Virginia Department of Health Professions
Board of Veterinary Medicine

Agenda

Virginia Board of Veterinary Medicine
Ad Hoc USP Committee

October 2, 2019
Board Room 1
12:00 p.m.

Call to Order – Autumn Halsey, LVT

- Welcome
- Emergency Egress Procedures

Ordering of Agenda – Ms. Halsey

Public Comment – Dr. Karras
The Board will receive all public comment related to compounding in the practice of veterinary medicine.at this time.

Discussion Items **Pages 1-130**

- Presentation on United States Pharmacopeia (USP) Compounding Requirements – Gigi Davidson, Pharmacist, Chair USP Compounding Expert Committee
- Compounding in Virginia veterinary practices – **Leslie Knachel/Elaine Yeatts**

New Business – Ms. Halsey

Next Meeting – Ms. Halsey/Ms. Knachel

Meeting Adjournment – Ms. Halsey

This information is in **DRAFT** form and is subject to change.

Virginia Board of Veterinary Medicine

Use of Compounded Drugs in Veterinary Practice

Guidance

Q: May a veterinarian prescribe a compounded drug product?

A: A Virginia licensed veterinarian may prescribe a compounded drug product by preparing a valid prescription pursuant to federal and state laws and regulations for an individual patient with which there exists a valid veterinarian-client-patient relationship. The client may obtain the compounded drug product from a pharmacy of their choice that is properly licensed by the Virginia Board of Pharmacy. The payment arrangements for a prescribed compounded drug product are not under the purview of the Board of Veterinary Medicine. However, a pharmacist must be compliant with the Virginia Board of Pharmacy regulation, 18VAC110-20-390(A), which states "*A pharmacist shall not solicit or foster prescription practice with a prescriber of drugs or any other person providing for rebates, 'kickbacks,' fee-splitting, or special charges in exchange for prescription orders unless fully disclosed in writing to the patient and any third party payor.*"

Q: May a veterinarian obtain compounded drug products from a pharmacy for administration in his/her office?

A: Yes, a Virginia licensed veterinarian may obtain compounded drug products from a pharmacy that is properly licensed by the Virginia Board of Pharmacy for *administration* in the course of their professional practice.

Q: May a veterinarian *dispense* a compounded drug product?

A: A veterinarian may dispense a compounded drug product as follows:

Drug Compounded by Veterinarian in Veterinary Facility
A veterinarian may dispense a compounded drug produce *if it is compounded by the veterinarian* pursuant to Virginia Code § 54.1-3410.2(J).

Drug Compounded by Pharmacy and Purchased by Veterinarian
A veterinarian may only dispense a compounded drug obtained from a pharmacy under the conditions set forth in § 54.1-3301(2) which states "… a veterinarian shall only be authorized to dispense a compounded drug, distributed from a pharmacy, when (i) the animal is his own patient, (ii) the animal is a companion animal as defined in regulations promulgated by the Board of Veterinary Medicine, (iii) the quantity dispensed is no more than a seven-day supply, (iv) the compounded drug is for the treatment of an emergency condition, and (v) timely access to a compounding pharmacy is not available, as determined by the prescribing veterinarian;…"

Q: What is the penalty for a licensee of the Virginia Board of Veterinary Medicine who is found to be dispensing compounded drug product not in accordance with federal law or the Virginia Drug Control Act?

A: The licensee may be subject to disciplinary action.

Applicable Laws

§ 54.1-3301. Exceptions.
This chapter shall not be construed to:
1. Interfere with any legally qualified practitioner of dentistry, or veterinary medicine or any physician acting on behalf of the Virginia Department of Health or local health departments, in the compounding of his prescriptions or the purchase and possession of drugs as he may require;
2. Prevent any legally qualified practitioner of dentistry, or veterinary medicine or any prescriber, as defined in § 54.1-3401 acting on behalf of the Virginia Department of Health or local health departments, from administering or supplying to his patients the medicines that he deems proper under the conditions of § 54.1-3303 or from causing drugs to be administered or dispensed pursuant to §§ 32.1-42.1 and 54.1-3408 except that a veterinarian shall only be authorized to dispense a compounded drug, distributed from a pharmacy, when (i) the animal is his own patient, (ii) the animal is a companion animal as defined in regulations promulgated by the Board of Veterinary Medicine, (iii) the quantity dispensed is no more than a seven-day supply, (iv) the compounded drug is for the treatment of an emergency condition, and (v) timely access to a compounding pharmacy is not available, as determined by the prescribing veterinarian;

§ 54.1-3401. Definitions.
"Compounding" means the combining of two or more ingredients to fabricate such ingredients into a single preparation and includes the mixing, assembling, packaging, or labeling of a drug or device (i) by a pharmacist, or within a permitted pharmacy, pursuant to a valid prescription issued for a medicinal or therapeutic purpose in the context of a bona fide practitioner-patient-pharmacist relationship, or in expectation of receiving a valid prescription based on observed historical patterns of prescribing and dispensing; (ii) by a practitioner of medicine, osteopathy, podiatry, dentistry, or veterinary medicine as an incident to his administering or dispensing, if authorized to dispense, a controlled substance in the course of his professional practice; or (iii) for the purpose of, or as incident to, research, teaching, or chemical analysis and not for sale or for dispensing. The mixing, diluting, or reconstituting of a manufacturer's product drugs for the purpose of administration to a patient, when performed by a practitioner of medicine or osteopathy licensed under Chapter 29 (§ 54.1-2900 et seq.), a person supervised by such practitioner pursuant to subdivision A 6 or A 19 of § 54.1-2901 or a person supervised by such practitioner or a licensed nurse practitioner or physician assistant pursuant to subdivision A 4 of § 54.1-2901 shall not be considered compounding.

§ 54.1-3410.2. Compounding; pharmacists' authority to compound under certain conditions; labeling and record maintenance requirements.
A. A pharmacist may engage in compounding of drug products when the dispensing of such compounded products is (i) pursuant to valid prescriptions for specific patients and (ii) consistent with the provisions of § 54.1-3303 relating to the issuance of prescriptions and the dispensing of drugs.

Pharmacists shall label all compounded drug products that are dispensed pursuant to a prescription in accordance with this chapter and the Board's [Pharmacy] regulations, and shall include on the labeling an appropriate beyond-use date as determined by the pharmacist in compliance with USP-NF standards for pharmacy compounding.

B. A pharmacist may also engage in compounding of drug products in anticipation of receipt of prescriptions based on a routine, regularly observed prescribing pattern.

Pharmacists shall label all products compounded prior to dispensing with (i) the name and strength of the compounded medication or a list of the active ingredients and strengths; (ii) the pharmacy's assigned control number that corresponds with the compounding record; (iii) an appropriate beyond-use date as determined by the pharmacist in compliance with USP-NF standards for pharmacy compounding; and (iv) the quantity.

C. In accordance with the conditions set forth in subsections A and B, pharmacists shall not distribute compounded drug products for subsequent distribution or sale to other persons or to commercial entities, including distribution to pharmacies or other entities under common ownership or control with the facility in which such compounding takes place; however, a pharmacist may distribute to a veterinarian in accordance with federal law.

Compounded products for companion animals, as defined in regulations promulgated by the Board of Veterinary Medicine, and distributed by a pharmacy to a veterinarian for further distribution or sale to his own patients shall be limited to drugs necessary to treat an emergent condition when timely access to a compounding pharmacy is not available as determined by the prescribing veterinarian.

*A pharmacist may, however, deliver compounded products dispensed pursuant to valid prescriptions to alternate delivery locations pursuant to § **54.1-3420.2.***
A pharmacist may provide a reasonable amount of compounded products to practitioners of medicine, osteopathy, podiatry, or dentistry to administer to their patients, either personally or under their direct and immediate supervision, if there is a critical need to treat an emergency condition, or as allowed by federal law or regulations. A pharmacist may also provide compounded products to practitioners of veterinary medicine for office-based administration to their patients.

Pharmacists who provide compounded products for office-based administration for treatment of an emergency condition or as allowed by federal law or regulations shall label all compounded products distributed to practitioners other than veterinarians for administration to their patients with (i) the statement "For Administering in Prescriber Practice Location Only"; (ii) the name and strength of the compounded medication or list of the active ingredients and strengths; (iii) the facility's control number; (iv) an appropriate beyond-use date as determined by the pharmacist in compliance with USP-NF standards for pharmacy compounding; (v) the name and address of the pharmacy; and (vi) the quantity. Pharmacists shall label all compounded products for companion animals, as defined in regulations promulgated by the Board of Veterinary Medicine, and distributed to a veterinarian for either further distribution or sale to his own patient or administration to his own patient with (a) the name and strength of the compounded medication or list of the active ingredients and strengths; (b) the facility's control number; (c) an appropriate beyond-use date as determined by the pharmacist in compliance with USP-NF standards for pharmacy compounding; (d) the name and address of the pharmacy; and (e) the quantity.

E. Pharmacists shall ensure compliance with USP-NF standards for both sterile and non-sterile compounding.

*J. Practitioners who may lawfully compound drugs for administering or dispensing to their own patients pursuant to §§ **54.1-3301**, **54.1-3304**, and **54.1-3304.1** shall comply with all provisions of this section and the relevant Board regulations.*

USP 795

Printed on: Wed Jul 31 2019, 14:45:37 pm
Printed by: Sammy Johnson
Not Yet Official as of: 31-Jul-2019
To be Official on 1-Dec-2019
DocId: GUID-98DCB48D-DC23-4A63-AD2E-01CA8979FB7E_3_en-US
Printed from: https://online.uspnf.com/uspnf/document/GUID-98DCB48D-DC23-4A63-AD2E-01CA8979FB7E_3_en-US

⟨795⟩ PHARMACEUTICAL COMPOUNDING—NONSTERILE PREPARATIONS

Change to read:

1. INTRODUCTION AND SCOPE

This chapter describes the minimum standards to be followed when preparing compounded nonsterile preparations (CNSPs) for humans and animals. For purposes of this chapter, nonsterile compounding is defined as combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer's labeling, or otherwise altering a drug or bulk drug substance to create a nonsterile medication.

The requirements in this chapter must be followed to minimize harm, including death, to human and animal patients that could result from 1) excessive microbial contamination, 2) variability from the intended strength of correct ingredients (e.g., ±10% of the labeled strength), 3) physical and chemical incompatibilities, 4) chemical and physical contaminants, and/or 5) use of ingredients of inappropriate quality.

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

1.1 Scope

CNSPS SUBJECT TO THE REQUIREMENTS IN THIS CHAPTER

CNSPs that must comply with this chapter include but are not limited to the following dosage forms:

- Solid oral preparations
- Liquid oral preparations
- Rectal preparations
- Vaginal preparations
- Topical preparations (i.e., creams, gels, ointments)
- Nasal and sinus preparations intended for local application (i.e., nasal sprays and nasal irrigation)
- Otic preparations

PRACTICES NOT SUBJECT TO THE REQUIREMENTS IN THIS CHAPTER

The following practices are not considered compounding and are not required to meet the requirements of this chapter:

Administration: Preparation of a single dose for a single patient when administration will begin within 4 hours of beginning the preparation is not required to meet the standards in this chapter.

Nonsterile radiopharmaceuticals: Compounding of nonsterile radiopharmaceuticals is not required to meet the standards in this chapter and is subject to the requirements in *Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging* ⟨825⟩.

Reconstitution: Reconstitution of a conventionally manufactured nonsterile product in accordance with the directions contained in the manufacturer approved labeling is not required to meet the standards in this chapter.

Repackaging: Repackaging of conventionally manufactured drug products is not required to meet the standards in this chapter (see *Good Repackaging Practices* ⟨1178⟩).

Splitting tablets: Breaking or cutting a tablet into smaller portions is not required to meet the standards in this chapter.

PERSONNEL AND SETTINGS AFFECTED

This chapter applies to all persons who prepare CNSPs and all places where CNSPs 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 pharmacies, hospitals and other healthcare institutions, patient treatment sites, and physicians' or veterinarians' practice sites.

The compounding facility's leadership and all personnel involved in preparing, storing, packaging, and transporting CNSPs are responsible for 1) ensuring that the applicable practices and quality standards in this chapter are continually and consistently applied to their operations, and 2) proactively identifying and remedying potential problems within their operations. Personnel engaged in the compounding of CNSPs must also comply with laws and regulations of the applicable regulatory jurisdiction.

The compounding facility must designate one or more individuals to be responsible and accountable for the performance and operation of the facility and personnel for the preparation of CNSPs. The responsibilities of the designated person(s) include but are not limited to:

- Overseeing a training program to ensure competency of personnel involved in compounding, handling, and preparing of CNSPs
- Selecting components
- Monitoring and observing compounding activities and taking immediate corrective action if deficient practices are observed
- Ensuring that standard operating procedures (SOPs) are fully implemented. The designated person(s) must ensure that follow-up is carried out if problems, deviations, or errors are identified
- Establishing, monitoring, and documenting procedures for the handling and storage of CNSPs and/or components of CNSPs

The designated person(s) must be identified in an SOP. If the compounding facility has only one person responsible for all of the compounding in the facility, then that person is the designated person.

2. PERSONNEL TRAINING AND EVALUATION

All personnel involved in the preparation and handling of CNSPs must be initially trained, must demonstrate competency, and must undergo refresher training every 12 months. Training and competency of personnel must be documented as described in *15. Documentation*.

A designated person must oversee a training program that describes the required training, the frequency of training, and the process for evaluating the competency of personnel involved in nonsterile compounding and handling of CNSPs. This program must equip personnel with knowledge and training in the required skills necessary to perform their assigned tasks.

Before beginning to prepare CNSPs independently, all compounding personnel must complete training and be able to demonstrate proficiency in the principles and hands-on skills of nonsterile manipulations for the type of compounding they will be performing. Proficiency must be demonstrated every 12 months in at least the following core competencies:

- Hand hygiene

- Garbing
- Cleaning and sanitizing
- Handling and transporting components and CNSPs
- Measuring and mixing
- Proper use of equipment and devices selected to compound CNSPs
- Documentation of the compounding process (e.g., Master Formulation Records and Compounding Records)

Steps in the training procedure must include the following:

- Read and understand this chapter, other applicable standards, and other relevant literature
- Understand and interpret Safety Data Sheets (SDSs) and, if applicable, Certificates of Analysis (COA)
- Read and understand procedures related to their compounding duties

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 be observed and guided throughout the training process. The personnel will then be expected to repeat the procedures independently, but under the direct supervision of the designated person(s) and/or trainer. Personnel will be permitted to perform the procedure without direct supervision only after independently demonstrating understanding and competency. Upon completion of the training program, the designated person(s) and/or trainer must document that the personnel has been trained and successfully completed competency assessments (see *15. Documentation*).

In addition to the initial and annual competency training and evaluation described in this section, a designated person should monitor and observe compounding activities and must take immediate corrective action if deficient practices are observed. SOPs must describe procedures for the monitoring and observing of compounding activities and personnel.

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.

3. PERSONAL HYGIENE AND GARBING

Individuals entering the compounding area must maintain personal hygiene. Individuals must evaluate whether they have a personal risk of potentially contaminating the compounding environment and CNSP (e.g., personnel with rashes, recent tattoos or oozing sores, conjunctivitis, or active respiratory infection). Individuals must report these conditions to the designated person(s). The designated person(s) is responsible for evaluating whether these individuals should be excluded from working in compounding areas before their conditions have resolved because of the risk of contaminating the CNSP and the environment.

3.1 Personnel Preparation

Personnel engaged in compounding must maintain hand hygiene and maintain cleanliness required for the type of compounding performed.

Before entering the compounding area, compounding personnel must remove any items that are not easily cleanable and that might interfere with garbing. At a minimum, personnel must:

- Remove personal outer garments (e.g., bandanas, coats, hats, jackets)
- Remove all hand, wrist, and other exposed jewelry, including piercings that could interfere with the effectiveness of garbing or hand hygiene (e.g., watches, rings that may tear gloves)
- Remove earbuds or headphones

The designated person(s) may permit accommodations as long as the quality of the environment and CNSP will not be affected.

3.2 Hand Hygiene

Personnel must perform hand hygiene when entering the compounding area to compound as described in *Box 3-1*. Alcohol hand sanitizers alone are not sufficient.

Box 3-1. Hand Hygiene Procedures

- 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 disposable towels or wipers.
- Allow hands and forearms to dry thoroughly before donning gloves.

To minimize the risk of cross-contaminating other CNSPs and contaminating other objects (e.g., pens and keyboards), gloves should be wiped or replaced before beginning a CNSP with different components.

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

3.3 Garb and Glove Requirements

Gloves must be worn for all compounding activities. Other garb (e.g., shoe covers, head and facial hair covers, face masks, gowns) should be worn as needed for the protection of personnel from chemical exposures and for prevention of preparation contamination and must be appropriate for the type of compounding performed. The garbing requirements and frequency of changing the garb must be determined by the facility and documented in the facility's SOPs.

Garb must be stored in a manner that minimizes contamination (e.g., away from sinks to avoid splashing). Visibly soiled garb or garb with tears or punctures must be changed immediately.

If gowns are worn, they may be re-used if not soiled. If used, gloves, shoe covers, hair covers, facial hair covers, face masks, or head coverings may not be re-used and must be replaced with new ones. If used, non-disposable garb, such as goggles, should be cleaned and sanitized with 70% isopropyl alcohol before re-use.

4. BUILDINGS AND FACILITIES

4.1 Compounding Space

Space must be specifically designated for nonsterile compounding. The method of designation (e.g., visible perimeter) must be described in the facility's SOP. Other activities must not be occurring in the space at the same time as compounding. The compounding space must be well-lighted and must be maintained in a clean, orderly, and sanitary condition, and in a good state of repair. Carpet is not allowed in the compounding space. Surfaces should be resistant to damage by cleaning and sanitizing agents.

The space must provide for the orderly placement of equipment and materials to prevent mix-ups among components, containers, labels, in-process materials, and finished CNSPs. The space should be designed, arranged, and used in a way that minimizes cross-contamination from non-compounding areas.

4.2 Storage Area

Compounding personnel must monitor temperatures in storage area(s) 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 for the CNSPs or components. The results of the temperature readings must be documented on a temperature log or stored in the continuous temperature recording device, and must be retrievable. All temperature monitoring equipment must be calibrated or verified for accuracy as recommended by the manufacturer or every 12 months if not specified by the manufacturer.

The compounding facility must adhere to SOPs to detect and prevent temperature excursions within storage area(s). When it is known that a CNSP or component has been exposed to temperatures either below or above the storage temperature limits for the CNSP or component, personnel must determine whether the CNSP or component integrity or quality has been compromised and, if so, the CNSP or component must be discarded.

All CNSPs, components, equipment, and containers must be stored off the floor and in a manner that prevents contamination and permits inspection and cleaning of the storage area(s).

4.3 Water Sources

A source of hot and cold water and an easily accessible sink must be available for compounding. The sink must be emptied of all items unrelated to compounding and cleaned when visibly soiled before being used to clean any equipment used in nonsterile compounding. The plumbing system must be free of defects that may contribute to the contamination of any CNSP. *Purified Water* (see *Water for Pharmaceutical Purposes* (1231)), distilled water, or reverse osmosis water should be used for rinsing equipment and utensils.

5. CLEANING AND SANITIZING

Cleaning and sanitizing of the surfaces in the nonsterile compounding area(s) must occur on a regular basis at the minimum frequencies specified in *Table 1* or, if compounding is not performed daily, cleaning and sanitizing must be completed before initiating compounding. Cleaning and sanitizing must be repeated when spills occur and when surfaces are visibly soiled.

Cleaning and sanitizing agents must be selected and used with consideration of compatibilities, effectiveness, and to minimize the potential to leave residues.

If cleaning and sanitizing are performed as separate steps, cleaning must be performed first.

Table 1. Minimum Frequency for Cleaning and Sanitizing Surfaces in Nonsterile Compounding Area(s)

Site	Minimum Frequency
Work surfaces	• At the beginning and end of each shift, after spills, and when surface contamination is known or suspected • Clean and sanitize the work surfaces between compounding CNSPs with different components
Floors	Daily, after spills, and when surface contamination (e.g., splashes) is known or suspected
Walls	Every 3 months, after spills, and when surface contamination (e.g., splashes) is known or suspected
Ceilings	When visibly soiled and when surface contamination is known or suspected
Storage shelving	Every 3 months, after spills, and when surface contamination (e.g., splashes) is known or suspected

6. EQUIPMENT AND COMPONENTS

6.1 Equipment

The equipment and supplies used for compounding a CNSP must be suitable for the specific compounding process. Equipment surfaces that contact components must not be reactive, additive, or sorptive, and must not alter the quality of the CNSPs. Disposable or dedicated equipment may be used to reduce the chance of bioburden and cross-contamination.

Equipment must be stored in a manner to minimize the risk of contamination and must be located to facilitate its use, maintenance, and cleaning. Equipment and devices used in the compounding or testing of compounded preparations must be inspected prior to use and, if appropriate, verified for accuracy as recommended by the manufacturer and at the frequency recommended by the manufacturer, or at least every 12 months, whichever is more frequent. After compounding, the equipment must be cleaned to prevent cross-contamination of the next preparation.

Weighing, measuring, or otherwise manipulating components that could generate airborne chemical particles [e.g., active pharmaceutical ingredients (APIs), added substances, conventionally manufactured products] must be assessed to determine if these activities must be performed in closed system processing device to reduce the potential exposure to personnel or contamination of the facility or CNSPs. Examples of closed system processing devices include containment ventilated enclosures (CVEs), biological safety cabinets (BSCs), or single-use containment glove bags. The process evaluation must be carried out in accordance with the facility SOP and the assessment must be documented.

If a BSC or CVE is used, it must be certified every 12 months according to requirements such as the current Controlled Environment Testing Association (CETA), NSF International, or American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE) guidelines, or other laws and regulations of the applicable regulatory jurisdiction.

