

DRAFT ASHP Guidelines on Compounding Sterile Preparations

Introduction and Scope

Purpose. Medication compounding is a fundamental part of pharmacy practice. Compounding personnel—responsible for compounding and dispensing compounded sterile preparations (CSPs) must ensure the CSPs are of correct ingredient identity, purity, strength (including stability and compatibility), sterility, and in appropriately labeled container closures.^{1, 2} It may be necessary to store CSPs before their anticipated use. The time from compounding to use of a CSP increases the risk that microbial growth will occur. There are strategies outlined by the United States Pharmacopeia (USP) and others that help mitigate these risks. When quality assurance and quality control systems are inadequate, personnel responsible for sterile compounding may not know that inaccurate or contaminated preparations are dispensed.^{3,4,5,6}

These guidelines are intended to help compounding personnel prepare CSPs of high quality and reduce the potential for harm to patients and consequences for compounding personnel. The recommendations in these guidelines are based on published data, when available; applicable regulations and standards; procedures used in similar industries; and expert opinion. These guidelines are a revision of the 2014 *ASHP Guidelines on Compounding Sterile Preparations*,⁷ with the goal of providing more current recommendations. For example, the revised USP chapter 797 (official on November 1, 2023) refers to compounding as Category 1, Category 2, or Category 3 CSPs, with revised methodology to replace the historic terms of low-, medium-, and high-risk compounding.¹ Furthermore, the definition of sterile compounding has been expanded to recognize that certain preparations are excluded from USP chapter 797 requirements if prepared following labeling approved by the Food and Drug Administration (FDA).

Many healthcare settings also use CSPs prepared by outside compounding pharmacies or outsourcing facilities. Although these guidelines may be useful in assessing the quality of CSPs prepared by outside compounding pharmacies, more information on the topic of outsourcing sterile compounding services is available in the *ASHP Guidelines on Outsourcing Sterile Compounding Services*.⁸

Finally, while these guidelines are generally applicable to all personnel who prepare CSPs and all facilities in which CSPs are prepared, pharmacists and other healthcare professionals responsible for the preparation, selection, and use of CSPs are urged to use professional judgment in interpreting and applying these guidelines to their specific circumstances. Users of these guidelines are cautioned that the information provided is current as of publication and are urged to consult current editions of original sources (e.g., laws, regulations, and applicable standards, including USP compendial standards) to ensure patient safety as well as legal and regulatory compliance.

Context of compounding activity. When approaching an activity that may be considered sterile compounding, there are certain conditions that impact the beyond use date (BUD) assignment or make the activity out of scope for all or parts of USP chapter 797.¹ These activities and conditions include:

- Scope of activity meeting definition of “sterile compounding”
- Dosage form and intended route of administration
- Allergenic extract prescription set
- Preparation per approved labeling
- Immediate-use compounding
- Future activation proprietary bag and vial system
- USP compounded monograph

Legal and regulatory considerations. Significant legal and regulatory changes have taken place since publication of the previous ASHP guidelines. The Drug Quality and Security Act was signed into law in November 2013, as an amendment to the federal Food, Drug, and Cosmetic Act (FD&C Act).⁹ Substantive changes to the FD&C Act included modifications to section 503A – Pharmacy Compounding, and the addition of section 503B – Outsourcing Facilities. Under the 503A regulations, most compounding is considered part of the practice of pharmacy and in most states is governed by state law and regulation.¹⁰ In most cases, extemporaneously compounded preparations must be prepared pursuant to a prescriber’s prescription for a specific patient. Compounding before receipt of a valid prescription order (“anticipatory compounding”) can be acceptable under section 503A in limited quantities if the compounding is based on a history of receiving valid prescription orders and the orders have been generated within an established relationship between the pharmacist and the patient or provider. Because compounding under section 503A is not required to follow current Good Manufacturing Practices (CGMPs), excessive anticipatory compounding and batch sizes should be limited.¹⁰ Section 503B of the FD&C Act created a new category of pharmacy compounding, an outsourcing facility.^{9,11,12} Facilities wishing to practice according to section 503B must register with the FDA as an outsourcing facility, follow CGMP practices, meet additional state requirements, and undergo periodic FDA inspections.¹² The detailed requirements of section 503B are outside the scope of these guidelines, but in general, 503B outsourcing facilities may produce large quantities of anticipatory CSPs and CSPs without a patient specific order as long as these products are not essentially copies of approved drugs, unless the drug is currently on shortage.

The FDA has additional guidance that expands on the agency’s current thinking regarding certain topics and other requirements that affect sterile compounding.¹³ Notably, the guidance document *Insanitary Conditions at Compounding Facilities* lists conditions that must be followed to comply with the FD&C Act for all practice settings.¹⁴ Certain requirements listed in FDA guidance documents differ slightly from USP chapter 797, so it is essential that compounders interpret these guidance documents carefully. Although FDA inspections of 503A compounding facilities within health systems are rare, FDA does have the purview to inspect any facility engaging in compounding.

On January 1, 2004, USP chapter 797, Pharmaceutical Compounding—Sterile Preparations, became official, replacing USP chapter 1206, Sterile Drug Products for Home Use.^{15,16} Since the initial publication in 2004, USP chapter 797 has undergone several revisions. A revised chapter became official in 2008.¹⁷ A new revision was published on November 1, 2022, with an official date of November 1, 2023.¹ State regulations and requirements continue to vary, with some states requiring full compliance with USP chapter 797, some have indirect references to the chapter, and some have additional regulations.¹⁸ The National Association of Boards of Pharmacy supports the incorporation of compounding regulations into state pharmacy practice legislation by including such wording in the association’s Model Rules and Model State Pharmacy Act.¹⁹ State boards of pharmacy should be consulted to determine the current status of sterile compounding regulations, as there are significant differences in regulations among states. Although state requirements may vary, the FD&C Act states that compounding “must comply with the standards of the United States Pharmacopoeia chapter on pharmacy compounding” and other applicable USP chapters.^{20,21}

Accreditation considerations. The Centers for Medicare & Medicaid Services (CMS) Hospital Conditions of Participation and Interpretive Guidelines, the Joint Commission, the Accreditation Commission for Health Care, DNV Healthcare’s National Integrated Accreditation for Healthcare Organizations, and other accrediting bodies include statements concerning safe practices for preparation and storage of sterile compounds.^{21, 22, 23,24} Clinics, long-term care facilities, home care organizations, rehabilitation facilities, and physician offices (all of which come under the purview of USP chapter 797) may all be subject to specific additional governance of sterile compounding practices, depending on the agencies regulating or accrediting the facility.¹ In addition, organizations compounding hazardous drugs may also be subject to the requirements in USP chapter 800 Hazardous Drugs – Handling in Healthcare Settings.^{25, 26}

Other compounding-related resources. ASHP provides several resources to assist in maintaining safe and compliant compounding practices. These include additional compounding-related guidelines and resources for training and competency of various personnel; in addition, ASHP has recognized USP chapter 797 as a relevant practice standard in the *ASHP Guidelines: Minimum Standard for Pharmacies in Hospitals*.^{9,26,27,28,29} Other professional organizations also provide guidance on specific aspects of compounding. Standards for prescribing, preparation, administration, and monitoring of parenteral nutrition are available through the American Society for Parenteral and Enteral Nutrition.³⁰ The Institute for Safe Medication Practices provides recommendations for preventing medication errors, including those involving CSPs.³¹ The Infusion Nurses Society offers standards, professional development, and resources for all aspects of infusion care.³² The Controlled Environment Testing Association (CETA) provides numerous CETA Application Guides (CAGs), to members (ask your certifier for a copy), for the proper use, cleaning, and certification of primary engineering controls (PECs) and buffer areas (generally referred to as “cleanrooms”).³³ *Guidelines for Hand Hygiene in Healthcare Settings*,³⁴ *Guidelines for*

Prevention of Intravascular Catheter-Related Infections,³⁵ *Guidelines for Environmental Infection Control in Healthcare Facilities*,³⁶ and *Protect Patients Against Preventable Harm from Improper Use of Single-dose/ Single-use Vials*,³⁷ all from the Centers for Disease Control and Prevention (CDC), serve as the backbone for most infection prevention practices in the United States. Safe infusion, injection, and medication vial practices have been addressed by CMS³⁸ and the Association for Professionals in Infection Control and Epidemiology.³⁹ The Association of Perioperative Registered Nurses (AORN) has recommended practices for medication safety in perioperative settings available for their members.⁴⁰

Compounding Categories and Special Considerations

Compounding Categories. The primary driver for CSP categories within USP chapter 797 are based on the environment of preparation, including segregated compounding areas (SCAs) or cleanroom suites. Each of the compounding categories requires compounding within a PEC. Category 1 CSPs usually have the PEC placed within an SCA, which is a non-classified area dedicated for compounding. A PEC placed in a cleanroom suite may also be classified as Category 1, which may be helpful in situations like cleanroom suite downtimes. Since Category 1 CSPs do not have the protections from a controlled International Organization for Standardization (ISO) classified environment, the preparation BUDs are limited to 12-hr at controlled room temperature or 24-hr when stored in the refrigerator. Category 2 CSPs require the PEC to be placed within a buffer room of a cleanroom suite, which must be accessed from an ISO-classified controlled environment anteroom. With a cleanroom suite, there are additional responsibilities and requirements to clean, disinfect, monitor, and sample to ensure the environment is properly maintained within required specifications. With the additional controls of a cleanroom suite, the BUD limits for Category 2 are greater than those of Category 1. Finally, Category 3 CSPs require compounding within a PEC located in a cleanroom suite, and there are additional preparation, personnel, and environmental controls that must be followed for all personnel and activities within the identified buffer room. These additional requirements and controls allow for Category 3 CSPs to receive BUD limits greater than those of Category 2, up to 180 days when all conditions are met.

Specialty preparations. Personnel, facilities, and compounding processes for allergenic extracts are different than the CSP categories and requirements described above. Section 21 of USP chapter 797 specifically outlines requirements and processes for use of allergenic extracts.¹

Nuclear pharmacies are regulated by the Nuclear Regulatory Commission and other applicable pharmacy laws and regulations. USP chapter 823, Radiopharmaceuticals for Positron Emission Tomography,⁴¹ provides the standards for production facilities. USP chapter 825, Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging provides standards for radiopharmaceuticals.⁴²

Immediate-use CSPs. Under certain conditions, CSPs can be prepared outside of an ISO Class 5 PEC, following USP chapter 797 requirements for “immediate-use CSPs.” There are various situations or practice settings where immediate-use compounding may occur frequently, such as in emergency departments, operating rooms, provider clinics, or surgery centers. Situations in which immediate-use compounding may occur include the following:

- A CSP with very short stability is being prepared.
- Pharmacy services are not available (e.g., stand-alone emergency room, in-home infusion).
- Waiting for compounding of a CSP by the pharmacy may lead to delays in care, patient harm, or poor outcomes (e.g., medical emergencies).

Within a health system, the pharmacy department should work with areas that routinely compound immediate-use CSPs to evaluate appropriateness or to determine whether CSPs can be prepared in advance and made available to the specific area.

Because immediate-use CSPs are not prepared in a PEC—protecting the sterility of the CSP—strict adherence to aseptic technique is essential, as are methods to reduce mix-up errors. Pharmacy should work with areas and disciplines involved in immediate-use compounding to ensure that a comprehensive training and competency program is in place to ensure proper aseptic techniques and practices.

USP chapter 797 allows a maximum BUD of 4 hours for immediate-use CSPs. In some practice settings, the 4-hour maximum BUD may be required, whereas other areas may not require the full duration. Careful consideration of hospital or health-system policy regarding the allowable BUD limits for immediate-use compounding should occur, with multidisciplinary input.

Proprietary bag and vial systems. The use of proprietary bag and vial systems can create operational efficiencies for both pharmacy and nursing. There are various manufacturers of these systems, and each has specific requirements for use, including different labeling for docking, activation, and storage. There are several key factors to assess when selecting a proprietary bag and vial system, including the following:

- Is the device pre-assembled directly to a fluid bag, or does it come as a separate component?
- If the device does not come pre-assembled to a fluid bag, what specifications are required of the fluid bag (e.g., specific manufacturers, volume limits, fluid types)?
- Are currently stocked vials compatible with the system (e.g., diameter of stopper enclosure, volume limit) or will use require purchasing of a vial with the device pre-assembled?
- Is the system compatible and approved to be used with both lyophilized powder and liquid vials?
- Does the system allow for docking and storage for future activation?
- If the system can be docked for future activation, what are the storage requirements

Training for docking, activation, and mixing CSPs using a proprietary bag and vial system is of the utmost importance. The training should include how to ensure the vial is properly attached to the system and secured, how to identify through physical signs that the system has been prematurely activated and thus may not be appropriate for use, how to ensure that all of the drug is transferred into the bag during activation, and other additional manufacturer-recommended training elements to ensure proper and safe use of the device.

Single-dose vials are intended to be used to prepare single doses; however, contents from single-dose/single-use vials may be used for multiple doses under Category 1, 2, or 3 conditions.³⁸ Single-dose vials may be used for up to 12 hours when accessed in an ISO Class 5 environment and stored according to manufacturer guidelines. This repackaging should only be performed by qualified healthcare personnel in accordance with the procedures described in these guidelines and in USP chapter 797.¹

Pharmacy bulk packages (PBPs), a type of vial containing many single doses,¹ may be used under Category 1, 2, or 3 conditions for the duration of time allowed per the manufacturer's labeling information, usually between 4 and 8 hours.⁴³ USP chapter 797 now allows all vial types to be removed from ISO Class 5 conditions for storage under appropriate storage conditions (e.g., the refrigerator, protected from light, etc.) during the allowable usage time for Category 1, 2, and 3 compounding.

Multiple-dose vials may be reused or saved up to the manufacturer's recommended BUD if facility policy does not require a shorter period.⁴⁴ If there is no manufacturer recommendation, multiple-dose vials may be reused or saved up to a maximum of 28 days or for a shorter period dictated by facility policy. Table 1 illustrates the dating for these products based on environmental conditions.

Table 1. Beyond-Use Date Limits for CSPs¹

Sterility Test (performed and passed)	Endotoxin Testing (performed and passed)	Sterilization Method (aseptic terminal) or	Starting Components (sterile nonsterile) or	Controlled Room Temperature (20°-25 °C)	Refrigerator (2°-8 °C)	Freezer (-25° to -10 °C)
Category 1 CSPs						
No	Not required	Either Method	Sterile or Nonsterile	12 hr	24 hr	N/A
Category 2 CSPs						

No	Not required	Aseptic Processing	Some Nonsterile	1 day	4 days	45 days
No	Not required	Aseptic Processing	Only Sterile	4 days	10 days	45 days
No	Not required	Terminal Sterilization	Sterile or Nonsterile	14 days	28 days	45 days
Yes	Required if using any nonsterile starting components**	Aseptic Processing	Sterile or Nonsterile	30 days	45 days	60 days
Yes	Required if using any nonsterile starting components**	Terminal Sterilization	Sterile or Nonsterile	45 days	60 days	90 days
Category 3 CSPs*						
Yes	Required if using any nonsterile starting components**	Aseptic Processing	Sterile or Nonsterile	60 days	90 days	120 days
Yes	Required if using any nonsterile starting components**	Terminal Sterilization	Sterile or Nonsterile	90 days	120 days	180 days

*Category 3 compounded sterile preparations (CSPs) have additional requirements, including environmental monitoring, application of sporicidal agents, personnel requirements, stability-indicating studies, and additional CSP testing not listed.

