ASHP Guidelines on Compounding Sterile Preparations

Purpose

The compounding of medications is a fundamental part of pharmacy practice. All compounding personnel, mainly pharmacists and pharmacy technicians, are responsible for compounding and dispensing sterile products and preparations of correct ingredient identity, purity (freedom from physical contaminants, such as precipitates,[1] and chemical contaminants), strength (including stability[2] and compatibility), and sterility and for dispensing them in appropriate containers that are labeled accurately and appropriately for the end user. In contemporary health care organizations, patients receive compounded sterile preparations (CSPs) that are stored for extended periods before use. It has long been recognized that extended storage of CSPs may allow for the growth of a pathological bioburden of microorganisms[3] and that patient morbidity and mortality can result from contaminated or incorrectly compounded sterile preparations.[4–9] When quality monitoring is inadequate, personnel responsible for sterile compounding may not know that inaccurate or contaminated products are dispensed.[10–13]

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; on expert opinion and procedures used in similar industries; and on applicable regulations and standards. These guidelines are a revision of the 2000 *ASHP Guidelines on Quality Assurance of Pharmacy-Prepared Sterile Products*,[14] with the goals of providing more current recommendations and harmonizing the ASHP guidelines with *United States Pharmacopeia* (*USP*) chapter 797, Pharmaceutical Compounding—Sterile Preparations.[15] To help achieve that harmonization, these guidelines employ the definitions and terminology of *USP* chapter 797 rather than those of the previous guidelines.

Many health care settings also use CSPs prepared by compounding pharmacies. Although these guidelines may be useful in assessing the quality of CSPs prepared by compounding pharmacies, more information on the topic of outsourcing sterile compounding services is available in the *ASHP Guidelines on Outsourcing Sterile Compounding Services*.[16]

Finally, while these guidelines are generally applicable to all personnel who prepare CSPs and all facilities in which CSPs are prepared, pharmacists and other health care 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.

Legal and Regulatory Considerations

Significant legal and regulatory changes have taken place since publication of the previous ASHP guidelines (Figure 1).

At the time of its publication, section 503A of the U.S. Food and Drug Administration Modernization Act (FDAMA) served to define the limits of legitimate compounding.[18] When section 503A of FDAMA was ruled unconstitutional in 2001, the delineation between compounding and manufacturing reverted to earlier regulations based on the Federal Food, Drug, and Cosmetics Act.[19] Under those regulations, compounding is considered part of the practice of pharmacy and in most states, is governed by state law and regulation. Manufacturing is regulated by the federal government through the auspices of the Food and Drug Administration (FDA). In most cases, extemporaneously compounded preparations must be prepared pursuant to a prescriber's prescription for a specific patient. Some states have specific regulations dealing with CSPs for office use. Some pharmacies whose primary purpose is preparing CSPs for hospitals and other facilities may be registered with the FDA as manufacturers and must adhere to federal good manufacturing practices. Some state boards of pharmacy permit one pharmacy to compound for another pharmacy under central fill regulations. Most pharmacies compound only pursuant to a prescriber's prescription and follow state regulations regarding compounding.

On January 1, 2004, *USP* chapter 797, Pharmaceutical Compounding—Sterile Preparations,[15] became official, replacing *USP* chapter 1206, Sterile Drug Products for Home Use.[20] The change from a chapter numbered above 1000 to a chapter below 1000 marked a change from an advisory standard to an enforceable one. *USP* chapter 797 has since been revised.[15] Some state regulations require full compliance with *USP* chapter 797, some have indirect references to the chapter, some do not mention the chapter, and some have additional regulations.[21] 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.[22] State boards of pharmacy should be consulted to determine the current status of sterile compounding regulations, as there are significant differences in regulation among states.

Accreditation Considerations

The Centers for Medicare and Medicaid Services (CMS) Hospital Conditions of Participation and Interpretive Guidelines, the Joint Commission, the American Osteopathic Association's Healthcare Facilities Accreditation Program, and DNV Healthcare's National Integrated Accreditation for Healthcare Organizations all include statements concerning safe practices for storage and preparation of sterile compounds.[23–26] Clinics, long-term care facilities, home care organizations, rehabilitation facilities, and physician offices (all of which come under the purview of *USP* chapter 797[15])

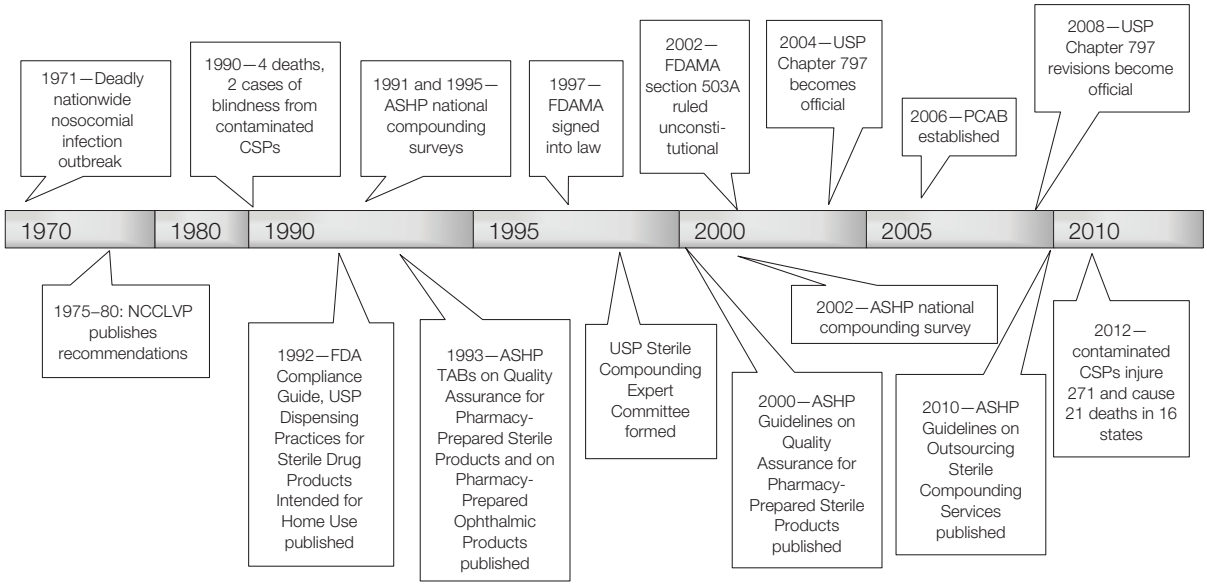

Figure 1. Evolution of Sterile Compounding Standards, 1970—2010. Adapted from *The ASHP Discussion Guide on USP Chapter <797> for Compounding Sterile Preparations*.[17] NCCLVP, National Coordinating Committee on Large Volume Parenterals; CSPs, compounded sterile preparations; USP, United State Pharmacopeia; TAB, technical assistance bulleting; FDAMA, Food and Drug Administration Modernization Act; PCAB, Pharmacy Compounding Accreditation Board.

may all be subject to specific additional governance of sterile compounding practices, depending on the agencies regulating or accrediting the facility. In addition, organizations preparing hazardous drugs[27,28] should comply with National Institute for Occupational Safety and Health (NIOSH) recommendations to ensure that compounding personnel are operating in a safe environment.[29,30]

Other Compounding-Related Guidelines

ASHP provides several guidelines for safe compounding practices[28,31,32] and a discussion guide on *USP* chapter 797[17] and has recognized *USP* chapter 797 as a relevant practice standard in the *ASHP Guidelines: Minimum Standard for Pharmacies in Hospitals.*[33] 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.[34,35] The Institute for Safe Medication Practices provides recommendations for preventing medication errors, including those involving CSPs.[36,37] The Infusion Nurses Society offers standards, professional development, and resources for all aspects of infusion care.[38] The Controlled Environment Testing Association (CETA) provides numerous CETA Application Guides (CAGs) for the proper use, cleaning, and certification of primary engineering controls (PECs) and buffer areas (generally referred to as "cleanrooms").[39–45] *Guidelines for Hand Hygiene in Healthcare Settings*,[46] *Guidelines for Prevention of Intravascular Catheter-Related Infections*,[47] *Guidelines for Environmental Infection Control in Healthcare Facilities*,[48] and *Protect Patients Against Preventable Harm from Improper Use of Single-dose/Single-use Vials,*[49] 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 CMS[50] and the Association for Professionals in Infection Control and Epidemiology,[51] and the Association of peri-Operative Registered Nurses has recommended practices for medication safety in perioperative settings.[52]

Physical Facilities and Equipment

Design and Functionality Requirements

Facility requirements are intended to establish a safe environment for compounding CSPs. The International Organization for Standardization (ISO) air cleanliness classification of the compounding environment is a critical measure that is affected by facility design.