If a CVE or other non-disposable device is used, it must be cleaned as described in *Table 2*.

Table 2. Minimum Frequency for Cleaning and Sanitizing Equipment in Nonsterile Compounding Area(s)

Site	Minimum Frequency
CVE	• At the beginning and end of each shift, after spills, and when surface contamination is known or suspected • Clean and sanitize the horizontal work surface of the CVE between compounding CNSPs with different components
Other devices and equipment used in compounding operations	• Before first use and thereafter in accordance with the manufacturer's recommendations • If no recommendation is available, after compounding CNSPs with different components

6.2 Components

The compounding facility must have written SOPs for the selection and inventory control of all components from receipt to use in a CNSP.

SDSs must be readily accessible to all personnel working with APIs and added substances located in the compounding facility. Personnel must be instructed on how to retrieve and interpret needed information.

COMPONENT SELECTION

A designated person must be responsible for selecting components to be used in compounding.

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
- In the United States, must be obtained from an FDA-registered facility
- Outside of the United States, must comply with laws and regulations of the applicable regulatory jurisdiction

All components other than APIs:

- Should be accompanied by a COA that verifies that the component meets the criteria in the *USP–NF* monograph, if one exists, and any additional specifications for the component
- In the United States, should be obtained from an FDA-registered facility
  - If it cannot be obtained from an FDA-registered facility, the designated person(s) must select a component that is suitable for the intended use
- Outside of the United States, must comply with laws and regulations of the applicable regulatory jurisdiction

COMPONENT RECEIPT

Upon receipt of components other than conventionally manufactured products, the COA must be reviewed to ensure that the component has met the acceptance criteria in a *USP–NF* monograph, if one exists. For components other than conventionally manufactured products, information including the receipt date, quantity received, supplier name, lot number, expiration date, and results of any in-house or third-party testing performed must be documented.

The date of receipt by the compounding facility must be clearly and indelibly marked on each component package that lacks a vendor expiration date. Packages of components (i.e., API and added substances) that lack a vendor's expiration date must not be used by the compounding facility after 3 years from

the date of receipt. A shorter expiration date must be assigned according to *Pharmaceutical Compounding—Sterile Preparations (797), 9.3 Components, Component Receipt* if the same component container is also used in sterile compounding or if the ingredient is known to be susceptible to degradation.

For each use, the lot must be examined for evidence of deterioration and other aspects of unacceptable quality. Once removed from the original container, components not used in compounding (e.g., excess after weighing) should be discarded and not returned to the original container to minimize the risk of contaminating the original container.

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

COMPONENT EVALUATION BEFORE USE

Before use, compounding personnel must visually re-inspect all components. Packages must be inspected to detect container breaks, looseness of the cap or closure, or deviation from the expected appearance or texture of the contents that might have occurred during storage.

Compounding personnel must ascertain before use that components are of the correct identity based on the labeling and have been stored under required conditions in the facility.

If the correct identity, strength, purity, and quality of components intended for preparation of CNSPs cannot be confirmed (e.g., containers with damaged or incomplete labeling), they must be immediately rejected. If they are not immediately discarded, they must be clearly labeled as rejected, and segregated to prevent their use before disposal.

COMPONENT HANDLING

All components must be handled in accordance with the manufacturer's instructions or per laws and regulations of the applicable regulatory jurisdiction. The handling must minimize the risk of contamination, mix-ups, and deterioration (e.g., loss of identity, strength, purity, and quality).

COMPONENT SPILL AND DISPOSAL

The facility must maintain chemical hazard and disposal information (e.g., SDSs) and must review and update its chemical hazard and disposal information every 12 months. The chemical hazard and disposal information (e.g., SDSs) must be made accessible to compounding personnel.

The facility must have an SOP for the management of nonhazardous component spills and disposal. If required by the SOP, these activities must be documented and corrective action taken.

The facility must have a readily accessible spill kit in the compounding area. The contents of the spill kit should be affixed to the packaging of the spill kit if not readily visible on the manufacturer's label.

All personnel who may be required to remediate a spill must receive training in spill management of chemicals used and stored at the compounding facility. Refresher training must be conducted every 12 months and documented for all personnel who may be required to clean up a spill.

Waste must be disposed of in accordance to laws and regulations of the applicable regulatory jurisdiction. The disposal of components must comply with laws and regulations of the applicable regulatory jurisdiction. For information on the handling of HDs, see (800).

7. MASTER FORMULATION AND COMPOUNDING RECORDS

7.1 Creating Master Formulation Records

A Master Formulation Record is a detailed record of procedures that describes how the CNSP is to be prepared. A Master Formulation Record must be created for each unique formulation of a CNSP. CNSPs are prepared according to the Master Formulation Record and the preparation information is documented on a Compounding Record (see *7.2 Creating Compounding Records*). Any changes or alterations to the Master Formulation Record must be approved and documented according to the facility's SOP. *Box 7-1* lists the information that must be included in a Master Formulation Record.

Box 7-1. Master Formulation Records

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

- Name, strength or activity, and dosage form of the CNSP
- Identities and amounts of all components
  - If applicable, relevant characteristics of components (e.g., particle size, salt form, purity grade, solubility)
- Container–closure system(s)
- Complete instructions for preparing the CNSP, including equipment, supplies, and a description of the compounding steps
- Physical description of the final CNSP
- Assigned beyond-use date (BUD) and storage requirements
- Reference source to support the assigned BUD and storage requirements
- If applicable, calculations to determine and verify quantities and/or concentrations of components and strength or activity of API
- Labeling requirements (e.g., shake well)
- Quality control (QC) procedures (e.g., pH testing, visual inspection) and expected results
- Other information needed to describe the compounding process and ensure repeatability (e.g., adjusting pH, temperature)

7.2 Creating Compounding Records

A Compounding Record documents the compounding of each CNSP. A Compounding Record must be created for all CNSPs. Each Compounding Record must be reviewed for completeness before the CNSP is released. The identifier of the person completing the review and the date of review must be documented on the Compounding Record. The Compounding Record must permit traceability of all components in the case of a recall or known quality issue. The Master Formulation Record can be used as the basis for preparing the Compounding Record. For example, a copy of the Master Formulation Record can be made that contains spaces to record the information needed to complete the Compounding Record. *Box 7-2* lists the information that must be included in a Compounding Record.

Box 7-2. Compounding Records

Compounding Records must include at least the following information:

- Name, strength or activity, and dosage form of the CNSP
- Date and time of preparation of the CNSP
- 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 CNSP
- Name, vendor or manufacturer, lot number, and expiration date of each component
- Weight or measurement of each component
- Total quantity compounded
- Assigned BUD and storage requirements
- If applicable, calculations to determine and verify quantities and/or concentrations of components and strength or activity of API
- Physical description of the final CNSP
- Results of quality control procedures (e.g., pH testing, visual inspection)
- Master Formulation Record reference for the CNSP

8. RELEASE INSPECTIONS

At the completion of compounding and before release and dispensing, the CNSP must be visually inspected to determine whether the physical appearance is as expected. Inspections must also confirm that the CNSP and its labeling match the Compounding Record and the prescription or medication order. Some CNSPs, as noted in their Master Formulation Record, also must be visually checked for certain characteristics (e.g., emulsions must be checked for phase separation). All checks and inspections, and if required, any other tests necessary to ensure the quality of the CNSP must be detailed in the facility's Master Formulation Records. Checks and inspections must be documented. Additional quality assurance (QA) and quality control activities are described in *12. Quality Assurance and Quality Control*. Pre-release inspection also must include a visual inspection of container–closure integrity (e.g., checking for leakage, cracks in the container, or improper seals). CNSPs with observed defects must be immediately discarded, or marked and segregated from acceptable units in a manner that prevents them from being released or dispensed.

9. LABELING

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 the article is enclosed, except any outer shipping container. The term label designates the part of the labeling on the immediate container. See *Labeling ⟨7⟩*.

Every dispensed CNSP must be labeled with adequate, legible identifying information to prevent errors during storage, dispensing, and use. All labeling must be in compliance with laws and regulations of the applicable regulatory jurisdiction.

The label on each immediate container of the CNSP must, at a minimum, display the following information:

- Assigned internal identification number (e.g., barcode, prescription, order, or lot number)
- Active component(s), and amounts, activities, or concentrations
- Dosage form
- Amount or volume in each container
- Storage conditions if other than controlled room temperature
- BUD

The labeling on the CNSP should display the following information:

- Route of administration
- Indication that the preparation is compounded

- Any special handling instructions
- Any warning statements that are applicable
- Name, address, and contact information of the compounding facility if the CNSP is to be sent outside of the facility or healthcare system in which it was compounded

Labeling operations must be controlled to prevent labeling errors and CNSP mix-ups. A final check must be conducted to verify that the correct label has been affixed to the finished CNSP. All labels must also comply with laws and regulations of the applicable regulatory jurisdiction.

10. ESTABLISHING BEYOND-USE DATES

10.1 Terminology

Each CNSP label must state the date, or the hour and date, beyond which the preparation cannot be used and must be discarded (i.e., the BUD). BUDs for CNSPs are calculated in terms of hours, days, or months.

BUDs and expiration dates are not the same. An expiration date identifies the time during which a conventionally manufactured drug product, active ingredient, 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 a 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.

10.2 Parameters to Consider in Establishing a BUD

BUDs for CNSPs should be established conservatively to ensure that the preparation maintains its required characteristics to minimize the risk of contamination or degradation.

When establishing a BUD for a CNSP, it is critical that personnel carefully consider the possible ways that the physical or chemical characteristics of the CNSP could change over time. The following factors must be considered:

- The chemical and physical stability properties of the API and any added substances in the preparation (e.g., if the API and added substances in the preparation are known to degrade over time and/or under certain storage conditions, which would reduce the strength of the preparation and/or produce harmful impurities)
- The compatibility of the container–closure system with the finished preparation (e.g., leachables, interactions, adsorption, and storage conditions)
- Degradation of the container–closure system, which can lead to a reduction in integrity of the CNSP
- The potential for microbial proliferation in the CNSP

10.3 Establishing a BUD for a CNSP

The BUDs indicate the days after the CNSP is prepared and beyond which the CNSP must not be used. The day that the preparation is compounded is considered Day 1. The BUDs in *Table 3* are based on the ability of the CNSP to maintain chemical and physical stability and to suppress microbial growth. *Table 3* represents the maximum BUDs for CNSPs that are packaged in tight, light-resistant containers unless conditions under *10.4 CNSPs Requiring Shorter BUDs* or *10.5 Extending BUDs for CNSPs* apply.

The aqueous and nonaqueous dosage forms in *Table 3* are defined based on the water activity (Aw) of the most similar drug product described in *Application of Water Activity Determination to Nonsterile Pharmaceutical Products (1112)*. In general, the use of Aw aids in assessing the susceptibility of CNSPs to microbial contamination and the potential for API degradation due to hydrolysis. Reduced Aw greatly assists in the prevention of microbial proliferation in conventionally manufactured products and is expected to convey the same benefit to CNSPs. The list of manufactured products in *Application of Water Activity Determination to Nonsterile Pharmaceutical Products (1112)*, *Table 2* is not exhaustive. However, it provides guidance on the Aw value of a particular CNSP and can assist personnel in determining the BUD by dosage form based on *Table 3*.

CNSPs with an Aw > 0.6 should contain suitable antimicrobial agents to protect against bacteria, yeast, and mold contamination from proliferation if inadvertently introduced during or after the compounding process. When antimicrobial preservatives are clinically contraindicated in a CNSP, storage of the preparation in a refrigerator is required if such storage does not change the physical or chemical properties of the CNSP (i.e., precipitation).

Table 3. Maximum BUD by Type of Preparation in the Absence of a *USP-NF* Compounded Preparation Monograph or CNSP-Specific Stability Information

Type of Preparation	BUDs (days)	Storage Temperature[a]
Non-preserved aqueous dosage forms[b]	14	Refrigerator
Preserved aqueous dosage forms[b]	35	Controlled room temperature or refrigerator
Nonaqueous dosage forms[c]	90	Controlled room temperature or refrigerator
Solid dosage forms[d]	180	Controlled room temperature or refrigerator

[a] See *Packaging and Storage Requirements (659)*.
[b] An aqueous preparation is one that has an Aw of > 0.6 (e.g., emulsions, gels, creams, solutions, sprays, or suspensions).
[c] Any preparation other than solid dosage forms that have a reduced Aw of ≤0.6 (e.g., suppositories, ointments, fixed oils, or waxes).
[d] Capsules, tablets, granules, powders.

10.4 CNSPs Requiring Shorter BUDs

A shorter BUD must be established under the following circumstances:

- If the API or any other components in the CNSP have an expiration date that is earlier than the BUD that could be assigned from *Table 3*, the expiration date supersedes the BUD and must be the assigned shortest date
- If the CNSP includes components from conventionally manufactured product(s), the BUD of the CNSP must not exceed the shortest remaining expiration date of any of those conventionally manufactured product(s)
- If the CNSP includes components from other compounded preparations, the BUD of the final CNSP must not exceed the shortest remaining BUD of any of those compounded preparations
- If the formulation is known to require a shorter BUD

10.5 Extending BUDs for CNSPs

CNSPS WITH A *USP–NF* MONOGRAPH

If there is a *USP–NF* compounded preparation monograph for the CNSP, the BUD must not exceed the BUD specified in the monograph.

CNSPS WITH STABILITY INFORMATION

The BUDs specified in *Table 3* for aqueous dosage forms and nonaqueous dosage forms may be extended up to maximum of 180 days if there is a stability study (published or unpublished) using a stability-indicating assay for the API(s), CNSP, and type of container–closure that will be used.

If the BUD of the CNSP is extended beyond the BUDs in *Table 3*, an aqueous CNSP should be tested for antimicrobial effectiveness (see *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 CNSP 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.

11. SOPS

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

One or more person(s) must be designated to ensure that SOPs are fully implemented. The designated person(s) must ensure that follow-up occurs if problems, deviations, or errors are identified.

12. QUALITY ASSURANCE AND QUALITY CONTROL

Quality assurance and quality control programs are necessary to ensure that consistently high-quality CNSPs are prepared. 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 CNSP. 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 CNSPs are conducted in accordance with 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. Designated person(s) responsible for the QA program must have the training, experience, responsibility, and authority to perform these duties. The overall QA and QC program must be reviewed at least once every 12 months by the designated person(s). The results of the review must be documented and appropriate action must be taken if needed.

13. CNSP PACKAGING AND TRANSPORTING

13.1 Packaging of CNSPs

SOPs must describe packaging of CNSPs. Personnel should select and use packaging materials that will maintain the physical and chemical integrity and stability of the CNSPs. Packaging materials must protect CNSPs from damage, leakage, contamination, and degradation, while simultaneously protecting personnel from exposure.

13.2 Transporting CNSPs

If transporting CNSPs, the facility must have written SOPs to describe the mode of transportation, any special handling instructions, and whether temperature monitoring devices are needed.

14. COMPLAINT HANDLING AND ADVERSE EVENT REPORTING

Compounding facilities must develop and implement SOPs for complaint and adverse event report receipt, acknowledgment, and handling and designate one or more person(s) to be responsible for handling them. Complaints may include concerns or reports on the quality and labeling of, or possible adverse reactions to, a specific CNSP.

14.1 Complaint Handling

The designated person(s) must ensure that all complaints are reviewed to determine whether the complaint indicates a potential quality problem with the CNSP. 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 CNSPs. Corrective action, if necessary, must be implemented for all potentially affected CNSPs. Consider whether to initiate a recall of potentially affected CNSPs and whether to cease nonsterile 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., e-mail, 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 CNSP, the prescription or medication order number, and the lot number, if one is assigned.

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 *15. Documentation*. A CNSP 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.

14.2 Adverse Event Reporting

The designated person(s) must ensure that reports of potential adverse events involving a CNSP are reviewed. If the investigation into an adverse event reveals a quality problem with a CNSP that is likely to affect other patients, those patients and prescribers potentially affected must be informed. The designated person(s) must review all adverse event reports as part of the QA and QC programs (see *12. Quality Assurance and Quality Control*). Adverse events must be reported in accordance with facility SOPs and all laws and regulations of the applicable regulatory jurisdiction. In addition, adverse events associated with a CNSP should be reported to the FDA through the MedWatch program for human drugs and through Form FDA 1932a for animal drugs.

15. DOCUMENTATION

All facilities where CNSPs 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 corrective actions for any failures
- Equipment records (e.g., calibration, verification, and maintenance reports)
- COA
- Receipt of components
- SOPs, Master Formulation Records, and Compounding Records
- Release inspection and testing records
- Information related to complaints and adverse events including corrective actions taken
- Results of investigation and corrective actions

Documentation must comply with all laws and regulations of the applicable regulatory jurisdiction. Records must be legible and stored in a manner that prevents their deterioration and/or loss. All required compounding records for a particular CNSP (e.g., Master Formulation Record, Compounding Record, and release inspection and testing results) must be readily retrievable for at least 3 years after preparation or as required by the laws and regulations of the applicable regulatory jurisdiction, whichever is longer.

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.

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

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.

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

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

Compounded nonsterile preparation (CNSP): A preparation intended to be nonsterile created by combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer's labeling, or otherwise altering of a drug or bulk drug substance.

Compounder: Personnel trained to compound preparations.

Compounding: The process of combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer's labeling, or otherwise altering a drug or bulk drug substance to create a nonsterile medication.

Compounding area: A space that is specifically designated for nonsterile compounding. A visible perimeter should establish the boundaries of the nonsterile compounding area.

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

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

Containment ventilated enclosure (CVE): A full or partial enclosure that uses ventilation principles to capture, contain, and remove airborne contaminants through high-efficiency particulate air (HEPA) filtration and to prevent their release into the work environment.
Conventionally manufactured product: A pharmaceutical dosage form, usually the subject of an FDA-approved application that is manufactured under current good manufacturing practice conditions.
Designated person(s): One or more individuals assigned to be responsible and accountable for the performance and operation of the facility and personnel for the preparation of CNSPs.
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. See (800).
Label: A display of written, printed, or graphic matter on the immediate container of any article.
Labeling: All labels and other written, printed, or graphic matter that are 1) on any article or any of its containers or wrappers, or 2) accompanying such an article.
Purified Water: The minimal quality of source water for the production of Purified Water is drinking water whose attributes are prescribed by the US Environmental Protection Agency (EPA), the EU, Japan, or the World Health Organization (WHO). This source water may be purified using unit operations that include deionization, distillation, ion exchange, reverse osmosis, filtration, or other suitable purification procedures. (See *Water for Pharmaceutical Purposes* (1231), *3. Waters Used for Pharmaceutical Manufacturing and Testing Purposes*, *3.1 Bulk Monographed Waters and Steam*, *3.1.1 Purified Water*.)
Preservative: A substance added to inhibit microbial growth.
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 CNSP.
Reconstitution: The process of adding a diluent to a conventionally manufactured product to prepare a solution or suspension.
Release inspection and testing: Visual inspection and testing performed to ensure that a preparation meets appropriate quality characteristics.
Sanitizing agent: An agent for reducing, on inanimate surfaces, the number of all forms of microbial life including fungi, viruses, and bacteria.
Specification: The tests, analytical methods, and acceptance criteria to which an API or other components, CNSP, container–closure system, equipment, or other material used in compounding CNSPs must conform to be considered acceptable for its intended use.
Stability: The extent to which a product or preparation retains physical and chemical properties and characteristics within specified limits throughout its expiration or BUD.

APPENDIX

Acronyms

API(s)	Active pharmaceutical ingredient(s)
ASHRAE	American Society of Heating, Refrigerating, and Air-Conditioning Engineers
Aw	Water activity
BSC(s)	Biological safety cabinet(s)
BUD(s)	Beyond-use date(s)
CETA	Controlled Environment Testing Association
CNSP(s)	Compounded nonsterile preparation(s)
COA	Certificate(s) of Analysis
CVE	Containment ventilated enclosure
FDA	Food and Drug Administration
HD(s)	Hazardous drug(s)
QA	Quality assurance
QC	Quality control
SDS(s)	Safety Data Sheet(s)
SOP(s)	Standard operating procedure(s)▲ (USP 1-Dec-2019)

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

Topic/Question	Contact	Expert Committee

Topic/Question	Contact	Expert Committee
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Most Recently Appeared In:
Pharmacopeial Forum: Volume No. 44(3)

Page Information:

USP42-NF37 2S - 9497
USP42-NF37 - 6951
USP41-NF36 - 6546

Current DocID: GUID-98DCB48D-DC23-4A63-AD2E-01CA8979FB7E_3_en-US

FAQs: <795> Pharmaceutical Compounding—Nonsterile Preparations

Last updated: May 31, 2019

1. Where can I find FAQs and other information on USP Compounding Standards?

For FAQs on other USP Compounding Standards, please see below:

- General Chapter <797> Pharmaceutical Compounding—Sterile Preparations
- General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings
- General Chapter <825> Radiopharmaceuticals– Preparation, Compounding, Dispensing, and Repackaging
- Compounded Preparation Monographs (CPMs)

2. What is the definition of nonsterile compounding?

For purposes of General Chapter <795>, nonsterile compounding is defined as combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer's labeling, or otherwise altering a drug or bulk drug substance to create a nonsterile medication.

3. To whom do the standards in General Chapter apply?

The chapter applies to all persons who prepare CNSPs and all places where CNSPs are prepared for human patients. This includes but is not limited to pharmacists, technicians, nurses, physicians, dentists, naturopaths, and chiropractors, in all places including but not limited to pharmacies, hospitals and other healthcare institutions, patient treatment sites, and physicians' practice sites. Personnel engaged in the compounding of CNSPs must additionally comply with laws and regulations of the applicable regulatory

jurisdiction. Compounding of nonsterile hazardous drugs (HDs) must additionally comply with General Chapter <800> *Hazardous Drugs—Handling in Healthcare Settings*.

