are used, they must be shown to achieve effective sterilization (see *Dry Heat Sterilization* ⟨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 compounding record.

11. MASTER FORMULATION AND COMPOUNDING RECORDS

11.1 Creating Master Formulation Records

A Master Formulation Record is a detailed record of procedures that describes how the CSP is to be prepared. A Master Formulation Record must be created for CSPs prepared for more than 1 patient and for CSPs prepared from nonsterile ingredient(s). Any changes or alterations to the Master Formulation Record must be approved and documented according to the facility's SOP. *Box 11-1* lists the information that must be included in a Master Formulation Record.

Box 11-1. Master Formulation Records

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

- Name, strength or activity, and dosage form of the CSP
- Identities and amounts of all ingredients
- Type and size of container–closure system(s)
- Complete instructions for preparing the CSP, including equipment, supplies, a description of the compounding steps, and any special precautions
- Physical description of the final CSP
- BUD and storage requirements
- Reference source to support the stability of the CSP
- 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 (e.g., steam, dry heat, irradiation, or filter)

11.2 Creating Compounding Records

A Compounding Record documents the compounding of each CSP. A Compounding Record must be created for all CSPs. The Compounding Record must be created to document the compounding process or repackaging process. A prescription or medication order or label may serve as the compounding record. If an ACD, workflow management system, or other similar equipment is used, the required information in the compounding record may be stored electronically as long as it is retrievable and contains the required information (see *Box 11-2*). A Master Formulation Record can serve as the basis for preparing the Compounding Record. For example, a copy of the Master Formulation Record can be made that contains spaces for recording the information needed to complete the Compounding Record. *Box 11-2* lists the information that must be included in a Compounding Record.

Box 11-2. Compounding Records

Compounding Records must include at least the following information:

- Name, strength or activity, and dosage form of the CSP
- Date and time of preparation of the CSP
- Assigned internal identification number (e.g., prescription, order, or lot number)
- A method to identify the individuals involved in the compounding process and verifying the final CSP
- Name of each component
- Vendor, lot number, and expiration date for each component for CSPs prepared for more than 1 patient and for CSPs prepared from nonsterile ingredient(s)
- Weight or volume of each component
- Strength or activity of each component
- Total quantity compounded
- Assigned BUD and storage requirements
- Results of QC procedures (e.g., visual inspection, filter integrity testing, pH testing)

If applicable, the Compounding Record must also include:

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

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., it is inspected for evidence of inappropriate visible particulates or other foreign matter, discoloration, or other defects). The CSP 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). CSPs with observed

defects must be discarded, or marked and segregated from acceptable units in a manner that prevents them from being released or dispensed.

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. A CSP with such defects must be immediately discarded, or marked and segregated from acceptable units in a manner that prevents it from being released or dispensed. Any defect may indicate sterility or stability problems, which should be investigated to determine the cause (see *18. Quality Assurance and Quality Control*).

12.2 Sterility Testing

Sterility testing is not required for Category 1 CSPs (see *Table 10*). If a Category 2 CSP is assigned a BUD that requires sterility testing (see *Table 11*), the testing must be performed according to ⟨71⟩ or a validated alternative method (see *Validation of Alternative Microbiological Methods* ⟨1223⟩) that is non-inferior to ⟨71⟩ testing.

If sterility testing is performed, the minimum quantity of each container to be tested for each media is specified in *Sterility Tests* ⟨71⟩, *Table 2*, and the number of containers required to be tested in relation to the batch size is specified in *Sterility Tests* ⟨71⟩, *Table 3*, except as described below.

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 *Sterility Tests* ⟨71⟩, *Table 3*, additional units must be compounded to be able to perform sterility testing as follows:

- If between 1 and 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 *Sterility Tests* ⟨71⟩, *Table 3* must be used.