Primary Engineering Controls (PECs). A PEC is a device or room that provides an ISO Class 5 environment for compounding CSPs. PECs all rely on a special type of high-efficiency particle air (HEPA) filter that is ≥99.99% efficient in removing particles as small as 0.3 microns in size (the most penetrating particle size [MPPS], which refers to the largest-sized particle that may escape the filter, although particles of all sizes may be captured). 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. (More information about HEPA filtration and first-air concepts can be found in the ASHP publications *Compounding Sterile Preparations,*[53] *Basics of Aseptic Compounding Technique,*[54] *Getting Started in Aseptic Compounding,*[55] and *Compounding Sterile Preparations: ASHP Video Guide to USP <797>.*[56])

PEC devices include laminar airflow workbenches (LAFWs), biological safety cabinets (BSCs), compounding

aseptic isolators (CAIs), and compounding aseptic containment isolators (CACIs) (Table 1). Properly designed, unidirectional airflow CAIs function in a similar manner as 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. Smoke tests of PECs assist a facility in verifying unidirectional airflow and lack of turbulence and reverse flows.

CAIs or CACIs located outside of an ISO Class 7 environment must be coupled with documentation from the manufacturer that the device will meet or exceed *USP* chapter 797 standards under these conditions and be dynamically tested on site to USP 797 and CETA requirements. If the CACI used for hazardous drug preparation is located outside the buffer area (see **Architecture**, below), it must be located in a segregated and dedicated area that maintains at least 0.01-inch water column negative pressure and maintains, at a minimum, 12 air changes per hour (ACPH).

Architecture. The sterile compounding area includes a well-lit buffer area and ante area (both are secondary engineering controls) and an area for storage of sterile products and supplies. 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. This area should provide adequate space for the PEC and may include a limited amount of shelving and/or carts for staging of compounding (not for storing stock). An ante area provides space for hand washing, garbing, and product decontamination; it also serves as a way to further segregate the buffer area from other, less-clean areas of the facility. Water sources, such as sinks or floor drains, are not permitted in the buffer area and should not be immediately adjacent to segregated compounding areas outside of a buffer area. A storage area outside the buffer and ante areas should provide adequate space for placement of sterile products and supplies.

The sterile compounding area (ante and buffer areas) may be constructed of either hard- or soft-walled enclosures, with the zones being delineated by open or closed architecture. Closed architecture is formed by walls and doors between the buffer and ante areas and is required for high-risk compounding (Table 2).

Open architecture has openings between the buffer and ante areas and relies on a defined airflow velocity to divide the two areas, which are marked by a line of demarcation; this type of facility may only be utilized for low- and medium-risk compounding. Demarcation lines should be indicated by colored tiles or other elements integrated into the flooring pattern but may be as simple as marking on the floor.

Table 1.
Primary Engineering Controls (PECs)

PEC Device	Used to Prepare Non-Hazardous CSPs	Used to Prepare Hazardous CSPs
Conventional	Laminar airflow workbench (LAFW)	Class II Biological safety cabinet (BSC)
Isolators	Compounding aseptic isolator (CAI)	Compounding aseptic containment isolator (CACI)

Facilities for preparation of radiopharmaceuticals have some different requirements. Refer to *USP* chapter 797[15] and other relevant standards for specifics.

Facilities without *USP* chapter 797-compliant ante areas and buffer areas may prepare low-risk, non-hazardous CSPs in a PEC within a segregated compounding area. A segregated compounding area is an unclassified space (i.e., an area with no specific ISO classification) and does not include ante or buffer areas. It is 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.[15] This architecture type is most often seen in satellite pharmacies, small hospitals, procedural areas, or clinics. The beyond-use dating for sterile preparations compounded in a segregated compounding area cannot exceed 12 hours (see **Expiration and Beyond-Use Dating**).

Buffer Areas

Air Supply. A buffer area differs from an ordinary ventilated room by having the following:

- Increased air supply.
- HEPA filtration (the filtered air should be introduced at the ceiling, with returns mounted low on the walls; ceiling-mounted returns should not be used) including a terminal air filter (a filter at the end of the heating, ventilation, and air conditioning [HVAC] ducting).
- Room pressurization.
- A perforated plate or swirl supply air diffuser (if an air diffuser is necessary); high-induction supply air diffusers should not be used in buffer areas.

Structural components must be coupled with HEPA filtration and air exchanges in order to provide a complete buffer area environment and proper ISO classifications. Buffer areas must meet or exceed ISO Class 7 air cleanliness standards. Ante areas must at least meet ISO Class 8 standards; ante areas opening into a negative pressure preparation area must meet ISO Class 7 standards. The number of ACPH is based upon air/room pressure, velocity or air handler capacity, HEPA flow restriction, duct size, the amount of processing completed on a daily basis, and temperature. ACPH must occur at a minimum of 30 times per hour in buffer and ante areas, but may need to be increased in high-traffic/high-volume areas in order to maintain the room's specified ISO classification (Table 2) under dynamic conditions. Facilities may incorporate the contribution of up to 15 air changes per hour from a LAFW in the total air changes per hours in a nonhazardous buffer area. By design, these devices filter room air as it passes through the HEPA filter.

Airflow within the room should be as steady as possible, having as few interruptions as possible. Within the PEC, it must be unidirectional,[39] with as few interruptions in steady airflow as possible. PEC placement within the room should be well designed, with PECs placed where they are least affected by opened doors, HVAC systems, or personnel traffic. For non-hazardous preparations, positive pressure is required between rooms physically divided by walls or doors (closed architecture style) and should be maintained at a minimum of positive 0.02 inch water column. If a room does not have physical barriers (i.e., has an open architecture

Table 2.
Facilities Features Required for Specific Types of Compounding (Data from *USP* Chapter 797[15] Except as Noted)

	Low-Risk with ≤12-hour BUD (Non-Hazardous)	Low-Risk (Non-Hazardous)	Medium-Risk (Non-Hazardous)	High-Risk (Non-Hazardous)	Hazardous Drugs
Architectural Style[a]	Segregated	Open or closed	Open or closed	Closed	Closed
Buffer zone ISO classification	N/A	ISO Class 7 or better	ISO Class 7 or better	ISO Class 7 or better	ISO Class 7 or better
Ante area ISO classification	N/A	ISO Class 8 (ISO Class 7 if opens into negative pressure area) or better	ISO Class 8 (ISO Class 7 if opens into negative pressure area) or better	ISO Class 8 (ISO Class 7 if opens into a negative pressure area) or better	ISO Class 7 or better
Minimum air exchanges for buffer area[b]	N/A	30	30	30	30
Minimum air exchanges for ante area[c]	N/A	20 if ISO 8; 30 if ISO 7	20 if ISO 8; 30 if ISO 7	20 if ISO 8; 30 if ISO 7	30
Pressure	N/A	Positive	Positive	Positive	Negative

[a]Architectural style ("open" and "closed") is not defined in *USP* chapter 797, but the concept of physical separation of ante areas and buffer rooms is described in the chapter. For the purposes of these guidelines, "closed architecture" indicates that the buffer and ante areas are separated by a door (i.e., are physically separate rooms) and maintain a pressure differential of no less than 0.02-inch water column positive pressure. "Open architecture" indicates that the buffer and ante areas are in one room, not separated by a door (i.e., not physically separated). Displacement airflow is used to separate open architecture spaces, with at least 40 feet per minute of airflow across the entire plane of the opening. A segregated compounding area contains a PEC within a restricted space.