** If applicable for specific intended route of administration.

The person who first punctures a multiple-dose container intended for re-use must note the BUD and other information required by facility policy (e.g., their initials) on the vial or attached label. A label indicating “use by” clarifies that the date is the BUD rather than the opening date. If a vial lacks a BUD, it should not be used and should be properly discarded.

Institutions should have infection control policies regarding the sharing of multiple-dose vials with multiple patients. The policies should be drafted in collaboration with the infection control department of the organization.

Batch compounding and sterility testing. Use of CSPs stored for extended periods of time is guided by the chemical stability of components and the sterility limits of the CSP defined above. If batches are prepared within Category 2 conditions, the desired BUD will determine whether sterility testing is required.⁴⁴

To extend the BUD beyond those specified for Category 2 CSPs, the pharmacy must meet Category 3 standards. The batch preparation’s master formulation record must reference the stability indicating study and specify the exact ingredients used in the stability study. Additionally, each batch or lot of products compounded must have sterility testing performed in accordance with USP chapter 71.⁴⁴ USP chapter 797 has maximum BUDs for Category 3 CSPs depending on storage temperatures and whether terminal sterilization is used. Batches requiring sterility testing must not exceed 250 units.¹

Batches of CSPs prepared as multiple-dose containers intended for administration to multiple patients ordinarily contain a preservative with sufficient antimicrobial effectiveness testing per USP chapter 51.⁴⁵ After puncture to provide the first dose from a container, the container

must be discarded after 28 days or the product's BUD, whichever is shorter.

It is ideal to receive complete sterility testing results prior to dispensing doses. If sterility testing results are not received prior to dispensing, procedures must be in place for daily observation of the sterility test specimens, immediate recall of dispensed CSPs, and notification of patients and their physicians if microbial or fungal growth is observed.¹ An investigation into the root cause of contamination must occur if sterility testing is positive.

Beyond-Use Dating (BUD) and Stability

Establishing BUDs. BUDs are assigned to CSPs, intermediate preparations (e.g., stock solutions), and containers (e.g., single dose vials) after they have been accessed. Prior to establishing a BUD, it is important to analyze the context of the assignment, applicable stability and sterility factors, and proper application of USP chapter 797.¹ It will also be prudent that any product or preparation that is assigned a BUD be properly labeled with clear communication of the BUD, so that healthcare workers know how to interpret the information and apply it to the situation, such as knowing what actions to take when the current date/time exceeds the listed BUD.

The term BUD may not be familiar or easily understood by healthcare professionals outside of pharmacy, which may lead to disruptive actions (e.g., prematurely discarding a CSP that is actively infusing on a patient). Therefore, organizations should consider careful selection of the BUD descriptor field listed on the immediate container of each CSP and avoid the term 'expires,' where applicable. The selected descriptor should be clear, outlined in policy, and included in staff training. Common improved field descriptors can include, but are not limited to 'use by,' 'spike by,' or 'start administration by,' which more accurately describe the intent and scope of a BUD.⁴⁶ Pharmacy should work with nursing to identify short-stability infusions that may require more frequent exchanging than allowed in nursing policy by default.

Stability factors. Stability is an important factor for evaluating and establishing a BUD for a CSP. A CSP's stability—and clinical effect—can be impacted by negligible changes to manufactured dosage forms, which requires pharmacists to evaluate various preparation-specific conditions that could impact stability. There are various forms of stability that must be assessed, including the following five:^{1,2}

- **Chemical:** each active ingredient retains its chemical integrity and labeled potency, within specified limits
- **Physical:** the original physical properties, including appearance, uniformity, dissolution, and suspendability, are retained
- **Therapeutic:** the therapeutic effect remains unchanged
- **Toxicological:** no significant increase in toxicity occurs
- **Container composition:** the container closure of the CSP should not interfere with stability and should withstand intended storage conditions (e.g. freezing).

While USP chapter 797 lists BUD limits for the various CSP categories, it does not allow default

BUDs to be assigned without stability data, like USP chapter 795.⁴⁷ USP chapter 797 cautions to assign conservative BUDs but provides guidance in the associated USP 797 FAQ document that the maximum allowable BUD limits in the chapter must not be exceeded in the absence of exact matching stability data.⁴⁸ Assignment of BUDs for CSPs must be based on stability and sterility. BUDs assigned to Category 3 CSPs must be supported with data from stability-indicating analytical method testing and container closure testing (described further in Extended BUD section).^{49,50} Additional testing is needed for Category 3 injections and ophthalmic solutions per USP 797. Category 3 CSPs using these data must be prepared according to the exact formulation as the tested conditions.

Sterility factors. There are numerous environmental, equipment, product, and personnel influences on the sterility of a CSP. Sterility assurance is achieved through interrelated controls that provide confidence that items are suitable for use as labeled. Sterility testing is a quality control test that can be used to improve confidence that any of the controls in place were functioning as designed, but it is important to note the irresolvable limitations in sterility testing, however. Pharmacists should put greater focus on sterility assurance controls that address influences on the sterility of CSPs, including but not limited to the following:⁴²

- Facility design
- Equipment design
- Equipment maintenance
- Personnel traffic flow
- Personnel practices and training
- Personnel hygiene and garbing
- Cleaning and disinfecting
- Heating, ventilation, and cooling (HVAC)
- Products and materials
- Product and material flow
- Sterilization and depyrogenation
- Storage conditions

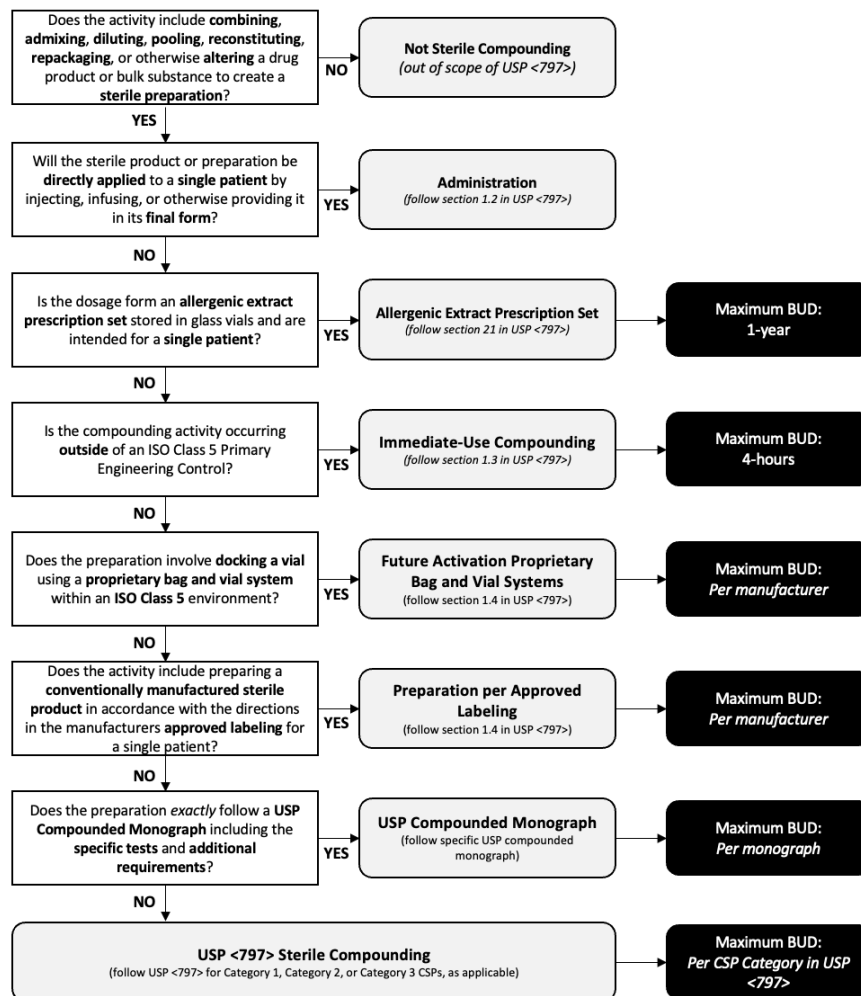
Application of USP chapter 797 BUDs. For CSPs that meet the definition of Category 1, Category 2, or Category 3 CSPs, there are several conditions to assess that will allow for proper and compliant BUD assignment, per USP chapter 797, including the following:¹

- Environment (the main driver for CSP category assignment)
- Sterility testing
- Endotoxin testing
- Sterilization method
- Starting components
- Storage conditions

The pharmacist must determine if sterility or stability serves as the limiting factor for proper BUD assignment. The BUD tables within USP chapter 797 provide “limits,” or maximum BUDs that can be assigned under each applicable CSP category when all conditions

are met. Therefore, if a CSP is stable for a shorter time than the corresponding BUD listed within the table, the BUD must be reduced to the stability timeframe as described in Figure 1.

Figure 1. USP chapter 797 activities and beyond-use date (BUD) assignment.



Extended BUDs. The term “extended BUD” has historically been used to describe longer BUDs assigned to CSPs after passing a USP chapter 71 sterility test compared to those in the 2008 version of USP chapter 797 for low-, medium-, or high-risk CSPs. The provision allowing for extending BUDs beyond the applicable tables within the chapter with sterility testing has been removed from the revised USP chapter 797 (official November 2023).¹ Instead, the tables now include BUD limits, including CSPs that have undergone and passed sterility testing. Further, a new type of compounding designed for “extended BUDs” has also been created, called Category 3 CSPs. This type of compounding allows compounders to use longer BUDs than those for Category 1 or Category 2 CSPs when certain conditions are met, including environmental monitoring, application of sporicidal agents, personnel requirements, stability-indicating studies, and additional CSP testing.

A required stability-indicating study for Category 3 CSPs quantifies the active pharmaceutical ingredient (API) in a sample and separates the API from excipients, degradants, and impurities using a validated analytical method. This type of study is distinctly different from a potency-over-time study, which cannot separate out these degradants and may lead to false conclusions on the stability of the CSP. The difference between the two tests or studies is in the validation of the analytical method.⁴³

An additional method that can be used to extend BUDs is to follow a USP compounded monograph for a specific preparation. A USP monograph contains a compounding formulation, acceptability criteria, packaging and storage, BUD, and labeling information. To achieve the listed BUDs, the compounded monograph must be followed exactly, including passing and performing the listed specific tests (e.g., pH [USP chapter 791], sterility tests [USP chapter 71], bacterial endotoxin test [USP chapter 85], particulate matter in injections [USP chapter 788]).^{1,44,45,51,52} Because USP monographs supersede the general chapters, the information within the monograph can be used when the requirements in the monograph differs from those in USP chapter 797.

Facilities and Environmental Controls

Physical facilities and equipment

Design and functionality requirements. Facility requirements are intended to establish a safe environment for compounding CSPs. The ISO air cleanliness classification of the compounding environment is a critical measure that is affected by facility design.¹

Primary engineering controls (PECs). A PEC is a device or room that provides laminar ISO Class 5 or better air for compounding CSPs. PECs all rely on a special type of high-efficiency particle air (HEPA) filter that meets minimum requirements of $\geq 99.97\%$ efficient in removing particles as small as 0.3 microns in size (the most penetrating particle size, which refers to the largest-sized particle that may escape the filter, although particles of all sizes may be captured).³³ The unidirectional (horizontal or vertical) HEPA-filtered air must provide sufficient velocity to sweep particles away from the direct compounding area and maintain unidirectional flow during preparation of CSPs.¹ Higher grade filters (e.g., ultra-low particulate air [ULPA] filters) may be used but may require considerations around HVAC capacity and impact on air changes. More information about primary and secondary engineering control function and oversight are available on the ASHP Compounding Resources website²⁹ and the FDA Compounding Quality Center of Excellence training resources.⁵³

PEC devices include laminar airflow systems (LAFS), which provide ISO Class 5 or better conditions with unidirectional HEPA-filtered airflow. LAFS category PECs include laminar airflow workbenches (LAFWs) and integrated vertical laminar flow zones (IVLFZ) within an ISO Class 7 or cleaner buffer room.¹ LAFWs and IVLFZs are appropriate only for nonhazardous

compounding. Class II and III biological safety cabinets (BSCs) are LAFS devices that are suitable for sterile hazardous drug compounding when externally exhausted.

Other types of PECs include restricted access barrier system (RABS) classified devices, which provide an enclosure that provides HEPA-filtered ISO Class 5 unidirectional air.¹ RABSs include compounding aseptic isolators (CAIs) and compounding aseptic containment isolators (CACIs). To be used to prepare Category 2 or 3 CSPs, RABSs must be placed within an ISO Class 7 or better clean room. The only type of RABS suitable for hazardous drug compounding is a CACI. Properly designed, unidirectional airflow RABSs function in a similar manner to LAFWs, but the direct compounding area does not interact with room air because it is within a closed system, with the air sweeping particles away from the compounding site. Pharmaceutical isolators are similar to RABSs but operate under continuous positive pressure and have an integral, automated decontamination system and use only decontaminated interfaces or rapid transfer ports for materials transfer.¹ Pharmaceutical isolators offer flexibility in their placement. For Category 1 CSPs, they may be placed within an unclassified SCA; for Category 2 or Category 3 CSPs, they must be placed in an ISO Class 8 or better room and do not require an anteroom. As of this publication, pharmaceutical isolators are rarely used in traditional compounding pharmacies. Table 2 provides a summary of PEC types used in sterile compounding, their suitability for use in hazardous drug compounding, and placement options.

Table 2. Primary Engineering Control (PEC) Types, Hazardous Compounding Suitability and Placement^{1,25}

PEC Type	Device Type	Suitable for Sterile Hazardous Drug Compounding?	Placement for Category 1 CSPs	Placement for Category 2, 3 CSPs
LAFS	LAFW	No	Unclassified SCA	ISO Class 7 positive pressure buffer room, with ISO class 8 or better ante room
	IVLFZ	No	N/A	ISO Class 7 positive pressure buffer room, with ISO class 8 or better ante room
	BSC	Yes*	Negative pressure, Unclassified SCA	ISO Class 7 negative pressure buffer room, with ISO class 7 or better ante room
RABS	CAI	No	Unclassified SCA	ISO Class 7 positive pressure buffer room, with ISO Class 8 or better ante room

	CACI	Yes*	Negative pressure, Unclassified SCA	ISO Class 7 negative pressure buffer room, with ISO Class 7 or better ante room
Pharmaceutical Isolator	Pharmaceutical Isolator	No	Unclassified SCA	ISO Class 8 or better positive pressure room

*If externally exhausted per USP chapter 800.²⁵

Abbreviations: PEC, primary engineering control; CSP, compounded sterile preparation; LAFS, laminar airflow system; LAFW, laminar airflow workbench; IVLFZ, integrated vertical laminar flow zone; BSC, biological safety cabinet; RABS, restricted access barrier system; CAI, compounding aseptic isolator; CACI, compounding aseptic containment isolator; SCA, segregated compounding area; ISO, International Organization for Standardization.