If sterility testing is performed according to ⟨71⟩, a *Sterility Tests* ⟨71⟩*, Method Suitability Test* must be performed to ensure that contamination can be recovered. If performing sterility testing according to ⟨71⟩, the *Sterility Tests* ⟨71⟩*, Test for Sterility of the Product to Be Examined, Membrane Filtration* method 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 2 injectable CSPs made from one or more nonsterile component(s) and assigned a BUD that requires sterility testing (see *Table 11*) must be tested to ensure that they do not contain excessive bacterial endotoxins (see ⟨85⟩). Category 2 injectable CSPs made 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 endotoxins limit in an official monograph or other CSP formula source, the CSP must not exceed the endotoxins limit calculated as described in ⟨85⟩ for the appropriate route of administration for humans. CSPs for non-human species must not exceed the endotoxin reference limits calculated as described in ⟨85⟩ based on the weight of the target animal 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

CSPs must be labeled with 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 in, 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⟩.

The label on the 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 amounts, activities, or concentrations
- Storage conditions if other than controlled room temperature
- BUD
- Route of administration

- 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 should indicate that the preparation is compounded.

If the CSP is to be sent outside of the facility in which it was compounded, the labeling must include the contact information of the compounding facility. The labeling of the CSP must also provide any applicable special handling instructions or warning statements.

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. Master Formulation Record, if required (see *11.1 Creating Master Formulation Records*); and
3. Compounding Record (see *11.2 Creating Compounding Records*)

All labels must also comply with laws and regulations of the applicable regulatory jurisdiction.

14. ESTABLISHING BEYOND-USE DATES

14.1 Terminology

Each CSP label must state the BUD, which is the date, or the hour and date, beyond which the preparation must not be used and must be discarded. The BUD is determined from the date/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 compendial 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 the conventionally manufactured product, API, or added substance may be dispensed or used (see *Labeling ⟨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 for a particular formulation in its container and at stated exposure conditions of illumination and temperature. See *Table 9* for a summary of terms.

Table 9. 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/time that preparation of the CSP is initiated.	Applies to all CSPs
Expiration Date	The time during which a product can be expected to meet the requirements of the compendial monograph, if one exists, or maintain expected quality provided it is kept under the specified storage conditions.	Applies to all conventionally manufactured products, APIs, and added substances

14.2 Parameters to Consider in Establishing a BUD

Multiple factors that affect sterility and chemical and physical stability must be considered when establishing BUDs for CSPs. BUDs should be established conservatively for CSPs 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 factors that may affect stability, including but not limited to:

- The chemical and physical properties of the drug and/or its formulation
- The compatibility of the container–closure system with the finished preparation (e.g., leachables, interactions, and storage conditions)

The BUDs for CSPs in *Table 10* and *Table 11* are based primarily on factors that affect the achievement and maintenance of sterility, which include, but are not limited to, the following:

- Environment in which the CSP is prepared (e.g., PEC in a cleanroom suite or SCA)
- Aseptic processing and sterilization method
- Starting components (e.g., sterile or nonsterile starting ingredients)
- Whether or not sterility testing is performed
- Storage conditions (e.g., packaging and temperature)

ASEPTIC PROCESSING AND STERILIZATION METHODS

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

1. **Aseptic processing**, which includes either 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.]
2. **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., dry heat, steam, irradiation).

Terminal sterilization is the preferred method of sterilization, unless the specific CSP or container–closure system cannot tolerate terminal sterilization. *Table 11* allows for longer BUDs for CSPs that are terminally sterilized than for aseptically processing CSPs because terminal sterilization using a verified method provides reasonable assurance that a CSP will be sterile.

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 in *Table 11* for CSPs that are aseptically processed from conventionally manufactured sterile starting component(s) than from one or more nonsterile starting component(s).

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 in *Table 11* if sterility testing results are within acceptable limits.

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 10* and *Table 11* 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 re-frozen.

CSPs may be stored under different storage conditions before they are used (e.g., CSPs may first be frozen, and then thawed in the refrigerator, and finally kept at controlled room temperature before administration). The storage time of a CSP must not exceed the original BUD placed on the CSP for its labeled storage 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 1 day 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 (i.e., controlled room temperature), the CSP must be used within the time frame for that storage condition (in this example, 1 day).

14.3 Establishing a BUD for a CSP

BUDs for CSPs must be established in accordance with *Table 10* for Category 1 CSPs and *Table 11* for Category 2 CSPs. One day is equivalent to 24 hours.