[b]If an ISO Class 5 recirculating device is in place, a minimum of 15 air changes per hour (ACPH) is sufficient if the ACPH is 30 between the device and the area supply HEPA filters.

[c]*USP* chapter 797 does not address the air changes in ISO Class 8 ante areas. The FDA Aseptic Processing Guide[57] recommends a minimum of 20 ACPH to maintain ISO 8. However, this is a minimum value intended for industry. Since ante areas for CSPs include ungowned personnel and other activities, a minimum of 30 ACPH is best practice for ISO Class 8 ante areas and required for ISO 7 ante areas.

style) and relies on a line of demarcation, the displacement airflow concept requiring air velocity of 40 feet per minute (0.2 meter per second) from the buffer area across the entire plane of line of demarcation into the ante area is required. Open architecture is not permitted in areas used for high-risk preparations.

When designing buffer areas, facilities must consider workflow patterns, such as how personnel performing double-checks will affect air quality. If supervisory personnel are not located in the buffer area, movement in and out of the buffer area is likely to increase airflow interruption. Communication devices should 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.

Surfaces. Surfaces of any kind in the buffer area and ante area 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. Walls and ceilings must be made of either hard plastic or epoxy-painted gypsum board. If ceiling tiles are used, they must be coated with hard polymer and caulked both around the perimeter and around each tile. Ceiling lights must be smooth, mounted flush, and sealed. Floors should be made of wide, heavy-duty sheet vinyl, rubber, or epoxy that is coved around the corners and rolled up onto the walls. Paint must be an epoxy, acrylic, or other non-porous sealant type.

Work surfaces should preferably be stainless steel, but at a minimum are required to be non-porous and easily sanitized. Carts and shelves, ideally made of stainless steel wire, 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.

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 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.

Power and Other Utility Interruptions

The facility's emergency management plan should include steps to meet patient-care needs during time of utility interruptions, including the need for CSPs. In some cases, immediate-use procedures may be safely implemented to meet some needs. Methods to identify and safely meet interim compounding needs or address patient-care needs with

noncompounded alternatives should be developed, put into standard operating procedures (SOPs), inserviced to staff, and tested as part of the organization's emergency planning process.

Pharmacy Compounding Devices

Pharmacy compounding devices are utilized to increase efficiency while decreasing the potential for human error. 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. All compounding devices must be monitored and validated for accuracy consistent with device manufacturer specifications.

Automated Compounding Devices (ACDs) are utilized to accurately combine multiple drugs and solutions into a single delivery container. These devices are most commonly used for parenteral nutrition preparation, but may be used for cardioplegia solutions, continuous renal replacement therapy, or other complex processes. *ASHP Guidelines on the Safe Use of Automated Compounding Devices for the Preparation of Parenteral Nutrition Admixtures*[32] should be consulted for further details on utilizing ACDs. Accuracy and precision testing for ACDs is required by *USP* chapter 797[15] and incorporate gravimetric, volumetric, and chemical analyses. These analyses, as determined by facility protocol, must be monitored and recorded on a daily basis, with evaluation for outliers occurring at least weekly.

Repeater 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.

Robotic systems automate the compounding and labeling of parenteral doses in syringes and bags using an enclosed chamber that must create an ISO Class 5 air cleanliness environment or better.

The proper use of ACDs, repeater pumps, robotic systems, and other compounding equipment used in the preparation of CSPs remains the responsibility of the pharmacist.

Cleaning and Disinfecting

Cleaning with a germicidal detergent and water will remove visible solids or soiling before disinfecting. Disinfecting removes microbial contamination. It is critical that an appropriate germicidal detergent and water be used to clean all surfaces of the buffer and ante areas in addition to all of the PECs. Great care must be exercised to avoid getting the HEPA filters wet during cleaning. Cleaning with a germicidal detergent will leave a residue that needs to be removed from work surfaces (e.g., counter and PEC surfaces). This residue is best removed by using sterile 70% isopropyl alcohol (IPA).

Appendix II of *USP* chapter 797[15] provides information on types of products that can be used for cleaning and disinfecting the ante and buffer areas, including floors, walls, and ceilings. Choice of cleaning and disinfection products should be approved by the organization's appropriate authority (e.g., the Infection Control Committee).

Policies and procedures must be developed to ensure consistent practices, including dilution of cleaning products. Table 3 describes the minimum frequency for cleaning surfaces used to compound low- and medium-risk CSPs in the sterile compounding area.

Table 3.
Minimum Frequency for Cleaning of Specific Sites (Reprinted with Permission from *USP* Chapter 797[15])

Site	Minimum Frequency
ISO Class 5 PEC	Beginning of each shift Before each batch Every 30 minutes when compounding After spills When surface contamination is known or suspected
Counters and easily cleanable work surfaces	Daily
Floors	Daily
Walls	Monthly
Ceilings	Monthly
Storage shelving	Monthly

Environmental Monitoring

Environmental monitoring and related documentation must be completed on a routine basis to ensure adequate environmental and personnel controls are in place to prevent contamination of CSPs. Ensuring a safe compounding environment requires viable and nonviable airborne particle testing, pressure differential or displacement airflow measurement, temperature monitoring, and surface disinfection sampling and assessment. Nonviable particles are particles that do not contain a living organism, such as particles shed from paper or dust. Viable particles are living organisms, such as bacteria or fungal spores, that require nonviable particles to travel. Monitoring of humidity,[39,44] sound,[39] and lighting[39] may also be considered by facilities to enhance the environmental monitoring program.

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, with possible additional times based on the type of testing:

- At the commissioning and certification of new facilities and equipment.
- Every six months during routine re-certification of equipment and facilities.
- 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.

Records of data collected through the monitoring program must be maintained as part of the overall quality assurance program of the facility. The data should 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. Table 4 provides an overview of environmental monitoring requirements.

Table 4.
Environmental Monitoring Requirements (Adapted from *USP* Chapter 797[15])

Parameter	Monitored By	Frequency
Temperature	Compounding personnel or facilities management staff (if electronic monitoring is centralized)	Documented daily (at a minimum)
Pressure differential or velocity across line of demarcation	Compounding personnel	Documented each shift (preferably), daily (at a minimum)
	Qualified certifier	At least every 6 months
Nonviable particles	Qualified certifier	At least every 6 months
Surface sampling	Compounding or laboratory personnel	Periodically, as defined by compounding and infection control personnel, at least every 6 months or after significant changes in procedures or cleaning practices
Electronic device sample of viable particles	Compounding personnel or qualified certifier	At least every 6 months

Table 5.
Controlled Temperatures (Data from *USP* General Notices and Requirements[58])

Storage Condition	Centigrade	Fahrenheit
Room temperature	20 to 25 °C	68 to 77 °F
Cold temperature (refrigerated)	2 to 8 °C	36 to 46 °F
Freezer (frozen)	–25 to –10 °C	–13 to 14 °F

Temperature Monitoring. 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 in a log. The facilities should maintain a comfortable room temperature (20 °C [68 ºF] or cooler) for properly garbed compounding personnel. If facilities use continuous temperature recording devices, they must be monitored and documented once daily to ensure they are functioning properly. Controlled temperature ranges are listed in Table 5.