Smoke tests of PECs assist a facility in verifying unidirectional airflow and lack of turbulence and reverse flows. They should also be used to educate compounders about air flow and zones lacking sufficient laminar airflow for aseptic manipulations or open container/exposed critical site placement.

Secondary engineering controls (SECs). PECs must be placed within an SEC that provides a controlled, well-lit, and comfortable environment for compounding activities.¹ There are two primary types of SECs: a cleanroom suite and an SCA.

Cleanroom suite. The cleanroom suite includes a buffer area and anteroom (both are SECs). A buffer area (or “cleanroom”) is defined as an area where a PEC is located and where activities such as preparation, compounding, and staging of CSPs occur. The buffer room is accessed from an adjoining anteroom. The buffer room should provide adequate space for the PEC and may include a limited amount of shelving and/or carts for staging compounding (not for storing stock). An anteroom provides space for garbing and product decontamination and may also host handwashing activities; it also serves to further segregate the buffer area from other, unclassified areas of the facility (i.e., an area with no specific ISO classification). The cleanroom suite (ante and buffer areas) must be constructed of hard-walled enclosures delineated by closed architecture (fixed walls and doors). Category 2 and 3 CSPs must be prepared within a cleanroom.

Segregated compounding area (SCA). This is an unclassified space and does not include ante or buffer areas. SCAs are required to be separated from activities that are not essential to the preparation of CSPs; not be located adjacent to food preparation sites, warehouses, or construction sites; and not have unsealed windows or doors that connect to the outdoors or high-traffic areas.¹ An SCA may have fixed walls and doors or be separated from general-use spaces using a line of demarcation. Facilities with SCAs should have staff maintain full cleansing and garbing procedures when preparing CSPs in the space.¹ This architecture type is most often seen in satellite pharmacies, small hospitals, procedural areas, or clinics. CSPs prepared within SCAs are limited to Category 1 BUD limits (see *Beyond-use dating*).

Environmental Control Standards. A cleanroom suite differs from an ordinary ventilated

room by having the following elements: increased air supply, room pressurization, and a pressure differential, described in Table 3.

Table 3. Secondary Engineering Control Air Control Standards ^{1,25}

Room Type	Is Recirculated Air Allowed?	Minimum ACPH	Pressure Differential (inch water column)	ISO Classifications
Nonhazardous buffer room	Yes (air returns with partial recirculation allowed)	30 (with at least 15 being provided by the room air supply)	$\geq +0.020$	ISO Class 7 or better
Hazardous buffer room	No (air must be exhausted without recirculation)	30	0.010 to 0.030	ISO Class 7 or better
Anteroom	Yes (air returns with partial recirculation allowed)	30 if ISO Class 7 20 if ISO Class 8	$\geq +0.020$	ISO Class 8 (ISO Class 7 if opens into a negative pressure area) or better
SCA	Air recirculation not restricted	No requirements	No requirements	Unclassified
C-SCA	No (air must be exhausted without recirculation)	12	0.010 to 0.030	Unclassified
Hazardous drug storage location	No (air must be exhausted without recirculation)	12	≤ -0.010	Unclassified

Abbreviations: ACPH - air changes per hour; ISO - International Organization for Standardization; SCA - segregated compounding area; C-SCA - containment SCA

Air supply. Cleanroom suites feature HEPA filtration where the filtered air must be introduced at the ceiling with a terminal air filter (a filter at the end of the HVAC ducting). Air return/exhaust ducts must be mounted low on the walls. Ceiling-mounted returns are not recommended, but if they are present, they require dynamic smoke visualization to demonstrate lack of air stagnation.

Room pressurization. SCAs and negative pressure hazardous drug storage locations do not require HEPA-filtered supply air and ISO-classified air quality standards. However, areas

where hazardous drugs will be stored or compounded (“containment SCAs”) do require negative pressurization to adjacent spaces and a minimum of 12 air changes per hour (ACPH).²⁵

Structural components must be coupled with HEPA filtration and air exchanges to provide a buffer area environment that meets or exceeds ISO Class 7 air cleanliness standards.¹ Ante areas must meet or exceed ISO Class 8 standards; ante areas opening into a negative pressure preparation area must meet ISO Class 7 standards. Room ACPHs are calculated based upon the volume of HEPA-filtered air supplied per minute and the size of the room. In rooms in which there are no hazardous substances, air supply can be calculated based on a combination of air supplied by the room supply vents and recirculated air from LAFS or recirculating filters. The air volume supplied by the room HVAC must be at least 15 ACPH.¹ Air within buffer room that contains hazardous substances must not be recirculated, therefore all of the air supply must be achieved through HVAC-supplied air.²⁵ Additional factors that may justify increasing ACPH above the minimum requirements include frequent entries and exits from the room, high-density rooms with multiple compounders, and high-volume compounding and stocking activities. In these instances, even if the room achieves ISO-classified air standards, it may not consistently stay within allowable viable air sample limits (see *Environmental monitoring*). In that case, increasing HEPA-filtered air supply (and ACPH) may reduce microbial out-of-limit results. Some rooms may require air change rates in excess of 100 ACPH to achieve ISO class air standards and consistently maintain viable air counts below action level or activities may be required to be limited within the space.

Airflow within the cleanroom suite should be free of stagnation and should avoid sweeping dirtier air from the floor toward compounding activities. PEC placement within buffer rooms should be considerate of traffic patterns and potential for air disruptions from overhead HEPA-filtered air supply vents.

When designing buffer areas, consider how workflow patterns may affect air quality, such as where personnel are positioned to perform double-checks or where materials staging will occur. If checking personnel are not located in the buffer area, movement in and out of the buffer area is likely to increase airflow interruption. Pass-throughs may minimize personnel entries and exits. Communication devices should also be used to minimize traffic between areas, and cameras may be installed to supplement supervision of staff or check compounding accuracy, if permitted by state regulations.

Pressure differential. Since positive- and/or negative-pressure rooms are required for cleanroom-based sterile compounding, the appropriate differential pressure must be maintained continuously. Pressure differentials between unclassified, ante, and buffer areas must be continuously monitored.^{1,25}

Pressure between ISO Class 7 positive-pressure areas and the general, non-classified space

must be at least 0.020 inches water column (WC). Similarly, a minimum pressure differential of positive 0.020 WC is required between each positively pressured ISO classified room, moving from areas of high air quality to lower air quality. Air quality is not synonymous with ISO classification; for example, a cleanroom suite may have a clean and dirty anteroom, both with ISO 7 classification, the pressure differential must be positive from the clean anteroom into the dirty anteroom.

Negative-pressure buffer rooms for hazardous compounding should have no less than -0.010 WC and no more than -0.030 WC negative to adjacent ISO Class 7 positive-pressure anterooms. Pressure differentials must be reviewed and documented each shift (at least daily) or by a continuous device with alarms.

Surfaces. USP Chapter 797 requires surfaces of any kind in the buffer and ante areas must be smooth, impervious, and easy to clean, with no cracks or crevices that could trap dust or contaminants. All materials used in the facilities must be non-shedding.¹ Walls and ceilings must be made of either hard plastic, epoxy-painted gypsum board, or other approved materials that promote cleanability. If ceiling tiles are used, they must be coated with hard polymer and caulked both around the perimeter and around each tile using 100% silicone. Ceiling lights must be smooth, mounted flush, and sealed. Floors should be made of heavy-duty sheet vinyl, rubber, or epoxy that is coved around the corners and rolled up onto the walls. Adjoining surfaces should be free of ledges that collect particulates and are difficult to clean. Paint must be an epoxy, acrylic, or other nonporous sealant type.

Work surfaces should preferably be stainless steel but at least must be nonporous, easily cleaned and disinfected, and able to withstand harsh cleaning agents. Carts and shelves, ideally made of flat stainless-steel shelving, nonporous plastic, or rustproof metal, should be easy to move and clean, if necessary. Office equipment (e.g., computers and components [including washable keyboard and mouse], telephones, printers) placed in the buffer area must be easily cleanable and placed in such a manner that they have no material impact on the ISO air cleanliness classification of the area. Any device placed within the ISO Class 5 space must be validated using a smoke study to determine its impact on unidirectional airflow and potential for creating turbulence. Additional testing should be completed to monitor the impact of particle-generating office equipment (e.g., printers), including dynamic particle count testing near the operating device and viable environmental monitoring sampling (air and surface).

SCAs do not have as many surface and fixture feature requirements as cleanroom suites. Minimally, they must be located away from unsealed windows, doors that connect to the outdoors, and traffic flow, which may impact the air quality within the PEC. SCAs should have at least 1 meter of free space around the PEC dedicated to sterile compounding activities.¹ Table 4 describes the comparison of surface and fixture minimum requirements between cleanrooms and SCAs.

Table 4. Comparison of Fixture Feature Requirements by Secondary Engineering Control Type^{1, 25}

Fixture Feature	Cleanroom Suite	SCA
General surface qualities	Smooth, impervious, free from cracks and crevices, and non-shedding to allow cleaning and disinfecting. Resistant to damage by cleaning and disinfecting agents. Avoid dust collecting on overhangs and ledges.	
Ceiling	Ceiling tiles (if used) must be washable and caulked around the room and tile perimeters. Lights must have smooth exterior surfaces and be flush mounted and sealed.	Ceiling tiles (if used) must be washable and caulking or clips may be recommended to avoid displacement during cleaning.
Walls	Fixed walls required between designated spaces. Material must be durable (epoxy painted or heavy-gauge polymer). Junctures with ceiling, walls, and floors must be sealed to eliminate cracks.	Only required for a C-SCA.
Returns/exhaust vents	Low on wall. Should be placed behind refrigerator compressors in negative-pressure buffer rooms.	Not required unless for a C-SCA.
Floors	Must be coved to meet wall.	
Lines of demarcation (LOD)	Required in the anteroom. Required in negative-pressure buffer room for donning and doffing PPE.	Not required but advisable if SCA lacks fixed walls defining space.
Doors	Doors required. Sweeps are not recommended (but may be necessary to fine-tune pressure control). Should interlock doors within the anteroom. Should be hands-free operation.	Only required for a C-SCA
Water sources	Inside (allowed on clean or dirty side of LOD or outside the anteroom). Floor drains not allowed. Sprinkler systems must be flush mounted and covered.	Handwashing sink should not be within 1 meter of primary engineering control.

Furniture	Carts and furniture should be nonporous. Casters and wheels should be cleanable. Equipment shouldn't leave the LOD without being disinfected prior to re-entry.
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Abbreviations: SCA - segregated compounding area; C-SCA - containment SCA - LOD, lines of demarcation; PPE - personal protective equipment

Water sources. Water sources such as sinks and eyewashes are not permitted in buffer areas.
¹ Floor drains are not allowed within a cleanroom suite. A sink associated with a cleanroom suite may be placed within the anteroom or outside of the anteroom in a clean, controlled area.

SCAs may have a sink within the SCA or in close proximity to the SCA. A sink must at least 1 m from a PEC. See Table 4 for a comparison of water source requirements between cleanrooms and SCAs.

Sinks should have hands-free operations. Consider avoiding open storage of clean supplies and garb within the splash radius of the sink (typically 1 m). Consider 0.2-micron point-of-use (POU) faucet filters in the event of waterborne bacteria recovery trends during viable air sampling.

Sprinkler systems should be recessed with easily cleanable covers. Exposed sprinkler heads are difficult to clean and are prone to damage during ceiling cleaning, which may lead to catastrophic flooding and damage within the cleanroom suite.

Lighting and sound. Appropriate lighting and sound protection are required to maintain a safe compounding environment. USP Chapter 1066—Physical Environments that Promote Safe Medication Use recommends that peak sound levels of 45 decibels should be targeted, as working under prolonged noise level conditions creates risks of impaired performance.⁵⁴ The National Institute for Occupational Safety and Health (NIOSH) has a different recommended threshold limit of 85 A-weighted decibels (dBA) averaged over an 8-hour period (time-weighted average [TWA]) as a recommended exposure limit.⁵⁵ NIOSH recommends employers implement a hearing conservation program, if noise exposure exceeds 85 dBA (8h TWA), which includes noise monitoring, hearing protection, and audiometric testing. NIOSH describes an estimate of noise levels of 85 dBA requiring someone to raise their voice to be heard from 3 feet away. A noise level of 95 dBA requires someone to shout to be heard from 3 feet away. Consider having workspace sound levels checked by a certifier if staff need to raise their voices to be heard by a nearby co-worker.

Adequate lighting is also important to minimize visual fatigue and improve accuracy and performance efficiency. Table 5 describes lighting level minimums recommended for various tasks. Consider having a certifier evaluate your workspace lighting levels at the time of activation and upon staff requests to modify lighting levels (e.g., ask to turn off hood lights because of headaches, ask to turn off room lights to decrease room temperature).

Table 5. USP Chapter 1066 Optimal Pharmacy Lighting Levels by Task⁵⁴

Task	Lighting Level Minimums
Computer entry	75 fc
Medication filling/checking	90-150 fc
Sterile compounding and preparation	100-150 fc
Pharmacy medication storeroom	50 fc

Abbreviation: fc - foot candles.

Renovations. To meet requirements for sterile compounding, many facilities choose to renovate existing space rather than construct new facilities. Whether designing a new area or retrofitting an existing one, the specific types (e.g., hazardous or nonhazardous) and risk levels of CSPs that will be prepared in the area should guide the facility design and construction. A plan for how operations will continue without interruption should be devised prior to construction. If renovations or construction occurs in adjacent areas to the cleanroom, careful containment strategies must be deployed using an infection control risk assessment process.⁵⁶

Power and Other Utility Interruptions. The facility's emergency management plan should include steps to meet patient care needs during time of utility interruptions ("downtime event"), including the need for CSPs. Essential pharmacy equipment, such as LAFWs and BSCs, should be on emergency generator backup power. Consider placing HVAC controls on uninterrupted power supply (UPS) to minimize troublesome system restarts of air supply and air damper controls. If PECs alone are continuing to run on emergency power, space can be treated as Category 1 for beyond-use dating. If intravenous (IV) compounding must occur during this downtime, it is essential to limit the movement of personnel into and out of the cleanroom suite. In case of power outages in which PECs are not on emergency back-up, immediate-use beyond-use dating must be implemented. Ideally, the following air handling parameters will be verified within limits before resuming compounding operations: air supply, air pressure differentials, temperature, humidity, and exhaust fan function (in negative-pressure environments). Upon reinstatement of HVAC controlled conditions, PECs and the cleanroom suite should be cleaned prior to returning to normal activities and full beyond-use dating. Internal testing can be conducted to evaluate the necessary level of cleaning required after various durations of power loss. Variables to test include power loss during operational hours or after hours. Continuing compounding operations during a downtime event may create elevated particle levels and microbial risk than an event occurring when the pharmacy is closed. All products compounded before the outage may be removed from the suite and processed normally.