4. How do I know what are requirements versus recommendations in the chapter?

Generally, requirements in a General Chapter are conveyed by use of the terms "must" or "shall". Recommendations are conveyed by use of the terms "should" and "may".

5. What does "official date" mean?

The USP "official date" indicates the date by which affected users are expected to meet the requirements of a particular standard. Ensuring compliance with the requirements of these standards is the responsibility of regulators such as the FDA, states, and other government authorities. USP has no role in enforcement.

All text in the United States Pharmacopeia (USP) or National Formulary (NF) that has reached its official date is "official text." Although all text of the *USP–NF* that has reached its official date is "official text," not all official text states requirements with which compendial users must comply. Some official text is intended to assist or guide compendial users or to serve informational purposes.

6. When do the revisions to General Chapter become official?

The revision of <795> published on June 1, 2019 will become "official" on December 1, 2019. The "official date" indicates the date by which affected users are expected to meet the requirements of a particular standard. However, ensuring compliance with the requirements of these standards is

the responsibility of regulators such as the FDA, states, and other government authorities. Regulatory bodies such as state boards of pharmacy may have a different official date. USP has no role in enforcement.

7. Is splitting tablets required to meet the standards in the chapter?

No, breaking or cutting a tablet into smaller portions is not required to meet the standards in this chapter.

8. Is reconstitution of conventionally manufactured products required to meet the standards in the chapter?

Reconstitution of a conventionally manufactured nonsterile product in accordance with the directions contained in the manufacturer approved labeling is not required to meet the standards in this chapter. Reconstitution that is not performed according to manufacturer approved labeling is considered nonsterile compounding and is subject to the requirements in the chapter.

9. Is administration out of the scope of the chapter?

Yes. The intent of the chapter is to establish minimum standards for practitioners when preparing compounded nonsterile preparations in order to minimize harm, including death, to human and animal patients. The scope of the chapter is intended to be limited to compounding and the standards are designed to help ensure a CNSP maintains its integrity up until the time when administration begins. Additionally, the preparation of a single dose for a single patient when administration will begin within 4 hours of beginning the preparation is not required to meet the requirements in the chapter.

10. Does the chapter address compounded radiopharmaceutical dosage forms?

No. Radiopharmaceuticals are not subject to the requirements in <795> but are subject to the requirements in General Chapter <825> *Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging*.

11. Are the temperatures in the chapter expressed in degrees Fahrenheit or Celsius?

Unless otherwise specified, all temperatures in the *USP-NF* are expressed in degrees centigrade (Celsius) (see also General Notices 8.180 *Temperatures*).

12. Are products manufactured by 503B facilities or conventionally manufactured products considered active pharmaceutical ingredients (APIs)?

No. The term "API" refers to a bulk drug substance (pure chemical substances), usually in powder or liquid form, which is intended to be used in compounding. API is distinguished from finished dosage forms.

13. Why were the categories of compounding (simple, moderate, and complex) in the previous chapter eliminated in the new revision?

The categories of compounding were originally adapted from <1075> *Good Compounding Practices* in 2011. The categories often led to confusion among users on how to apply the criteria and the chapter did not provide standards on how to use these categories in applying the compounding standards.

14. Who can be the designated person(s)?

The designated person is one or more individuals assigned to be responsible and accountable for the performance and operation of the facility and personnel for the preparation of compounded nonsterile preparations (CNSPs). Facilities must determine whether they have one or more

designated person, select the designated person, and determine how to allocate responsibility if there is more than one designated person.

15. Is the repackaging of a conventionally manufactured product required to meet the standards in the chapter?

No, repackaging of conventionally manufactured drug products is not required to meet the standards in this chapter (see also <1178> *Good Repackaging Practices*).

16. Since the section on Compounding for Animal Patients in the previous chapter was removed, does the chapter still apply to veterinary compounding?

The intent of the chapter is to establish minimum standards to help ensure quality of CNSPs, whether the CNSP is for human or animal patients. USP has no role in the enforcement of compounding chapters. Pursuant to *General Notices, 2.30 Legal Recognition*, ensuring compliance with USP standards is the responsibility of regulatory bodies. Regulators may choose to enforce the requirements of <795> with respect to veterinary compounding.

17. What garb is required for nonsterile compounding?

Gloves must be worn for all compounding activities. All other garb (e.g., shoe covers, head and facial hair covers, face masks, gowns) should be worn as required by the facility's Standard Operating Procedures (SOPs). Garb is recommended for the protection of personnel and to minimize the risk of CNSP contamination. The garb must be appropriate for the type of compounding performed. The garbing requirements and frequency of changing the garb must be determined by the facility and documented in the facility's SOPs.

18. Are gloves required to be wiped or changed before beginning to compound a CNSP with different components?

The chapter recommends wiping or replacing gloves before beginning to compound a CNSP with different components to minimize the risk of cross-contaminating other CNSPs and contaminating other objects. General Chapter <795> does not describe the use of specific wipes or agents to use for wiping gloves. Facilities must determine whether gloves should be changed or replaced and the appropriate wipe/agent to use if they are wiped.

19. Can gowns be reused for multiple days if not soiled?

If gowns are worn, they may be re-used if not soiled. If gowns are visibly soiled or have tears or punctures, they must be changed immediately. Facilities must determine the frequency for changing gowns.

20. Is a compounding space required to be in an enclosed room (i.e., with walls and doors)?

No. While a room may be used as the compounding space, the chapter does not require a separate room. The chapter requires a space that is specifically designated for nonsterile compounding. A visible perimeter should establish the boundaries of the nonsterile compounding area.

21. What is considered an appropriate temperature range to store CNSPs or components?

The storage area must be maintained at a temperature that is appropriate for the CNSPs and components. The storage conditions for the CNSP would be dependent on the assigned beyond-use date (BUD) and CNSP-specific properties (see <795>, *10.2 Parameters to Consider in Establishing a BUD*). The storage conditions for components may be provided by the manufacturer

or vendor on the labeling and/or specified in the USP monograph for that component (see also <659>).

22. Since reconstitution and repackaging are not considered compounding and are out of scope of the chapter, can they still be performed in the designated compounding space?

Yes, other activities may be performed in the compounding space when compounding is not occurring. The chapter requires that a compounding space be designated for nonsterile compounding, however, the space is not required to be dedicated for sole use in compounding. Other activities may occur in the compounding space but they must not be occurring in the space at the same time as compounding.

23. Can non-compounding personnel clean and sanitize the compounding space?

Facilities must determine the appropriate personnel for cleaning and sanitizing the compounding space. The chapter does not specify who may perform the cleaning and sanitization procedures.

24. What is the difference between cleaning and sanitizing?

Cleaning is the process of removing soil (e.g., organic and inorganic material) from objects and surfaces, normally accomplished by manually or mechanically using water with detergents or enzymatic products. Sanitizing is the process of reducing, on inanimate surfaces, the number of all forms of microbial life including fungi, viruses, and bacteria.

25. Are containment ventilated enclosures (CVEs) required for nonsterile compounding?

No. The chapter requires facilities to assess particle-generating activities (e.g., weighing, measuring, or other manipulation of components) to determine whether a closed system processing device is needed. The chapter does not require a closed system processing device but does require facilities to perform a process evaluation to determine whether a device is needed. A closed system processing device reduces the potential exposure to personnel and contamination to the facility from airborne particles that weighing, measuring, or otherwise manipulating components could generate. A CVE is one example of a closed system processing device; other examples include BSCs and single-use containment glove bags.

26. Why are APIs required to be obtained from an FDA-registered facility and components other than APIs only recommended to be obtained from an FDA-registered facility?

The Federal Food, Drug, and Cosmetic Act requires compounded preparations to be prepared from bulk drug substances that are obtained from FDA-registered facilities. The Expert Committee recognizes that there may be some components other than APIs that cannot be obtained from an FDA-registered facility, thus, it is a recommendation that these components be obtained from an FDA-registered facility.

27. Are all CNSPs required to be labeled, regardless of whether they are dispensed?

Yes. CNSPs must be labeled with the information specified in *9. Labeling* regardless of whether or not they are dispensed.

28. What is water activity (Aw)?

Aw is the measure of free water in a pharmaceutical dosage form. Aw is used in accessing the susceptibility of CNSPs to microbial contamination and the

potential for API degradation due to hydrolysis. A lower Aw is associated with a lower risk of microbial contamination. Thus, dosage forms such as suppositories, ointments, fixed oils, or waxes which have an Aw ≤ 0.6 have a BUD of 90 days. Dosage forms that have an Aw > 0.6 such as emulsions, gels, creams, solutions, sprays, and suspensions have a BUD of 14 or 35 days depending on whether it is non-preserved or preserved, respectively.

29. Are compounders expected to measure the Aw of CNSPs to determine the BUD?

No, the chapter does not require compounders to measure Aw for CNSPs. Aw is intended to be used as a guide for assigning BUD. General Chapter <795> provides examples of dosage forms that have an Aw ≤ 0.6 and those that have an Aw > 0.6. Additionally, General Chapter <1112> *Application of Water Activity Determination to Nonsterile Pharmaceutical Products* provides a list of products and corresponding Aw in *Table 2*.

30. Why is the BUD for nonaqueous dosage forms with an Aw ≤ 0.6 (e.g., suppositories, ointments, fixed oils, or waxes) limited to 90 days?

Although many nonaqueous formulations, including anhydrous oil formulations, may be stable for a long period of time, this is not consistently demonstrated for all nonaqueous formulations. For example, a stability-indicating assay of doxycycline compounded in oil exhibited degradation before 90 days. Additionally, there are other ingredients that may oxidize or otherwise react with the fatty acids in the oil. The chapter provides a conservative approach due to numerous examples where preparations in oil are not stable for 180 days. Further, the chapter allows the BUD of CNSPs to be extended up to 180 days if there is a stability study using a stability-indicating assay (see <795>, *10.5 Extending BUDs for CNSPs*).

31. If a stability study shows that a CNSP is stable for longer than 180 days, can that BUD be assigned?

No. General Chapter <795> specifies that the BUD for CNSPs may be extended up to a maximum of 180 days if there is a stability study (published or unpublished) using a stability-indicating assay for the API(s), CNSP, and type of container–closure that will be used. If the CNSP is aqueous, the chapter additionally recommends testing for antimicrobial effectiveness for extending BUDs beyond those contained in *Table 3 (see 10.5 Extending BUDs for CNSPs*).

However, if there is a *USP–NF* compounded preparation monograph for the CNSP, the BUD must not exceed the BUD specified in the monograph. As stated in General Notices 3.10, monograph requirements supersede the requirements of General Chapters.

32. If I extend the BUD beyond those described in *Table 3. Maximum BUD by Type of Preparation in the Absence of a USP-NF Compounded Preparation Monograph or CNSP Specific Stability Information*, why does the CNSP have to be tested for antimicrobial effectiveness?

The chapter allows an extension of BUD if there is stability data supported by a stability-indicating study. Although the CNSP may be stable, the CNSP may be susceptible to microbial proliferation especially from prolonged and repeated use. Antimicrobial effectiveness testing is recommended and only needs to be performed once for a particular CNSP. If a range of concentration is used in the same CNSP formulation and stored under the same conditions, the antimicrobial effectiveness test can be conducted for the highest and lowest concentrations. The results can be extrapolated for the concentrations within the range studied (e.g., bracketed study design).

33. Is there a difference between testing stability with a strength (potency) or a stability-indicating method?

Yes, a strength (potency) over time test determines the amount of active ingredient in a preparation, however, it may not be able to separate the active ingredient from its degradation products and impurities for quantitation depending on the analytical methods used for the test. A stability-indicating method will be able to quantitate the active ingredient and its degradation products or related impurities in the preparation by separating the active ingredient from its degradation products and impurities, and to show a change in the concentration of the active ingredient with increasing storage time. A stability-indicating method is used to determine stability of a drug and used to establish the Beyond-Use Date. (See article, "Strength and Stability Testing for Compounded Preparations.")

USP 797

Printed on: Wed Jul 31 2019, 14:31:01 pm
Printed by: Sammy Johnson
Not Yet Official as of: 31-Jul-2019
To be Official on 1-Dec-2019
DocId: GUID-A4CAAA8B-6F02-4AB8-8628-09E102CBD703_4_en-US
Printed from: https://online.uspnf.com/uspnf/document/GUID-A4CAAA8B-6F02-4AB8-8628-09E102CBD703_4_en-US

⟨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 (a)].

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.[12] 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). 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

ISO Class	Particle Count[b]/m³
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 suites: 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
LAFS	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
	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
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[a]	Monthly

Site	Cleaning	Disinfecting	Applying Sporicidal
Work surface(s) outside the PEC	Daily	Daily[a]	Monthly
Floor(s)	Daily	Daily[a]	Monthly
Wall(s), door(s), and door frame(s)	Monthly	Monthly[a]	Monthly
Ceiling(s)[c]	Monthly	Monthly[a]	Monthly
Storage shelving and bins	Monthly	Monthly[a]	Monthly
Equipment outside the PEC(s)	Monthly	Monthly[a]	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 date 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 *8. 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°)
	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
Aseptically processed CSPs	Yes	30 days	45 days	60 days
Terminally sterilized CSPs	No	14 days	28 days	45 days

Preparation Characteristics		Storage Conditions		
Compounding Method	Sterility Testing Performed and Passed	Controlled Room Temperature (20°–25°)	Refrigerator (2°–8°)	Freezer (−25° to −10°)
	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 container: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
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)

[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.

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

Topic/Question	Contact	Expert Committee
<797> PHARMACEUTICAL COMPOUNDING--STERILE PREPARATIONS	Jeanne H. Sun Manager, Compounding +1 (301) 230-3361	CMP2015 Compounding 2015

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. 44(5)

Page Information:

USP42-NF37 2S - 9508
USP42-NF37 - 6959
USP41-NF36 - 6554

Current DocID: GUID-A4CAAA8B-6F02-4AB8-8628-09E102CBD703_4_en-US

FAQs: <797> Pharmaceutical Compounding—Sterile Preparations

Last updated: May 31, 2019

1. Where can I find FAQs and other information on USP Compounding Standards?

For FAQs on USP Compounding Standards, please see below:

- General Chapter <795> Pharmaceutical Compounding—Nonsterile Preparations
- General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings
- General Chapter <825> Radiopharmaceuticals– Preparation, Compounding, Dispensing, and Repackaging
- Compounded Preparation Monographs (CPMs)

2. What is the definition of sterile compounding?

For the purposes of General Chapter <797>, 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. However, administration and preparation per approved labeling are out of the scope of the chapter as described in *1.2 Administration and 1.4 Preparation Per Approved Labeling*, respectively.

3. To whom do the standards in General Chapter <797> apply?

This chapter applies to all persons who prepare CSPs and all places where CSPs are prepared for human patients. This includes, but is not limited to, pharmacists, technicians, nurses, physicians, 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' practice sites.

Please note, compounding of sterile hazardous drugs (HDs) must additionally comply with General Chapter <800> *Hazardous Drugs—Handling in Healthcare Settings*.

4. Does the chapter apply to veterinary compounding?

The intent of the chapter is to establish minimum standards to help ensure quality of CSPs, whether the CSP is for human or animal patients. USP has no role in the enforcement of compounding chapters. Pursuant to *General Notices, 2.30 Legal Recognition*, ensuring compliance with USP standards is the responsibility of regulatory bodies. Regulators may choose to enforce the requirements of <795> with respect to veterinary compounding.

5. How do I know what are requirements versus recommendations in the chapter?

Generally, requirements in a General Chapter are conveyed by use of the terms "must" or "shall". Recommendations are conveyed by use of the terms "should" and "may".

6. What does "official date" mean?

The USP "official date" indicates the date by which affected users are expected to meet the requirements of a particular standard. Ensuring compliance with the requirements of these standards is the responsibility of regulators such as the FDA, states, and other government authorities. USP has no role in enforcement.

All text in the United States Pharmacopeia (USP) or National Formulary (NF) that has reached its official date is "official text." Although all text of the USP–NF that has reached its official date is "official text," not all official text states requirements with which compendial users must comply. Some official text is intended to assist or guide compendial users or to serve informational purposes.

7. When do the revisions to General Chapter become official?

The revision of <797> published on June 1, 2019 will become "official" on December 1, 2019. The "official date" indicates the date by which affected users are expected to meet the requirements of a particular standard. However, ensuring compliance with the requirements of these standards is the responsibility of regulators such as the FDA, states, and other government authorities. Regulatory bodies such as state boards of pharmacy may have a different official date. USP has no role in enforcement.

8. Are the temperatures expressed degrees in Fahrenheit or Celsius?

Unless otherwise specified, all temperatures in the USP-NF are expressed in degrees centigrade (Celsius) (see also General Notices 8.180 *Temperatures*).

9. Are products manufactured by 503B facilities or conventionally manufactured products considered active pharmaceutical ingredients (APIs)?

No. The term "API" refers to a bulk drug substances (pure chemical substances), usually in powder or liquid form, which is intended to be used in compounding as opposed to a finished dosage forms.

10. Who can be the designated person(s)?

The designated person is one or more individuals assigned by the facility to be responsible and accountable for the performance and operation of the

facility and personnel for the preparation of compounded sterile preparations (CSPs). Facilities must determine whether they have one or more designated person, select the designed person, and determine how to allocate responsibility if there is more than one designated person.

11. Does docking and activation of a proprietary bag and vial system for immediate administration in accordance with the manufacturer's labeling instructions have to occur under ISO 5 conditions?

No. Docking and activation of proprietary bag and vial systems in accordance with the manufacturer's labeling for immediate administration to an individual patient is not required to meet the standards in this chapter.

12. When is docking a proprietary bag and vial system required to meet the standards of this chapter?

Docking proprietary bag and vial systems for *future activation and administration* is considered compounding and must be performed in accordance with this chapter.

13. Is the repackaging of a conventionally manufactured product required to meet the standards in the chapter?

Yes, 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.

14. Is administration out of the scope of the chapter?

Yes. The intent of the chapter is to establish minimum standards for practitioners when preparing CSPs in order to minimize harm, including death, to human and animal patients. The scope of the chapter is intended to be limited to compounding and the standards are designed to help ensure a

CSP maintains its integrity up until the time when administration begins. Standard precautions such as the Centers for Disease Control and Prevention's (CDC's) safe injection practices apply to administration (see *1.2 Administration*).

15. Does a conventionally manufactured sterile product prepared for administration to a single patient in accordance with manufacturer's approved labeling outside of ISO Class 5 conditions have to be administered within 4 hours of reconstitution or mixing if it meets all the conditions in *1.4 Preparation Per Approved Labeling*?

No. When all of the conditions in 1.4 Preparation Per Approved Labeling are met, the storage information in the manufacturer's approved labeling may be followed.

16. What is the difference between compounding for immediate use and preparing a conventionally manufactured sterile product for administration?

Preparation of a single dose of a conventionally manufactured sterile product in accordance with the approved labeling that includes information about the diluent to be used, the resultant strength, storage time, and container closure system is not considered compounding. Compounding for immediate use involves mixing up to three different sterile products to make a CSP. Immediate use CSPs must be used within 4 hours following the start of preparation (see *1.3 Immediate Use CSPs*).

17. Is withdrawing a dose from a container of a conventionally manufactured sterile product, without any further manipulation, for immediate administration to a patient considered compounding?

No, withdrawing a dose from a container of a conventionally manufactured sterile product without any further manipulation is considered administration and is out of the scope of <797>.

18. When compounding immediate use CSPs, can more than three individual containers of a sterile product be used?

The immediate use CSPs provision states that the preparation must not involve more than 3 different sterile products. Two or more of the same sterile product may be used as long as there are not more than three different sterile products. For example, two vials of drug are reconstituted using two vials of sterile water for injection and added to an intravenous bag may be considered immediate use as long as the criteria listed in *1.3 Immediate Use CSPs* are met. As another example, when the CSP requires combining 4 vials of the same component into a single bag of diluent, only 2 different sterile products are used to prepare the CSP.

19. Can a single-dose container be used to prepare doses for more than one patient when compounding an immediate use CSP?

No. One of the conditions of the immediate use CSP provision specifies that any unused starting components 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 when used for preparing immediate use CSPs.

20. Why does the immediate use CSPs provision allow for administration to begin within 4 hours following the start of the preparation?

The immediate use CSPs provision was revised to allow up to 4 hours for beginning administration based on the lag phase of microbial growth, during which potential bacterial cells are adjusting to their environment and change very little, and they do not immediately start reproducing. On average, exponential reproduction may not start for 4 to 6 hours.[1] In the event bacterial cells were inadvertently introduced into a CSP, it would not immediately start

replicating, and therefore there is a window of time in which a CSP can be held prior to administration.

[1]For example, see:

Daquigan N et al. Early recovery of Salmonella from food using a 6-hour non-selective pre-enrichment and reformulation of tetrathionate broth. Front Microbiol. 2016;7:2103.
Jarvis, Basil. Statistical Aspects of the Microbiological Examination of Foods, Third Edition. Academic Press, 2016.
Ryan, Kenneth et al. Sherris Medical Microbiology, Sixth Edition. McGraw-Hill Education, 2014.
Wang J et al. A novel approach to predict the growth of Staphylococcus aureus on rice care. Front Microbiol. 2017;8:1140.

21. Is it considered compounding if the steps used to prepare a single dose of a conventionally manufactured product are different from the directions contained in the manufacturer's approved labeling?

Yes. Any compounding (e.g., mixing, reconstituting) that is not performed according to the manufacturer's approved labeling is considered sterile compounding and is subject to the requirements in the chapter.

22. Does the chapter address compounded radiopharmaceutical dosage forms?

No. Radiopharmaceuticals are not subject to the requirements in <797> but are subject to the requirements in General Chapter <825> *Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging*.