Pressure Differential or Air Displacement. Since positive- and/or negative-pressure rooms are required for sterile compounding, the appropriate differential pressure or air displacement velocities must be maintained. If closed architecture is used, a pressure differential between general, ante, and buffer areas must be monitored. A facility with open architecture design must monitor the differential airflow across the opening between ante and buffer areas.

A pressure gauge or velocity meter must be in place to monitor airflow between relevant areas. Pressure between ISO Class 7 positive-pressure areas and the general area must be at least 5 Pa (0.02-inch water column). Negative pressure areas should have no less than 2.5 Pa (0.01-inch water column) negative pressure to adjacent positive pressure. A monitored pressure indicator must be installed to ensure proper pressurization. If differential airflow is used as a measure, the velocity must be at least 0.2 meter per second (40 feet per minute).

Results of pressure differential and/or velocity of air displacement must be reviewed and documented each shift (at least daily) or by a continuous device with alarms.

Nonviable Airborne Particle Testing Program. 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 Certification Guide for Sterile Compounding Facilities (CAG-003-2006).[39] PECs such as LAFWs, BSCs, CAIs, and CACIs must be certified every 6 months and whenever the device is relocated or serviced. Both primary (LAFWs, BSCs, CAIs, and CACIs) and secondary engineering controls (buffer areas and ante areas) must be checked for total particle counts every 6 months according to the manufacturer's specifications or CETA recommendation and when a device or room is relocated or altered. Thresholds for each ISO class are presented in Table 6.

Viable Airborne Particle Testing Program. Classified space (PECs and buffer and ante areas) must undergo routine viable particle testing. The testing plan should include the required sample locations, method of collection, frequency, the volume of air to be tested, and the time of day testing will occur. Testing must occur every 6 months in all compounding areas (PECs, buffer areas, ante areas, and areas adjacent to segregated compounding areas) as part of the overall compounding recertification process. The method of testing must be impaction via an electronic air sampling device, as settling plates alone are not considered an acceptable method.

Sampling plans should be detailed and include all high-traffic locations within the compounding area 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. In segregated compounding areas, sampling should include locations within the ISO Class 5 PEC and other areas in close proximity to the PEC.

Viable particle testing must be performed using a general microbiological growth medium, such as sterile nutrient

Table 6.
Particle Limits for Sterile Compounding Areas (Adapted from *USP* Chapter 797[15])

	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

Table 7.
Viable Environmental Monitoring Recommended Action Levels for Microbial Contamination (Adapted from *USP* Chapter 797[15])

ISO Classification	Recommended Action Levels for Microbial Contamination (CFUs/m^3)[a]
5	1[b]
7	10
8 or above	100

[a]CFUs/m^3, colony-forming units per cubic meter.
[b]Samples from ISO Class 5 environments should normally yield no microbiological contaminants.

agar. In facilities that compound high-risk preparations, testing must also be done with a medium that supports fungal growth, such as malt extract. The growth medium should be incubated (outside of the sterile preparation area) according to the manufacturer's recommendations.

Sample data must be reviewed as a means of evaluating control of the compounding environment. Results above recommended action levels (see Table 7) should prompt reevaluation of work practices, cleaning procedures, and HEPA filtration. Any microbial growth that results from viable environment sampling must be identified to the genus level by microbiology personnel. If any highly pathogenic organisms (e.g., gram-negative rods or yeasts) are identified, infection control specialists should immediately be consulted to assist in formulating a response to the situation.

Surface Disinfection Sampling and 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, at a minimum, every 6 months or when significant procedural or cleaning changes are implemented. A specific plan detailing the location of each sample must be devised so that the same locations are repeated with each testing session. Contact plates require pressing a plate directly to the surface being tested, while swabbing requires swabbing an area, submersing the swab in the correct amount of diluent, and then swabbing onto or into a sterile nutrient agar surface. Agar plates will leave a residue on contact surfaces that must be cleaned with sterile water and disinfected with sterile 70% IPA.

Results must be reported in colony-forming units (CFUs) per plate. Reevaluation of work practices and cleaning procedures should occur if the CFU count exceeds the suggested action levels (Table 8). Investigation into the source of contamination should be undertaken, the sources eliminated, and the area cleaned and re-sampled.

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

Expiration and Beyond-Use Dating

A manufacturer's expiration date is the date assigned pursuant to manufacturer testing. The drug product is guaranteed by the manufacturer to be safe and effective up to the listed date when products are stored as described in the product labeling.

A beyond-use date (BUD) is the date or time after which administration of a CSP shall not be initiated. As described in previous ASHP guidelines[14] and in *USP* chapter 797,[15] the BUD is determined from the date or time the preparation is compounded, its chemical stability, and the sterility limits described later in these guidelines. Both the stability of the components and the sterility limits described above must be taken into consideration when determining BUDs, and the BUD must be the shorter of the sterility dating or chemical stability dating. Information regarding stability dating procedures and defaults can be found in *USP* chapter 795, Pharmaceutical Compounding—Non-Sterile Preparations,[59] and other published literature sources.[60,61]

Processes such as thin-layer chromatography (TLC) and high-performance liquid chromatographic (HPLC) assays are the most reliable means of determining the stability of a product and should be used in place of theoretical predictions of stability when published literature is not available. The use of commercial reference laboratories that offer qualitative and quantitative testing may serve as a key resource for end-product testing.

Risk Level Classification

In these guidelines, as in previous ASHP guidelines[14] and *USP* chapter 797,[15] CSPs are stratified by potential risk of

Table 8.
Recommended Action Levels for Personnel Testing (Adapted from *USP* Chapter 797[15])

	PEC	Buffer Area	Ante Area
Viable airborne particle testing action levels for contamination (CFUs per cubic meter [1000 L] of air per plate)	>1	>10	>100
Surface sample contamination (CFUs per plate)	>3	>5	>100
Glove fingertip sampling	>3	N/A	N/A

[a]CFUs = colony-forming units.

microbial contamination into three primary categories: low-, medium-, and high-risk CSPs, with an additional category for CSPs intended for immediate use[15] and a sub-category for low-risk CSPs intended for use within 12 hours.[15] The potential risk is based on the danger of exposing multiple patients to microbial bioburden and based on microbial growth factors influenced by product storage time, temperature and product ability to support microbial growth, surface and time exposure of critical sites, and microbial bioburden in the environment. Compounding personnel must determine the appropriate risk level and the appropriate BUD for use based upon chemical stability and the potential for microbial, physical, or chemical contamination during compounding. In making a risk-level determination, compounding personnel must evaluate where the preparation is being made, the number of components or the number of aseptic breaches needed to compound the preparation, and the complexity of the compounding process. When circumstances make risk-level assignment unclear, guidelines for the more stringent risk level should prevail. For examples and a comparison of the risk levels, requirements, and BUDs to be used in risk-level determination, see Table 9.

Low-Risk CSPs
This category encompasses simple admixtures involving closed-system transfer, measuring, and mixing of three or fewer commercially manufactured sterile products (including the infusion solution). Low-risk compounding conditions must include all of the following:

- CSPs are compounded using aseptic technique within an ISO Class 5 PEC (e.g., LAFW, BSC, CAI, or CACI) that is located within an ISO Class 7 buffer area with an ISO Class 8 ante area.
- Each container, including the final container, may not be entered more than twice to prepare the CSP.
- Compounding is limited to aseptic manipulations of disinfected containers using sterile needles and syringes.

Low-Risk CSPs for Use Within 12 Hours. Under limited circumstances, sterile compounding may occur in a segregated compounding area (such as a satellite pharmacy or dedicated sterile compounding space) in which the ISO Class 5 PEC is not located within an ISO Class 7 buffer area. A segregated compounding area is a designated space, either a demarcated area or room, in which compounding is restricted to preparing low-risk, nonhazardous CSPs with a beyond-use time of no more than 12 hours from the time of preparation. All other requirements for low-risk CSPs must be followed, with the exception that the ISO Class 5 PEC is not required to be located within an ISO Class 7 buffer area. The PEC must be separate from other operations, including sinks and other water sources or drains, and away from unsealed windows or doors that connect to high traffic areas, construction, warehouses, or food preparation areas. Distinct labeling for conveying short BUDs should be considered.