Methods to identify and safely meet interim compounding needs or address patient care needs with non-compounded alternatives should be developed, put into standard operating procedures (SOPs), in-serviced to staff, and tested as part of the organization's emergency planning process. Working with certifiers and the facility's environmental monitoring

program to determine what facility excursion limits are during various situations of HVAC control loss (e.g., air supply maintained but pressure out of range, air supply reduced but pressures maintained) is recommended.

Caution should be exercised if UPS accessories are used when emergency generator power is not available. These devices will allow compounding staff time to complete their current CSP and safely shut down LAFWs or BSCs they are working in. These devices generate and blow particulates with fans, are hard to clean, and will add to the thermal load of the compounding suite, so it would be ideal to place the UPS devices outside the cleanroom suite if possible.

Environmental and Microbiological Monitoring

Routine monitoring

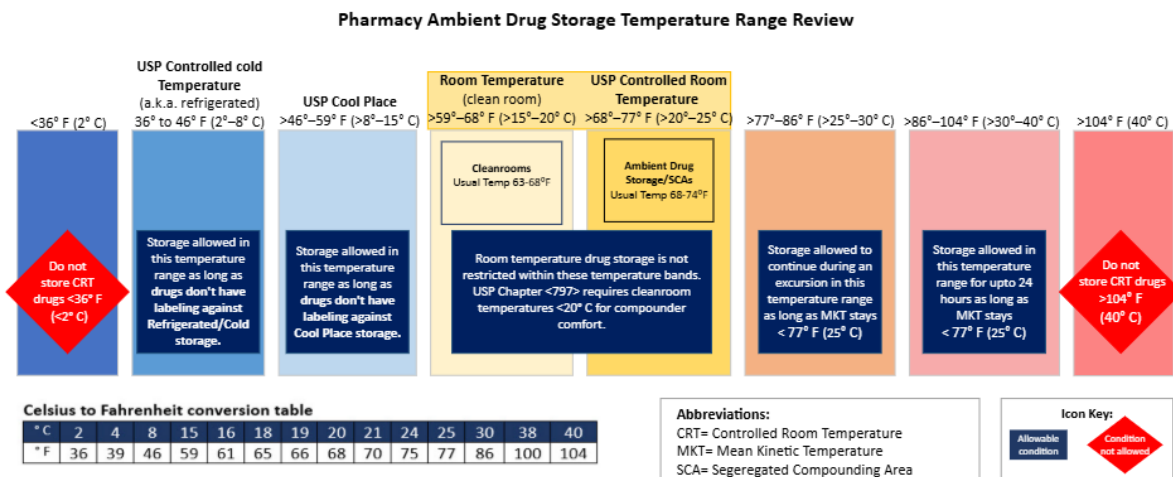
Temperature and humidity monitoring. To minimize the risk of microbial growth, as well as to provide a comfortable work environment, the cleanroom suite should maintain a temperature of 20°C (68 °F) or cooler and a relative humidity less than 60%.¹ Any controlled temperature area used for compounding sterile preparations or for storage of sterile products or CSPs must be monitored at least once daily and results documented, ideally using a continuous recording device. If facilities use continuous recording devices, they must be monitored and documented once daily to ensure they are functioning properly.

All temperature and humidity monitoring instruments must be verified for accuracy yearly or per manufacturer recommendations. Elevated temperature and humidity levels can contribute to conditions that promote microbial proliferation and/or stored drug degradation.⁵⁷ Consider monitoring humidity and temperature levels in conjunction with viable environmental monitoring results as a part of out-of-limit result investigations. Humidity levels below 20-30% can result in static electricity and may be damaging to electronics or lead to cross contamination of powders. Low humidity may also be drying and cause excessive skin shedding by personnel. Organizations should consider establishing a lower humidity threshold if any of the previously mentioned issues are of concern. In humid summer months, pharmacies may need to consider increasing room temperatures to maintain a relative humidity below 60%, due to their inverse relationship.¹²

Compounders may choose to store some drugs within cleanroom settings that are indicated for 'controlled room temperature' storage. While cleanroom environments are typically maintained at temperatures below 20°C, this should not conflict with the storage requirements for most medications labeled for "controlled room temperature". According to USP <659>, medications labeled for storage at controlled room temperature (20°C to 25°C) may alternatively be stored in a cool place or refrigerated, unless otherwise specified in the individual monograph or on the label. A cool place is defined as 8°C to 15°C.⁵⁸ Cleanroom temperatures are typically controlled between 15°C to 20°C. This zone is above cool place conditions and should be technically sufficient for room temperature storage of all medications. Medications with warnings against storage in cool or cold conditions (i.e., 'do

not refrigerate') may need to be evaluated in the event a temperature excursion occurs below 15°C. See Figure 2 for an explanation of various temperature definitions outlined in USP Chapter 659 and how they intersect with temperature ranges suggested in USP Chapter 797 for optimal sterile compounding conditions.

Figure 2 Pharmacy Ambient Drug Storage Temperature Range Review^{1,58}



Engineering control certification. Certification of all classified areas must occur at commissioning, every 6 months, and if there are any changes to the area, such as relocation of a PEC, construction, HVAC maintenance or repair, or any other alteration that could affect the environmental state of control.^{1,33} Additionally, if there is concern about CSP contamination, recertification should be performed as part of the root-cause investigation. PECs must be recertified after any significant maintenance or repairs, such as HEPA filter replacement, installation of permanent devices (e.g., a camera), or electrical repair. Certification includes airflow testing, HEPA filter integrity testing, total particulate count, and airflow smoke pattern testing. All tests except HEPA filter integrity must be performed in dynamic operating conditions. Dynamic conditions must mimic normal operating processes, such as material transfer, personnel movement, and compounding processes. The number of personnel present in each PEC and SEC must be documented and reviewed as part of the record of the certification. Certification documents must include certification equipment calibration certificates.

HEPA leak testing. Over time, HEPA filters may develop leaks (most commonly due to puncture or liquid exposure). Leak testing ensures the HEPA filter is properly seated, sealed, and maintains integrity. Dynamic conditions of the cleanroom are not required, and patient-specific compounding should not occur during this test. If a filter fails, it must be repaired or replaced, and certification testing repeated. It is advisable to have spare replacement HEPA filters available for critical compounding locations where CSP Category 2 and 3 maintenance is important for patient care (e.g., home infusion pharmacies, acute care pharmacies).

Total particulate counts/nonviable airborne particle testing. Total particulate counts do not differentiate between viable and nonviable particles. Nonviable particles, which are particles that do not contain a living organism, such as particles shed from paper or dust; these are counted as part of the total particulate count. Particulate counts must be performed in each classified area and PEC under dynamic conditions. Table 6 describes the particulate counts must meet ISO standards for air quality in controlled environments.

Table 6. Particle Limits for Sterile Compounding Areas (Adapted from USP Chapter 797)¹.

	Primary Engineering Controls (LAFW, BSC, CAI, CACI)	Buffer Area and Ante Area Opening into a Negative-Pressure Room	Ante Area Opening Only into a Positive-Pressure Room
ISO Class	5	7	8
Limit on number of ≥ 0.5 -micron particles/m ³ of air	3,520	352,000	3,520,000

Abbreviations: LAFW - laminar airflow workbench; BSC - biological safety cabinet; CAI - compounding aseptic isolator; CACI - compounding aseptic containment isolator; ISO - International Organization for Standardization

Determination of the ISO classification of an area or device is dependent on nonviable particle testing (“certification”), which must be completed by qualified personnel complying with the requirements of USP chapter 797. Certification standards established in CETA’s Certification Guide for Sterile Compounding Facilities (CAG-003) provides a consolidated reference of USP chapter 797 certification requirements for PECs and SECs.³³ Both PECs (e.g., LAFWs, BSCs, CAIs, and CACIs) and SECs (buffer areas and anterooms) must be certified every 6 months according to the manufacturer’s specifications or CETA recommendations and whenever the device is relocated or serviced. The certification report must be reviewed by the USP 797 required designated person to ensure corrective actions are completed for out-of-range results.

Environmental monitoring. Environmental monitoring, including documentation, review, and trending of results, is critical for establishing and maintaining a state of control in the compounding environment. Adequate environmental and personnel controls must be tested and validated by trained and competent individuals to ensure a safe compounding environment that will be sufficient to prevent contamination of CSPs. Pharmacies must implement written procedures for microbial air and surface monitoring.

Viable volumetric impact air and surface sampling ensure that a facility’s policies and procedures as well as engineering systems are working in conjunction to attain a state of control.

Each element of the monitoring program must be included in a sampling plan with sample

locations, methods of collection, sampling frequency, and other specifics depending on the type of monitoring being performed. The environmental monitoring sampling frequency must occur at a minimum as listed below:

- At the commissioning and certification of new facilities and equipment.
- After any facility or equipment maintenance, including construction or remodeling of adjacent departments or work on shared air handlers.
- At any point when problems are identified with products, preparations, or employee technique or if a CSP is suspected to be the source of a patient infection.
- In response to any change that could impact the environment, such as changes in cleaning agents.

Records of data collected through the monitoring program must be maintained as part of the facility's overall quality assurance program. The data must be reviewed by management personnel, or their designees, and by the facility's Infection Control Committee to ensure that the findings of the reports are addressed. Trends must be reviewed, and corrective action documented.

Microbiological Monitoring

Equipment and materials. Microbial monitoring of both surfaces and air should be performed using a general growth media such as trypticase soy agar (TSA) with neutralizing additives. TSA will support both bacterial and fungal growth. Alternatively, a dual culture plate method using a general growth media such as trypticase soy agar (TSA) and a selective fungal media such as malt extract agar (MEA) or Sabouraud dextrose agar (SDA) may be used. The pharmacy must verify certificates of analysis for each lot of growth media to confirm it meets expected growth promotion tests, pH, and sterilization requirements.¹

An impact air sampler is needed for viable airborne particle testing.¹ Impact air samplers are calibrated to sample a measured volume of air by pulling air across media plates to capture viable microbial particles present. Impact air samplers come in various configurations that allow for one or more media plates to be sampled concurrently. Impact air samplers must be serviced and calibrated as prescribed by the manufacturer.

Two temperature ranges and incubation periods are required for growth media: a range of 30-35°C for at least 48 hours for bacterial organisms and 20-25°C for at least 5 days to support fungal organisms.¹ As 20-25°C is at or below ambient temperatures in some environments, at least one incubator must have cooling capabilities to maintain the required temperature range. Incubator temperatures must be monitored manually or continuously, and the results of all temperature monitoring must be reviewed and documented as described in facility SOPs.

Viable airborne particle testing. Viable particles are living organisms, such as bacteria or fungal spores, that require nonviable particles to travel. Particles must be collected using an impaction air sampler that collects at least 1000 L of air at each sampling location.¹ Per USP

Chapter 797 revisions, a multiplier can no longer be used to collect less than 1000 L of air (i.e., collecting 500 L and multiplying colony-forming unit [CFU] count by 2). Every ISO classified space (PECs and buffer and ante areas), and areas adjacent to SCAs must be tested. Categories 1 and 2 must undergo routine viable airborne particle testing at least every 6 months to maintain certification. Category 3 facilities must perform impact air sampling monthly.¹ Additional testing may be done to understand seasonal impact on the compounding environment or when out-of-specification results are obtained, in which case re-testing will need to occur to verify return to a state of control. More frequent monitoring may be required for facilities based on facility design and activity levels. A risk assessment of compounding activities must be performed to determine the appropriate location for viable testing. The testing plan should include a map of the required sample locations, method of collection, frequency, the volume of air to be tested, and the time-of-day testing will occur.

Sampling plans should be detailed and include all high-traffic locations within the cleanroom and any sites prone to contamination. Turbulence caused by airflow disruption, such as within an ISO Class 5 LAFW or doorways, should be included in the testing plan, along with areas where garbing, cleaning, labeling, and staging occur. Sampling should be conducted under conditions of maximum occupancy of the compounding space. In SCAs, sampling should include locations within the ISO Class 5 PEC and other areas close to the PEC.

Table 7 describes sample data that must be reviewed to evaluate control of the compounding environment. Results above recommended action levels should prompt reevaluation of work practices, cleaning procedures, and HEPA filtration. Microbial growth above the action levels stated in Table 7 requires identification to the genus level.¹

Table 7. Recommended Action Levels¹

	ISO 5 (PEC)	ISO 7	ISO 8
Viable airborne particle testing action levels for contamination (CFU per cubic meter [1000 L] of air per plate)	>1 CFU	>10 CFU	>100 CFU
Surface sample contamination (CFU per plate)	>3 CFU	>5 CFU	>50 CFU

Abbreviations: ISO - International Organization for Standardization; PEC - primary engineering control; CFU - colony-forming unit

Surface assessment. Touch contamination originating from contaminated work surfaces must be minimized and prevented if possible. Surface sampling provides facilities with a snapshot of the effectiveness of their disinfection procedures (including technique and cleaning products) and must be part of the overall quality assurance plan. Using a sterile nutrient agar contact plate for flat surfaces or swabs for equipment and other non-flat

surfaces, sampling must be performed in all ISO-classified areas on a periodic basis, monthly at a minimum for Categories 1 and 2, or when the following occur:

- Significant procedural or cleaning changes are implemented
- In response to contaminated CSPs
- When staff issues with technique have been observed
- When a surface sample comes back out of specification¹

Facilities performing Category 3 compounding must perform surface sampling weekly and include ISO Class 5 PEC surface samples as a part of each batch. A specific plan detailing the location of each sample must be devised so that the same locations are repeated with each testing session. At a minimum, the following areas must be sampled:

- Each classified room
- Interior of each ISO Class 5 PEC
- Pass-throughs connected to classified areas

Sampling locations within these spaces should be monitored using a risk-based approach, focusing on areas such as equipment within the PEC, staging areas next to the PEC, and any frequently touched work surfaces in the flow of aseptic processes. If there are material storage areas in the anteroom or buffer room, these materials could be surface sampled to ensure proper material movement SOPs are followed. Contact plates require pressing a plate directly to the surface being tested, while irregular surfaces can be sampled over an area of approximately 2" x 2", using a sterile-water-wetted swab and then rubbing the swab onto a sterile nutrient agar surface. Agar plates will leave a residue on contact surfaces that must be cleaned and disinfected.⁵⁹

Incubation and reporting. Media plates must be placed in the incubator inverted (lid down) as this allows condensation to collect on the lid rather than the growth surface. If using a single general growth media (e.g., TSA), it is first incubated at 30-35 °C for no less than 48 hr.¹ After the first incubation, plates must be checked for growth, and the number of distinct colonies of growth documented. After reading, the plates must be incubated at 20-25 °C for at least 5 more days.¹ After the second incubation, the number of distinct colonies of growth should be documented. The total number of colonies after the second incubation will be the final CFU count. Ideally, incubating media will be monitored daily (on operational days) to monitor for growth before colony overlap makes CFU counting difficult.