23. Who can be the designated person(s)?

It is the responsibility of the facility to determine who is the designated person(s). The designated person is one or more individuals assigned by the facility to be responsible and accountable for the performance and operation of the facility and personnel for the preparation of CSPs. Facilities must determine whether they have one or more designated person, select the designated person, and determine how to allocate responsibility if there is more than one designated person.

24. Is documentation of gloved fingertip and thumb sampling and media-fill testing only required when results exceed action levels?

No. All results of the evaluations must be documented and 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 the 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.

25. Why are incubation conditions different for media-fill testing, gloved fingertip and thumb sampling, and environmental air and surface sampling?

Environmental air and surface samples and gloved fingertip and thumb samples are incubated at a high temperature and then a low temperature. Incubation at a lower temperature first may compromise recovery of gram-positive cocci which are often associated with humans. The incubation conditions are consistent with General Chapter <1116> *Microbiological Control and Monitoring of Aseptic Processing Environments*. Media-fill test samples are incubated at a low temperature and then a high temperature to detect a broad spectrum of microorganisms. The incubation time and

temperatures for media-fill test samples are consistent with FDA Guidance for Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practices.

26. What is the correct order of garbing?

General Chapter <797> does not specify an order of garbing. Garb must be donned and doffed in an order that reduces the risk of contamination. The order of garbing and location where garbing occurs would depend on the type of garbing used (e.g., sterile gowns) and the placement of the sink (e.g., if the sink is located inside or outside of the ante-room). The order of garbing must be determined by the facility and documented in the facility's SOP.

27. Can donning and doffing activities by different personnel occur in the same room at the same time?

The chapter recommends (but does not require) that donning and doffing not occur in the ante-room or the segregated compounding area (SCA) at the same time. Personnel must be aware of activity in the room to ensure that the integrity of garb is not compromised. For example, if one person is performing hand hygiene while another is donning a gown, personnel must consider the risk of contaminating the gown (e.g., from potential splashing).

28. What are examples of methods to cover jewelry that cannot be removed?

Examples of jewelry that cannot be removed are dermal piercings (also known as a microdermal piercing), which is a piercing that is held in place with a dermal anchor that is installed underneath the skin. Facilities must determine the appropriate method for covering dermal piercings to minimize the risk of contaminating the CSP and the environment. For example, depending on the location of the piercing, an adhesive bandage or head cover may be used to cover the jewelry.

29. Are wedding rings permitted to be worn under sterile gloves?

The chapter requires removing all hand jewelry that could interfere with the effectiveness of garbing or otherwise increase the risk of contamination of the CSP. Wedding rings may potentially compromise the integrity of the glove (e.g., tearing).

30. Are 3 pairs of gloves required for using a compounding aseptic isolator (CAI) or compounding aseptic containment isolator (CACI)?

If using a CAI or CACI, the chapter recommends disposable gloves to be worn inside gloves attached to the restricted-access barrier system (RABS) sleeves. However, the chapter requires sterile gloves to be worn over the gloves attached to the RABS sleeves. The use of disposable gloves inside of gloves attached to the RABS sleeve is intended to maintain the cleanliness of the gloves attached to the RABS sleeve which may collect sweat or other touch contaminants. Sterile gloves outside of the gauntlet gloves help minimize the risk of contamination to the environment and the CSP.

31. If I am compounding Category 1 CSPs in an SCA, do I have to wear the same garb as when compounding Category 2 CSPs in a cleanroom suite?

Yes. Minimum garbing requirements are not stratified based on facility design. The chapter lists the minimum garbing requirements to protect the CSP and the environment. Sterile gloves are required for preparing CSPs inside an ISO Class 5 PEC.

32. Can gowns be re-used?

Yes. 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. Garb must be replaced immediately if it becomes visibly soiled or if its integrity is compromised.

Additionally, gowns and other garb must be stored in a manner that minimizes contamination (e.g., away from sinks to avoid splashing).

33. Why must the HEPA filter be located in the ceiling of the buffer and ante-rooms?

Placement of HEPA filters in the ceiling eliminates the potential for post-filtration contamination of the air-stream. Air distribution systems with duct-mounted HEPA filters are susceptible to introduction of unfiltered air into the airstream after the air is filtered. HEPA filter placement in the ventilation duct is difficult to leak test and susceptible to contamination, especially in the event of water leakage or other breaches. Ceiling mounted filters help facilitate testing and servicing.

34. Why are CAIs and CACIs required to be placed in an ISO Class 7 buffer room with an ISO Class 8 ante-room for preparing Category 2 CSPs?

The PEC must be located in a controlled environment for preparing Category 2 CSPs to minimize the risk of contamination. Movement of materials in and out of the RABS (e.g., CAI or CACI) in unclassified air carries a higher risk of contamination. Placement of the RABS in a classified area mitigates the risk of inadvertent contamination of CSPs with the longer BUDs that are permitted for Category 2 CSPs.

35. Does the Integrated Vertical Laminar Flow Zone (IVLFZ) require 100% HEPA filter coverage in the ceiling? Can returns be under the work table?

The chapter requires "full coverage of HEPA filters above the work surface" but does not specify 100% coverage. HEPA filters must cover the entire area above the work tables. However, even if HEPA filters cover the entire ceiling above the table of an IVLFZ, there may be less than 100% coverage.

Returns must be positioned where they create the best "pull" of air across the work surface. Returns may be on the wall behind the table at a height where the return straddles the table. A portion of the air is drawn into the section of return above the table and a portion of the air is drawn around the front of the table to the area of the return below the table. If the returns are only located under the table, the table should be positioned in such a way to allow air to pass between the wall and the table to the return. The chapter does note that 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.

36. Can a containment ventilated enclosure (CVE) be used for presterilization procedures (e.g., weighing, mixing nonsterile components)?

Presterilization procedures must be performed in a single-use containment glove bag, CVE, BSC, or CACI to minimize the risk of airborne contamination.

37. Are pass-throughs required to have interlocking doors?

The chapter recommends that pass-through doors be interlocking. However, if a pass-through is used, both doors must never be opened at the same time.

38. How are visual smoke studies performed in rooms where air returns are not located low on the wall?

A visual smoke study uses a visible source of smoke, which is neutrally buoyant, to verify an absence of stagnant airflow where particulates can accumulate.

39. What is the difference between a pharmaceutical isolator and a RABS (i.e., a CAI or CACI)?

Unlike RABS, pharmaceutical isolators are different in that they contain 4 major elements: controlled workspace, transfer device, access device, and a decontamination system. A pharmaceutical isolator is equipped with a generator that distributes a sporicidal agent throughout the chamber.

If the isolator is used to prepare Category 2 CSPs, it must be placed in an ISO Class 8 or better positive pressure room. In contrast, if the CAI or CACI is used to prepare Category 2 CSPs, the CAI or CACI must be placed in a cleanroom suite with an ISO Class 7 or better positive pressure buffer room with an ISO Class 8 or better positive pressure ante-room.

40. Can magnehelic gauges be used for monitoring pressure differentials?

Yes, magnehelic gauges may be used to monitor pressure. The quantitative results from the pressure monitoring device must be reviewed and documented at least daily on the days when compounding is occurring. Users should note that magnehelic gauges do not warn or alert personnel to events where there is a loss of pressure whereas there other pressure monitoring systems may have audible or visible alarms.

41. Why is the frequency of surface sampling changed to monthly?

Surface sampling was previously required "periodically" which was interpreted differently by users (e.g., monthly, quarterly, or biannually). The change to monthly surface sampling is intended to provide an additional measure of control and monitoring in between viable air monitoring and certification requirements every 6 months. Monthly surface sampling provides additional data for trending and allow for monitoring of contamination risks.

42. Why are sinks allowed to be placed outside of the ante-room? Does the sink placement in contradict the sink placement requirements in ?

In facilities with cleanroom suites, 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. Sinks are permitted outside of the ante-room to offer more flexibility to the cleanroom design and help minimize the risk of contamination from water sources to the classified areas.

In facilities preparing HDs in a cleanroom suite, General Chapter <800> requires the sink to be placed in the ante-room at least 1 meter away from the entrance of the HD buffer room to avoid contamination migration into the negative pressure HD buffer room. There are no conflicts for the sink placement in <797> and <800>. Facilities compounding sterile HDs must meet the requirements in both <797> and <800>.

43. Is an SCA required to be in an enclosed room (i.e., walls and doors)?

No. An SCA is defined as 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.

44. Is certification of the compounding area required to be performed using the current Controlled Environment Testing Association (CETA) certification guide for *Sterile Compounding Facilities*?

No, facilities may use the CETA certification guide or an equivalent guideline. Facilities must determine the appropriate certification guide to use for certifying their compounding area.

45. How many microbiological air and surface samples are required based on the size of classified areas?

Microbiological air and surface monitoring must be conducted in all classified areas to confirm that the required environment quality is maintained. The microbiological air and surface sampling must be facility specific and must be described in the facility's Standard Operating Procedures (SOPs). The chapter does not specify a minimum number of samples based on the size of the room. Facilities must determine the appropriate number of locations and select the locations of sampling based on their relationship to the activities performed in the area.

46. Do microorganisms need to be identified to the genus level regardless of action level?

No, an attempt must be made to identify any microorganisms recovered to the genus level if the levels measured during sampling exceed the action levels in the chapter.

47. What is the rationale for only requiring an attempt to identify any microorganisms recovered to the genus level if the levels measured during sampling exceed the action levels in the chapter?

48. What is the difference between cleaning and disinfecting?

Cleaning is the process of removing residues (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces. Disinfecting is the process of destroying fungi, viruses, and bacteria on inanimate surfaces and objects. Applying a sporicidal agent is used to destroy bacterial and fungal spores and is expected to kill all vegetative microorganisms.

49. What is a one-step disinfectant cleaner?

A one-step disinfectant cleaner is 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.

It is important to note that sterile isopropyl alcohol (IPA) is not a one-step disinfectant cleaner.

50. Where can I find examples or sources of EPA-registered one-step disinfectant cleaners?

USP cannot endorse particular products. Users may research one-step disinfectant cleaners or contact cleaning/disinfecting agent manufacturers to get more information on available products.

51. What surfaces of the SCA does table containing the minimum frequencies of cleaning, disinfecting, and applying sporicidal agents (Table 8) apply?

The minimum frequencies in Table 8 apply to all surfaces within the perimeter of the SCA. These include the PEC(s), walls, floors, ceilings, work surfaces, equipment, and storage shelving and bins located within the perimeter of the SCA.

52. Does the equipment inside a PEC need to be cleaned?

Yes, the chapter requires equipment inside of the PEC to be cleaned, disinfected, and a sporicidal agent applied (see *Table 8*).

53. Are cleaning supplies required to be sterile?

No, cleaning tools are not required to be sterile. The chapter does state that all cleaning supplies (e.g., wipers, sponges, and mop heads) with the exception of tool handles and holders must be low-lint. Further, the chapter recommends that wipes, sponges, and mop heads be disposable.

54. Are cleaning agents required to be sterile?

No, cleaning agents are not required to be sterile.

55. Where can I find information about the minimum contact time for the cleaning, disinfecting, and sporicidal agents used?

Users should refer to the manufacturer's directions or published data for the minimum contact time for the agent used. The minimum contact time may differ based on the intended purpose. For example, an agent may have a 1-minute contact time to be bactericidal and a 3-minute contact time to be sporicidal.

56. Does the chapter require a separate cleaning and disinfecting step in addition to applying a sporicidal agent?

The chapter requires cleaning and disinfecting of the compounding areas. These steps can be combined if an EPA-registered one-step disinfectant is used. One-step disinfectants have been formulated to be effective in the presence of light to moderate soiling without a separate cleaning step. Sporicidal agents must be used at least monthly. Some EPA-registered disinfectant cleaners may also have sporicidal properties. If the sporicidal agent is an EPA-registered (or equivalent) one-step disinfectant sporicidal cleaner, separate cleaning and disinfecting steps are not required.

57. Is a Biological Safety Cabinet the only PEC that has a removable work surface tray?

No. CAIs, CACIs, and some LAFWs have removable work trays.

58. Why are APIs required to be obtained from an FDA-registered facility and components other than APIs only recommended to be obtained from an FDA-registered facility?

The Federal Food Drug and Cosmetic Act requires compounded preparations to be prepared from bulk drug substances that are obtained from FDA-registered facilities. The Expert Committee recognizes that there may be

some components other than APIs that cannot be obtained from an FDA-registered facility, thus, it is a recommendation that these components be obtained from an FDA-registered facility.

59. What is the difference between aseptic processing and terminal sterilization?

Aseptic processing includes either 1) compounding with only sterile starting ingredient(s), or 2) compounding with nonsterile ingredient(s) followed by sterilization by filtration. Aseptic processing is not terminal sterilization.

Terminal sterilization includes compounding with sterile and/or nonsterile starting ingredient(s) and subsequent sterilization with a process intended to achieve a probability of a nonsterile unit (PNSU) of 10^{-6} (e.g., dry heat, steam, irradiation).

60. Can stoppered and crimped empty vials be sterilized using steam heat?

Sealed containers must be able to generate steam internally to be sterilized by steam heat. Stoppered and crimped empty vials must contain a small amount of sterile water to generate steam (see also <1229> *Sterilization of Compendial Articles*).

61. Why is a prefiltration step with a filter of a pore size of 1.2 µm required before sterilization procedures?

A prefiltration step with a filter of a pore size of 1.2 µm removes particulate matter in the solution before sterilization.

62. What is the PNSU for CSPs sterilized by filtration?

A PNSU value cannot be applied to CSPs that are sterilized by filtration because sterilization by filtration is not terminal sterilization.

63. Is a biological indicator required for each sterilization cycle using steam or dry heat?

Yes, the effectiveness of the steam and dry heat sterilization method must be verified and documented with each run or load using an appropriate biological indicator.

64. What is required to be documented for the visual inspection of the CSP and the container-closure system?

All CSPs must be visually inspected to determine whether the physical appearance of the CSP is as expected. Visible quality characteristics (e.g., discoloration, visible particulates, cloudiness) may be documented. Results of visual inspection of the container-closure system (e.g. checking for leakage, cracks in the container, or improper seals) may be documented.

65. Why should CSPs administered epidurally have the same endotoxin limit as that of intrathecally administered CSPs?

CSPs delivered by implanted pumps may be administered over a long period of time and may be compounded from nonsterile components. Bacterial endotoxin testing helps ensure that CSP do not contain excessive bacterial endotoxins. Although <797> refers to General Chapter <85> *Bacterial Endotoxins Test* for calculating endotoxin limits for the appropriate route of administration, <85> does not address products administered epidurally or administered directly into the central nervous system. Compounders should be aware that endotoxin testing is also important for CSPs administered epidurally.

66. What is the difference between the beyond-use date (BUD) and "hang time" (e.g., administration time)?

The BUD is the date or the hour and date after which the CSP must not be used. BUDs applies to CSPs and are not intended to limit the time during which a CSP is administered (e.g., infused). "Hang time" is often used to refer to the amount of time during which a CSP or conventionally manufactured product (e.g. pre-mix, large volume parenteral solution) may be infused before which either the tubing or the medication must be changed. General Chapter <797> does not address administration time (e.g., hang time).

67. How does the storage conditions affect the BUD of a CSP?

Generally, longer BUDs are permitted for CSPs stored in colder conditions than for CSPs stored at controlled room temperature as colder temperatures have been shown to slow the growth of most microorganisms.

68. Are BUDs cumulative?

No, BUDs must not be additive. The storage time of a CSP must not exceed the original BUD placed on the CSP for its labeled storage condition. For example, a CSP that is assigned a BUD based on storage at room temperature cannot subsequently be refrigerated or frozen in order to extend the original BUD assigned. Likewise, the BUD of a frozen CSP must not be extended based on storage at room temperature when it is thawed.

69. Can the BUD of Category 2 CSPs be extended beyond those in *Table 11. BUDs for Category 2 CSPs*?

The chapter states that BUDs for Category 2 CSPs must be established in accordance with *Table 11*. However, if there is a compounded preparation monograph for a particular CSP formulation, that BUD may be assigned if the CSP is prepared according to the monograph and all monograph requirements are met (e.g., Specific Tests). *General Notices 3.10* states that

where the requirements of a monograph differ from the requirements in an applicable general chapter, the monograph requirements apply and supersede the general chapter. In the absence of a compounded preparation monograph, the chapter does not allow for extension of BUDs beyond those in *Table 11*. BUDs must be assigned conservatively and must take into account factors such as validated stability-indicating assays and testing for sterility, endotoxins, container-closure integrity, and particulate matter.

70. Why is the BUD for aseptically prepared Category 2 CSPs using only sterile ingredients 4 days when stored at controlled room temperature?

The previous version of <797> specified a storage time of 48 hours and 30 hours at controlled room temperature for low- and medium-risk level CSPs, respectively. The longer BUD in the revised chapter is based on a risk based approach to balance the need for quality CSPs and to facilitate patient access. Further, the revised chapter contains additional requirements (e.g., facility and engineering controls and surface sampling) to help mitigate risks of inadvertent contamination.

71. Is a conventionally manufactured single-dose container required to be stored in an ISO Class 5 PEC in order for it to be allowed to be used for up to 12 hours?

No, opened or punctured conventionally manufactured single-dose containers may be stored outside of an ISO Class 5 PEC. However, the chapter does require that the conventionally manufactured single-dose container be entered or punctured inside of an ISO Class 5 PEC. These containers may be used up to 12 hours after initial entry or puncture provided that the storage requirements (e.g., controlled room temperature, cold temperature) are maintained. Opened single-dose ampules must not be stored for any period of time.

72. Are conventionally manufactured sterile topical ophthalmic products considered multiple-dose containers?

No, <659> *Packaging and Storage Requirements* defines multiple-dose containers as a container–closure system that holds a sterile medication for *parenteral administration* (*injection or infusion*) that has met antimicrobial effectiveness testing requirements, or is excluded from such testing requirements by FDA regulation. Therefore, the requirement that multiple-dose containers not be used for more than 28 days unless otherwise specified on the labeling does not apply to conventionally manufactured sterile topical products.

73. If the approved labeling of a pharmacy bulk package describes a long storage time (e.g., 14 days), can the pharmacy bulk package be stored and used for that period of time?

Users should carefully review the manufacturer's approved labeling for pharmacy bulk packages. Some approved labeling may provide a storage time based on stability (e.g., 14 days) as well as a shorter time (e.g., 4 hours) based on the risk of microbial contamination. Users must use the shorter storage time specified in the manufacturer's approved labeling. The pharmacy bulk package must be used according to the manufacturer's approved labeling.

74. Do compounded pH solutions affect the BUD assigned to the final CSP?

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. If a nonsterile pH solution is compounded and used within 6 hours for a single CSP or a single batch, the pH solution would not be assigned a BUD, and therefore would not affect the BUD assigned to the final CSP. The nonsterile pH solution is considered to be part of the

compounding process. However, if a pH solution is prepared and stored, it must be sterilized within 6 hours and must be treated as a compounded stock solution. Sterilized and stored pH solutions must be assigned a BUD and the BUD must be taken into account when assigning a BUD to the final CSP.

75. What is an example of assigning a BUD to compounded stock solutions and their subsequent CSPs?

A compounder wants to reconstitute a conventionally manufactured sterile product and further dilute it to prepare a subsequent CSP (see *16.2 Use of Compounded Single-Dose CSPs and CSP Stock Solutions*).

- Day 1: a 2 gram single-dose conventionally manufactured container of powder for solution is reconstituted with 8 mL of a conventionally manufactured diluent, yielding 10 mL of 200 mg/mL of drug (CSP-A, original CSP). CSP-A is assigned a BUD of 10 days because it is aseptically processed, has not passed sterility testing, was prepared from only sterile starting components, and will be stored in a refrigerator (see *Table 11*).
- Day 3: CSP-A is entered or punctured in ISO Class 5 PEC, where 10 mL of CSP-A solution is further diluted with 40 mL of diluent, yielding 50 mL solution of 40 mg/mL of drug (CSP-B, a finished CSP). CSP-B is aseptically processed, has not passed sterility testing, was prepared from only sterile starting components, and will be stored in a refrigerator. 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. Therefore, the assigned BUD for CSP-B will be 7 days (10 days minus the 3 lapsed days of CSP-A), because that is the shortest BUD of all of its individual components.
    - Additionally, CSP-A must be used within 12 hours of initial entry/puncture or its originally assigned BUD, whichever is shorter, and the remainder must be discarded.

76. What are allergenic extracts?

Allergenic extracts are 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 extract prescription sets are 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 Biological License Application (BLA) for the licensed biological products.

77. Does *21. Compounding Allergenic Extracts* apply to physician and pharmacy settings?

Yes, the provisions in 21. Compounding Allergenic Extracts apply regardless of where the allergenic extract is compounded 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.

78. Why are the BUDs for compounded allergenic extracts longer than those required for Category 1 and Category 2 CSPs?

Because of certain characteristics of allergenic extracts and allergy practice (e.g., preservative systems and risk of anaphylaxis), preparation of allergenic extract prescription sets is not subject to the requirements in this chapter that are applicable to other sterile CSPs. Further, FDA provides additional guidance for preparation of allergenic extracts in the FDA Guidance for

Mixing, Diluting, or Repackaging Biological Products Outside of the Scope of an Approved Biologics License Application.

USP 800

Add the following:

▲⟨800⟩ HAZARDOUS DRUGS—HANDLING IN HEALTHCARE SETTINGS

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click https://www.uspnf.com/rb-gc-800-20191201

Change to read:

▲▲ (RB 1-Dec-2019)

1. INTRODUCTION AND SCOPE

This chapter describes practice and quality standards for handling hazardous drugs (HDs) to promote patient safety, worker safety, and environmental protection. Handling HDs includes, but is not limited to, the receipt, storage, compounding, dispensing, administration, and disposal of sterile and nonsterile products and preparations.