Medium-Risk CSPs
This category encompasses preparations requiring more complex compounding processes, including:

- Multiple doses of sterile products combined or pooled to prepare a product that will be administered either to multiple patients (i.e., batching of syringes or large volumes), or one patient on multiple occasions (e.g., preparation for use over several days).[49]
- More than three commercially available sterile products are used to produce the compound.
- More complex compounding processes (e.g., total parenteral nutrition).

All requirements for low-risk compounding regarding location and aseptic technique must be followed.

High-Risk CSPs
High-risk CSPs are those

- Prepared from nonsterile ingredients, including manufactured products not intended for sterile routes of administration;
- Compounded using a nonsterile device prior to terminal sterilization;
- Containing nonsterile water that are stored for more than 6 hours before sterilization;
- Exposed to conditions worse than ISO Class 5 air quality for longer than 1 hour, if they contain or are compounded from sterile contents of commercially manufactured products or CSPs without antimicrobial preservatives;
- Containing bulk ingredients whose chemical purity and content strength are not verified by labeling and documentation from suppliers or by direct determination; or
- Prepared by compounding personnel who are improperly garbed or gloved.

Presterilization procedures for high-risk level CSPs, such as weighing and mixing, shall be completed in no worse than an ISO Class 8 environment.

CSPs in this category must be terminally sterilized before administration to patients. Terminal sterilization is defined by the FDA as the application of a lethal process

Table 9.
CSP Risk Levels and Beyond-Use Dates (BUDs) (Adapted from *USP* Chapter 797[15])[a]

Risk Category	Compounding Location	Garbing Required	Aseptic Technique Required	Examples	BUDs of CSP Stored at		
					Room Temperature	Refrigerated	Frozen (≤ 10 °C)
Low-risk	ISO Class 5 PEC, ISO Class 7 buffer area, ISO Class 8[b] ante area	Yes	Yes	Reconstitution of a single-dose vial, single preparation of a small volume parenteral, single large volume IV replacement fluids with no more than 3 components	48 hours	14 days	45 days
Low-risk with < 12-hour BUD	ISO Class 5 PEC segregated from other operations	Yes	Yes	Same as low-risk examples, non-hazardous preparations only	12 hours	12 hours	N/A
Medium-risk	ISO Class 5 PEC, ISO Class 7 buffer area, ISO Class 8[b] ante area	Yes	Yes	Batched syringes, total parenteral nutrition, ophthalmic preparations made from sterile products, pooled admixtures, batch-compounded preparations without bateriostatic additives, preparations made using automated compounders or other automated devices, elastomeric pumps	30 hours	9 days	45 days
High-risk	ISO Class 5 PEC, ISO Class 7 buffer area, ISO Class 7 ante area	Yes	Yes	CSPs prepared from bulk, nonsterile components or in final containers which are not sterile; preparations that must be terminally sterilized before administration	24 hours	3 days	45 days
Immediate-use	Medication preparation areas should be clean, uncluttered, and functionally separate[c]	No	Yes	Emergent use preparations such as epidurals prepared by anesthesia for immediate injection or infusion, diagnostics, any non-hazardous preparations that might cause harm due to delays in administration	1 hour	N/A	N/A

[a]ISO = International Organization for Standardization, PEC = primary engineering control, IV = intravenous.
[b]Ante area must be ISO 7 if it opens into a negative pressure buffer area.
[c]*Source*: The Joint Commission. MM.05.01.07, EP2.[24]

(e.g., steam under pressure or autoclaving) to sealed containers for the purpose of achieving a sterility assurance level of less than 10^{-6} or a probability of 1 nonsterile unit per 1 million sterilized units.[57] For CSPs that are heat-labile and cannot be processed as above, sterilization using an alternative method, such as a sterilizing grade 0.22 micron filter, must be done. Filtration only achieves a sterility assurance level of 10^{-3}, which is only 1 nonsterile unit per one thousand filtrated units. All filters used to sterilize CSPs must undergo filter integrity (bubble-point) testing.

Immediate-Use CSPs

The immediate-use category should be reserved for emergent use or situations in which adhering to low-risk compounding procedures would add additional risk due to delays in patient care. Examples of such situations may include cardiopulmo-

nary resuscitation, diagnostic procedures, or short-stability medications that must be prepared immediately before administration outside health care facilities (e.g., in home infusion or emergency care at the accident site or in an ambulance). Immediate-use CSPs do not need to be compounded in an ISO Class 5 environment and garbing and gowning are not required, as long as all of the following criteria are met:

- Hand hygiene per CDC recommendations[46];
- Aseptic technique is followed;
- No hazardous drugs are used;
- Only simple transfer of no more than three sterile, non-hazardous drugs in the manufacturer's original containers are involved in the compounding, and no more than two entries into any one container occur;
- No more than 1 hour elapses from the time compounding commences to the time administration to the patient begins (although best practice dictates that there are no intervening steps between compounding and administration);
- No batching or storage of CSPs occurs; and
- The preparation is labeled with patient identification, names and amounts of all ingredients, name or initials of preparer, and exact 1-hour BUD and time.

If CSPs prepared for immediate use are not administered within 1 hour, they must be properly discarded. All medications must be labeled to meet regulatory and accreditation standards and in accordance with facility policy.

Point-of-Care Activation Systems

Point-of-care (POC) activation systems (i.e., vial/bag systems) create a physical barrier between components (fluid and medication) that can be activated to allow the components to mix. These devices are designed to create a closed system by which the end user activates the components just prior to the administration of the medication. BUDs for these products are based on the individual manufacturer's recommendations for labeling and dating. Table 10 provides a summary of manufacturer-recommended BUDs for POC systems at time of publication. To decrease potential for contamination and errors, POC systems that will be attached and stored for longer than 1 hour prior to activation should be assembled (but not activated) by pharmacy staff within an ISO Class 5 environment. Activation of the devices should be completed at the point of care just prior to administration.

Ampuls, Single-Dose, and Multiple-Dose Containers

Ampuls may not be reused or saved at any time during the compounding process. To minimize particulate contamination, 5 micron filter straws or filter needles must be used when withdrawing contents of ampuls. Refer to the drug labeling for manufacturer's recommendations concerning filtration.

The environmental conditions in which drug vials are entered determine the BUD for the CSP. Single-dose vials are intended to be used to prepare single doses; however, in times of critical need, contents from unopened single-dose/single-use vials may be repackaged for multiple patients.[49] This repackaging should only be performed by qualified health care personnel in accordance with the procedures described in these guidelines and in *USP* chapter 797.[15]

Pharmacy bulk packages (PBPs), a type of vial containing many single doses,[65] must be considered a single-dose vial for purposes of determining BUDs. Manufacturer's information for each PBP contains recommended BUDs, which are usually between 4 and 8 hours.

Multiple-dose vials may be reused or saved up to the manufacturer's recommended BUD, if they are not opened in a direct patient-care area and if facility policy does not require a shorter period.[66] 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 11 illustrates the dating for these products based on environmental conditions.

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., his or her 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.

Table 10.
Beyond-Use Date (BUD) at Room Temperature for Point-of-Care Activated Devices Assembled in ISO Class 5 Environment[a]

Device	Company	BUD[b]	Applicable Products
ADD-Vantage[62]	Hospira	30 days from date diluent removed from overwrap	
Mini-Bag Plus[63]	Baxter	15 days from date diluent removed from overwrap	50 and 100 mL bags
Mini-Bag Plus[63]	Baxter	30 days from date diluent removed from overwrap	100 mL containers docked with the following drugs: cefazolin 1 g, cefuroxime (Zinacef) 750 mg, ceftriaxone (Rocephin) 1 g, aztreonam (Azactam) 1 g, piperacillin and tazobactam (Zosyn) 3.375 g
addEASE[64]	B. Braun	70 days	When connected to 50 mL and 100 mL bags
		56 days	When connected to Excel 250 mL bags

[a]Information is current as of January 2011. The manufacturer's package insert should always be checked for the most current recommendation for dating.
[b]BUD for assembled but not activated system.