Alternatively, each location may be sampled with two media devices (dual plate method). Both plates may be a general growth media such as TSA, or one could be a selective media for fungal growth (e.g., MEA or SDA). One TSA plate device is incubated at 30-35 °C for no less than 48 hours, and the second TSA plate (or fungal selective media, if using) must incubated at 20-25 °C for no less than 5 days. At the end of each incubation period, distinct colonies of growth on each plate are counted.

Results must be reported in CFUs per plate. If using the dual sampling method, each device

must be examined and documented, and action limits applied to each device separately (i.e., counts of dual plates are not combined). Reevaluation of work practices and cleaning procedures should occur if the CFU count exceeds the suggested action levels (Table 7). Investigation into the source of contamination should be undertaken, the sources eliminated, and the area cleaned and re-sampled. Compounding personnel re-education is important but should not be the only outcome of any investigation.

Environmental monitoring and quality assurance programs may be completed by a limited number of personnel in any given facility, but the actions of all compounding personnel may affect critical elements of compliance. All compounding personnel should be familiar with facility policies and procedures specific to CSPs, even if the procedures are not typically their responsibility.

Personnel and Competency

Personnel responsibilities. All personnel involved in making or overseeing CSPs must be trained and qualified before working independently. The amount of training required will depend on the individual's experience and level of oversight. There must be a designated person who is ultimately responsible for ensuring that training programs are sufficient and complete. The individuals performing the compounding, and the designated person (or persons responsible) with direct oversight of compounding personnel, are required to complete all training competencies outlined below in **Personnel Compounding Competency**. The responsibility of direct oversight should be defined in policy and should include specific activities and job functions that constitute oversight. These responsibilities encompass the ability to observe, assess, and intervene to ensure adherence to aseptic technique and procedures during sterile compounding procedures. Technologies, such as remote video monitoring or automation, can augment or aid in these roles, but should not be used as a direct sole replacement for these responsibilities.

Additionally, oversight should not be delegated to individuals who are off-site or otherwise removed from the day-to-day compounding environment, as proximity is essential for meaningful engagement and accountability.

Other individuals involved in the compounding process, such as those who restock or clean the compounding area, perform in-process checks or final verification of CSPs, and others, such as maintenance personnel or certifiers, must have training and competency checked as outlined by the facility SOPs. Each organization should define the required competencies required for individuals with oversight of compounding personnel. For example, individuals with direct oversight, like supervisors or pharmacists who check compounded preparations who do not perform sterile compounding but enter compounding environments, may be required to perform a media fill test annually. Individuals that do not enter compounding areas, but check final products, may be required to only perform an initial medial fill test.

Compounding personnel are responsible for ensuring that CSPs are accurately identified, measured, diluted, mixed, purified, sterilized, packaged, sealed, labeled, stored, dispensed, distributed, and disposed of if not used.¹ Emphasis should be on the need to maintain quality standards for the control of processes, components, and environments, and for the skill and knowledge of personnel who prepare CSPs.

Compounding personnel must understand and demonstrate competency in aseptic technique and in use of the products and systems used in CSP preparation, such as needles, syringes, administration sets, fluid containers, and compounding devices. There are numerous resources to assist with understanding and demonstration of aseptic principles and compounding techniques.^{29,53} Personnel must understand the types of PECs, HEPA filtration, and airflow concepts that are critical to sterile compounding.

Policies should be developed in conjunction with employee health or infection control personnel to set thresholds for health status fitness for compounding personnel, including conditions that may present a higher contamination risk to the environment or product such as weeping sores, rashes, conjunctivitis, recent tattoos, or respiratory infections.

Compounding areas. Compounding personnel must understand the purposes of and relationships between ante, buffer, segregated, and storage areas.¹ A systematic process of entering and exiting the various areas is necessary to minimize contamination. Food, drinks, and gum are prohibited in all these areas. Because paper and labels may shed, thus producing nonviable particles, paper products should be low-linting, designed for cleanrooms, and only used if essential to the compounding process. Printers, label printers, and other forms of technology that assist the compounding process may be permissible if acceptable particle counts can be maintained. As a best practice, these technologies should be positioned immediately adjacent to an air return to immediately remove any particles from the ISO-classified space. Corrugated cardboard packaging must be restricted from classified area or SCA, and should be eliminated from any clean storage area. All products and components such as needles, syringes, and tubing should be removed from their outer cardboard packaging and decontaminated by wiping the individual packages (if not in an overwrap) with a suitable agent (e.g., 70% IPA, disinfectant, sporicidal) prior to entering the buffer area. It is strongly recommended to use an EPA-registered sporicidal agent at this stage, to prevent undue spore contamination downstream. When used for sterile compounding, items in plastic or foil overwrap should remain in the overwrap until introduced into the ISO Class 5 PEC, at which point they should be opened with the overwrap discarded immediately.⁶⁰ Items stored in the buffer area but not in an overwrap must be decontaminated again prior to entering the PEC, as items may become contaminated by dust or other particles during storage in the buffer area.

Personnel compounding competency. Touch contamination remains the primary cause of microbial contamination during sterile compounding.^{60,61} For this reason, personnel training and assessment of competency are of the utmost importance to ensure the lowest possible

risk of contamination due to human error. The frequency of training and competency assessments are dependent on the types and categories of CSPs produced by the individual or within the facility.

USP chapter 797 stipulates a formal process for using immediate-use BUD for certain compounding practices.¹ Products that are compatible, stable, produced using 3 or fewer sterile product components, and for which administration starts within 4 hours following the start of the preparation may be classified as an immediate-use product. Immediate-use products are not subject to all processes and competency requirements described below. Instead, a written SOP must be in place to ensure that aseptic techniques, processes, and procedures are followed. The person performing immediate use sterile compounding must be trained and tested to demonstrate competency. The institution may determine training and competency requirements.

Compounding competency requirements are generally the same for individuals compounding Categories 1 and 2 CSPs. There are more stringent requirements for individuals and institutions compounding Category 3 CSPs.

Individuals must demonstrate knowledge and competency of core skills before starting sterile compounding, and again at least every 12 months. Core areas include hand hygiene; garbing; cleaning and disinfection; calculations, measuring, and mixing; aseptic technique; achieving and/or maintaining sterility; use of equipment; documentation of the compounding process; principles of HEPA-filtered unidirectional airflow within the ISO Class 5 area; proper use of PECs; and principles of movement of materials and personnel within the compounding area.

Additional training and demonstrated competency assessment in garbing, hand hygiene, and aseptic manipulation are required initially, and again at least every 6 months for all staff involved in the compounding of sterile products.

Hygiene and garbing. Proper preparation for sterile compounding must include effective hand hygiene and garbing. To minimize the number of particles and bacteria introduced into the sterile compounding area, all outer jackets and sweaters, visible jewelry, and cosmetics must be removed prior to initiating the handwashing and garbing processes.¹ Personal electronic devices (e.g., cell phones, earbuds) and any associated attachments must be removed prior to hand hygiene and garbing and should not be used within the sterile compounding area. Nails should be clean and neatly trimmed, nail products should not be worn, and eyeglasses should be wiped down.

Hand hygiene procedures include the following¹:

- Washing hands, under the fingernails, wrists, and arms up to the elbow for 30 seconds with a facility-approved soap
 - Drying hands and arms with non-shedding disposable towels
 - Sanitizing hands with application of a waterless, alcohol-based hand rub (ABHR)
- Garbing occurs in the ante area and should be sequenced from “dirtiest” to

“cleanest.” The exact order will depend on the placement of the sink and must be outlined in the facility’s SOPs¹:

- Don shoe covers, hair and beard covers, and a mask
- Perform hand hygiene
- Don gown, fastened securely at the neck and wrists
- Sanitize hands using an ABHR and allow hands to dry
- Don sterile powder-free gloves (must occur in an ISO-classified room or SCA)
- Sanitize gloves with application of 70% sterile IPA and allow gloves to dry

Facilities compounding Category 3 CSPs must meet additional garbing requirements, including not allowing any exposed skin in the buffer room, outer garb must be sterile, and not reusing garb. To demonstrate competency of the garbing and hygiene process, all compounding personnel must complete an initial garbing competency no fewer than 3 separate times. These 3 garbing attempts must be successful in succession and repeated until 3 successive successful completions occur. This garbing competency includes both a visual observation of the garbing process and a gloved fingertip and thumb sampling test of both hands.

Gloves must be inspected by personnel routinely during the compounding process to check for tears or holes. The gloves should be disinfected with sterile 70% IPA immediately before compounding, regularly throughout the compounding process and each time contaminated items are touched. Additionally, the FDA considers it an insanitary condition if gloved hands are not sanitized before re-entry into the ISO class 5 environment.¹⁴

When exiting the compounding area during a work shift, gowns that are not soiled may be removed and retained in the ante area and re-worn during the same work shift. All other garb, including gloves, must be removed. When re-entering the compounding area, proper hand hygiene and garbing must be completed again.

If a RABS is used as the PEC, compounding personnel must glove, and garb as described above. Additionally, disposable gloves should be worn inside the gloves attached to the RABS sleeves. Sterile gloves must be worn over the gloves attached to the RABS sleeve, and RABS sleeves and gloves should be changed per the manufacturer’s recommendations and as defined by facility SOPs.

Glove fingertip testing. Glove fingertip and thumb testing is an integral and required part of ensuring competency in the garbing process.¹ Immediately following each of the 3 successive garbing evaluations described above, a glove fingerprint and thumb sampling occurs for both hands. Each sampling occurs after a complete hand hygiene and full garbing procedure. The gloved fingerprint and thumb sample occurs following garbing, but prior to sterile 70% IPA being applied to the gloves. To complete a gloved fingerprint and thumb sampling, the individual will use one sampling media device per hand and collect samples from each finger and thumb by rolling the fingertip and thumb pads over the surface. The sampling device

should contain general microbial growth agar supplemented with neutralizing additives to support both bacterial and fungal growth. These samples should be incubated at 30-35 °C for no less than 48 hr then at 20-25 °C for no less than 5 days. The number of CFUs is recorded per hand, and the action level is determined by the total number of CFUs for both hands. The CFU action level for the gloved fingertip and thumb test following garbing is >0.

Remediation of any failure should include retraining and repeating the entire competency sequence outlined in policies and procedures. Hygiene and garbing competencies must be successfully completed at least every 6 months for personnel compounding Category 1 and 2 CSPs, and at least every 3 months for personnel compounding Category 3 CSPs.

Aseptic manipulation competency. Prior to compounding patient CSPs, personnel must successfully complete an aseptic manipulation competency.¹ The goal of this competency is to provide an objective evaluation of aseptic technique. The process consists of a visual observation, media-fill testing, gloved fingerprint and thumb sampling on both hands, and a surface sampling of the direct compounding area. The media-fill test process should be outlined in the facility SOPs and designed to simulate the most difficult and challenging aseptic compounding procedures an individual will be expected to perform. All components should be replaced with soybean-casein digest media. The media-fill test elements should include the following: length of the process; number of additions or transfers; number, type and complexity of manipulations; and number of personnel in the buffer room or SCA. The testing should take place under conditions that reflect a realistic workflow, such as at the end of a shift, to simulate the worst-case scenario environment for compounding sterile preparations. Once started, the test should be completed without interruption.

Immediately following the media-fill test, a gloved fingertip and thumb sampling must be performed on both hands inside the PEC. The sampling plates and incubation process is the same as described above. The CFU action level for the gloved fingerprint and thumb sampling test following the media fill test is >3.

Following the gloved fingertip and thumb sampling, surface sampling should occur in the direct compounding area. Failure of the media fill test, gloved fingertip and thumb sampling, or the surface sampling constitutes a failure of the aseptic manipulation competency.

USP 797 outlines minimum requirements for performing media-fill testing for compounders involved in aseptic compounding practices. Certain types of fully automated robotic compounding devices—usually producing their own ISO Class 5 airflow within a restricted access barrier system—perform all of the aseptic manipulations of a CSP with limited human intervention or exposure. For these types of devices, media-fill testing should be performed on the device following the same requirements and testing frequency as outlined in USP 797 based on either Category 2 or Category 3 requirements. The individual staff operating such devices may not need to perform a media-fill themselves, if they are not involved in any aseptic compounding practice. If significant modifications to the fully automated robotic

device is needed to perform different types of dosage forms (e.g., syringes, bags), a media-fill test should be designed for each type of dosage form and repeated at the same frequency as described.

Aseptic manipulation competencies must be successfully completed at least every 6 months for personnel compounding Category 1 and 2 CSPs, and at least every 3 months for personnel compounding Category 3 CSPs.

Growth media requirements. Sterile nutrient agar for media-fill testing and other materials are available from multiple vendors. The media-fill testing growth media should use a soybean-casein digest media, which may also be sold as tryptic soy agar/broth.¹ Completed media-fill tests should be incubated at both 20-25 °C and 30-35 °C for at least 7 days each. The processes and order must be described in the facility SOPs. Failure is indicated by visible turbidity or appearance of visual growth in one or more containers on or before 14 days. Gloved fingerprint and thumb and surface sampling should be performed using products and processes as described above.¹

Personnel responsibilities for handling, preparation, and disposal of cytotoxic and other hazardous agents. The Occupational Safety and Health Administration (OSHA) requires that employers and employees are made aware of the hazards of all chemicals used in the workplace, including medications.⁶² At a minimum, compounding personnel of reproductive age should confirm in writing that they understand the risks of handling hazardous drugs.¹ Personnel at high risk of exposure to hazardous drugs should be enrolled in a medical surveillance program. In many larger facilities, the employee health department will determine who should be enrolled. Specific guidance about surveillance for healthcare workers exposed to hazardous drugs is available from NIOSH,⁶³ as is a list of drugs NIOSH considers hazardous.⁶⁴ NIOSH has also published their procedure for reviewing and classifying hazardous drugs to help aid in maintaining an organization-specific hazardous drug list. The risks of occupational exposure to hazardous drugs and their potential effects on compounding personnel should be conveyed to employees during employee orientation and in an ongoing manner through continuing education and monitoring at least annually. Training and competency programs should be provided in addition to competencies for compounding of nonhazardous sterile drugs, with details of differentiating the garbing, storage, preparation, and disposal procedures for hazardous drugs. USP chapter 800 requires that training, at a minimum, include the following:²⁵

- Safe aseptic manipulation practices
- Negative pressure techniques when compounding
- Proper utilization of a BSC or CACI
- Correct use of closed-system transfer devices, if used
- Containment, cleanup, and disposal procedures for breakages and spills
- Treatment of personnel contact and inhalation exposure

OSHA requires more general training on chemical label elements and safety data sheet

format.⁶² When training or evaluating competency, facilities may choose products to objectively evaluate hazardous drug compounding technique. These products use dyes or fluorescence to determine personnel technique and assess for spills or hazardous drug exposures.