This chapter applies to all healthcare personnel who handle HD preparations and all entities that store, prepare, transport, or administer HDs (e.g., pharmacies, hospitals and other healthcare institutions, patient treatment clinics, physicians' practice facilities, or veterinarians' offices). Personnel who may potentially be exposed to HDs include, but are not limited to: pharmacists, pharmacy technicians, nurses, physicians, physician assistants, home healthcare workers, veterinarians, and veterinary technicians.

Entities that handle HDs must incorporate the standards in this chapter into their occupational safety plan. The entity's health and safety management system must, at a minimum, include:

- A list of HDs
- Facility and engineering controls
- Competent personnel
- Safe work practices
- Proper use of appropriate Personal Protective Equipment (PPE)
- Policies for HD waste segregation and disposal

The chapter is organized into the following main sections:

1. Introduction and Scope
2. List of Hazardous Drugs
3. Types of Exposure
4. Responsibilities of Personnel Handling Hazardous Drugs
5. Facilities and Engineering Controls
6. Environmental Quality and Control
7. Personal Protective Equipment
8. Hazard Communication Program
9. Personnel Training
10. Receiving
11. Labeling, Packaging, Transport, and Disposal
12. Dispensing Final Dosage Forms
13. Compounding
14. Administering

2. LIST OF HAZARDOUS DRUGS

The National Institute for Occupational Safety and Health (NIOSH) maintains a list of antineoplastic and other HDs used in healthcare. An entity must maintain a list of HDs, which must include any items on the current NIOSH list that the entity handles. The entity's list must be reviewed at least every 12 months. Whenever a new agent or dosage form is used, it should be reviewed against the entity's list.

The NIOSH list of antineoplastic and other HDs provides the criteria used to identify HDs. These criteria must be used to identify HDs that enter the market after the most recent version of the NIOSH list, or that the entity handles as an investigational drug. If the information available on a drug is deemed insufficient to make an informed decision, consider the drug hazardous until more information is available.

Box 1: Containment Requirements

- Drugs on the NIOSH list that must follow the requirements in this chapter include:
  - Any HD API
  - Any antineoplastic requiring HD manipulation
- Drugs on the NIOSH list that do not have to follow all the containment requirements of this chapter if an assessment of risk is performed and implemented include:
  - Final dosage forms of compounded HD preparations and conventionally manufactured HD products, including antineoplastic dosage forms that do not require any further manipulation other than counting or repackaging (unless required by the manufacturer)
- For dosage forms of other HDs on the NIOSH list, the entity may perform an assessment of risk to determine alternative containment strategies and/work practices

Some dosage forms of drugs defined as hazardous may not pose a significant risk of direct occupational exposure because of their dosage formulation (e.g., tablets or capsules—solid, intact medications that are administered to patients without modifying the formulation). However, dust from tablets and capsules may present a risk of exposure by skin contact and/or inhalation. An assessment of risk may be performed for these dosage forms to determine alternative containment strategies and/or work practices. If an assessment of risk is not performed, all HDs must be handled with all containment strategies defined in this chapter.

The assessment of risk must, at a minimum, consider the following:

- Type of HD (e.g., antineoplastic, non-antineoplastic, reproductive risk only)
- Dosage form
- Risk of exposure
- Packaging
- Manipulation

If an assessment of risk approach is taken, the entity must document what alternative containment strategies and/or work practices are being employed for specific dosage forms to minimize occupational exposure. If used, the assessment of risk must be reviewed at least every 12 months and the review documented.

3. TYPES OF EXPOSURE

Routes of unintentional entry of HDs into the body include dermal and mucosal absorption, inhalation, injection, and ingestion (e.g., contaminated foodstuffs, spills, or mouth contact with contaminated hands). Containers of HDs have been shown to be contaminated upon receipt. Both clinical and nonclinical personnel may be exposed to HDs when they handle HDs or touch contaminated surfaces. *Table 1* lists examples of potential routes of exposure based on activity.

Table 1. Examples of Potential Opportunities of Exposure Based on Activity

Activity	Potential Opportunity of Exposure
Receipt	• Contacting HD residues present on drug containers, individual dosage units, outer containers, work surfaces, or floors
Dispensing	• Counting or repackaging tablets and capsules
Compounding and other manipulations	• Crushing or splitting tablets or opening capsules • Pouring oral or topical liquids from one container to another • Weighing or mixing components • Constituting or reconstituting powdered or lyophilized HDs • Withdrawing or diluting injectable HDs from parenteral containers • Expelling air or HDs from syringes • Contacting HD residue present on PPE or other garments • Deactivating, decontaminating, cleaning, and disinfecting areas contaminated with or suspected to be contaminated with HDs • Maintenance activities for potentially contaminated equipment and devices
Administration	• Generating aerosols during administration of HDs by various routes (e.g., injection, irrigation, oral, inhalation, or topical application) • Performing certain specialized procedures (e.g., intraoperative intraperitoneal injection or bladder instillation) • Priming an IV administration set
Patient-care activities	• Handling body fluids (e.g., urine, feces, sweat, or vomit) or body-fluid-contaminated clothing, dressings, linens, and other materials
Spills	• Spill generation, management, and disposal
Transport	• Moving HDs within a healthcare setting
Waste	• Collection and disposal of hazardous waste and trace contaminated waste

4. RESPONSIBILITIES OF PERSONNEL HANDLING HAZARDOUS DRUGS

Each entity must have a designated person who is qualified and trained to be responsible for developing and implementing appropriate procedures; overseeing entity compliance with this chapter and other applicable laws, regulations, and standards; ensuring competency of personnel; and ensuring environmental control of the storage and compounding areas. The designated person must thoroughly understand the rationale for risk-prevention policies, risks to themselves and others, risks of non-compliance that may compromise safety, and the responsibility to report potentially hazardous situations to the management team. The designated person must also be responsible for the oversight of monitoring the facility and maintaining reports of testing/sampling performed in facilities, and acting on the results.

All personnel who handle HDs are responsible for understanding the fundamental practices and precautions and for continually evaluating these procedures and the quality of final HDs to prevent harm to patients, minimize exposure to personnel, and minimize contamination of the work and patient-care environment.

Change to read:

5. FACILITIES AND ENGINEERING CONTROLS

HDs must be handled under conditions that promote patient safety, worker safety, and environmental protection. Signs designating the hazard must be prominently displayed before the entrance to the HD handling areas. Access to areas where HDs are handled must be restricted to authorized personnel to protect persons not involved in HD handling. HD handling areas must be located away from breakrooms and refreshment areas for personnel, patients, or visitors to reduce risk of exposure.

Designated areas must be available for:

- Receipt and unpacking
- Storage of HDs
- Nonsterile HD compounding (if performed by the entity)
- Sterile HD compounding (if performed by the entity)

Certain areas are required to have negative pressure from surrounding areas to contain HDs and minimize risk of exposure. Consideration should be given to uninterrupted power sources (UPS) for the ventilation systems to maintain negative pressure in the event of power loss.

5.1 Receipt

Antineoplastic HDs and all HD APIs must be unpacked (i.e., removal from external shipping containers) in an area that is neutral/normal or negative pressure relative to the surrounding areas. HDs must not be unpacked from their external shipping containers in sterile compounding areas or in positive pressure areas.

5.2 Storage

HDs must be stored in a manner that prevents spillage or breakage if the container falls. Do not store HDs on the floor. In areas prone to specific types of natural disasters (e.g., earthquakes) the manner of storage must meet applicable safety precautions, such as secure shelves with raised front lips.

Antineoplastic HDs requiring manipulation other than counting or repackaging of final dosage forms and any HD API must be stored separately from non-HDs in a manner that prevents contamination and personnel exposure. These HDs must be stored in an externally ventilated, negative-pressure room with at least 12 air changes per hour (ACPH). Non-antineoplastic, reproductive risk only, and final dosage forms of antineoplastic HDs may be stored with other inventory if permitted by entity policy.

Sterile and nonsterile HDs may be stored together, but HDs used for nonsterile compounding should not be stored in areas designated for sterile compounding to minimize traffic into the sterile compounding area.

Refrigerated antineoplastic HDs must be stored in a dedicated refrigerator in a negative pressure area with at least 12 ACPH [e.g., storage room, buffer room, or containment segregated compounding area (C-SCA)]. If a refrigerator is placed in a negative pressure buffer room, an exhaust located adjacent to the refrigerator's compressor and behind the refrigerator should be considered.

5.3 Compounding

Engineering controls are required to protect the preparation from cross-contamination and microbial contamination (if preparation is intended to be sterile) during all phases of the compounding process. Engineering controls for containment are divided into three categories representing primary, secondary, and supplementary levels of control. A containment primary engineering control (C-PEC) is a ventilated device designed to minimize worker and environmental HD exposure when directly handling HDs. The containment secondary engineering control (C-SEC) is the room in which the C-PEC is placed. Supplemental engineering controls [e.g., closed-system drug-transfer device (CSTD)] are adjunct controls to offer additional levels of protection. *Appendix 2* provides examples for designs of HD compounding areas.

Sterile and nonsterile HDs must be compounded within a C-PEC located in a C-SEC. The C-SEC used for sterile and nonsterile compounding must:

- Be externally vented
- Be physically separated (i.e., a different room from other preparation areas)
- Have an appropriate air exchange (e.g., ACPH)
- Have a negative pressure between 0.01 and 0.03 inches of water column relative to all adjacent areas

The C-PEC must operate continuously if it supplies some or all of the negative pressure in the C-SEC or if it is used for sterile compounding. If there is any loss of power to the C-PEC, or if repair or moving occurs, all activities occurring in the C-PEC must be suspended immediately. If necessary, protect the unit by covering it appropriately per the manufacturer's recommendations. Once the C-PEC can be powered on, decontaminate, clean, and disinfect (if used for sterile compounding) all surfaces and wait the manufacturer-specified recovery time before resuming compounding.

A sink must be available for hand washing. An eyewash station and/or other emergency or safety precautions that meet applicable laws and regulations must be readily available. Care must be taken to locate water sources and drains in areas where their presence will not interfere with required ISO classifications. Water sources and drains must be located at least 1 meter away from the C-PEC.

For entities that compound both nonsterile and sterile HDs, the respective C-PECs must be placed in separate rooms, unless those C-PECs used for nonsterile compounding are sufficiently effective that the room can continuously maintain ISO 7 classification throughout the nonsterile compounding activity. If the C-PECs used for sterile and nonsterile compounding are placed in the same room, they must be placed at least 1 meter apart and particle-generating activity must not be performed when sterile compounding is in process.

5.3.1 NONSTERILE COMPOUNDING

In addition to this chapter, nonsterile compounding must follow standards in *Pharmaceutical Compounding—Nonsterile Preparations (795)*. A C-PEC is not required if manipulations are limited to handling of final dosage forms (e.g., counting or repackaging of tablets and capsules) that do not produce particles, aerosols, or gasses.

The C-PECs used for manipulation of nonsterile HDs must be either externally vented (preferred) or have redundant–HEPA filters in series. Nonsterile HD compounding must be performed in a C-PEC that provides personnel and environmental protection, such as a Class I Biological Safety Cabinet (BSC) or Containment Ventilated Enclosure (CVE). A Class II BSC or a compounding aseptic containment isolator (CACI) may also be used. For occasional nonsterile HD compounding, a C-PEC used for sterile compounding (e.g., Class II BSC or CACI) may be used but must be decontaminated, cleaned, and disinfected before

resuming sterile compounding in that C-PEC. A C-PEC used only for nonsterile compounding does not require unidirectional airflow because the critical environment does not need to be ISO classified.

The C-PEC must be placed in a C-SEC that has at least 12 ACPH. *Table 2* summarizes the engineering controls required for nonsterile HD compounding.

Due to the difficulty of cleaning HD contamination, surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets in the nonsterile compounding area must be smooth, impervious, free from cracks and crevices, and non-shedding.

Table 2. Engineering Controls for Nonsterile HD Compounding

C-PEC	C-SEC Requirements
• Externally vented (preferred) or redundant–HEPA filtered in series • Examples: CVE, Class I or II BSC, CACI	• Externally vented • 12 ACPH • Negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas

5.3.2 STERILE COMPOUNDING

In addition to this chapter, sterile compounding must follow standards in ⟨797⟩.

All C-PECs used for manipulation of sterile HDs must be externally vented. Sterile HD compounding must be performed in a C-PEC that provides an ISO Class 5 or better air quality, such as a Class II or III BSC or CACI. Class II BSC types A2, B1, or B2 are acceptable. For most known HDs, type A2 cabinets offer a simple and reliable integration with the ventilation and pressurization requirements of the C-SEC. Class II type B2 BSCs are typically reserved for use with volatile components. *Appendix 3* describes the different types of BSCs.

A laminar airflow workbench (LAFW) or compounding aseptic isolator (CAI) must not be used for the compounding of an antineoplastic HD. A BSC or CACI used for the preparation of HDs must not be used for the preparation of a non-HD unless the non-HD preparation is placed into a protective outer wrapper during removal from the C-PEC and is labeled to require PPE handling precautions.

The C-PEC must be located in a C-SEC, which may either be an ISO Class 7 buffer room with an ISO Class 7 ante-room (preferred) or an unclassified containment segregated compounding area (C-SCA). If the C-PEC is placed in a C-SCA, the beyond-use date (BUD) of all compounded sterile preparations (CSPs) prepared must be limited as described in ⟨797⟩ for CSPs prepared in a segregated compounding area. *Table 3* summarizes the engineering controls required for sterile HD compounding.

Table 3. Engineering Controls for Sterile HD Compounding

Configuration	C-PEC	C-SEC	Maximum BUD
ISO Class 7 buffer room with an ISO Class 7 ante-room	• Externally vented • Examples: Class II BSC or CACI	• Externally vented • 30 ACPH • Negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas	As described in ⟨797⟩
Unclassified C-SCA	• Externally vented • Examples: Class II BSC or CACI	• Externally vented • 12 ACPH • Negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas	As described in ⟨797⟩ for CSPs prepared in a segregated compounding area

ISO Class 7 buffer room with an ISO class 7 ante-room: The C-PEC is placed in an ISO Class 7 buffer room that has fixed walls, HEPA-filtered supply air, a negative pressure between 0.01 and 0.03 inches of water column relative to all adjacent areas and a minimum of 30 ACPH.

The buffer room must be externally vented. Because the room through which entry into the HD buffer room (e.g., ante-room or non-HD buffer room) plays an important role in terms of total contamination control, the following is required:

- Minimum of 30 ACPH of HEPA-filtered supply air
- Maintain a positive pressure of at least 0.02 inches of water column relative to all adjacent unclassified areas
- Maintain an air quality of ISO Class 7 or better

An ISO Class 7 ante-room with fixed walls is necessary to provide inward air migration of equal cleanliness classified air into the negative pressure buffer room to contain any airborne HD. A hand-washing sink must be placed in the ante-room at least 1 meter from the entrance to the HD buffer room to avoid contamination migration into the negative pressure HD buffer room.

Although not a recommended facility design, if the negative-pressure HD buffer room is entered though the positive-pressure non-HD buffer room, the following is also required:

- A line of demarcation must be defined within the negative-pressure buffer room for donning and doffing PPE
- A method to transport HDs, HD CSPs, and HD waste into and out of the negative pressure buffer room to minimize the spread of HD contamination. This may be accomplished by use of a pass-through chamber between the negative-pressure buffer area and adjacent space. The pass-through chamber must be included in the facility's certification to ensure that particles are not compromising the air quality of the negative-pressure buffer room. A refrigerator pass-through must not be used. Other methods of containment (such as sealed containers) may be used.

HD CSPs prepared in an ISO Class 7 buffer room with an ISO Class 7 ante-room may use the BUDs described in ⟨797⟩, based on the categories of CSP, sterility testing, and storage temperature.

Containment segregated compounding area (C-SCA): The C-PEC is placed in an unclassified C-SCA that has fixed walls, a negative pressure between 0.01 and 0.03 inches of water column relative to all adjacent areas, and a minimum of 12 ACPH. The C-SCA must be externally vented. A hand-washing sink must be placed at least 1 meter from C-PEC and may be either inside the C-SCA or directly outside the C-SCA.

Only ▲Category 1▲ (CN 1-Dec-2019) HD CSPs may be prepared in a C-SCA. HD CSPs prepared in the C-SCA must not exceed the BUDs described in ⟨797⟩ for CSPs prepared in a segregated compounding area.

5.4 Containment Supplemental Engineering Controls

Containment supplemental engineering controls, such as CSTDs, provide adjunct controls to offer an additional level of protection during compounding or administration. Some CSTDs have been shown to limit the potential of generating aerosols during compounding. However, there is no certainty that all CSTDs will perform adequately. Until a published universal performance standard for evaluation of CSTD containment is available, users should carefully evaluate the performance claims associated with available CSTDs based on independent, peer-reviewed studies and demonstrated contamination reduction.

A CSTD must not be used as a substitute for a C-PEC when compounding. CSTDs should be used when compounding HDs when the dosage form allows. CSTDs must be used when administering antineoplastic HDs when the dosage form allows. CSTDs known to be physically or chemically incompatible with a specific HD must not be used for that HD.

6. ENVIRONMENTAL QUALITY AND CONTROL

Environmental wipe sampling for HD surface residue should be performed routinely (e.g., initially as a benchmark and at least every 6 months, or more often as needed, to verify containment). Surface wipe sampling should include:

- Interior of the C-PEC and equipment contained in it
- Pass-through chambers
- Surfaces in staging or work areas near the C-PEC
- Areas adjacent to C-PECs (e.g., floors directly under C-PEC, staging, and dispensing area)
- Areas immediately outside the HD buffer room or the C-SCA
- Patient administration areas

There are currently no studies demonstrating the effectiveness of a specific number or size of wipe samples in determining levels of HD contamination. Wipe sampling kits should be verified before use to ensure the method and reagent used have been tested to recover a specific percentage of known marker drugs from various surface types found in the sampled area. There are currently no certifying agencies for vendors of wipe sample kits.

There is currently no standard for acceptable limits for HD surface contamination. Common marker HDs that can be assayed include cyclophosphamide, ifosfamide, methotrexate, fluorouracil, and platinum-containing drugs. An example of measurable contamination would be cyclophosphamide levels >1.00 ng/cm², which were shown in some studies to result in uptake of the drug in exposed workers. If any measurable contamination is found, the designated person must identify, document, and contain the cause of contamination. Such action may include reevaluating work practices, re-training personnel, performing thorough deactivation, decontamination, cleaning, and improving engineering controls. Repeat the wipe sampling to validate that the deactivation/decontamination and cleaning steps have been effective.

7. PERSONAL PROTECTIVE EQUIPMENT

Personal Protective Equipment (PPE) provides worker protection to reduce exposure to HD aerosols and residues. Additional PPE may be required to handle the HDs outside of a C-PEC, such as treating a patient or cleaning a spill. The NIOSH list of antineoplastic and other HDs provides general guidance on PPE for possible scenarios that may be encountered in healthcare settings. Disposable PPE must not be re-used. Reusable PPE must be decontaminated and cleaned after use.

Gowns, head, hair, shoe covers, and two pairs of chemotherapy gloves are required for compounding sterile and nonsterile HDs. Two pairs of chemotherapy gloves are required for administering injectable antineoplastic HDs. Gowns shown to resist permeability by HDs are required when administering injectable antineoplastic HDs. For all other activities, the entity's SOP must describe the appropriate PPE to be worn based on its occupational safety plan and assessment of risk (if used). The entity must develop SOPs for PPE based on the risk of exposure (see *Types of Exposure*) and activities performed.

Appropriate PPE must be worn when handling HDs including during:

- Receipt
- Storage
-

Transport

- Compounding (sterile and nonsterile)
- Administration
- Deactivation/decontamination, cleaning, and disinfecting
- Spill control
- Waste disposal

7.1 Gloves

When chemotherapy gloves are required, they must meet American Society for Testing and Materials (ASTM) standard D6978 (or its successor). Chemotherapy gloves should be worn for handling all HDs including non-antineoplastics and for reproductive risk only HDs. Chemotherapy gloves must be powder-free because powder can contaminate the work area and can adsorb and retain HDs. Gloves must be inspected for physical defects before use. Do not use gloves with pin holes or weak spots.

When used for sterile compounding, the outer chemotherapy gloves must be sterile. Chemotherapy gloves should be changed every 30 minutes unless otherwise recommended by the manufacturer's documentation and must be changed when torn, punctured, or contaminated. Hands must be washed with soap and water after removing gloves.

7.2 Gowns

When gowns are required, they must be disposable and shown to resist permeability by HDs. Gowns must be selected based on the HDs handled. Disposable gowns made of polyethylene-coated polypropylene or other laminate materials offer better protection than those made of uncoated materials. Gowns must close in the back (i.e., no open front), be long sleeved, and have closed cuffs that are elastic or knit. Gowns must not have seams or closures that could allow HDs to pass through.

Cloth laboratory coats, surgical scrubs, isolation gowns, or other absorbent materials are not appropriate protective outerwear when handling HDs because they permit the permeation of HDs and can hold spilled drugs against the skin, thereby increasing exposure. Clothing may also retain HD residue from contact, and may transfer to other healthcare workers or various surfaces. Washing of non-disposable clothing contaminated with HD residue should only be done according to facility policy as drug residue may be transferred to other clothing. Potentially contaminated clothing must not be taken home under any circumstances.

Gowns must be changed per the manufacturer's information for permeation of the gown. If no permeation information is available for the gowns used, change them every 2–3 hours or immediately after a spill or splash. Gowns worn in HD handling areas must not be worn to other areas in order to avoid spreading HD contamination and exposing other healthcare workers.