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 medium-risk batches are prepared and assigned a BUD within those limits, no sterility testing is required. However, if those limits are exceeded, each batch must be tested for sterility according to the requirements of *USP* chapter 71.[67]

Facilities that wish to store CSPs for periods longer than those described above must complete sterility testing for each batch to determine the extended BUD. Each batch of any risk-level CSP intended for storage outside the limits described above must be tested for sterility, according to the requirements of *USP* chapter 71, *Sterility Tests*.[67] The results must be evaluated along with stability data to establish the extended BUD. The policies and procedures of the individual facility must outline the processes used to determine extended BUDs.

Batches of high-risk CSPs prepared as multiple-dose vials intended for administration to multiple patients, batches of high-risk CSPs exposed for more than 12 hours to temperatures of 2 to 8 °C (36 to 46 ºF) or for more than 6 hours to temperatures above 8 °C (46 ºF) before sterilization, or batches of more than 25 identical, single-dose, high-risk CSPs must undergo sterilization and microbial and bacterial endotoxin (pyrogen) testing prior to dispensing or administration. Sterility testing, as outlined in *USP* chapter 71, must be completed prior to dispensing or administration.[67] *USP* Membrane Filtration*, USP* Direct Inoculation of the Culture Medium*,* or another testing method that produces verification results statistically comparable with those methods may be utilized.[67]

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. An investigation into the root cause of contamination must occur if sterility testing is positive.

All high-risk CSPs prepared in batches of more than 25 units, with the exception of inhalation or ophthalmic preparations, must be tested to ensure that they do not contain excessive bacterial endotoxins, as described in *USP* chapter 85, Bacterial Endotoxins Test,[68] and *USP* chapter 151, Pyrogen Test.[69] Endotoxin limits (reported in *USP* endotoxin units/hour/kg or units/hour/m^2), if established, are included in the official monograph for the product or may be found in other formula sources. If specific endotoxin limits are not available, default guidance can be found in *USP* chapter 85.[68]

For high-risk preparations, batches of 25 or fewer CSPs do not require sterility testing.[15] However, facilities should consider sterility testing of such CSPs as part of their quality assurance plans to ensure that proper procedures are being followed.

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, high-risk CSPs, parenteral nutrition) in their own facility. Facilities considering outsourcing compounding should consult the *ASHP Guidelines on Outsourcing Sterile Compounding Services*.[16] The decision to use CSPs prepared by outside compounding pharmacies should be reviewed and approved by hospital leadership,[23,70] and such use should only occur in accordance with written policies and procedures.

Administration of CSPs

USP chapter 797 does not include any specifications for administration or timing during this crucial period of the drug delivery cycle. CDC provides the most comprehensive guidance regarding administration of intravenous medications, including administration times, frequency of infusion set changes, use of filters, and prevention of catheter-related infections.[38,47]

Personnel

Personnel Responsibilities

The term *compounding personnel* refers to any individual involved in compounding sterile preparations, regardless of profession. Compounding personnel are responsible for ensuring that CSPs are accurately identified, measured, diluted, and mixed and are correctly purified, sterilized, packaged, sealed, labeled, stored, dispensed, distributed, and disposed of if not used. Emphasis should be on the need to

Table 11.
Beyond-Use Dates for Ampuls, Single-Dose, and Multiple-Dose Containers (Adapted from *USP* Chapter 797[15])

Container	Opened and Maintained within an ISO Class 5 Environment	Opened Outside an ISO Class 5 Environment or Taken from ISO Class 5 Conditions to Less Clean Air
Ampuls	One time use; cannot be stored	One time use; cannot be stored
Single-dose vials	One time use, cannot be stored; contents of unopened vial may be repackaged in times of critical need[49]	One time use; cannot be stored
Pharmacy bulk packages	6 hours[a]	Not intended for use outside ISO 5 environment
Multiple-dose vials	28 days[a]	28 days[a]

[a]Unless otherwise specified by manufacturer.

maintain quality standards for the control of processes, components, and environments and for the skill and knowledge of personnel who prepare CSPs.

Accurate identification and inspection of quality and purity of non-sterile chemicals or non-sterile ingredients are necessary for the integrity of the finished preparations. Upon arrival from the manufacturer and subsequently after opening, bulk packages should be inspected for breaks in the package or closure integrity and for proper appearance, color, odor, and texture.

If nonsterile ingredients are not official *USP* or *National Formulary* products, compounding personnel must require a Certificate of Analysis from the manufacturer to accompany the products.[59] Once a product is received from the manufacturer, the date of receipt must be clearly marked on each package. If a manufacturer's expiration date is not provided, chemicals should be given a three-year BUD from the time of opening unless inspection or testing deems the product within drug monograph specification (if available) to be used for a longer time.[59]

Compounding personnel must have an understanding of how combining different agents in a preparation may affect bioavailability, compatibility (visual and chemical), pH, and concentration effects. Factors that influence stability (e.g., temperature, pH, sorption, photolysis, and chemical degradation) must be carefully evaluated and supported by references or appropriate testing.

Compounding personnel must understand and demonstrate competency in aseptic technique and for the products and systems used in CSP preparation, such as needles, syringes, administration sets, fluid containers, and compounding devices. Aseptic principles and techniques are explained in depth in *Compounding Sterile Preparations*[53] and demonstrated in *Basics of Aseptic Compounding Technique*,[54] *Getting Started in Aseptic Compounding,*[55] and *Compounding Sterile Preparations: ASHP's Video Guide to Chapter <797>*.[56] 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. Compounding personnel with weeping sores, rashes, conjunctivitis, or respiratory infections must not participate in compounding processes until these conditions resolve.

Hygiene and Garbing. Proper preparation for sterile, nonhazardous drug compounding must include effective hand hygiene and garbing procedures. To minimize the number of particles introduced into the sterile compounding area and to minimize the risk of bacteria, all outer jackets and sweaters, visible jewelry, and cosmetics must be removed prior to initiating the handwashing and garbing processes. Personal electronic devices (e.g., cell phones, MP3 players) and any associated attachments must be removed prior to hand hygiene and garbing and should not be used within the sterile compounding area.

Hand hygiene must be performed prior to and after gowning and includes:

- Washing hands, under the fingernails, wrists, and up to the elbow for 30 seconds with a facility-approved agent.
- Drying hands and arms with nonshedding disposable towels or an electronic hand dryer.
- Sanitizing hands with application of a waterless, alcohol-based hand rub (ABHR) with persistent activity prior to donning sterile gloves.

Garbing occurs in the ante area and should be sequenced as follows (from "dirtiest" to "cleanest"):

- 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.
- Enter the buffer area (if facility layout dictates, this step may occur after the following two steps).
- Don sterile powder-free gloves.
- Sanitize the gloves with application of 70% sterile IPA and allow gloves to dry.

Studies support the use of sterile rather than nonsterile gloves in the reduction of initial bioburden.[71] Furthermore, nonsterile gloves run the risk of cross-contamination from hands touching multiple gloves as they are removed from a stock box or container. Gloves must be inspected by personnel on a routine basis during the compounding process to check for tears or holes. The gloves should be disinfected with sterile 70% IPA throughout the compounding process and each time contaminated items are touched.

When high-risk compounding operations prior to terminal sterilization occur, personnel must glove and garb as stated above.