The BUDs in *Table 10* and *Table 11* for CSPs are based on the risk of microbial contamination or not achieving sterility despite implementation of the requirements in this chapter. Therefore, it is assumed that the CSP formulation will remain chemically and physically stable, and its packaging will 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 *Table 10* or *Table 11*. Additionally, the BUD must not exceed the shortest remaining expiration date or BUD of any of the starting components, regardless of the source.

Table 10 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 10. BUDs for Category 1 CSPs

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

Table 11 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 11. BUDs for Category 2 CSPs

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

14.4 Multiple-Dose CSPs

A compounded multiple-dose container is designed to contain more than 1 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 injections). 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 CSP. A multiple-dose CSP must additionally pass antimicrobial effectiveness testing in accordance with *Antimicrobial Effectiveness Testing* ⟨51⟩. The compounder may rely on 1) antimicrobial effectiveness testing that is conducted (or contracted for) once for each formulation in the particular container–closure system in which it will be packaged or 2) antimicrobial effectiveness testing results provided by an FDA-registered facility or published in peer-reviewed literature sources if 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 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 *Package Integrity Evaluation—Sterile Products* ⟨1207⟩). The container–closure integrity test needs to be conducted only once on each formulation and fill volume in the particular container–closure system in which the multiple-dose CSP will be packaged.

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 medication 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 hours after initial entry or puncture as long as the storage requirements during that 12-hour 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 1 dose of a drug product (see *Packaging and Storage Requirements* ⟨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 *Packaging and Storage Requirements* ⟨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 finished 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 finished CSP(s). The BUD of a CSP prepared from one or more compounded components may not exceed the shortest BUD of any of the individual starting components (see *14. Establishing Beyond-Use Dates*).

16.1 Use of Compounded Multiple-Dose CSPs

A multiple-dose CSP is designed to contain more than 1 dose of medication, 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 *14.4 Multiple-Dose CSPs*. Multiple-dose CSPs must be stored under the conditions upon which its BUD is based (e.g., refrigerator, 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.

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, controlled room temperature). The component CSP may be used for sterile compounding for up to 12 hours or its assigned BUD, whichever is shorter, and any remainder must be discarded.

17. SOPs

Facilities that prepare CSPs must develop SOPs for the compounding process and other support activities. A designated person 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 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 able 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 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 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 SOPs that ensure that all aspects of the preparation of CSPs are conducted in accordance with the requirements in this chapter and laws and regulations of the applicable regulatory jurisdiction. A designated person 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 SOPs must describe the roles, duties, and training of the personnel responsible for each aspect of the QA program. 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:

1. 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), and
2. Determine whether a recall is 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 disposition and reconciliation of the recalled CSP

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 (e.g., state board of pharmacy, state health department).

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 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, mail). The record must contain the name of the complainant or 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 facility SOPs and all laws and regulations of the applicable regulatory jurisdiction. In addition, adverse events potentially associated with the quality of the CSP should be reported to the applicable jurisdictional regulatory body (e.g., state boards of pharmacy, state health departments, FDA's MedWatch program for human drugs, or FDA Form 1932a for animal drugs).

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

Processes and techniques for handling, storing, packaging, and transporting CSPs must be outlined in 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 at least once daily 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 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, Master Formulation Records (when used), and Compounding Records
- Release inspection and testing records
- Information related to complaints and adverse events
- Results of investigations and corrective actions

Documentation must comply with all laws and regulations of the applicable jurisdiction. Records must be legible and stored in a manner that prevents their deterioration and/or loss. All required compounding records for a particular CSP (e.g., Master Formulation Record, Compounding Record, and release testing results) must be readily retrievable for at least 3 years after preparation or as required by laws and regulations of the applicable regulatory jurisdiction, 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)]. Because patients must be maintained on a maintenance dose of prepared concentrated allergenic extracts for a period of time longer than the BUDs specified for Category 1 and Category 2, longer BUDs are required for prescription sets to achieve effective therapy.

Allergenic extracts prescription sets must follow standards at least as stringent as those in this section:

Personnel Qualifications

1. A designated person with training and expertise in allergen immunotherapy is responsible for ensuring that personnel who will be preparing allergen immunotherapy are trained, evaluated, and supervised.
2. 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.
3. Annual personnel training and competency must be documented. Personnel must demonstrate proficiency in these procedures by passing written or electronic testing before they can be allowed to compound allergenic extract prescription sets.
4. Before being allowed to independently compound, all compounders must successfully complete gloved fingertip and thumb sampling on both hands (see *Box 2-1* 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 procedure. After the initial competency evaluation, compounding personnel must successfully complete gloved fingertip and thumb sampling at least every 12 months thereafter.