7.3 Head, Hair, Shoe, and Sleeve Covers

Head and hair covers (including beard and moustache, if applicable), shoe covers, and sleeve covers provide protection from contact with HD residue. When compounding HDs, a second pair of shoe covers must be donned before entering the C-SEC and doffed when exiting the C-SEC. Shoe covers worn in HD handling areas must not be worn to other areas to avoid spreading HD contamination and exposing other healthcare workers.

Disposable sleeve covers may be used to protect areas of the arm that may come in contact with HDs. Disposable sleeve covers made of polyethylene-coated polypropylene or other laminate materials offer better protection than those made of uncoated materials.

7.4 Eye and Face Protection

Many HDs are irritating to the eyes and mucous membranes. Appropriate eye and face protection must be worn when there is a risk for spills or splashes of HDs or HD waste materials when working outside of a C-PEC (e.g., administration in the surgical suite, working at or above eye level, or cleaning a spill). A full-facepiece respirator provides eye and face protection. Goggles must be used when eye protection is needed. Eye glasses alone or safety glasses with side shields do not protect the eyes adequately from splashes. Face shields in combination with goggles provide a full range of protection against splashes to the face and eyes. Face shields alone do not provide full eye and face protection.

7.5 Respiratory Protection

Personnel who are unpacking HDs that are not contained in plastic should wear an elastomeric half-mask with a multi-gas cartridge and P100-filter until assessment of the packaging integrity can be made to ensure no breakage or spillage occurred during transport. If the type of drug can be better defined, a more targeted cartridge can be used.

Surgical masks do not provide respiratory protection from drug exposure and must not be used when respiratory protection from HD exposure is required. A surgical N95 respirator provides the respiratory protection of an N95 respirator, and like a surgical mask, provides a barrier to splashes, droplets, and sprays around the nose and mouth.

For most activities requiring respiratory protection, a fit-tested NIOSH-certified N95 or more protective respirator is sufficient to protect against airborne particles. However, N95 respirators offer no protection against gases and vapors and little protection against direct liquid splashes (see the Centers for Disease Control and Prevention's (CDC's) Respirator Trusted-Source information).

Fit test the respirator and train workers to use respiratory protection. Follow all requirements in the Occupational Safety and Health Administration (OSHA) respiratory protection standard (29 CFR 1910.134). An appropriate full-facepiece, chemical cartridge-type respirator or powered air-purifying respirator (PAPR) should be worn when there is a risk of respiratory exposure to HDs, including when:

- Attending to HD spills larger than what can be contained with a spill kit
- Deactivating, decontaminating, and cleaning underneath the work surface of a C-PEC
- There is a known or suspected airborne exposure to powders or vapors

7.6 Disposal of Used Personal Protective Equipment

Consider all PPE worn when handling HDs to be contaminated with, at minimum, trace quantities of HDs. PPE must be placed in an appropriate waste container and further disposed of per local, state, and federal regulations. PPE worn during compounding should be disposed of in the proper waste container before leaving the C-SEC. Chemotherapy gloves and sleeve covers (if used) worn during compounding must be carefully removed and discarded immediately into a waste container approved for trace contaminated waste inside the C-PEC or contained in a sealable bag for discarding outside the C-PEC.

8. HAZARD COMMUNICATION PROGRAM

Entities are required to establish policies and procedures that ensure worker safety during all aspects of HD handling. The entity must develop SOPs to ensure effective training regarding proper labeling, transport, storage, and disposal of the HDs and use of Safety Data Sheets (SDS), based on the Globally Harmonized System of Classification and Labeling of Chemicals (GHS).

Elements of the hazard communication program plan must include:

- A written plan that describes how the standard will be implemented
- All containers of hazardous chemicals must be labeled, tagged, or marked with the identity of the material and appropriate hazard warnings
- Entities must have an SDS for each hazardous chemical they use (29 CFR 1910.1200)
- Entities must ensure that the SDSs for each hazardous chemical used are readily accessible to personnel during each work shift and when they are in their work areas
- Personnel who may be exposed to hazardous chemicals when working must be provided information and training before the initial assignment to work with a hazardous chemical, and also whenever the hazard changes
- Personnel of reproductive capability must confirm in writing that they understand the risks of handling HDs

9. PERSONNEL TRAINING

All personnel who handle HDs must be trained based on their job functions (e.g., in the receipt, storage, compounding, repackaging, dispensing, administrating, and disposing of HDs). Training must occur before the employee independently handles HDs. The effectiveness of training for HD handling competencies must be demonstrated by each employee. Personnel competency must be reassessed at least every 12 months. Personnel must be trained prior to the introduction of a new HD or new equipment and prior to a new or significant change in process or SOP. All training and competency assessment must be documented.

The training must include at least the following:

- Overview of entity's list of HDs and their risks
- Review of the entity's SOPs related to handling of HDs
- Proper use of PPE
- Proper use of equipment and devices (e.g., engineering controls)
- Response to known or suspected HD exposure
- Spill management
- Proper disposal of HDs and trace-contaminated materials

10. RECEIVING

The entity must establish SOPs for receiving HDs. HDs should be received from the supplier in impervious plastic to segregate them from other drugs and to allow for safety in the receiving and internal transfer process. HDs must be delivered to the HD storage area immediately after unpacking.

PPE, including chemotherapy gloves, must be worn when unpacking HDs (see *Personal Protective Equipment*). A spill kit must be accessible in the receiving area.

The entity must enforce policies that include a tiered approach, starting with visual examination of the shipping container for signs of damage or breakage (e.g., visible stains from leakage, sounds of broken glass). *Table 4* summarizes the steps for receiving and handling of damaged shipping containers.

Table 4. Summary of Requirements for Receiving and Handling Damaged HD Shipping Containers

If the shipping container appears damaged	• Seal container without opening and contact the supplier • If the unopened package is to be returned to the supplier, enclose the package in an impervious container and label the outer container "Hazardous" • If the supplier declines return, dispose of as hazardous waste

If a damaged shipping container must be opened	• Seal the container in plastic or an impervious container • Transport it to a C-PEC and place on a plastic-backed preparation mat • Open the package and remove undamaged items • Wipe the outside of the undamaged items with a disposable wipe • Enclose the damaged item(s) in an impervious container and label the outer container "Hazardous" • If the supplier declines return, dispose of as hazardous waste • Deactivate, decontaminate, and clean the C-PEC (see *Deactivating, Decontaminating, Cleaning, and Disinfecting*) and discard the mat and cleaning disposables as hazardous waste

When opening damaged shipping containers, they should preferably be transported to a C-PEC designated for nonsterile compounding. If a C-PEC designated for sterile compounding is the only one available, it must be disinfected after the decontamination, deactivation, and cleaning step before returning to any sterile compounding activity.

Damaged packages or shipping cartons must be considered spills that must be reported to the designated person and managed according to the entity's SOPs. Segregate HDs waiting to be returned to the supplier in a designated negative pressure area. Clean-up must comply with established SOPs.

11. LABELING, PACKAGING, TRANSPORT AND DISPOSAL

The entity must establish SOPs for the labeling, packaging, transport, and disposal of HDs. The SOPs must address prevention of accidental exposures or spills, personnel training on response to exposure, and use of a spill kit. Examples of special exposure-reducing strategies include small-bore connectors (such as Luer Lock) and syringes, syringe caps, CSTDs, the capping of container ports, sealed impervious plastic bags, impact-resistant and/or water-tight containers, and cautionary labeling.

11.1 Labeling

HDs identified by the entity as requiring special HD handling precautions must be clearly labeled at all times during their transport. Personnel must ensure that the labeling processes for compounded preparations do not introduce contamination into the non-HD handling areas.

11.2 Packaging

Personnel must select and use packaging containers and materials that will maintain physical integrity, stability, and sterility (if needed) of the HDs during transport. Packaging materials must protect the HD from damage, leakage, contamination, and degradation, while protecting healthcare workers who transport HDs. The entity must have written SOPs to describe appropriate shipping containers and insulating materials, based on information from product specifications, vendors, and mode of transport.

11.3 Transport

HDs that need to be transported must be labeled, stored, and handled in accordance with applicable federal, state, and local regulations. HDs must be transported in containers that minimize the risk of breakage or leakage. Pneumatic tubes must not be used to transport any liquid HDs or any antineoplastic HDs because of the potential for breakage and contamination.

When shipping HDs to locations outside the entity, the entity must consult the Transport Information on the SDS. The entity must ensure that labels and accessory labeling for the HDs include storage instructions, disposal instructions, and HD category information in a format that is consistent with the carrier's policies.

11.4 Disposal

All personnel who perform routine custodial waste removal and cleaning activities in HD handling areas must be trained in appropriate procedures to protect themselves and the environment to prevent HD contamination. Disposal of all HD waste, including, but not limited to, unused HDs and trace-contaminated PPE and other materials, must comply with all applicable federal, state, and local regulations.

12. DISPENSING FINAL DOSAGE FORMS

HDs that do not require any further manipulation, other than counting or repackaging of final dosage forms, may be prepared for dispensing without any further requirements for containment unless required by the manufacturer or if visual indicators of HD exposure hazards are present (e.g., HD dust or leakage).

Counting or repackaging of HDs must be done carefully. Clean equipment should be dedicated for use with HDs and should be decontaminated after every use. Tablet and capsule forms of antineoplastic HDs must not be placed in automated counting or packaging machines, which subject them to stress and may create powdered contaminants.

13. COMPOUNDING

Entities and personnel involved in compounding HDs must be compliant with the appropriate USP standards for compounding including ⟨795⟩ and ⟨797⟩. Compounding must be done in proper engineering controls as described in *Compounding*. When compounding HD preparations in a C-PEC, a plastic-backed preparation mat should be placed on the work surface of the C-PEC. The mat should be changed immediately if a spill occurs and regularly during use, and should be discarded at the end of the daily compounding activity. Disposable or clean equipment for compounding (such as mortars and pestles, and spatulas) must be dedicated for use with HDs.

Bulk containers of liquid and API HD must be handled carefully to avoid spills. If used, APIs or other powdered HDs must be handled in a C-PEC to protect against occupational exposure, especially during particle-generating activities (such as crushing tablets, opening capsules, and weighing powder).

14. ADMINISTERING

HDs must be administered safely using protective medical devices and techniques. Examples of protective medical devices include needleless and closed systems. Examples of protective techniques include spiking or priming of IV tubing with a non-HD solution in a C-PEC and crushing tablets in a plastic pouch.

Appropriate PPE must be worn when administering HDs. After use, PPE must be removed and disposed of in a waste container approved for trace-contaminated HD waste at the site of drug administration. Equipment (such as tubing and needles) and packaging materials must be disposed of properly, such as in HD waste containers, after administration.

CSTDs must be used for administration of antineoplastic HDs when the dosage form allows. Techniques and ancillary devices that minimize the risk posed by open systems must be used when administering HDs through certain routes. Administration into certain organs or body cavities (e.g., the bladder, eye, peritoneal cavity, or chest cavity) often requires equipment for which locking connections may not be readily available or possible.

Healthcare personnel should avoid manipulating HDs such as crushing tablets or opening capsules if possible. Liquid formulations are preferred if solid oral dosage forms are not appropriate for the patient. If HD dosage forms do require manipulation such as crushing tablet(s) or opening capsule(s) for a single dose, personnel must don appropriate PPE and use a plastic pouch to contain any dust or particles generated.

15. DEACTIVATING, DECONTAMINATING, CLEANING, AND DISINFECTING

All areas where HDs are handled and all reusable equipment and devices must be deactivated, decontaminated, and cleaned. Additionally, sterile compounding areas and devices must be subsequently disinfected.

The entity must establish written procedures for decontamination, deactivation, and cleaning, and for sterile compounding areas disinfection. Additionally, cleaning of nonsterile compounding areas must comply with (795) and cleaning of sterile compounding areas must comply with (797). Written procedures for cleaning must include procedures, agents used, dilutions (if used), frequency, and documentation requirements.

All personnel who perform deactivation, decontamination, cleaning, and disinfection activities in HD handling areas must be trained in appropriate procedures to protect themselves and the environment from contamination. All personnel performing these activities must wear appropriate PPE resistant to the cleaning agents used, including two pairs of chemotherapy gloves and impermeable disposable gowns (see *Personal Protective Equipment*). Additionally, eye protection and face shields must be used if splashing is likely. If warranted by the activity, respiratory protection must be used.

The deactivating, decontaminating, cleaning, and disinfecting agents selected must be appropriate for the type of HD contaminant(s), location, and surface materials. The products used must be compatible with the surface material. Consult manufacturer or supplier information for compatibility with cleaning agents used. Agents used for deactivation, decontamination, and cleaning should be applied through the use of wipes wetted with appropriate solution and not delivered by a spray bottle to avoid spreading HD residue. All disposable materials must be discarded to meet EPA regulations and the entity's policies. Perform cleaning in areas that are sufficiently ventilated. *Table 5* summarizes the purpose and example agents for each step.

Table 5. Cleaning Steps

Cleaning Step	Purpose	Example Agents
Deactivation	Render compound inert or inactive	As listed in the HD labeling or other agents which may incorporate Environmental Protection Agency (EPA)-registered oxidizers (e.g., peroxide formulations, sodium hypochlorite, etc.)
Decontamination	Remove HD residue	Materials that have been validated to be effective for HD decontamination, or through other materials proven to be effective through testing, which may include alcohol, water, peroxide, or sodium hypochlorite
Cleaning	Remove organic and inorganic material	Germicidal detergent
Disinfection (for sterile manipulations)	Destroy microorganisms	EPA-registered disinfectant and/or sterile alcohol as appropriate for use

15.1 Deactivation

Deactivation renders a compound inert or inactive. Residue from deactivation must be removed by decontaminating the surface.

There is no one proven method for deactivating all compounds. The ultimate goal should be complete surface decontamination. Products that have known deactivation properties (EPA-registered oxidizing agents that are appropriate for the intended use) should be used when possible. Care should be taken when selecting materials for deactivation due to potential adverse effects (hazardous byproducts, respiratory effects, and caustic damage to surfaces). Damage to surfaces is exhibited by corrosion to stainless steel surfaces caused by sodium hypochlorite if left untreated. To prevent corrosion, sodium hypochlorite must be neutralized with sodium thiosulfate or by following with an agent to remove the sodium hypochlorite (e.g., sterile alcohol, sterile water, germicidal detergent, or sporicidal agent).

15.2 Decontamination

Decontamination occurs by inactivating, neutralizing, or physically removing HD residue from non-disposable surfaces and transferring it to absorbent, disposable materials (e.g., wipes, pads, or towels) appropriate to the area being cleaned. When choosing among various products available for decontaminating HDs, consideration should be given to surface compatibility and facility requirements. It is imperative to adhere to manufacturer's use instructions. Because of the growing number of assays available for HDs, additional surface wipe sampling is now possible and should be done to document the effectiveness of any agent used for decontamination of HD residue from work surfaces (see *Environmental Quality and Control*).

The amount of HD contamination introduced into the C-PEC may be reduced by wiping down HD containers. The solution used for wiping HD packaging must not alter the product label. The work surface of the C-PEC must be decontaminated between compounding of different HDs. The C-PEC must be decontaminated at least daily (when used), any time a spill occurs, before and after certification, any time voluntary interruption occurs, and if the ventilation tool is moved.

C-PECs may have areas under the work tray where contamination can build up. These areas must be deactivated, decontaminated, and cleaned at least monthly to reduce the contamination level in the C-PEC. Accessing this area may be difficult. Deactivate, decontaminate, and clean as much as possible of the C-PEC surfaces before accessing the area under the work tray. When deactivating, decontaminating, and cleaning the area under the work tray of a C-PEC, the containment airflows are compromised by opening the cabinets. To provide protection to the worker performing this task, respiratory protection may be required.

15.3 Cleaning

Cleaning is a process that results in the removal of contaminants (e.g., soil, microbial contamination, HD residue) from objects and surfaces using water, detergents, surfactants, solvents, and/or other chemicals. Cleaning agents used on compounding equipment should not introduce microbial contamination. No cleaning step may be performed when compounding activities are occurring.

15.4 Disinfection

Disinfection is a process of inhibiting or destroying microorganisms. Before disinfection can be adequately performed, surfaces must be cleaned. Disinfection must be done for areas intended to be sterile, including the sterile compounding areas.

16. SPILL CONTROL

All personnel who may be required to clean up a spill of HDs must receive proper training in spill management and the use of PPE and NIOSH-certified respirators (see *Personal Protective Equipment*). Spills must be contained and cleaned immediately only by qualified personnel with appropriate PPE. Qualified personnel must be available at all times while HDs are being handled. Signs must be available for restricting access to the spill area. Spill kits containing all of the materials needed to clean HD spills must be readily available in all areas where HDs are routinely handled. If HDs are being prepared or administered in a non-routine healthcare area, a spill kit and respirator must be available. All spill materials must be disposed of as hazardous waste.

The circumstances and management of spills must be documented. Personnel who are potentially exposed during the spill or spill clean up or who have direct skin or eye contact with HDs require immediate evaluation. Non-employees exposed to an HD spill should follow entity policy, which may include reporting to the designated emergency service for initial evaluation and completion of an incident report or exposure form.

SOPs must be developed to prevent spills and to direct the clean up of HD spills. SOPs must address the size and scope of the spill and specify who is responsible for spill management and the type of PPE required. The management of the spill (e.g., decontamination, deactivation, and cleaning) may be dependent on the size and type of spill. The SOP must address the location of spill kits and clean-up materials as well as the capacity of the spill kit. Written procedures should address use of appropriate full-facepiece, chemical cartridge-type respirators if the capacity of the spill kit is exceeded or if there is known or suspected airborne exposure to vapors or gases.

17. DOCUMENTATION AND STANDARD OPERATING PROCEDURES

The entity must maintain SOPs for the safe handling of HDs for all situations in which these HDs are used throughout a facility. The SOPs must be reviewed at least every 12 months by the designated person, and the review must be documented. Revisions in forms or records must be made as needed and communicated to all personnel handling HDs.

The SOPs for handling of HDs should include:

- Hazard communication program
- Occupational safety program
- Designation of HD areas
- Receipt
- Storage
- Compounding
- Use and maintenance of proper engineering controls (e.g., C-PECs, C-SECs, and CSTDs)
- Hand hygiene and use of PPE based on activity (e.g., receipt, transport, compounding, administration, spill, and disposal)
- Deactivation, decontamination, cleaning, and disinfection
- Dispensing
- Transport
- Administering
- Environmental monitoring (e.g., wipe sampling)
- Disposal
- Spill control
- Medical surveillance

Personnel who transport, compound, or administer HDs must document their training according to OSHA standards (see OSHA Standard 1910.120 Hazardous Waste Operations and Emergency Response) and other applicable laws and regulations.

18. MEDICAL SURVEILLANCE

Medical surveillance is part of a comprehensive exposure control program complementing engineering controls, safe work processes, and use of PPE. Healthcare workers who handle HDs as a regular part of their job assignment should be enrolled in a medical surveillance program. The general purpose of surveillance is to minimize adverse health effects in personnel potentially exposed to HDs. Medical surveillance programs involve assessment and documentation of symptom complaints, physical findings, and laboratory values (such as a blood count) to determine whether there is a deviation from the expected norms.

Medical surveillance can also be viewed as a secondary prevention tool that may provide a means of early detection if a health problem develops. Tracking personnel through medical surveillance allows the comparison of health variables over time in individual workers, which may facilitate early detection of a change in a laboratory value or health condition. Medical surveillance programs also look for trends in populations of workers. Examining grouped data compared with data from unexposed workers may reveal a small alteration or increase in the frequency of a health effect that would be obscured if individual workers' results alone were considered.

Medical surveillance evaluates the protection afforded by engineering controls, other administrative controls, safe work processes, PPE, and worker education about the hazards of the materials they work with in the course of their duties. The data-gathering elements of a medical surveillance program are used to establish a baseline of workers' health and then to monitor their future health for any changes that may result from exposure to HDs.

Elements of a medical surveillance program should be consistent with the entity's Human Resource policies and should include:

- Development of an organized approach to identify workers who are potentially exposed to HDs on the basis of their job duties
- Use of an entity-based or contracted employee health service to perform the medical surveillance while protecting the confidentiality of the employees' personal medical information
- Initial baseline assessment (pre-placement) of a worker's health status and medical history. Data elements collected include a medical (including reproductive) history and work history to assess exposure to HDs, physical examination, and laboratory testing. Methods used to assess exposure history include a review of:
  - Records of HDs handled, with quantities and dosage forms
  - Estimated number of HDs handled per week
  - Estimates of hours spent handling HDs per week and/or per month
  - Performance of a physical assessment and laboratory studies linked to target organs of commonly used HDs, such as a baseline complete blood count. Biological monitoring to determine blood or urine levels of specific HDs is not currently recommended in surveillance protocols, but may have a role in the follow-up of acute spills with a specific agent.
- Medical records of surveillance should be maintained according to OSHA regulation concerning access to employee exposure and medical records
- Monitoring workers' health prospectively through periodic surveillance using the elements of data gathering described above (updated health and exposure history, physical assessment, and laboratory measures, if appropriate)
- Monitoring of the data to identify prevention failure leading to health effects; this monitoring may occur in collaboration with the employee health service
- Development of a follow-up plan for workers who have shown health changes suggesting toxicity or who have experienced an acute exposure. This follow-up should include evaluation of current engineering and administrative controls and equipment to ensure that all systems are appropriately and accurately implemented (see *Follow-Up Plan*)
- Completion of an exit examination when a worker's employment at the entity ends, to document the information on the employee's medical, reproductive, and exposure histories. Examination and laboratory evaluation should be guided by the individual's history of exposures and follow the outline of the periodic evaluation

18.1 Follow-Up Plan

The occurrence of exposure-related health changes should prompt immediate re-evaluation of primary preventive measures (e.g., administrative and engineering controls, PPE, and others). In this manner, medical surveillance acts as a check on the effectiveness of controls already in use.