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 and replaced, and proper hand hygiene must be completed before re-entering the compounding area. When CAIs are utilized, compounding personnel must glove and garb as above, unless the manufacturer of the isolator provides written documentation based on environmental testing that any or all of the components of personnel hygiene and garbing are not required based on the PECs of the facility where the device is located.

Proper garb should always be used with CACIs, because personnel will be handling hazardous materials. Vials may be contaminated, even upon delivery,[72–74] and the garb is needed to protect compounding personnel from unexpected drug residue and from inadvertent spills.

Compounding Areas. Compounding personnel must understand the purposes of and relationships between ante, buffer, segregated, and storage areas. A systematic process of entering and exiting the various areas is necessary to minimize contamination. Food, drinks, and gum are prohibited in all of these areas. Since shedding from paper and labels provides a source of nonviable particles, only paper products essential to the compounding process should be allowed in the buffer area. Corrugated cardboard packaging must be eliminated from buffer areas and should be eliminated from ante areas, with all products and components such as needles, syringes, and tubing removed from their outer cardboard packaging and decontaminated by wiping the individual packages (if not in an overwrap) with a suitable disinfectant (e.g.,70% IPA) prior to entering the buffer area.

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 immediately before placing in the PEC and the overwrap immediately discarded.[75] Items stored in the buffer area but not in an overwrap must be decontaminated again prior to entering the PEC, as items may be stored in a buffer area for an extended period of time and may become contaminated by dust or other particles.

Packaging and Labeling

Packaging and subsequent labeling are critical to patient safety. Packaging must be appropriate to preserve both sterility and stability until the BUD. Proper labeling requires an understanding of compounding risk levels and how to determine BUDs based on both stability and sterility.

Labels for single compounded preparations must, at a minimum, include the following:

- Names of active ingredients,
- Amounts or concentrations of active ingredients,
- BUD and time,
- Storage requirements, and
- Identification of responsible compounding personnel.

Labels for batch-prepared CSPs must also include:

- Control or lot number,
- Appropriate auxiliary labeling (including precautions), and
- Device-specific instructions (when appropriate).

Federal and state regulations and accreditation requirements may necessitate 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. 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. Visual inspection should assess particulate matter, coring, cloudiness, leaks, and container and closure integrity.

Compounding accuracy checks must comply with federal and state dispensing regulations and include accuracy 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 via cameras or other devices, by video recordings, or by keeping the used additive containers and syringes with the final product until checked. The check ideally should be performed by someone other than the compounder to decrease confirmation bias. Accuracy can be further verified by weighing when applicable and practical. When using an ACD, specific gravity values must be independently confirmed after being entered to ensure proper volumes are delivered during the compounding process.

Storage of CSPs

Temperatures of areas used for storage on patient-care and procedural units, including room temperature and in refrigerators, freezers, and warmers, must be monitored and recorded daily. On at least a monthly basis, compounding personnel or designated pharmacy personnel should evaluate storage areas for appropriate secure conditions, separation of drugs and food, and proper use and disposal of single- and multiple-dose vials.

Control and Oversight of IV Solutions

Some facilities delegate storage and distribution of parenteral solutions to materials management. Since the products are prescription drugs, the pharmacy must maintain oversight, including selection of appropriate products, package sizes, and forms; safe and secure storage; and temperature control. IV solutions that contain medications (e.g., potassium chloride, heparin, dopamine, dextran, mannitol) or high-risk agents (e.g., sterile water, sodium chloride greater than 0.9%, and parenteral nutrition components) should be stored in and distributed by the pharmacy.

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, and 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. Pneumatic tube delivery may require additional padding around containers to ensure that heat and light exposure and impact are minimized. 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 preparations should always be delivered in a bag 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. Handling and exposure instructions should be legibly displayed on the outside of shipping containers. 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).

Redispensing CSPs

If facility policy allows redispensing 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. There must be policies and procedures in place to provide assurance of proper storage conditions for each product or preparation (e.g., refrigeration, protection from light, package integrity) before redispensing. CSPs must not be redispensed if package integrity has been compromised, including temperature variations.

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 be made aware of the hazards of all chemicals used in the workplace, including drugs.[76] Compounding personnel of reproductive capability shall confirm in writing that they understand the risks of handling hazardous drugs.[15] Personnel at high risk of exposure to hazardous drugs should be enrolled in a medical surveillance program. In many larger facilities, the employee's health department will determine who should be enrolled. Specific guidance about surveillance for health care workers exposed to hazardous drugs is available from NIOSH,[77] as is a list of drugs NIOSH considers hazardous.[27] 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 non-hazardous sterile drugs, with details of differentiating the garbing, storage, preparation, and disposal procedures for hazardous drugs. *USP* chapter 797 requires that training, at a minimum, include:

- Safe aseptic manipulation practices.
- Negative pressure techniques when compounding.
- Proper utilization of a BSC or CACI.
- Correct use of closed-system transfer devices (CSTDs), if used.
- Containment, cleanup, and disposal procedures for breakages and spills.
- Treatment of personnel contact and inhalation exposure.[15]

OSHA requires more general training on chemical label elements and safety data sheet (SDS) format.[76] When training or evaluating competency, facilities may choose products to objectively evaluate hazardous drug compounding technique. These products utilize 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*.[28]

Personnel Responsibilities for Specialty Preparations

Specialty preparations (e.g., allergen extracts, radiopharmaceuticals, and evolving technology and therapeutics such as biologics and nanotechnology) provide specific treatments for patients and require specialized procedures to be followed. Although compounding of intradermal or subcutaneous injections of allergen extracts would ideally occur under conditions for similar risk-level CSPs, they may not necessarily be subject to the same personnel, environmental, and storage requirements as for other CSPs of a similar risk level, as long as the following criteria outlined by *USP* chapter 797,[15] in conjunction with the American Academy of Otolaryngic Allergy and the Joint Council of Allergy, Asthma and Immunology,[78] are met:

- Compounding process involves simple transfer using sterile components and allergen products.
- All allergen extracts contain effective preservatives to prevent microbial growth.
- All hand hygiene, garbing, and gloving procedures for low-risk compounding, with the exception of donning shoe covers, must be followed.
- Ampul necks and vial stoppers are disinfected by wiping with sufficient amounts of sterile 70% IPA to ensure that the critical sites remain wet for 10 seconds and are allowed to dry.
- Direct contact contamination of critical sites is minimized by utilizing aseptic compounding.
- Multiple-dose vials are labeled with the name of one patient and a BUD and storage temperature range based on manufacturer recommendations or published literature. Single-dose extracts are not to be stored for subsequent use after entry.

Nuclear pharmacies are regulated by the Nuclear Regulatory Commission as well as other applicable pharmacy laws and regulations. *USP* chapter 823, Radiopharmaceuticals for Positron Emission Tomography,[79] provides the standards for production facilities. Once the components for use in positron emission tomography are released as finished preparations, handling, manipulation, and use are considered compounding by *USP* chapter 797[15] and for the purposes of these guidelines. Low-risk-level radiopharmaceuticals are those compounded from sterile components with a volume of less than 100 mL for a single-dose injection or no more than 30 mL taken from a multiple-dose container.[15] These radiopharmaceutical preparations must be compounded in an ISO Class 5 PEC within an ISO Class 8 environment.

Non-radiopharmaceuticals compounded in nuclear pharmacies must be compounded under full USP 797 compliant conditions. The radiopharmaceutical exemption in USP chapter 797[15] does not apply to non-radiopharmaceuticals.

The concept of limiting radiation exposure to a level that is as low as reasonably achievable (ALARA) must be adhered to for handling, compounding, and visual inspection of products. Technetium-99m/molybdenum-99 generator system operations and storage must occur within an ISO Class 8 environment and must further comply with all manufacturer's recommendations and federal and state regulations. Manufacturer's guidelines for BUDs should be followed for radiopharmaceutical multiple-dose vials that

are compounded with technetium-99m and exposed to ISO Class 5 conditions with no direct contact contamination.