Definitions of hazardous drugs and proper handling of hazardous drugs, including receiving, distribution, stocking, inventorying, preparation, transport, and disposal, are all concepts discussed in detail in the *ASHP Guidelines on Handling Hazardous Drugs*.²⁶

Compounding Operations

Pharmacy compounding devices. Pharmacy compounding devices are used to increase efficiency while decreasing the potential for human error and human contamination by decreasing the number of manipulations that compounding personnel make to a sterile product. Devices that do not create their own ISO Class 5 environment must be located within an ISO Class 5 PEC and adhere to applicable standards for accuracy and precision.¹ Efforts must be taken to demonstrate that the device does not interfere with laminar airflow by creating turbulence or disrupting first airflow over any critical site. All compounding devices must be monitored and validated for accuracy consistent with device manufacturer specifications.¹

Automated compounding devices (ACDs) are used to accurately combine multiple drugs and solutions into a single delivery container. These devices are commonly used for parenteral nutrition preparation but may be used for cardioplegia solutions, continuous renal replacement therapy, or other repetitive processes. The *ASHP Guidelines on the Safe Use of Automated Compounding Devices for the Preparation of Parenteral Nutrition Admixtures* should be consulted for further details on utilizing ACDs.²⁷ Accuracy and precision testing for ACDs is required by USP chapter 797 and incorporates gravimetrics, with specific gravity, and volumetric testing.¹ These analyses, as determined by facility SOPs, must be monitored and recorded on a daily basis, with evaluation for outliers occurring at least weekly. A quarterly trend report is recommended to identify potential issues with accuracy and precision of ACDs.

Single channel pumps are devices used to pump a preset volume of fluid in a consistent and reproducible manner. They must be calibrated according to manufacturer specifications, which may depend on the volume and frequency of use. Single channel pumps should be calibrated to ensure accuracy when fluids are changed, or when there is a change in fluid viscosity, change in speed of the device, or movement of the device. Outlier results or out of range specification trending should lead to the devices being taken out of service and repaired per the manufacturer's guidance.

Robotic systems automate the compounding, repackaging, and labeling of parenteral doses. The robotic system must create an ISO Class 5 air cleanliness environment at minimum or else, the robotic technology must be placed in a dedicated ISO Class 5 or better rated device.¹

Robotic devices may use various safety technologies, including barcode technology, image technology, and gravimetrics to ensure safety of the sterile products compounding by minimizing the human element. Informational USP chapter 1211–Sterility Assurance outlines the benefits of using these types of robotic devices that would be classified as automation and separative technologies to accomplish the goal of reducing or eliminating personnel-borne contamination from manual compounding.⁶⁵

Robotic systems’ capacity to compound hazardous or nonhazardous medications is determined by the manufacturer’s specifications. Robotic systems can produce preparations more accurately and with less contamination than manual preparation with pharmacy personnel. Robotic protocols can vary from patient-specific doses to batch compounding as determined by the robotic technology used in concert with the facility’s needs.

The proper use of ACDs, single channel pumps, robotic systems, and other compounding equipment used in the preparation of CSPs remains the responsibility of the compounding pharmacist and designated quality control pharmacy staff.¹

Cleaning and disinfecting. Maintaining a sanitary environment for sterile compounding requires diligent cleaning and disinfecting of the cleanroom, equipment, pass-throughs, and all classified spaces.¹⁹ Microbial control, to acceptable levels, can be achieved through appropriate selection of cleaning and disinfectant agents and the use of proper techniques, contact time, and frequency of application. It is important to recognize the properties of each agent used, including chemical grade, sterility, spectrum of activity, mechanism of action, contact time for desired effect, mixing instructions (if not ready-to-use), safety profile, necessary personnel protective equipment, residue after drying, and impact to surfaces (e.g., corrosive to stainless steel)—which can be obtained through evaluation of the labeling or EPA approval documents for EPA-registered disinfectants.^{66,67} Furthermore, formulary selection should include an evaluation of the compatibility between the agents, as mixing some chemicals can inactivate ingredients or create harmful byproducts (e.g., mixing bleach and isopropyl alcohol [IPA] can create chloroform, and mixing bleach and peracetic acid can create chlorine gas, which are toxic byproducts).⁶⁸

The EPA lists registered disinfectants based on their approved use and claims against certain common pathogens. Each claim—bactericidal, virucidal, fungicidal, sporicidal, tuberculocidal—requires a specific standardized test using targeted species and measurement of agent contact time on surfaces. For sporicidal efficacy and contact times, EPA’s “List K: Antimicrobial Products Registered with EPA for Claims Against *Clostridium difficile* spores” should be consulted.⁶⁷ One-step disinfectant cleaners are designed to accomplish both cleaning (i.e., removing surface substances) and disinfecting (i.e., destroying surface microbes), but are only effective if the surfaces are lightly to moderately soiled. If the surface is grossly contaminated, a precleaning step must be used. The use of sterile water or IPA may be considered as a pre-cleaning and/or post-cleaning step to effectively remove soiling or residue from use of certain cleaning and disinfecting agents.

While selected disinfectants may have a broad spectrum of activity, they do not effectively destroy every bacterium, fungus, virus, or spore. Thus, when using any cleaning or disinfecting agent within the PEC, they must be sterile. Not all disinfectants may come sterile from the manufacturer, due to incompatibilities with sterilization filters or chemical breakdown when subject to terminal sterilization (e.g., gamma irradiation). While nonsterile cleaners and disinfectants can be used for other areas within the cleanroom suite, it may be prudent to only stock sterile agents to prevent inadvertent use within the PEC. Most disinfectants may not be effective against spores; thus periodic use of a sporicidal agent must be included in the cleaning and disinfecting program. The practice of additional disinfectant rotation—where disinfectants of different mechanisms of action or spectrum of activity are swapped for use periodically—is not recommended unless supported by the basis of historical environmental monitoring data. Within a cleanroom environment, microbes are usually present in low populations, not actively growing, and thus the development of microbial resistance to disinfectants is less likely to occur. If a specific organism is isolated frequently, the use-dilution method test can be used to confirm susceptibility to formulary disinfectants.⁶⁹ In the context of USP chapter 797, the application and use of sterile 70% IPA is separated from disinfectant application frequencies, as IPA is prone to drying/evaporation much quicker than the required contact time to achieve broad spectrum disinfection, and thus additional disinfectants must be used.

The environmental monitoring program (e.g., surface sampling) within the cleanroom suite should be used to support proper formulary selection of agents and cleaning frequency or personnel technique and be approved by the organization's appropriate authority (e.g., the Infection Prevention and Control Committee). The use of vaporized hydrogen peroxide or ionized hydrogen peroxide should be approached with significant caution. Consultation with cleanroom cleaning professionals, industrial hygiene, employee safety and health, infection prevention, and a microbiologist should be considered prior to using these agents to ensure efficacy, employee safety, and reduce risks of harm to equipment.

Packaging, labeling, and compounding records. Packaging and subsequent labeling are critical to patient safety. Packaging must be appropriate to preserve both sterility and stability until the BUD.¹ As a best practice, labeling on CSPs should be alcohol resistant to avoid issues with smudging or darkening of information on labels. Proper labeling requires an understanding of compounding risk levels and how to determine BUDs based on both stability and sterility.

See Table 8 for minimal requirements for labeling of CSPs. Compounding records should be created for all compounded preparations within the institution. The items listed above should all be completed as part of the compounding record. Compounding records of CSPs prepared for more than one patient or from nonsterile starting ingredients should also contain lot number, expiration date, and National Drug Code information for components. These records may be stored on paper or electronically. When products are prepared as part of a batch,

single doses should be trackable to the original compounding record in the event of a quality concern. If an IV workflow system is used as the master formulation and compounding record, it should be ensured that the system documents all necessary components of master formula and compounding record in an extractable format. Master formulation records are required for all CSPs prepared for multiple patients or from nonsterile starting ingredients.

Table 8. Minimum Requirements for Compounding Documentation and Labels

	Required Elements	
Master Formulation Record	Name of CSP Strength or Activity of CSP Dosage form of the CSP Identities and quantities of ingredients Type and Size of container closure system Complete instructions including: • Equipment • Supplies • Compounding Steps	Strength or Activity of CSP Physical description of the final CSP BUD and Storage Requirements Stability References Quality Control procedures Any additional information to ensure repeatability
Compounding Record	Name of the CSP Strength or Activity of the CSP Dosage form of the CSP Date and Time of Preparation Assigned internal identification (lot or Rx number) Identification of individual preparing the CSP Name of each component	Vendor, lot, and expiration for each component Weight or volume of each component Strength or activity of each component Total quantity compounded Final Yield
Label	Assigned internal identification (lot or Rx number) Active ingredients and their activity, amount, or concentration Storage condition (if other than controlled Room temperature) Beyond-Use-Date Total Amount Dosage Form	Route of administration Special Handling Instructions Warning Statements The compounding facility name and contact (if the CSP is sent outside of the facility in which it is compounded)

Federal and state regulations and accreditation bodies may require additional label information before the CSP is dispensed to a specific patient.

Verification of compounding accuracy and sterility incorporates physical inspection, ensuring compounding accuracy processes are in place, and (when applicable) sterility and endotoxin testing.¹ Finished preparation evaluation is the responsibility of compounding personnel and should be performed during the compounding process and when the preparation leaves the storage area. A visual inspection should assess the presence of particulate matter, coring, cloudiness, or leaks, as well as container and closure integrity.

Compounding accuracy checks must include precision of the product or preparation and the labeling. Prescription orders, compounding procedures, records, and materials used to prepare the compounds should be evaluated. A process should be implemented to confirm that the compounding process and end-preparation testing are properly done. Checking procedures should follow facility policy and procedures and may be accomplished through a variety of mechanisms, including those assisted by technology. All products should be validated using the product barcode via technology interfaced with the EHR. Final product verification (including correct amounts) may be completed through live, in-person verification prior to completing the compounding process, or retrospectively via cameras or other devices, by video recordings or pictures, or by gravimetric weight validation. The “syringe-pull-back” method of checking syringes pulled back to the volume injected is not recommended, as there is no guarantee that the volume pulled back in the empty syringe is the same as that used in compounding. The check should be performed by someone other than the compounder to decrease confirmation bias. Accuracy can be further verified using technology such as barcode verification and gravimetrics when available.

Storage of CSPs. Temperatures of areas used for storage on patient care and procedural units, including room temperature storage units, refrigerators, freezers, and warmers, should be monitored with a continuous monitoring device, and must be monitored and recorded daily at a minimum. Sensors used for temperature monitoring should be calibrated annually. CSPs must be stored securely both in the pharmacy and on patient care units, limiting access to pharmacy staff and staff authorized to handle and administer drugs. Data supporting stability of CSPs should be referenced to determine the need for unique storage conditions, including temperature of storage and exposure to light.

Auxiliary labels or statements applied to CSPs should align with recommendations from the Institute of Safe Medication Practices (ISMP) and Emergency Care Research Institute (ECRI) that emphasize limited and purposeful application to avoid overload and enhance effectiveness.⁷⁰ When used, auxiliary labels or statements should follow a standardized format, considering color, icons, and placement on the CSP. To reduce the risk of human error, such as omission, automation (e.g. printed on CSP labels) should be employed where feasible to apply these labels or statements. Additionally, while some accreditation bodies require specific auxiliary labels (e.g., “refrigerate” for CSPs requiring refrigerated storage), broader requirements may vary and can include alerts for agents like paralytics.

Transporting CSPs. All personnel involved in the handling, transport, or storage of CSPs, whether they are compounding personnel or not, must be properly trained to complete these tasks.¹ The performance of all personnel, including contractors, must be monitored for compliance with facility policies. Transportation methods for CSPs should be evaluated, as some forms of transportation, such as pneumatic tube systems, may adversely affect stability or integrity of some CSPs. Pneumatic tube or other automated delivery systems may require additional padding or security measures to ensure appropriate storage during transport. Some preparations may degrade if shaken, and therefore personnel, including pharmacy and nursing personnel, should be aware of which preparations may not be delivered via a pneumatic tube device.

Hazardous drug transport must incorporate measures to maintain CSP integrity while minimizing the risk of drug residue exposure to patients, personnel, and the environment. These CSPs should always be delivered in a bag marked as hazardous to prevent leakage or accidental exposure during transport, and they should not be delivered using a pneumatic tube device due to the risk of contamination to the environment if breakage occurs. Cleaning protocols for pneumatic tube systems are inadequate for hazardous drug contamination throughout the system.

Transport may occur outside of the compounding facility to other facilities or directly to patients. In these situations, compounding personnel must ensure physical integrity, sterility, and stability are maintained during transit. Proper packaging must be chosen to prevent contamination, leaks, damage, and temperature variations and to protect the end recipients and transporting personnel from harm. If non-health-system staff are involved in transport of the CSP, tamper-evident packaging should be used. Handling and exposure instructions should be legibly displayed on the outside of shipping containers as required by the transporter. BUDs, storage instructions, and disposal instructions for out-of-date preparations must be available to recipients, and recipients must be able to properly store CSPs (e.g., in a refrigerator or freezer, if necessary). Refrigeration methods during transport should be verified to ensure appropriate temperatures are maintained during transport.

Re-dispensing CSPs. If facility policy allows re-dispensing of CSPs, the process must only be done by compounding personnel to ensure continued sterility, purity, and stability. Facilities must determine how to track original preparation and thaw dates (if applicable) and be able to detect product tampering. Policies and procedures must be in place to provide assurance of proper storage conditions for each product or preparation (e.g., refrigeration, protection from light, package integrity) before re-dispensing. CSPs must not be re-dispensed if package integrity has been compromised, including temperature excursions. CSPs stored directly in patient rooms should not be re-dispensed, unless the outer packaging has been properly disinfected.

Special Populations and Use Cases

Pediatrics. Pediatric patients have unique compounding needs for many reasons. Most pediatric doses cannot be served by commercially available unit-of-use doses. In select cases, different concentrations may be required to dose pediatric patients. Many pediatric infusion doses are prepared as syringes, rather than as IV bags. For these reasons, special considerations should be provided for pediatric doses to ensure the safe and consistent preparation of pediatric products.

Stock solutions have long been a mainstay of pediatric sterile compounding. These allow for preparation of multiple doses from a single dilution, rather than making a separate dilution for each individual dose. Stock solutions can be given a BUD consistent with the rest of the chapter at the time of preparation. However, once the stock solution begins to be used for preparing individual doses, the stock solution can only be used for 12-hr due to the lack of preservatives. The BUD assigned to individual doses should be either based on the original date labeled on the stock solution or otherwise assigned in accordance with USP chapter 797, whichever is shorter (see Table 1).¹

As an example, if a stock solution is prepared from single dose vials and preservative-free diluent under Category 2 conditions and refrigerated, up to a 10-day BUD may be applied per Table 13 of USP chapter 797 (see Table 1) without performing sterility testing. If the stock solution is stored for three days and then used to prepare a patient-specific dose that will be stored at controlled room temperature (a 4-day BUD), the patient-specific dose can be assigned a 4-day BUD because the combined BUD does not exceed the original stock solution BUD. If instead, the stock solution is used 7 days after preparation, only 3 days remain, so only a 3-day BUD could be applied to the patient-specific dose.