5. Compounding personnel must have their sterile technique and related practices evaluated every 12 months as demonstrated by successful completion of a media-fill test (see *Box 2-2*).

6. 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.

7. 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.

Personnel Hygiene and Garbing

8. Before beginning compounding of allergen immunotherapy prescription sets, personnel must perform hand hygiene (see *Box 3-1*) and garbing procedures according to facility SOPs.

9. The minimum garb requirements include:

- Low-lint garment with sleeves that fit snugly around the wrists and that is enclosed at the neck (e.g., gowns or coveralls)
- Low-lint, disposable covers for head that cover the hair and ears and, if applicable, disposable cover for facial hair
- Face mask
- Sterile powder-free gloves

10. Compounding personnel must rub sterile 70% IPA onto all surfaces of the gloves and allow them to dry thoroughly throughout the compounding process.

Facilities

11. The compounding process must occur in an ISO Class 5 PEC or in a dedicated allergenic extracts compounding area (AECA). The PEC or AECA used to compound 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 meter 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 every 6 months (see *5. Certification and Recertification*).
- If used, a visible perimeter must establish the boundaries of the AECA.
    - Access to the AECA during compounding must be restricted to authorized personnel.
    - During compounding activities, no other activity is permitted in the AECA.
    - The surfaces of walls, floors, fixtures, shelving, counters, and cabinets in the AECA must be cleanable.
    - Carpet is not allowed in the AECA.
    - Surfaces should be resistant to damage by cleaning and sanitizing agents.
    - 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.
    - Dust-collecting overhangs such as utility pipes, ledges, and windowsills should be minimized. If overhangs or ledges are present, they must be easily cleanable.
    - 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.

Cleaning and Disinfecting

12. In a PEC, all interior surfaces of the PEC must be cleaned and disinfected daily and when surface contamination is known or suspected. Apply sterile 70% IPA to the horizontal work surface between each prescription set.

13. In an AECA, all work surfaces in the AECA where direct compounding is occurring must be cleaned and disinfected daily and when surface contamination is known or suspected. Apply sterile 70% IPA to the horizontal work surface between each prescription set.

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

14. 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 extracts prescription sets.

Establishing BUDs

15. 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.

Labeling

16. The label of each vial of an allergenic extract prescription set must display the following prominently and understandably:

- Patient name
- Type and fractional dilution of each vial, with a corresponding vial number
- BUD
- Storage conditions

Shipping and Transport

17. 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.

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

Documentation

19. 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:

- SOPs describing all aspects of the compounding process
- Personnel training records, competency assessments, and qualification records including corrective actions for any failures
- Certification reports of the PEC, if used, including corrective actions for any failures
- Temperature logs for the refrigerator(s)
- Compounding records for individual allergenic extract prescription sets (see *Box 21-1*)
- Information related to complaints and adverse events
- Investigations and corrective actions

Box 21-1. Compounding Records for Individual Allergenic Extract Prescription Sets

Compounding Records must include at least the following information:

- Name, concentration, volume, vendor or manufacturer, lot number, and expiration date for each component
- Date and time of preparation of the allergenic extract
- Assigned internal identification number
- A method to identify the individuals involved in the compounding process and verifying the final CSP
- Total quantity compounded
- Assigned BUD and storage requirements
- Results of QC procedures (e.g., visual inspection, second verification of quantities)

GLOSSARY

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.

Added substances: Ingredients that are necessary to compound a preparation but are 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 ingredients, excipients, and pharmaceutical ingredients.

Administration: The direct application of a sterile medication to a single patient by injecting, infusing, or otherwise providing a sterile medication 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.

Allergenic extract prescription set: Combinations of licensed allergenic extracts which 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.

Allergenic extracts: Biological substances 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 extracts compounding area (AECA): A designated, unclassified space, area, or room with a visible perimeter that is suitable for preparation of allergenic extract prescription sets.

Ante-room: 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 ante-room 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, 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.