Personnel Compounding Competency

Touch contamination remains the primary cause of microbial contamination in sterile compounding.[71,80] For this reason, personnel training and assessment of competency are of utmost importance to ensure the lowest possible risk for contamination due to human error. For low- and medium-risk operations, training and competency assessment are required initially upon hire or upon transfer to compounding responsibilities, and again at least every 12 months for all staff involved in the compounding of sterile products. High-risk operations require more frequent assessments, and staff must be evaluated upon hire or transfer and again at least every six months.

As part of the training competency assessment, a written test that evaluates knowledge about proper compounding SOPs, aseptic technique, cleaning and garbing, environmental monitoring, calculations, risk levels and BUDs, and quality assurance principles must be successfully completed. Thresholds for passing the written examination should be set by the facility. While written tests assess knowledge, hands-on observation of daily duties assesses for proper technique. Personnel should be able to demonstrate at least the following in a hands-on, witnessed assessment, as applicable to their compounding responsibilities:

- Proper hand hygiene technique (see Appendix III of *USP* chapter 797[15] for a sample assessment form).
- Proper gloving and garbing technique, including successful glove fingertip test (see Appendix III of *USP* chapter 797[15] for a sample assessment form).
- Proper aseptic technique, including successful media-fill test (see Appendix IV of *USP* chapter 797[15] for a sample assessment form).
- Proper cleaning and disinfecting procedures, including successful surface sampling test (see Appendix V of *USP* chapter 797[15] for a sample assessment form and Appendix II for information about cleaning products).
- Competency in the compounding of hazardous drugs.
- Competency in the compounding of allergen extracts.
- Competency in the compounding of radiopharmaceuticals.
- Competency in the use of sterile devices, such as filter needles, injection port adapters, sterile fluid transfer devices, and CSTDs.
- Competency in the use of pharmacy compounding devices.
- Ability to fill pump reservoirs.
- Competency to perform end-product testing and sterilization.

USP chapter 797[15] requires specific assessments to be completed using sterile nutrient agar growth media to test for potential contamination. Personnel-specific examples of this type of testing include media-fill testing of aseptic technique and glove fingertip testing of compounding personnel.

Media-Fill Testing

As described in *USP* chapter 797, the media-fill component of personnel assessment provides an objective evaluation of aseptic technique.[15] Media-fill tests should be customized to mimic the most challenging preparations compounded by personnel on a regular basis in a specific facility. Testing should occur at least every 12 months for personnel who compound low- and medium-risk preparations, while testing at least every 6 months is required for personnel involved in compounding high-risk preparations. The actual testing should take place under conditions that reflect realistic workflow, such as the end of a shift, to simulate a worst-case scenario environment for compounding sterile preparations. Once started, the test should be completed without interruption. Fluid culture media are available commercially for low- and medium-risk evaluations. High-risk assessments may utilize nonsterile nutrient medium in a powder form, which may be diluted and sterilized by filter methods. Finished tests should be incubated per manufacturer's recommendations. If incubators are in the pharmacy, they must be placed outside the sterile compounding area. Ideally, the facility's microbiology services should incubate and read the tests, providing an independent evaluation by qualified individuals. Turbidity in the culture media signifies failure of the media-fill testing and requires retesting of compounding personnel. Personnel who fail these tests will require re-training and may not compound sterile preparations until tests have been repeated with successful results.

Glove Fingertip Testing

Three sets of glove fingertip evaluations must be completed with no growth prior to personnel being allowed to compound sterile preparations. This initial testing involves compounding personnel completing all necessary hand hygiene and garbing procedures (with the exception of applying sterile 70% IPA to gloves). Immediately upon completion of these procedures, the glove fingertip and thumb samples from each hand are placed on sterile nutrient agar plates. The samples should be incubated (such as by the facility's microbiology personnel) according to manufacturer standards. This test must be successfully completed three times initially, then at least every 12 months. Personnel compounding high-risk products must successfully complete the test at least every 6 months. Suggested thresholds for contamination limits can be found in Table 6. Patterns of failures (personnel, media, or facility) must be evaluated as part of the facility's quality assurance plan. Qualified microbiology personnel and the facility's infection control practitioner should be consulted.

Growth Media Requirements

Sterile nutrient agar for media-fill testing, plates for fingertip testing, and surface testing materials are available from multiple vendors. *USP* chapters 797 and 1116 provide specifications and requirements.[15,81] The media-fill testing growth media and viable airborne particle plates should utilize a Soybean-Casein Digest medium, which may also be sold as Tryptic Soy Agar/Broth. The agar plates for glove fingertip testing and surface testing should utilize general nutrient agar with neutralizing agents such as lecithin and polysorbate 80.

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 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.

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 who are responsible for making sure that 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*—easily accessible written record or log that demonstrates that the SOP is being performed routinely and properly.
- *Revision*—documentation of the date that an SOP has been reviewed and the name of the reviewer.

USP chapter 797[15] lists and recommends SOPs and should be reviewed to guide the pharmacy department in developing, writing, and implementing SOPs. There should be SOPs written to address tasks or procedures in the following general categories:

- *Personnel*—training, education, skills, competency evaluations, and responsibilities.
- *Facilities*—access, cleaning, maintenance, use, monitoring, and testing.
- *Equipment*—calibration, maintenance, cleaning, certification, verification, and use.
- *Supplies*—ordering, storing, certification, inspection, and disposal.
- *Compounding procedures*—preparation of various sterile compounded medications (e.g., batches, total parenteral nutrition, hazardous drugs, epidural, patient-controlled analgesia, or ophthalmics), formulas, assigning BUDs, handling, and packaging.
- *Safety*—injuries, hazardous spills, and accidental exposures.
- *Quality assurance*—inspection of CSPs, testing of CSPs, BUDs, delivery, and storage of final CSPs, patient monitoring, adverse event reporting, and personnel and environmental monitoring.
- *Administration*—record keeping and management.

All significant procedures performed in a pharmacy should be covered by SOPs and documentation. These procedures should be routinely reviewed and modified for improvements at least annually.

Quality Assurance Program

The purpose of a quality assurance program is to provide a mechanism for monitoring, evaluating, correcting, and improving activities and processes. A quality assurance program should review and analyze objective data and use these data to develop action plans. 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.

Activities and processes that are identified based on their high frequency, high risk, or problem-prone nature should have specific monitoring and evaluation criteria assigned for objective and measurable assessment. The quality assurance program should encompass any and all activities that are included in previous sections of this document as elements which should be assessed and documented. This includes, but is not limited to:

- Personnel training and assessment,
- Environmental monitoring, and
- Equipment calibration and maintenance.

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

A critical part of any quality assurance program is proper documentation, corrective action, and follow-up. Institutions must determine how results will be reported and evaluated, including development of action limits and thresholds. Thresholds and follow-up mechanisms must be in place prior to initiating a quality assurance program or immediately after collecting initial benchmark data. Responsible persons for completing these tasks should be identified and trained, if necessary, in the proper execution of the quality assurance plan. Results of monitoring and measurements should be reported within and outside of the department responsible for compounding practices to committees such as Infection Control and Quality Improvement.

If corrective action is needed, the problem should be resolved as soon as possible. Assessment of problems with compounding errors, evident contamination during preparation, quarantine, or patterns of personnel or environmental monitoring outside the established parameters require for-

mal follow-up. A root cause analysis, including participation by other facility experts such as infection control personnel, should be completed.[82] For situations needing more time for corrective measures, an action plan should be developed and followed. Indicators and effectiveness of the quality assurance program should be reassessed annually.

New technologies, procedures, and policies should be incorporated on an as-needed basis. A failure mode and effects analysis of new techniques can serve as a valuable proactive assessment of the ease and value prior to introduction into the compounding process.[83]

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