The entity should take the following actions:

- Perform a post-exposure examination tailored to the type of exposure (e.g., spills or needle sticks from syringes containing HDs). An assessment of the extent of exposure should be conducted and included in a confidential database and in an incident report. The physical examination should focus on the involved area as well as other organ systems commonly affected (i.e., the skin and mucous membranes for direct contact or inhalation; the pulmonary system for aerosolized HDs). Treatment and laboratory studies will follow as indicated and be guided by emergency protocols
- Compare performance of controls with recommended standards; conduct environmental sampling when analytical methods are available
- Verify and document that all engineering controls are in proper operating condition
- Verify and document that the worker complied with existing policies. Review policies for the use of PPE and employee compliance with PPE use and policies. Review availability of appropriate PPE (see *Personal Protective Equipment*)
- Develop and document a plan of action that will prevent additional exposure of workers

Ensure confidential, two-way communication between the worker and the employee health unit(s) regarding notification, discussions about a change in health condition, or detection of an adverse health effect

- Provide and document a follow-up medical survey to demonstrate that the plan implemented is effective
- Ensure that any exposed worker receives confidential notification of any adverse health effect. Offer alternative duty or temporary reassignment
- Provide ongoing medical surveillance of all workers at risk for exposure to HDs to determine whether the plan implemented is effective

GLOSSARY

Active pharmaceutical ingredient (API): Any substance or mixture of substances intended to be used in the compounding of a drug 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.
Alternative duty: Performance of other tasks that do not include the direct handling of HDs.
Ante-room: An ISO Class 7 or cleaner room where personnel hand hygiene, garbing procedures, and other activities that generate high particulate levels are performed. The ante-room is the transition room between the unclassified area of the facility and the buffer room.
Assessment of risk: Evaluation of risk to determine alternative containment strategies and/or work practices.
Beyond-use date (BUD): The date or time beyond which a compounded preparation cannot not be used and must be discarded (see <795> and <797>). The date or time is determined from the date or time when the preparation was compounded.
Biological safety cabinet (BSC): A ventilated cabinet often used for preparation of hazardous drugs. These cabinets are divided into three general classes (Class I, Class II, and Class III). Class II BSCs are further divided into types (Type A1, Type A2, Type B1, and Type B2). See *Appendix 3* for details.
Buffer room: A type of C-SEC under negative pressure that meets ISO Class 7 or better air quality where the C-PEC that generates and maintains an ISO Class 5 environment is physically located. Activities that occur in this area are limited to the preparation and staging of components and supplies used when compounding HDs.
Chemotherapy glove: A medical glove that meets the ASTM Standard Practice for Assessment of Resistance of Medical Gloves to Permeation by Chemotherapy Drugs (D6978) or its successor.
Classified space: An area that maintains an air cleanliness classification based on the International Organization for Standardization (ISO).
Cleaning: The process of removing soil (e.g., organic and inorganic material) from objects and surfaces, normally accomplished by manually or mechanically using water with detergents or enzymatic products.
Closed-system drug-transfer device (CSTD): A drug-transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of HD or vapor concentrations outside the system.
Compounded preparation: A nonsterile or sterile drug or nutrient preparation that is compounded in a licensed pharmacy or other healthcare-related facility in response to or anticipation of a prescription or a medication order from a licensed prescriber.
Compounding aseptic containment isolator (CACI): A specific type of CAI that is designed for the compounding of sterile HDs. The CACI is designed to provide worker protection from exposure to undesirable levels of airborne drugs throughout the compounding and material transfer processes and to provide an aseptic environment with unidirectional airflow for compounding sterile preparations.
Compounding aseptic isolator (CAI): An isolator specifically designed for compounding sterile, non-hazardous pharmaceutical ingredients or preparations. The CAI is designed to maintain an aseptic compounding environment throughout the compounding and material transfer processes.
Compounding personnel: Individuals who participate in the compounding process.
Containment primary engineering control (C-PEC): A ventilated device designed and operated to minimize worker and environmental exposures to HDs by controlling emissions of airborne contaminants through the following:

- The full or partial enclosure of a potential contaminant source
- The use of airflow capture velocities to trap and remove airborne contaminants near their point of generation
- The use of air pressure relationships that define the direction of airflow into the cabinet
- The use of HEPA filtration on all potentially contaminated exhaust streams

Containment secondary engineering control (C-SEC): The room with fixed walls in which the C-PEC is placed. It incorporates specific design and operational parameters required to contain the potential hazard within the compounding room.
Containment segregated compounding area (C-SCA): A type of C-SEC with nominal requirements for airflow and room pressurization as they pertain to HD compounding.
Containment ventilated enclosure (CVE): 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.
Deactivation: Treatment of an HD contaminant on surfaces with a chemical, heat, ultraviolet light, or another agent to transform the HD into a less hazardous agent.
Decontamination: Inactivation, neutralization, or removal of HD contaminants on surfaces, usually by chemical means.
Doff: To remove PPE.
Don: To put on PPE.
Disinfection: The process of inhibiting or destroying microorganisms.
Engineering control: Primary, secondary, and supplemental devices designed to eliminate or reduce worker exposure to HDs.
EPA-registered disinfectant: Antimicrobial products registered with the Environmental Protection Agency (EPA) for healthcare use against pathogens specified in the product labeling.
Externally vented: Exhausted to the outside
Final dosage form: Any form of a medication that requires no further manipulation before administration.
Globally Harmonized System of Classification and Labeling of Chemicals (GHS): A system for standardizing and harmonizing the classification and labeling of chemicals.

Goggles: Tight-fitting eye protection that completely covers the eyes, eye sockets, and facial area that immediately surrounds the eyes. Goggles provide protection from impact, dust, and splashes. Some goggles fit over corrective lenses.
Hazardous drug (HD): Any drug identified by at least one of the following 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: An extended-medium, dry-type filter in a rigid frame, having a minimum particle collection efficiency of 99.97% for particles with a mass median diameter of 0.3 µm when tested at a rated airflow in accordance with MIL STD 282 using IEST Recommended Standard RP-CC001.5.
Negative-pressure room: A room that is maintained at a lower pressure than the adjacent areas; therefore the net flow of air is into the room.
Pass-through: An enclosure with interlocking doors that is positioned between two spaces for the purpose of reducing particulate transfer while moving materials from one space to another. A pass-through serving negative-pressure rooms needs to be equipped with sealed doors.
Personal protective equipment (PPE): Items such as gloves, gowns, respirators, goggles, faceshields, and others that protect individual workers from hazardous physical or chemical exposures.
Positive-pressure room: A room that is maintained at a higher pressure than the adjacent areas; therefore, the net flow of air is out of the room.
Repackaging: The act of removing a product from its original primary container and placing it into another primary container, usually of smaller size.
Safety data sheet (SDS): An informational document that provides written or printed material concerning a hazardous chemical. The SDS is prepared in accordance with the HCS (previously known as a Material Safety Data Sheet (MSDS)).
Spill kit: A container of supplies, warning signage, and related materials used to contain the spill of an HD.
Standard operating procedure (SOP): Written procedures describing operations, testing, sampling, interpretation of results, and corrective actions that relate to the operations that are taking place.
Supplemental engineering control: An adjunct control (e.g., CSTD) that may be used concurrently with primary and secondary engineering controls. Supplemental engineering controls offer additional levels of protection and may facilitate enhanced occupational protection, especially when handling HDs outside of primary and secondary engineering controls (e.g., during administering).
Unclassified space: A space not required to meet any air cleanliness classification based on the International Organization for Standardization (ISO).

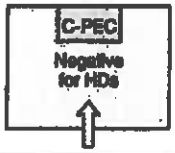
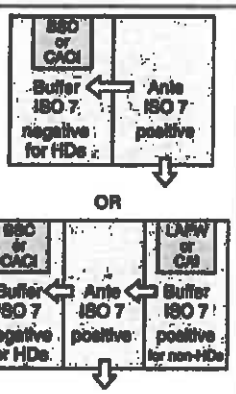
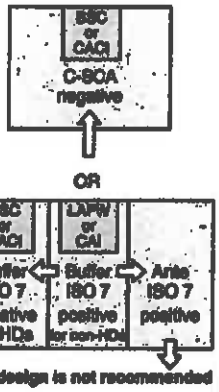
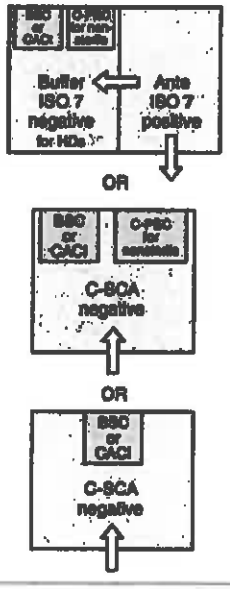
APPENDICES

Appendix 1: Acronyms

ACPH	Air changes per hour
API	Active pharmaceutical ingredient
ASTM	American Society for Testing and Materials
BSC	Biological safety cabinet
BUD	Beyond-use date
CACI	Compounding aseptic containment isolator
CAI	Compounding aseptic isolator
CDC	Centers for Disease Control and Prevention
C-PEC	Containment primary engineering control
C-SCA	Containment segregated compounding area
C-SEC	Containment secondary engineering control
CSP	Compounded sterile preparation
CSTD	Closed-system drug-transfer device
CVE	Containment ventilated enclosure
EPA	Environmental Protection Agency
GHS	Globally Harmonized System of Classification and Labeling of Chemicals

HCS	Hazard Communication Standard
HD	Hazardous drug
HEPA	High-efficiency particulate air
IV	Intravenous
LAFW	Laminar airflow workbench
NIOSH	National Institute for Occupational Safety and Health
ONS	Oncology Nursing Society
OSHA	Occupational Safety and Health Administration
PAPR	Powered air-purified respirator
PPE	Personal protective equipment
SDS	Safety Data Sheet
SOP	Standard operating procedure
ULPA	Ultra-low particulate air
UPS	Uninterrupted power source

Appendix 2: Examples of Designs for Hazardous Drug Compounding Areas[a]

Use	Optimal Primary and Secondary Control	Maximum ACPH	Limitations Primary and Secondary Control	Minimum ACPH	Notes for limitations
Nonsterile HD compounding		12			
Sterile HD compounding		30		12 30 30	Maximum BUD as described in <797> for segregated compounding area. If this design is in place, measures must be taken to avoid contamination of the positive-pressure buffer room. Maximum BUD as described in <797>.
Both sterile HD and nonsterile HD compounding	A separate room for sterile and nonsterile compounding is recommended			30 12 12	For rooms used for both sterile and nonsterile compounding, particle-generating activity must not be performed when sterile compounding is in process. C-PECs must be at least 1 meter apart. Maximum BUD as described in <797> for segregated compounding area. Maximum BUD as described in <797> for segregated compounding area.

[a] The arrows indicate direction of airflow.

Appendix 3: Types of Biological Safety Cabinets

Class I: A BSC that protects personnel and the environment but does not protect the product/preparation. A minimum velocity of 75 linear feet/minute of unfiltered room air is drawn through the front opening and across the work surface, providing personnel protection. The air is then passed through a HEPA/ULPA (ultra-low particulate air) filter, either into the room or to the outside in the exhaust plenum, providing environmental protection.
Class II: Class II (Types A1, A2, B1, and B2) BSCs are partial barrier systems that rely on the movement of air to provide personnel, environmental, and product/preparation protection. Personnel and product/preparation protection are provided by the combination of inward and downward airflow captured by

the front grille of the cabinet. Side-to-side cross-contamination of products/preparations is minimized by the internal downward flow of HEPA/ULPA filtered air moving toward the work surface and then drawn into the front and rear intake grilles. Environmental protection is provided when the cabinet exhaust air is passed through a HEPA/ULPA filter.

Type A1 (formerly, Type A): These Class II BSCs maintain a minimum inflow velocity of 75 feet/minute; have HEPA-filtered, down-flow air that is a portion of the mixed down-flow and inflow air from a common plenum; may exhaust HEPA-filtered air back into the laboratory or to the environment through an exhaust canopy; and may have positive-pressure contaminated ducts and plenums that are not surrounded by negative-pressure plenums. Type A1 BSCs are not suitable for use with volatile toxic chemicals and volatile radionuclides.

Type A2 (formerly, Type B3): These Class II BSCs maintain a minimum inflow velocity of 100 feet/minute; have HEPA-filtered, down-flow air that is a portion of the mixed down-flow and inflow air from a common exhaust plenum; may exhaust HEPA-filtered air back into the laboratory or to the environment through an exhaust canopy; and have all contaminated ducts and plenums under negative pressure or surrounded by negative-pressure ducts and plenums. If these cabinets are used for minute quantities of volatile toxic chemicals and trace amounts of radionuclides, they must be exhausted through properly functioning exhaust canopies.

Type B1: These Class II BSCs maintain a minimum inflow velocity of 100 feet/minute; have HEPA-filtered, down-flow air composed largely of uncontaminated, recirculated inflow air; exhaust most of the contaminated down-flow air through a dedicated duct exhausted to the atmosphere after passing it through a HEPA filter; and have all contaminated ducts and plenums under negative pressure or surrounded by negative-pressure ducts and plenums. If these cabinets are used for work involving minute quantities of volatile toxic chemicals and trace amounts of radionuclides, the work must be done in the directly exhausted portion of the cabinet.

Type B2 (total exhaust): These Class II BSCs maintain a minimum inflow velocity of 100 feet/minute; have HEPA-filtered, down-flow air drawn from the laboratory or the outside; exhaust all inflow and down-flow air to the atmosphere after filtration through a HEPA filter without recirculation inside the cabinet or return to the laboratory; and have all contaminated ducts and plenums under negative pressure or surrounded by directly exhausted negative-pressure ducts and plenums. These cabinets may be used with volatile toxic chemicals and radionuclides.

Class III: The Class III BSC is designed for work with highly infectious microbiological agents and other hazardous operations. It provides maximum protection for the environment and the worker. It is a gas-tight enclosure with a viewing window that is secured with locks and/or requires the use of tools to open. Both supply and exhaust air are HEPA/ULPA filtered. Exhaust air must pass through two HEPA/ULPA filters in series before discharge to the outdoors.

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▲▲ (RB 1-Dec-2019)

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

Topic/Question	Contact	Expert Committee
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Most Recently Appeared In:
Pharmacopeial Forum: Volume No. 41(2)

Page Information:

USP42-NF37 - 7002
USP41-NF36 2S - 9212
USP41-NF36 - 6598

Current DocID: GUID-5D76173F-5CB6-47B8-815E-7C275A916085_5_en-US

FAQs: <800> Hazardous Drugs—Handling in Healthcare Settings

Last updated: May 31, 2019

The following are responses provided by members of the USP Compounding Expert Committee. Responses have been provided for informational purposes only, and should not be construed as an official interpretation of USP text or relied on to demonstrate compliance with USP standards or requirements.

1. Where can I find FAQs and other information on USP Compounding Standards?

For FAQs on other USP Compounding Standards, please see below:

- General Chapter <795> Pharmaceutical Compounding—Nonsterile Preparations
- General Chapter <797> Pharmaceutical Compounding—Sterile Preparations
- General Chapter <825> Radiopharmaceuticals– Preparation, Compounding, Dispensing, and Repackaging
- Compounded Preparation Monographs (CPMs)

2. What is a hazardous drug?

A hazardous drug is any drug identified as hazardous or potentially hazardous by the National Institute for Occupational Safety and Health (NIOSH) on the basis of at least one of the following six criteria: carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity in humans, organ toxicity at low doses in humans or animals, genotoxicity, and new drugs that mimic existing hazardous drugs in structure or toxicity. NIOSH maintains a list of antineoplastic and other hazardous drugs used in healthcare settings.

3. What is the purpose of this chapter?

The purpose of the chapter is to describe practice and quality standards for handling hazardous drugs in healthcare settings and help promote patient safety, worker safety, and environmental protection. The chapter defines processes intended to minimize the exposure of hazardous drugs in healthcare settings. The chapter was developed by the USP Compounding Expert Committee with the assistance of the USP Compounding with Hazardous Drugs Expert Panel and government liaisons from the U.S. Food and Drug Administration (FDA) and the U.S. Centers for Disease Control and Prevention (CDC) including NIOSH. The chapter was published for the first time for public comment in March 2014. Based on the public comments received, the chapter was revised and proposed for another round of public comments in December 2014. The chapter was revised again and published in the *USP-NF* in February 2016.

4. Why was the chapter developed?

The public health need for developing <800> was based on published reports of adverse effects in healthcare personnel from occupational exposure to hazardous drugs.[1] General Chapter <800> was developed based on existing guidance documents published by NIOSH, American Society of Health-System Pharmacists (ASHP), and the Oncology Nursing Society (ONS). ASHP published a Technical Assistance Bulletin in 1986 and NIOSH published an alert on preventing occupational exposure in 2004. There was a known risk of hazardous drug exposure in healthcare settings from published medical reports, but there was no enforceable standard to minimize the potential risk of exposure.

[1] Sessink PJ, Bos RP. Drugs hazardous to healthcare workers. Evaluation of methods for monitoring occupational exposure to cytostatic drugs. *Drug*

Saf. April 1999; 20(4): 347-59. Venitt S, Crofton-Sleigh C, Hunt J, Speechley V, Briggs K. Monitoring exposure of nursing and pharmacy personnel to cytotoxic drugs: urinary mutation assays and urinary platinum as markers of absorption. Lancet. Jan 1984;1(8368): 74-7. (See also https://www.cdc.gov/niosh/topics/antineoplastic/default.html).

5. What is the intent of this chapter?

Chapter <800> was written to protect all workers, patients, and the general public who may be accessing facilities where hazardous drugs (HDs) are prepared. This includes, but is not limited to, pharmacists, technicians, nurses, physicians, physician assistants, home healthcare workers, veterinarians, and veterinary technicians. Under the chapter, if any workers come into contact with HDs, they must receive HD training, and be assessed for an understanding of the training. All personnel who handle HDs are responsible for understanding the fundamental practices and precautions and for continually evaluating these procedures and the quality of final HDs to prevent harm to patients, minimize exposure to personnel, and minimize contamination of the work and patient-care environment.

6. In which settings is the chapter relevant?

USP General Chapter <800> is relevant to all healthcare personnel who handle HD preparations and all entities that store, prepare, transport, or administer HDs (e.g., pharmacies, hospitals and other healthcare institutions, patient treatment clinics, physicians' practice facilities, or veterinarians' offices).

7. *NEW* How do I know what are requirements versus recommendations in the chapter?

Generally, requirements in a General Chapter are conveyed by use of the terms "must" or "shall". Recommendations are conveyed by use of the terms "should" and "may".

8. *UPDATED* What is the compendial status of <800>?

From a compendial standpoint, a USP general chapter numbered below <1000> becomes applicable and compendially required through reference in *General Notices*, a monograph, or another applicable general chapter numbered below <1000>.

General Chapters <795> and <797> are made applicable and compendially required through reference in *General Notices* (See *General Notices* 3.10.30). In addition, <795> and <797> are made applicable and compendially required for specific formulations where there is a USP Compounded Preparation monograph that makes reference to these chapters.

General Chapters <795> and <797> have been revised to include cross-references to <800>. These cross-references make <800> an applicable general chapter for facilities that are compendially required to implement <795> and <797>. For hazardous drugs, this means only when a licensed pharmacist or physician is "compounding" (as that term is defined in <795> and <797>) would <795>/<797> and <800> be applicable and compendially required.

USP plays no role in enforcement, and thus, state and other regulators may make their own determinations regarding the applicability and enforceability of <800> to entities within their jurisdiction. It is possible for states and other regulators to require broader implementation of, and compliance with,

<800>, i.e., for facilities engaged in activities that are beyond the scope of nonsterile and sterile compounding covered by <795> and <797>.

9. *UPDATED* Is the chapter relevant to the administration of HDs and preparation of conventionally manufactured sterile products per approved labeling?

From a scientific standpoint, the principles of <800> are broadly applicable to hazardous drug handling activities across all facility types. USP encourages the widespread adoption and use of <800> across all healthcare settings.

General Chapter <800> is made applicable and compendially required through references in General Chapter <797> and <795>. The requirements in <800> would be applicable and compendially required **only to the extent to which USP General Chapters <795> and <797> apply**. For hazardous drugs, this means only when a licensed pharmacist or physician is "compounding" (as that term is defined in <795> and <797>) would <800> be applicable and compendially required. Since administration and preparation of conventionally manufactured sterile products per approved labeling (as described in <797>) is out of scope of <797>, General Chapter <800> is not applicable or compendially required in these contexts.

USP plays no role in enforcement, and thus, state and other regulators may make their own determinations regarding the applicability and enforceability of <800> to entities within their jurisdiction. It is possible for states and other regulators to require broader implementation of, and compliance with, <800>, i.e., for facilities engaged in activities that are beyond the scope of nonsterile and sterile compounding covered by <795> and <797>.

10. *UPDATED* When will General Chapter <800> become official?

USP published a revision bulletin that specifies that the official date of the chapter will be December 1, 2019. The official date of <800> is aligned with the official date of <797> and <795>, to provide a unified approach to quality compounding.

11. *UPDATED* What does "official date" mean?

The USP "official date" indicates the date by which affected users are expected to meet the requirements of a particular standard. Ensuring compliance with the requirements of these standards is the responsibility of regulators such as the FDA, states, and other government authorities. USP has no role in enforcement.

Although all text of the *USP–NF* that has reached its official date is "official text," not all official text states requirements with which compendial users must comply. Some official text is intended to assist or guide compendial users or to serve informational purposes.

12. Does the anticipated December 1, 2019 official date of <800> impact my current or early adoption of the general chapter?

No. USP encourages adoption and implementation of General Chapter <800> to help ensure a quality environment and protection of healthcare workers and patients when hazardous drugs are handled.