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.

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.

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 ante-room.

Category 1 CSP: A CSP that is assigned a BUD of 12 hours or less at controlled room temperature or 24 hours 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 is assigned a BUD of greater than 12 hours at controlled room temperature or greater than 24 hours refrigerated that is compounded in accordance with all applicable requirements for Category 2 CSPs in this chapter.

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.

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

Cleaning agent: An agent for the removal of residues (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.

Cleanroom suite: A classified area that consists of both an ante-room 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 or bulk drug substance to create a sterile medication.

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.

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 ventilated enclosure: A 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 FDA-approved application, and 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 compounding facility and personnel in 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 disinfectant agents 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 *Dynamic operating conditions*). This test is not appropriate for ISO Class 7 or ISO Class 8 cleanrooms that do not have unidirectional airflow (see *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).

Excipients: See *Added substances*.

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.

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, coveralls), 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).

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.

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 work tables and effective placement of air returns.

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

Laminar airflow system (LAFS): A device or zone within a buffer area 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 ante-room.

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.

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.

Multiple-dose container: A container of sterile medication for parenteral administration (e.g., injection or infusion) that is designed to contain more than 1 dose of the medication. A multiple-dose container is usually required to meet the antimicrobial effectiveness testing criteria. See *Packaging and Storage Requirements* ⟨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 non-porous surface in the presence of light to moderate organic soiling without a separate cleaning step.

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

Perimeter: A visible demarcation that defines the boundaries of the SCA or AECA (e.g. a visible line or wall).

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 *Packaging and Storage Requirements* ⟨659⟩*, Injection Packaging Systems, Pharmacy bulk package*.

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.]

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.

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.

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, unclassified space, area, or room with a defined perimeter that contains a PEC and is suitable for preparation of Category 1 CSPs only.

Single-dose containers: A container of sterile medication 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 *Packaging and Storage Requirements* ⟨659⟩*, Injection Packaging Systems, Single-dose container*.

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

Sporicidal agent: 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 *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 membranes: Filter membranes that are documented to retain 100% of a culture of 10^7 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-µm or 0.2-µm pore size.

Terminal sterilization: The application of a lethal process (e.g., dry heat, steam, 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.

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.

Workflow management system: Technology comprised of hardware and software that allows for automation to assist in the verification of components of, and preparation of, CSPs and to document components and processes.

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 where particulates can accumulate. This test does not need to be performed under dynamic operating conditions and is not appropriate for PECs (see *Dynamic airflow smoke pattern test*).

APPENDIX

Acronyms

ACD	Automated compounding device
ACPH	Air changes per hour
AECA	Allergenic extracts compounding area
APIs	Active pharmaceutical ingredient(s)
BLA	Biological License Application
BMBL	Biosafety in Microbiological and Biomedical Laboratories
BSC(s)	Biological safety cabinet(s)
BUD(s)	Beyond-use date(s)
CACI	Compounding aseptic containment isolator
CAI	Compounding aseptic isolator
CDC	Centers for Disease Control and Prevention
CETA	Controlled Environment Testing Association
cfu	Colony-forming units
COA(s)	Certificate(s) of analysis
CSP(s)	Compounded sterile preparation(s)
CVE	Containment ventilated enclosure
DCA(s)	Direct compounding area(s)
ECV(s)	Endotoxin challenge vial(s)
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
HD(s)	Hazardous drug(s)
HEPA	High-efficiency particulate air
HVAC	Heating, ventilation, and air conditioning

Acronyms *(continued)*

IPA	Isopropyl alcohol
ISO	International Organization for Standardization
IVLFZ	Integrated vertical laminar flow zone
LAFS	Laminar airflow system
LAFW(s)	Laminar airflow workbench(es)
MEA	Malt extract agar
PEC(s)	Primary engineering control(s)
PNSU	Probability of a nonsterile unit
PPE	Personal protective equipment
QA	Quality assurance
QC	Quality control
RABS	Restricted-access barrier system
SAL	Sterility assurance level
SCA	Segregated compounding area
SDA	Sabouraud dextrose agar
SEC(s)	Secondary engineering control(s)
SOP(s)	Standard operating procedure(s)
TSA	Trypticase soy agar▲ USP 1-Dec-2019