Hospitals should use the same standardized concentration for pediatric patients as for adult patients when practical. There are occasions, however, when adult concentrations may not work for a pediatric patient, sometimes due to the inability to measure a small dose. Hospitals should validate the smallest volume measurable with syringe and syringe pump manufacturers.

Whenever possible, pediatric compounding should be segregated from adult doses, including where medications are compounded, prepared, checked, and stored. How this segregation is done may vary based on the volume of pediatric care provided. Some health systems may dedicate entire pharmacies or clean rooms to pediatrics, but for those with smaller pediatric volume, this may be done by creating separate pediatric batch processes and having dedicated staff responsible for pediatric compounding for all or part of their shift. Organizations that prepare adult and pediatric TPNs may have separate automated compounding devices or set ups to decrease risk of compounding errors of pediatric doses using higher concentrated adult components.

Multiple-dose topical ophthalmic solutions. Multiple-dose CSPs generally require preservatives and additional testing to ensure that a preparation meets USP chapter 51 standards of antimicrobial effectiveness testing.⁴⁵ Within the revised USP chapter 797, testing is not required when certain conditions are met, for example with compounded topical ophthalmic solutions. USP chapter 797 requires specific requirements to prepare multiple dose topical ophthalmic preparations including the preparations must be made under Category 2 conditions, be used by a single patient, and containers should not be used for more than 24 hours if stored between doses at room temperature or used for more than 72 hours if stored in the refrigerator between doses.

Administration of CSPs

USP chapter 797 does not include any specifications for administration or timing of CSPs. CDC provides the most comprehensive guidance regarding administration of IV medications, including administration times, frequency of infusion set changes, use of filters, and prevention of catheter-related infections.^{32,35}

Outsourced CSPs

Outsourcing the preparation of CSPs to pharmacies that specialize in sterile compounding provides an option for facilities that cannot or do not wish to prepare all or some types of CSPs (e.g., radiopharmaceuticals, nonsterile-to-sterile CSPs, parenteral nutrition) in their own facility. The decision to use outsourcing facilities considering outsourcing compounding should consult the *ASHP Guidelines on Outsourcing Sterile Compounding Services*.⁸

The decision to use CSPs prepared by outside compounding pharmacies should be reviewed and approved by hospital leadership,⁷¹ and such use should only occur in accordance with written policies and procedures. Health systems should have procedures for validating facilities used for outsourcing and may include information obtained from the facility prior to purchase.^{8,71} Procedures should be developed by pharmacists familiar with organizational needs, regulations, and the FDA inspection processes for outsourcing facilities.

Quality and Governance

SOP development. SOPs are documents containing detailed, step-by-step instructions on how to perform a task or procedure so that all personnel consistently perform the task or procedure in the same, safe manner. SOPs are part of a good quality assurance program within the pharmacy. They provide assurance that

- Equipment and facilities are properly maintained in good working order.
- Personnel are properly educated, trained, and evaluated.
- Supplies are received, stored, and disposed of properly and meet compendial standards.
- All tasks and procedures are performed uniformly and documented.

- Procedures for out-of-specification (OOS) conditions are available.

In addition to numerous required SOPs, USP chapter 797 requires three specific written programs: training, microbiological monitoring, and quality assurance/quality control.¹

An SOP provides detailed instructions (step-by-step), can be used for training or reference, and ensures compliance with regulatory requirements, whereas a program is generally more comprehensive and broader in scope. A program outlines overall applicable policies, procedures, and guidelines and is the foundation of compliance efforts. It provides a framework for developing SOPs and may include objectives, responsibilities, performance criteria, monitoring, or evaluation methods. The three program requirements outlined in USP chapter 797 may provide an opportunity to collaborate with other departments and disciplines within the hospital to provide maximum value. These departments could include accreditation, life safety, infection prevention, laboratory, industrial hygiene, facilities management, nursing, anesthesia, and educational departments. Refer to Table 9 for USP 797 specific program requirements.

Table 9. USP Chapter 797 Required Program Elements¹

Personnel Training and Evaluation Program Describes required training, frequency, process for evaluating individuals requiring competency assessment. Equips personnel with knowledge and training to perform assigned tasks. SOP should specify training required.
Microbial Air and Surface Monitoring Program Provides information on the environmental quality of the compounding area. Identifies environmental quality trends over time, identifies potential contamination sources, and allows for implementation of corrective actions. Develops written procedures for air and surface monitoring. Describes sampling methods and locations (including a map). Completes out-of-limit corrective action investigations.
Quality Assurance and Quality Control Program Must have SOPs that ensure each preparation step adheres to regulatory standards. Establishes system controls to ensure: - Adherence to procedures. - Prevention and detection of errors and quality problems. - Evaluation of complaints and adverse events. - Investigation and corrective actions. Must be reviewed every 12 months and be led by individual(s) trained, qualified, and experienced with quality assurance oversight.

- Adherence to procedures.
- Prevention and detection of errors and quality problems.
- Evaluation of complaints and adverse events.
- Investigation and corrective actions.

Must be reviewed every 12 months and be led by individual(s) trained, qualified, and experienced with quality assurance oversight.

All significant procedures performed in a pharmacy should be covered by SOPs. Documentation materials should also be included. USP outlines areas where SOPs are

required. These procedures must be reviewed at least annually and modified for improvements when new processes, training, or procedures are implemented at the facility. Staff must be notified of SOP changes. The facility should track the acknowledgement of notification and/or comprehension of the changes by personnel.

There are several components that should be included in an SOP:

- Title: should clearly identify the task.
- SOP number: an internal department number assigned by the organization to identify it.
- Author(s): the name of the person or persons who write the SOP so that problems and revisions can be addressed.
- Date effective: date when the SOP is implemented into the compounding routine.
- Authorization signature: person or committee that approves the SOP.
- Responsibility: person or persons-in-charge responsible for ensuring the SOP is performed properly.
- Purpose of the procedure: brief explanation of why the SOP is necessary or being implemented.
- Equipment and supplies required: list of equipment and supplies needed to perform the SOP.
- Procedure: detailed step-by-step explanation that can be easily followed by different individuals with the same results. The instructions should be concise to minimize any required interpretation.
- References: references should be listed to support the implementation and use of the SOP.
- Documentation form (as applicable): easily accessible written record or log that demonstrates that the SOP is being performed routinely and properly.
- Revision: documentation of the date an SOP has been reviewed and the reviewer's name.

Quality assurance and quality control program. A quality assurance program provides a mechanism for monitoring, evaluating, correcting, and improving activities and processes. A quality assurance program should review and analyze objective data and then use the data to develop action plans. By trending and analyzing data, facilities should actively work to correct problems detected and improve activities and processes as needed. Any plan designed to correct problems should include follow-up parameters to make certain actions were taken and were effective.

All activities and processes should have specific monitoring and evaluation criteria assigned for objective and measurable assessment. Trending of this information is critical to the success of the quality assurance program. The quality assurance program should encompass all activities and equipment that are included in previous sections of this document as elements which should be assessed and documented. This includes personnel training and assessment, environmental monitoring, and equipment calibration and maintenance.

1530

1531 It is critical to develop a measure of assessment that builds *in situ* audits. Employee
1532 competency assessment, while being actively visually assessed, does not adequately show
1533 real-world behaviors. Development of auditing tools, such as video recording or
1534 unannounced observations, can reveal actual technique and behaviors. Audit results should
1535 be shared with compounding staff, and behavioral audit findings should be reviewed with the
1536 employee and followed up within a pre-determined window to confirm that behavioral
1537 changes were sustained. Re-observed compounder behavior deviations should result in
1538 formal, documented re-education, competency assessments, and re-observations.

1539

1540 Specific quality assurance measures, pursuant to each risk level compounded in a facility,
1541 include routine cleaning and disinfection, air quality testing, visual confirmation of proper
1542 garbing procedures, review of all orders and preparations to ensure accuracy of compounded
1543 products, and visual inspection of final CSPs to confirm the absence of particulate matter or
1544 leakage.

1545

1546 A critical part of any quality assurance program is proper documentation, corrective action,
1547 and follow up. Institutions must determine how OOS results will be reported and evaluated,
1548 including development of action limits and thresholds. Thresholds and follow-up mechanisms
1549 must be in place prior to initiating a quality assurance program or immediately after collecting
1550 initial benchmark data.

1551

1552 Documentation should be tracked through a Corrective Action and Preventive Action (CAPA)
1553 process. The CAPA review should include, but is not limited to, the following:

1554

- Date of event
- Name of employee completing the assessment
- Patient information (if applicable)
- Who reported a complaint or identified the issue
- Who was notified of the complaint
- Brief description of the situation
- Assess impacted areas or processes
- Assess risk type and severity
- Immediate steps taken to correct the situation
- Documentation of investigation (if applicable)
- Follow-up actions taken
- Planned preventative actions to prevent event from recurring
- Review of process changes for results (if applicable)
- Documentation of a review of the CAPA once planned tasks are complete by an approved reviewer

1569

1570 Individuals responsible for completing these tasks should be identified and trained in the
1571 proper execution of the quality assurance plan. Results of monitoring and measurements that

are OOS should be reported within and outside of the department responsible for compounding practices to committees such as infection control and quality improvement. When corrective actions are identified, the identified issue should be resolved as soon as possible and documented on the facility's CAPA form.

Assessment of problems with compounding errors, evident contamination during preparation, quarantine, or patterns of personnel or environmental monitoring outside the established parameters require CAPA form completion, staff education, and root cause analysis. A root cause analysis, including participation by other facility experts such as infection control personnel, should be completed as soon as possible after all departmental staff have been interviewed.⁷² For situations that require more time for corrective measures, an interim action plan should be developed and reviewed at regular intervals until the corrective measure has been fully implemented. Indicators and effectiveness of the quality assurance program should be reassessed annually.

New technologies, procedures, and policies should be evaluated and added to appropriate quality assurance reviews as soon as implementation occurs. A failure mode and effects analysis of new techniques and technologies can serve as a valuable proactive assessment of the ease and value prior to introduction into the compounding process and be utilized to create quality assurance audit processes.^{31,73}

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References

1. USP. General Chapter, <797> Pharmaceutical Compounding—Sterile Preparations.

- 1615 USP-NF. Rockville, MD: USP. Official May 1, 2024.
- 1616 2. USP. General Chapter, <1191> Stability Considerations in Dispensing Practice. USP–
1617 NF. Rockville, MD: USP. Official May 1, 2018.
- 1618 3. Guynn JB Jr, Poretz DM, Duma RJ. Growth of various bacteria in a variety of
1619 intravenous fluids. *Am J Hosp Pharm*. 1973; 30(4):321–325.
- 1620 4. Selenic D, Dodson DR, Jensen B, Arduino MJ, Panlilio A, Archibald LK. Enterobacter
1621 cloacae bloodstream infections in pediatric patients traced to a hospital pharmacy.
1622 *Am J Health Syst Pharm*. 2003;60(14):1440-1446. doi:10.1093/ajhp/60.14.1440
- 1623 5. Moehring RW, Lewis SS, Isaacs PJ, et al. Outbreak of bacteremia due to Burkholderia
1624 contaminans linked to intravenous fentanyl from an institutional compounding
1625 pharmacy. *JAMA Intern Med*. 2014;174(4):606-612.
1626 doi:10.1001/jamainternmed.2013.13768
- 1627 6. Sacks GS. Microbial contamination of parenteral nutrition--how could it
1628 happen?. *JPEN J Parenter Enteral Nutr*. 2011;35(4):432.
1629 doi:10.1177/0148607111412193
- 1630 7. American Society of Health System Pharmacists. ASHP guidelines on compounding
1631 sterile preparations. *Am J Health Syst Pharm*. 2014;71(2):145-166.
1632 doi:10.2146/sp140001
- 1633 8. American Society of Health-System Pharmacists. ASHP guidelines on outsourcing
1634 sterile compounding services. *Am J Health-Syst Pharm*. 2015; 72:1664–75.
- 1635 9. Office of the Federal Register, National Archives and Records Administration. (2013,
1636 November 26). Public Law 113 - 54 - Drug Quality and Security Act. [Government].
1637 U.S. Government Publishing Office. Accessed August 18, 2025.
1638 <https://www.govinfo.gov/app/details/PLAW-113publ54>
- 1639 10. U.S. Food and Drug Administration. Pharmacy Compounding of Human Drug
1640 Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act. Guidance
1641 for Industry. Accessed August 19, 2025.
1642 <https://www.fda.gov/media/94393/download>
- 1643 11. U.S. Food and Drug Administration. Information for Outsourcing Facilities. March
1644 2022. Accessed August 19, 2025. [https://www.fda.gov/drugs/human-drug-](https://www.fda.gov/drugs/human-drug-compounding/information-outsourcing-facilities)
1645 [compounding/information-outsourcing-facilities](https://www.fda.gov/drugs/human-drug-compounding/information-outsourcing-facilities)
- 1646 12. U.S. Food and Drug Administration. Current Good Manufacturing Practice—
1647 Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B
1648 of the FD&C Act Guidance for Industry. Accessed August 19, 2025.
1649 <https://www.fda.gov/media/88905/download>
- 1650 13. U.S. Food and Drug Administration. Guidances I Drugs. Accessed August 19, 2025.
1651 [https://www.fda.gov/drugs/guidance-compliance-regulatory-](https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs)
1652 [information/guidances-drugs](https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs)
- 1653 14. U.S. Food and Drug Administration. Insanitary Conditions at Compounding Facilities
1654 Guidance for Industry. Accessed August 19, 2025. [https://www.fda.gov/regulatory-](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/insanitary-conditions-compounding-facilities-guidance-industry)
1655 [information/search-fda-guidance-documents/insanitary-conditions-compounding-](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/insanitary-conditions-compounding-facilities-guidance-industry)
1656 [facilities-guidance-industry](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/insanitary-conditions-compounding-facilities-guidance-industry)
- 1657 15. Pharmaceutical compounding-sterile preparations (general information chapter

- 797). In: The United States pharmacopeia, 27th rev., and The national formulary, 22nd ed. Rockville, MD: The United States Pharmacopeial Convention, 2004:2350-70.
16. Sterile drug products for home use (general information chapter 1206). In: The United States pharmacopeia, 23rd rev., and The national formulary, 19th ed. Rockville, MD: The United State Pharmacopeial Convention; 1995:2130–43. [no longer official]
17. Pharmaceutical compounding—sterile preparations (general information chapter 797). In: The United States pharmacopeia, 31st rev., and the national formulary, 26th ed., second supplement. Rockville, MD: United States Pharmacopeial Convention; 2008. [no longer official]
18. National Association of Boards of Pharmacy [NABP]. NABP Survey of Pharmacy Law 2025. Mount Prospect, IL: 2025.
19. National Association of Boards of Pharmacy. Model Pharmacy Act/Rules. Accessed August 19, 2025. <https://nabp.pharmacy/members/board-resources/model-pharmacy-act-rules/>
20. Pharmacy compounding. 21 U.S.C. § 353a. Accessed August 19, 2025 <https://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title21-section353a&num=0&edition=prelim>
21. Centers for Medicare & Medicaid Services [CMS]. Revised Hospital Guidance for Pharmaceutical Services and Expanded Guidance Related to Compounding of Medications (2016). Accessed August 19, 2025. <https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/Policy-and-Memos-to-States-and-Regions-Items/Survey-and-Cert-Letter-16-01>
22. Comprehensive accreditation manual for hospitals: the official handbook. Oakbrook Terrace, IL: The Joint Commission; 2023. Accessed August 19, 2025. https://store.jcrinc.com/assets/1/14/CAH23_samplepages.pdf
23. Accreditation Commission for Health Care. Accreditation 101. Accessed August 19, 2025. <https://www.achc.org/about-accreditation/>
24. DNV. NIAHO® Accreditation Requirements, Interpretive Guidelines and Surveyor Guidance for acute care hospitals. Accessed August 19, 2025. <https://www.dnv.us/supplychain/healthcare/standards/niaho-ac-dl.html>
25. USP. General Chapter <800> Hazardous Drugs—handling in healthcare settings. USP–NF. Rockville, MD: USP. Official July 1, 2020.
26. Power LA, Coyne JW. ASHP Guidelines on Handling Hazardous Drugs. *Am J Health Syst Pharm.* 2018;75(24):1996–2031. doi:10.2146/ajhp180564
27. American Society of Hospital Pharmacists. ASHP guidelines: minimum standard for pharmacies in hospitals. *Am J Health Syst Pharm.* 2013;70(18):1619–1630. doi:10.2146/sp130001
28. Iredell B, Mourad H, Nickman NA, et al. ASHP Guidelines on the Safe Use of Automated Compounding Devices for the Preparation of Parenteral Nutrition Admixtures. *Am J Health Syst Pharm.* 2022;79(10):730–735.