13. Have there been updates or changes to the chapter since it was published on February 1, 2016?

Yes, there have been minimal editorial changes to the chapter. USP publishes errata if it discovers erroneously published text that does not accurately reflect the intended requirements as approved by the Council of Experts. In

the errata table, enter "800" in the field "Search by Monograph" to view errata associated with General Chapter <800>.

14. Other than the change to the official date, are there other expected substantive changes to USP General Chapter?

No. The only part of USP General Chapter <800> that is expected to change is the official date, which is expected to be changed to December 1, 2019.

15. How can I obtain a copy of General Chapter?

You may download a copy of USP General Chapter <800>.

Note: This chapter alone is not sufficient for a comprehensive approach to safe handling of hazardous drugs. Additional chapters are required for complete implementation; see USP Compounding Compendium or *USP–NF*.

16. Have there been any documented/published studies involving harm related to handling of HDs?

Yes, there are several studies demonstrating risks associated with handling HDs. Some of references are included in the References section of USP General Chapter <800>.

17. Can repackaging containers of commercially available HD oral liquids into prescription containers or unit-dose packages be considered under an assessment of risk?

Yes, final dosage forms of commercially available HD oral liquids that do not require any further manipulation other than pouring and repackaging may be considered under an assessment of risk.

18. Can I do an assessment of risk for an entire group of HDs (i.e. Group 1, Group 2, or Group 3) instead of listing each individual HD?

No. The assessment of risk must list each drug and dosage form individually. Dosage forms of drugs within the same group might not have the same risk of exposure. For example, priming an intravenous line may have more risk of exposure than dispensing tablets without further manipulation. HDs appear on the NIOSH list based on different characterizes, such as specific reproductive risks. The facility may have the same information for several drugs or dosage forms, but the facility's list needs to be specific to the drug and dosage form.

19. Can the reconstitution, mixing, and diluting of Group 2 and 3 HDs on the NIOSH list be performed under an assessment of risk?

Yes. The reconstitution, mixing, and dilution of dosage forms of Group 2 and 3 HDs may be considered under an assessment of risk.

20. What are alternative containment strategies that may be employed under an assessment of risk?

The purpose of an assessment of risk is to identify mitigation (alternate) strategies for handling dosage forms of HDs to minimize exposure to personnel in the healthcare setting. Some examples of alternative strategies include purchasing HDs in unit-of-use packaging or unit-dose packaging, reassignment of pregnant personnel, and use of additional PPE.

21. If a NIOSH Group 1 HD is supplied as a ready to administer intramuscular injection, does expelling air from the syringe prior to administration require following all of the containment requirements in the chapter?

No. If the NIOSH Group 1 HD is a final dosage form that is being prepared for immediate administration, an assessment of risk may be performed to

determine alternative containment strategies and/or work practices. Section 14 of the chapter ("Administering") states that CSTDs must be used for administration of antineoplastic HDs when the dosage form allows.

22. Where does the designated person obtain training? How much training does the designated person need?

Any training should begin with reading the chapter in it is entirety. All of the requirements for HD handling are defined in the chapter and the chapter provides many references to other source documents. If additional training is required, many professional organizations conduct training and continuing education programs on the subject. The chapter does not specify a minimum number of training hours. The designated person must have a thorough understanding of the standards to be able to develop and implement appropriate procedures; oversee entity compliance with the chapter and other applicable laws, regulations, and standards; ensure competency of personnel; and ensure environmental control of the storage and compounding areas.

23. Are there requirement for posting signs that HDs are being handled in the facility?

Signs are not required to be posted at the entrance of facilities. However, signs designating the hazard must be prominently displayed before the entrance to the HD handling areas. Additionally, signs must be available for restricting access to areas where HD spills occur.

24. Can sterile and nonsterile HDs be stored together?

See Section 5.2 of the Chapter for guidance on storage. Sterile and nonsterile HDs may be stored together, but HDs used for nonsterile compounding should not be stored in areas designated for sterile compounding to minimize traffic into the sterile compounding area. Antineoplastic HDs requiring

manipulation other than counting or repackaging of final dosage forms and any HD active pharmaceutical ingredient (API) must be stored separately from non-HDs in a manner that prevents contamination and personnel exposure. These HDs must be stored in an externally ventilated, negative-pressure room with at least 12 air changes per hour (ACPH). Non-antineoplastic, reproductive risk only, and final dosage forms of antineoplastic HDs may be stored with other inventory if permitted by entity policy. Refrigerated antineoplastic HDs must be stored in a dedicated refrigerator in a negative pressure area with at least 12 ACPH [e.g., storage room, buffer room, or containment segregated compounding area (C-SCA)].

25. Can refrigerated non-antineoplastic HDs be stored with antineoplastic HDs?

Yes, a refrigerator must be dedicated to HD storage and located in a negative pressure room with at least 12 ACPH. Refrigerated antineoplastic HDs must be stored in this dedicated refrigerator. HD APIs requiring refrigeration must also be stored according to the Chapter. Other HDs may be stored in this dedicated refrigerator or may be stored with other inventory if an assessment of risk has been performed and implemented.

26. Where should the sink be located?

Care must be taken to locate water sources and drains in areas where their presence will not interfere with required ISO classifications. Water sources and drains must be located at least 1 meter away from the Containment Primary Engineering Control (C-PEC). Within an ISO classified area, a hand-washing sink must be placed in the ante-room at least 1 meter from the entrance to the HD buffer room to avoid contamination migration into the negative pressure HD buffer room. Within an unclassified C-SCA, a hand-

washing sink must be placed at least 1 meter from C-PEC and may be either inside the C-SCA or directly outside the C-SCA.

27. Is the Containment Secondary Engineering Control (C-SEC) required to be externally vented through high-efficiency particulate air (HEPA) filtration?

No, an erratum was published on May 26, 2016 to remove the requirement that the C-SEC be externally vented through HEPA filtration. The C-SEC must still be externally vented.

28. Is the C-PEC used for sterile compounding required to be exhausted to the outside or can the C-PEC be recirculated into the negative pressure C-SEC which is exhausted to the outside of the building?

The Chapter requires that all C-PECs used for manipulation of sterile HDs must be externally vented. Sterile HD compounding must be performed in a C-PEC that provides an ISO Class 5 or better air quality, such as a Class II or III biological safety cabinet (BSC) or compounding aseptic containment isolator (CACI). Class II BSC types A2, B1, or B2 are acceptable. C-PECs used for pre-sterilization procedures such as weighing and mixing must be either externally vented (preferred) or have redundant–HEPA filters in series and must provide personnel and environmental protection, such as a Class I BSC or Containment Ventilated Enclosure (CVE). A Class II BSC or a CACI may also be used.

29. Can non-HDs and HDs be compounded in C-PECs located in the same C-SEC?

Separate rooms (C-SECs) are required for sterile, nonsterile, HD, and non-HD compounding with two exceptions:

1. Per section 5.3 Compounding, for entities that compound both nonsterile and sterile HDs, the respective C- PECs must be placed in separate rooms, unless those C-PECs used for nonsterile compounding are sufficiently effective that the room can continuously maintain ISO 7 classification throughout the nonsterile compounding activity. If the C-PECs used for sterile and nonsterile compounding are placed in the same room, they must be placed at least 1 meter apart and particle-generating activity must not be performed when sterile compounding is in process; and
2. Per section 5.3.2 Sterile Compounding, a BSC or CACI used for the preparation of HDs must not be used for the preparation of a non-HD unless the non-HD preparation is placed into a protective outer wrapper during removal from the C-PEC and is labeled to require PPE handling precautions.

30. Can a Laminar Airflow Workbench (LAFW) or compounding aseptic isolator (CAI) be used for compounding a non-antineoplastic HD?

Section 5.3.2 specifies that a LAFW cannot be used for compounding an antineoplastic HD. However, for handling non-antineoplastic and reproductive risk HDs, each facility may conduct an assessment of risk and implement strategies different than those required in the chapter. A LAFW does not provide any protection for the worker from the HD. A LAFW or CAI may be used for non-antineoplastic HDs, however, alternative containment strategies and/or work practices must be determined during the assessment of risk.

31. *UPDATED* Can a BSC or CACI used for compounding HDs be used for compounding non-HDs?

If a non-HD is prepared in a C-PEC where HDs have been prepared, then the non-HD must be handled and labeled as an HD. The non-HD preparation must be placed into a protective outer wrapper during removal from the C-

PEC and must be labeled to require PPE handling precautions. All associated materials and wrappers should be discarded as HD waste because the preparation and associated materials have potentially been contaminated by exposure to HDs.

32. Can the negative pressure to the C-SEC be reduced or turned off when the room is not in use?

No, the C-SEC must maintain a negative pressure of 0.01 to 0.03 inches of water column relative to all adjacent areas at all times.

33. Can the ACPH in the C-SEC be set below the minimum requirement when the C-SEC is not in use?

No, the C-SEC must have an appropriate air exchange (e.g., 12 or 30 ACPH) at all times.

34. May a CACI, isolator, robotic device, or similar device be used to compound a sterile HD outside of a C-SEC?

No. A CACI, isolator, robotic device, or similar device may act as the C-PEC if it meets the containment requirements of the chapter as well as the requirements listed in <797>. However, the device must be placed in C-SEC meeting all of the requirements in the chapter.

35. Can the C-PEC be used to create 100% of the external venting for the C-SEC?

Yes, if that C-PEC can function appropriately as the sole source of exhaust from a room.

36. Are closed-system drug-transfer devices (CSTDs) required for compounding HDs?

No, the Chapter does not require a CSTD for compounding HDs, although it is recommended. However, the Chapter does require that CSTDs be used when administering antineoplastic HDs when the dosage form allows.

37. Is there a protocol for evaluating the performance of the different CSTDs available?

NIOSH initially created a draft containment test protocol for barrier-type CSTDs which it released for public comment in September 2015. Following substantial comment, NIOSH announced their intent to develop a second draft protocol, applicable to both barrier & air-cleaning (filtration) CSTDs in September 2016 and held a public meeting on the topic in November 2016. The comment period for this "universal" protocol has been extended several times. Neither protocol has been released in final form.

38. How can a CSTD be chemically incompatible with a HD?

Depending on the chemical composition of the drug being compounded and the composition of the CSTD device, chemical incompatibilities may exist. In March 2015, FDA warned against the use of bendamustine with CSTDs, syringes, and adapters containing polycarbonate or acrylonitrile-butadiene-styrene (ABS). The component in bendamustine (N, N-dimethylacetamide (DMA)) dissolved the ABS or polycarbonate on contact.

39. What is meant by "fixed walls"?

Fixed walls are solid hard wall modular or 'stick-build' construction. According to the Chapter, fixed walls are required to prevent the egress of HD contamination from the C-SEC (either a C-SCA or HD buffer room) as well as ingress of contamination into the ISO Class 7 HD buffer room.

40. Are pressure gauges required to monitor the pressure differential between the C-SEC and the adjacent areas?

The entity must be compliant with the appropriate USP standards for compounding including <795> and/or <797> and in accordance with applicable federal, state, and local regulations. Presence of a pressure gauge and at least daily monitoring is currently required for sterile compounding per USP <797>. However, pressure monitoring is not addressed in nonsterile compounding per USP <795>, so entities should follow applicable federal, state, and local regulations. Presence of a pressure gauge and at least daily monitoring of negative pressure storage areas and nonsterile compounding areas helps ensure pressure requirements are continually maintained in these areas.

41. Is environmental wipe sampling required?

No. The chapter recommends but does not require the performance of environmental wipe sampling. Some common marker HDs that can be assayed include cyclophosphamide, ifosfamide, methotrexate, fluorouracil, and platinum-containing drugs. If no wipe sampling kit is available for the specific HDs used by the entity, the performance of environmental wipe sampling would not be appropriate.

42. Why is environmental wipe sampling recommended when there is currently no standard for acceptable limits on HD surface contamination?

Environmental wipe sampling for HD surface residue should be performed to verify containment. Contamination in any amount indicates a lack of containment. Wipe sampling kits need to be evaluated to ensure they are appropriate for HDs used by the entity. If contamination is found, the chapter states that the designated person must identify, document, and contain the cause of contamination. Such action may include reevaluating work practices,

re-training personnel, performing thorough deactivation, decontamination, cleaning, and improving engineering controls. Repeat the wipe sampling to validate that the deactivation/decontamination and cleaning steps have been effective.

43. Does every area where HDs are handled require environmental sampling?

The chapter recommends, but does not require, the performance of environmental "wipe sampling." The term "sampling" indicates that a portion, or sample, of the entire population be tested.

44. What are the acceptable limits for HD surface contamination?

There is currently no standard for acceptable limits for HD surface contamination. Contamination in any amount indicates a lack of containment and must be addressed.

45. Are the PPE and Engineering Controls specified in Table 5 of the current NIOSH list required?

<800> requires entities to maintain a list of HDs that include any items on the current NIOSH list that the entity handles. However, the list of PPE and engineering controls in Table 5 of the 2016 NIOSH list is a recommendation and may be used to guide the development of the entity's policy. Section 7 of <800> states that "gowns, head, hair, shoe covers, and two pairs of chemotherapy gloves are required for compounding sterile and nonsterile HDs. Two pairs of chemotherapy gloves are required for administering antineoplastic HDs. Gowns shown to resist permeability by HDs are required when administering injectable antineoplastic HDs. For all other activities, the entity's Standard Operating Procedures (SOPs) must describe the appropriate PPE to be worn based on its occupational safety plan and assessment of risk

(if used). The entity must develop SOPs for PPE based on the risk of exposure and activities performed."

46. What PPE is required for administering HDs?

For administering all antineoplastic HDs, two pairs of chemotherapy gloves tested to ASTM D6978 standard must be worn. For administering injectable antineoplastic HDs, gowns shown to resist permeability by HDs must be worn in addition to two pairs of chemotherapy gloves. For administering other HDs, the entity must establish policies describing the PPE required. Table 5 of the NIOSH List provides additional recommendations for PPE based on the HD formulation and activity.

47. Are compounders required to remove all PPE when leaving the compounding area?

Yes, all PPE would need to be removed when leaving the HD compounding area. The goal is to contain all hazardous contamination within the negative pressure room.

48. Can gowns be re-worn during the same day if a compounder leaves the HD compounding area?

Disposable PPE must not be re-used. Consider all PPE worn when handling HDs to be contaminated with, at minimum, trace quantities of HDs. PPE must be placed in an appropriate waste container and further disposed of per local, state, and federal regulations. PPE worn during compounding should be disposed of in the proper waste container before leaving the C-SEC.

49. What documentation is required to show that a gown will resist permeability by HDs?

Gowns used for HD handling must be shown to resist permeability by HDs which can be determined by testing against ASTM F739-12. Manufacturers of gowns used for handling HDs should provide results of ASTM F739-12 testing. The gown manufacturer should be able to provide permeability data for commonly used HDs.

50. Is an entity required to have two sets of equipment, one set for compounding HDs and another second set for compounding non-HDs?

General Chapter <800> states that "disposable or clean equipment for compounding (such as mortars and pestles, and spatulas) must be dedicated for use with HDs." This refers to equipment (or parts of equipment) that comes in direct contact with HDs. Equipment that does not come in direct contact with HDs may be shared between HD and non-HD compounding areas provided it is deactivated, decontaminated, and cleaned before it is removed from the HD area. Equipment used in HD compounding must be operated in the C-SEC unless it is operated as a closed system (e.g. certain mixers, terminal sterilization using an autoclave, or convection oven).

51. During nonsterile compounding with HD APIs, are all steps of the compounding process required to be performed in the C-PEC?

General Chapter <800> states that "bulk containers of liquid and API HD must be handled carefully to avoid spills. If used, APIs or other powdered HDs must be handled in a C-PEC to protect against occupational exposure, especially during particle-generating activities (such as crushing tablets, opening capsules, and weighing powder)." It is recognized that under some circumstances, it is not possible to perform all steps of the compounding process in the C-PEC (e.g. due to equipment size or function). It is important for the safety of personnel that powdered HDs be weighed and mixed to the wet stage or made into capsules in the C-PEC. Once nonvolatile, non-

antineoplastic, powdered HDs are wet, an assessment of risk may be performed to determine alternative containment strategies and/or work practices. The NIOSH list of antineoplastic and other HDs provides general guidance on PPE for possible scenarios that may be encountered in healthcare settings including instances where a C-PEC cannot be used.

52. Where should HD APIs be handled prior to sterilization when compounding sterile HDs?

In addition to <800>, sterile compounding must follow standards in <797> which states that presterilization procedures for high-risk level CSPs, such as weighing and mixing, shall be completed in no worse than an ISO Class 8 environment. Per <800>, presterilization procedures for high-risk level HD CSPs can occur in the HD ISO Class 7 negative pressure buffer room if the C-PEC used for the nonsterile presterilization procedures is sufficiently effective that the room can continuously maintain ISO 7 classification. If the C-PECs used for sterile and nonsterile compounding are placed in the same room, they must be placed at least 1 meter apart and particle-generating activity must not be performed when sterile compounding is in process. Alternatively, an ISO Class 8 or better negative pressure room could be used. An ISO Class 7 negative pressure room would be necessary if it leads directly into the HD ISO 7 negative pressure buffer room.

53. Does the chapter apply if the HD is dissolved in a liquid dosage form and does not become an aerosol or gas?

HDs that do not require any further manipulation, other than counting or repackaging of final dosage forms, may be prepared for dispensing without any further requirements for containment unless required by the manufacturer or if visual indicators of HD exposure hazards are present (e.g., HD dust or

leakage). Consideration must be given to the aerolization of HDs in liquid formulations.

54. If the HD is a liquid dosage form, may it be compounded in a positive pressure non-HD cleanroom?

No, HD CSPs must be filtered in a BSC or CACI located in an ISO 7 room with negative pressure of 0.01 to 0.03 inches of water and 30 ACPH.

55. Can an assessment of risk be performed on concentrated solutions of HDs (i.e. hormone concentrates)?

No, concentrated solutions of HDs (i.e. hormone concentrates) is an HD API that is further manipulated into a final dosage form and is subject to the containment requirements in <800>. General Chapter <800> defines an API as "any substance or mixture of substances intended to be used in the compounding of a drug 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."

56. What kind of materials may be used for the cabinets and counters in the nonsterile compounding room?

The chapter states that cabinets in the nonsterile compounding area must be smooth, impervious, free from cracks and crevices, and non-shedding but does not limit or define the specific materials that may be used.

57. Do personnel of reproductive capability include both male and females?

Yes, the chapter applies to anyone capable of reproduction.

58. What PPE is required for receiving HDs?

At least one pair of chemotherapy gloves tested to ASTM D6978 standard must be worn when unpacking HDs (see section 10. Receiving). The entity's policies must address if any additional PPE is required. Table 5 of the 2016 NIOSH List of Antineoplastics and Other Hazardous Drugs in Healthcare Settings provides additional recommendations for PPE and engineering controls based the formulation of HD and the activity. The entity's policy should address situations where HDs are received in intact containers and where HDs are received in containers that may be damaged.

59. Are suppliers required to ship HDs in impervious plastic?

No, the chapter recommends that suppliers ship HDs in impervious plastic to segregate them from other drugs and allow for safety in the receiving and internal transfer process.

60. Does the HD return waiting area have to be separate from the regular HD storage area?

No, a separate area is not required. HDs waiting to be returned to the supplier must be segregated in a designated negative pressure area. The regular HD storage area may be designated for this purpose.

61. What container materials are considered impervious?

The type of impervious packaging will vary with the situation and type of HD. Impervious packaging may be "soft" or "firm". HDs must be transported in containers that minimize the risk of breakage or leakage.

62. What is the tiered approach for receiving HDs?

The tiers will be defined by the entity's SOPs based on considerations such as the facility design and types of HDs being handled.

63. What must be on the label for HDs?

HDs identified by the entity as requiring special HD handling precautions must be clearly labeled at all times during their transport. Labeling must be compliant with the appropriate USP standards for compounding including <795> and/or <797> and in accordance with applicable federal, state, and local regulations.

64. What kind of packaging containers can be used for packaging HDs?

The chapter states that packaging containers and materials must be selected to maintain physical integrity, stability, and sterility (if needed) of the HDs during transport. Packaging materials must protect the HD from damage, leakage, contamination, and degradation, while protecting healthcare workers who transport HDs. The entity must have written SOPs to describe appropriate shipping containers and insulating materials, based on information from product specifications, vendors, and mode of transport. Other sources of information may include the chemical or formula and the SDS. In addition, there are multiple chapters in the USP Compounding Compendium that describes packaging.

65. Can HDs be transported in pneumatic tubes, robots, or patient carts?

Each facility must conduct an assessment of risk and develop SOPs accordingly. HDs must be transported in containers that minimize the risk of breakage or leakage. Pneumatic tubes must not be used to transport any liquid HDs or any antineoplastic HDs because of the potential for breakage and contamination.

66. Are personnel involved in waste removal and cleaning required to don PPE?

Yes, personnel must wear appropriate PPE based on their assigned tasks.

67. What if the employee wants to keep their medical records private from the employer?

Medical surveillance is recommended but not required by the chapter. The entity may choose to use a contracted employee health service to perform the medical surveillance while protecting the confidentiality of the employees' personal medical information.

68. What "health variables" should be followed over time for individual workers?

The chapter recommends an initial baseline assessment (pre-placement) of a worker's health status, medical history, and collection of data elements including a medical (including reproductive) history and work history to assess exposure to HDs, physical examination, and laboratory testing. Methods used to assess exposure history include a review of:

- Records of HDs handled, with quantities and dosage forms
- Estimated number of HDs handled per week
- Estimates of hours spent handling HDs per week and/or per month
- Performance of a physical assessment and laboratory studies linked to target organs of commonly used HDs such as a baseline complete blood count.

69. In a medical surveillance program, how does an employer obtain data from the unexposed workers for comparison to the exposed workers?

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