- doi:10.1093/ajhp/zxac004
29. American Society of Health-System Pharmacists [ASHP]. ASHP Compounding Resource Center. Accessed August 19, 2025. <https://www.ashp.org/pharmacy-practice/resource-centers/compounding>
30. Boullata JI, Gilbert K, Sacks G, et al. A.S.P.E.N. clinical guidelines: parenteral nutrition ordering, order review, compounding, labeling, and dispensing. *JPEN J Parenter Enteral Nutr*. 2014;38(3):334-377. doi:10.1177/0148607114521833
31. Institute for Safe Medication Practices [ISMP]. ISMP Guidelines for Sterile Compounding and the Safe Use of Sterile Compounding Technology. ISMP; 2022. August 19, 2025. <https://www.ismp.org/resources/guidelines-sterile-compounding-and-safe-use-sterile-compounding-technology> <https://home.ecri.org/blogs/ismp-resources/guidelines-for-sterile-compounding-and-the-safe-use-of-sterile-compounding-technology>
32. Gorski LA, Hadaway L, Hagle ME et al. Infusion Therapy Standards of Practice, 8th Ed. *J Infus Nurs*. 2021; 44:S1-S224.
33. Controlled Environment Testing Association. *CETA Certification Guide for Sterile Compounding Facilities for USP Compliance*. CAG-003: 2022. Accessed September 8, 2025.
34. Centers for Disease Control and Prevention. Guideline for Hand Hygiene in Health-Care Settings: Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. *MMWR* 2002; 51(RR16):1–45. Accessed August 19, 2025. <https://www.cdc.gov/mmwr/PDF/rr/rr5116.pdf>
35. O’Grady NP, Alexander M, Burns LA, et al; Guidelines for the Prevention of Intravascular Catheter-Related Infections, 2011. Centers for Disease Control and Prevention, 2012 (updated July 2017). August 19, 2025. https://www.cdc.gov/infection-control/media/pdfs/guideline-bsi-h.pdf?CDC_AAref_Val=https://www.cdc.gov/infectioncontrol/pdf/guidelines/bsi-guidelines-H.pdf
36. Sehulster L, Chinn RY; CDC; HICPAC. Guidelines for environmental infection control in health-care facilities. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC). *MMWR Recomm Rep*. 2003;52(RR-10):1-42.
37. CDC. Injection Safety. Preventing Unsafe Injection Practices. Accessed August 19, 2025. https://www.cdc.gov/injection-safety/hcp/clinical-safety/?CDC_AAref_Val=https://www.cdc.gov/injectionsafety/cdcposition-singleusevial.html
38. CMS.gov. Safe Use of Single Dose/Single Use Medications to Prevent Healthcare-associated Infections (memo 12-35-ALL; June 15, 2012). Accessed August 19, 2025. <https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/Policy-and-Memos-to-States-and-Regions-Items/Survey-and-Cert-Letter-12-35>
39. Dolan SA, Arias KM, Felizardo G et al. APIC position paper: Safe injection, infusion,

- 1744 and medication vial practices in health care (2016). Accessed August 19, 2025.
1745 [https://www.apic.org/Resource /TinyMceFileManager/Position_Statements/2016A](https://www.apic.org/Resource/TinyMceFileManager/Position_Statements/2016A)
1746 [PICSIPPositionPaper.pdf](https://www.apic.org/Resource/TinyMceFileManager/Position_Statements/2016A)
- 1747 40. Association of periOperative Registered Nurses [AORN]. AORN eGuidelines+.
1748 Medicine Safety. Accessed August 19, 2025. Subscription Required.
1749 <https://aornguidelines.org/guidelines/content?sectionid=173722338&view=book>
- 1750 41. USP. General Chapter <823> Positron Emission Tomography Drugs for Compounding,
1751 Investigational, and Research Uses. USP–NF. Rockville, MD: USP. Official prior to
1752 2013.
- 1753 42. USP. General Chapter <825> Radiopharmaceuticals—Preparation, Compounding,
1754 Dispensing, and Repackaging. USP–NF. Rockville, MD: USP. Official January 1, 2024.
- 1755 43. USP. General Chapter <7> Labeling. USP–NF. Rockville, MD: USP. Official September
1756 1, 2023.
- 1757 44. CDC. Injection Safety. Safe Injection Practices to Prevent Transmission of Infections
1758 to Patients. From: 2007 Guideline for Isolation Precautions: Preventing Transmission
1759 of Infectious Agents in Healthcare Settings. Accessed August 19, 2025.
1760 https://www.cdc.gov/injectionsafety/ip07_standardprecaution.html
- 1761 44. USP. General Chapter <791> pH. USP–NF. Rockville, MD: USP. Official August 1,
1762 2024.
- 1763 45. USP. General Chapter <71> Sterility test. USP–NF. Rockville, MD: USP. Official prior
1764 to 2013. USP. General Chapter <71> Sterility test. USP–NF. Rockville, MD: USP.
1765 Official prior to 2013.
- 1766 45. USP. General Chapter <51> Antimicrobial effectiveness testing. USP–NF. Rockville,
1767 MD: USP. Official May 1, 2018
- 1768 46. Hansen KN, Kienle PC. Defining storage and administration terms for CSPs. *PPPMag*.
1769 2024;21:2. Accessed August 19, 2025. <https://www.pppmag.com/article/3234>
- 1770 47. USP. General Chapter <795> Pharmaceutical compounding – nonsterile
1771 preparations. USP–NF. Rockville, MD: USP; Official Nov 1, 2023.
- 1772 48. USP 797 FAQ updated on December 11, 2023. Question 183. Accessed August 19,
1773 2025. https://go.usp.org/USP_GC_797_FAQs?_gl=1*h3fkk6*_gcl_au*MTMyNTUyMTA4OS4xNzQ2NjQ2OTc4*_ga*MTY2MzY2M4MjYyNi4xNjczNDI0NjYw*_ga_DTGQ04CR27*cze3NDY2NDY5NzckbzUzJGcwJHQxNzQ2NjQ2OTc3JGowJGwwJGgw
- 1774 [7*cze3NDY2NDY5NzckbzUzJGcwJHQxNzQ2NjQ2OTc3JGowJGwwJGgw](https://go.usp.org/USP_GC_797_FAQs?_gl=1*h3fkk6*_gcl_au*MTMyNTUyMTA4OS4xNzQ2NjQ2OTc4*_ga*MTY2MzY2M4MjYyNi4xNjczNDI0NjYw*_ga_DTGQ04CR27*cze3NDY2NDY5NzckbzUzJGcwJHQxNzQ2NjQ2OTc3JGowJGwwJGgw)
- 1775 49. USP. General Chapter <1225> Validation of Compendial Methods. USP–NF. Rockville,
1776 MD: USP. Official August 1, 2017.
- 1777 50. USP. General Chapter <1207> Package Integrity Evaluation – Sterile Products. USP–
1778 NF. Rockville, MD: USP. Official August 1, 2016.
- 1779 51. USP. General Chapter <85> Bacterial endotoxins test. USP–NF. Rockville, MD: USP.
1780 Official May 1, 2018.
- 1781 52. USP. General Chapter <788> Particulate matter in injections. USP–NF. Rockville, MD:
1782 USP. Official May 1, 2023.
- 1783 53. U.S. Food and Drug Administration. Compounding Quality Center of Excellence.
1784 Accessed August 19, 2025. [https://www.fda.gov/drugs/human-drug-](https://www.fda.gov/drugs/human-drug-compounding/compounding-quality-center-excellence)
1785 [compounding/compounding-quality-center-excellence](https://www.fda.gov/drugs/human-drug-compounding/compounding-quality-center-excellence)
1786

54. USP. General Chapter <1066> Physical environments that promote safe medication use. USP-NF. Rockville, MD: USP. Official August 1, 2015.
55. Centers for Disease Control and Prevention. The National Institute for Occupational Safety and Health (NIOSH). Noise and Hearing Loss. Accessed August 19, 2025. <https://www.cdc.gov/niosh/topics/noise/noise.html#:~:text=NIOSH%20established%20a%20recommended%20exposure,loss%20over%20their%20working%20lifetime.>
56. Centers for Disease Control and Prevention. Healthcare-Associated Infections (HAIs). Infection Control Assessment and Response (ICAR) Tool for General Infection Prevention and Control (IPC) Across Settings. Accessed August 19, 2025. https://www.cdc.gov/healthcare-associated-infections/php/toolkit/icar.html?CDC_AAref_Val=https://www.cdc.gov/hai/prevent/infection-control-assessment-tools.html
57. Haycocks N, Goldschmidt NA, Thomsen U. Temperature & Humidity Requirements in Pharmaceutical Facilities. *Pharmaceutical Engineering*. September/October 2021. Accessed August 19, 2025. <https://ispe.org/pharmaceutical-engineering/september-october-2021/temperature-humidity-requirements-pharmaceutical>.
58. USP. General Chapter <659> Packaging and Storage Requirements. USP–NF. Rockville, MD: USP. Official April 1, 2021.
59. Controlled Environment Testing Association. *CETA Applications Guide for Viable Environmental Monitoring for Sterile Compounding Facilities*. CAG-009: 2023. Accessed September 8, 2025.
60. Kastango ES, Wagner JT, Kastango KB, Kastango NE, Wagner TJ. Generation of particulate matter during handling of needle and syringe packaging. *Am J Health Syst Pharm*. 2008;65(15):1443-1450. doi:10.2146/ajhp070444
60. Trissel LA, Gentempo JA, Saenz LM et al. Effect of two work practice changes on the microbial contamination rates of pharmacy-compounded sterile preparations. *Am J Health-Syst Pharm*. 2007; 64:837-841.
61. Thomas M, Sanborn MD, Couldry R. I.V. admixture contamination rates: traditional practice site versus a class 1000 cleanroom. *Am J Health Syst Pharm*. 2005;62(22):2386-2392. doi:10.2146/ajhp050078
62. U.S. Occupational Safety and Health Administration [OSHA]. Hazard Communication Standard (revised 2012). Accessed August 19, 2025. www.osha.gov/dsg/hazcom/index.html.
63. NIOSH [2023]. Managing hazardous drug exposures: information for healthcare settings. By Hodson L, Ovesen J, Couch J, Hirst D, Lawson C, Lentz TJ, MacKenzie B, Mead K. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2023-130, Accessed September 8, 2025. <https://doi.org/10.26616/NIOSH-PUB2023130>
64. NIOSH [2024]. NIOSH list of hazardous drugs in healthcare settings, 2024. By Ovesen JL, Sammons D, Connor TH, MacKenzie BA, DeBord DG, Trout DB, O’Callaghan JP, Whittaker C. Cincinnati, OH: U.S. Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No.

- 2025-103 (Supersedes 2016-161), Accessed September 8, 2025.
<https://doi.org/10.26616/NIOSHPUB2025103>
65. USP. General Chapter <1211> Sterilization and sterility assurance of compendial articles. USP–NF. Rockville, MD: USP; Official May 1, 2019.
66. United States Environmental Protection Agency. Selected EPA-registered disinfectants. Accessed August 19, 2025. <https://www.epa.gov/pesticide-registration/selected-epa-registered-disinfectants>
67. U. S. Environmental Protection Agency. EPA’s Registered Antimicrobial Products Effective Against *Clostridioides difficile* (C. diff) Spores [List K] Accessed August 19, 2025. <https://www.epa.gov/pesticide-registration/list-k-antimicrobial-products-registered-epa-claims-against-clostridium>
68. World Health Organization. Environmental Health Criteria 216: Disinfectants and disinfectant by products. Accessed August 19, 2025.
https://apps.who.int/iris/bitstream/handle/10665/42274/WHO_EHC_216.pdf
69. USP. General Chapter <1072> Disinfectants and Antiseptics. USP–NF. Rockville, MD: USP. Official prior to 2013.
70. Institute for Safe Medication Practices. ISMP targeted medication safety best practices for hospitals. Published 2025. Accessed August 26, 2025.
https://www.ismp.org/system/files/resources/2024-02/ISMP_TargetedMedicationSafetyBestPractices_Hospitals_021524_MS5818%20%281%29.pdf
71. U.S. Centers for Medicare & Medicaid Services. Hospitals: Conditions for Coverage & Participation. CMS. Published [date unknown]. Accessed October 3, 2025.
<https://www.cms.gov/medicare/health-safety-standards/conditions-coverage-participation/hospitals>
72. Agency for Healthcare Research and Quality Patient Safety Network (AHRQ PSNet). Patient safety 101: root cause analysis. Accessed August 19, 2025.
<https://psnet.ahrq.gov/primer/root-cause-analysis>
73. DeRosier J, Stalhandske E, Bagian JP, Nudell T. Using health care Failure Mode and Effect Analysis: the VA National Center for Patient Safety's prospective risk analysis system. *Jt Comm J Qual Improv*. 2002;28(5):248-209. doi:10.1016/s1070-3241(02)28025-6