Hospital Pharmacy–USP Compounding Standards

Environmental Requirements for USP 795 & 797 Compliance

This technology report summarizes the environmental requirements for compounded sterile preparations (CSPs) and for compounded nonsterile preparations (CNSPs). Compounding occurs in the following settings:

- Hospitals
- Outpatient treatment clinics
- Infusion facilities
- Pharmacies
- Physician offices
- Long-term care facilities

This report is based on the current industry guidelines listed in the following section, as well as the experience of knowledgeable healthcare facility designers.

Regulatory requirements constantly evolve. This technology report is based on United States Pharmacopeia (USP) <797> proposed revision dated July 2018 and USP <795> proposed revision dated March 2018. Section 503A of the Federal Food, Drug, and Cosmetic Act states that compounded preparations prepared by a licensed pharmacist or physician qualify for an exemption from the requirements of current Good Manufacturing Practice (CGMP) if they are compounded in compliance with the USP chapters on pharmacy compounding.

Current USP Guidelines

- The current version of USP <797> became official on June 1, 2008.
- An update to USP <797> was proposed for public comment on July 27, 2018.
- The proposed update to USP <797> is expected to be official on December 1, 2019.

USP <795> Facility Requirements

USP <795> describes the minimum practices and quality standards for the preparation of CNSPs.

CNSPs must be prepared in a space that is specifically designated for compounding. The compounding area must be separated from the rest of the facility. Nonsterile preparations must be compounded in a separate and distinct space from sterile compounding.

Any activity that may result in airborne contamination (powder substance) must be performed in a containment ventilated enclosure (CVE).

CVE

A full or partial enclosure that uses ventilation principles to capture, contain, and remove airborne contaminates through high-efficiency particulate air (HEPA) filtration.

USP <797> Facility Requirements

USP <797> describes the minimum practices and quality standards for the preparation of CSPs.
USP <797> divides CSPs into two classifications: Category 1 and Category 2 preparations. The definition and requirements are as follows:

**Category 1:**
- Category 1 CSPs are those with an assigned beyond-use date (BUD) of 12 hours or less at controlled room temperature or 24 hours or less if refrigerated.
- Category 1 CSPs must be prepared in a primary engineering control (PEC) which provides an ISO Class 5 environment. The PEC may be located in an ISO Class 7 buffer area (see category 2 requirements) or in a segregated compounding area (SCA).
- An SCA is a designated, unclassified space, area, or room in which a PEC is located for the purpose of preparing category 1 CSPs.

**Category 2:**
- Category 2 CSPs are those with an assigned BUD of greater than 12 hours at controlled room temperature or greater than 24 hours if refrigerated.
- Category 2 CSPs must be prepared in a PEC which provides an ISO Class 5 environment. The PEC must be located in a designated operational clean area which includes an ante-area and a buffer area.

**Equipment (Primary Controls)**

Although the ventilation system designer does not normally select the type of ventilated cabinets that are used within the compounding area, the designer must know the type of protection (personnel, product, and/or environment) provided by the units. This knowledge ensures that the ventilation system design will address the exhaust and makeup air requirements of these cabinets.

Cabinets provide a constant, even airflow that creates a barrier across the face of the work area while also maintaining a constant flow inside the cabinet.

**ISO Class 5 Environment**—USP <797> requires that CSP preparation take place in an ISO Class 5 PEC. This requirement means that airflow within the PEC uses HEPA filters to remove any particles.

<table>
<thead>
<tr>
<th>PEC Types</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BioSafety Cabinet (BSC)</td>
<td>A ventilated cabinet with unidirectional HEPA-filtered airflow and HEPA-filtered exhaust to protect the worker from hazardous drugs</td>
</tr>
<tr>
<td>Compounding Aseptic Isolator (CAI)</td>
<td>A type of restricted-access barrier system (RABS) that uses HEPA filtration to provide an ISO Class 5 clean-air environment designed for the compounding of sterile non-hazardous drugs</td>
</tr>
<tr>
<td>Compounding Aseptic Containment Isolator (CACI)</td>
<td>A type of RABS that uses HEPA filtration to provide an ISO Class 5 clean-air environment designed for the compounding of sterile hazardous drugs</td>
</tr>
<tr>
<td>Isolator</td>
<td>An enclosure that provides HEPA-filtered ISO Class 5 unidirectional air operated at a continuously higher pressure than its surrounding environment and decontaminated using an automated system</td>
</tr>
<tr>
<td>Laminar Airflow System (LAFS)</td>
<td>A device or zone within a buffer area that provides an ISO Class 5 or better environment for sterile compounding; the system provides a unidirectional HEPA-filtered airflow</td>
</tr>
<tr>
<td>Laminar Airflow Workbench (LAFW)</td>
<td>A device that is a type of LAFS that provides an ISO Class 5 or better environment for sterile compounding; the device provides a unidirectional HEPA-filtered airflow</td>
</tr>
<tr>
<td>Restricted-Access Barrier System (RABS)</td>
<td>An enclosure that provides HEPA-filtered ISO Class 5 unidirectional air and that allows for the ingress and/or egress of materials through defined openings that have been designed and validated to preclude the transfer of contamination and that generally are not to be opened during operations</td>
</tr>
</tbody>
</table>

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2. Classification of air cleanliness; ISO Class 5 is equivalent to 100 particles per ft³ or 3520 particles per m³ of 0.5 µm per m³ or larger.
**Failure of Cabinet** – The impact that a cabinet failure will have on the room environment must be considered during the design process. For example, consider a system with the following cabinets: Negative pressure barrier isolators, Class II BSC Type B1, and Class II BSC Type B2. If the building exhaust or cabinet exhaust fails, the cabinet will become pressurized, causing airflow from the work area to flow back into the room. Therefore, these cabinets should have their exhaust ducted to the outside.

**Continuous Monitoring** – Typically, cabinet manufacturers provide a magnehelic gauge to provide visual confirmation of cabinet operation. Failure of the building exhaust system will not be apparent to the user because the cabinet supply blower will continue to operate. Therefore, a pressure-independent monitor should be installed to sound an audible alarm and shut off the BSC supply fan if a failure occurs.

**Building Exhaust** – Typically, cabinets that exhaust air to the outside are connected to the building's existing exhaust system. To maintain steady cabinet flow conditions, the pressure relationships inside the cabinet and between the cabinet and the exhaust ducts must be held constant. Cabinets will require either a hard connection or a thimble connection to the exhaust duct. The type of connection depends on the type of cabinet.

BSCs and glove boxes require constant exhaust airflow to contain contamination and to protect products in the cabinet. If BSCs are connected to a central exhaust system that also serves variable-volume fume hoods, the variation in total system exhaust can upset the pressure relationships between the airflows in the cabinet, allowing contaminants to either escape the cabinet or to enter the cabinet workbench area. To avoid this problem, BSCs can be equipped with constant-air-volume controllers. In situations where constant-air-volume controllers are required, they should be integrated into the building automation system (BAS) so that historical data, alarms, and alarm acknowledgements can be collected and archived to document compliance with regulatory requirements.

**Design Requirements for CSP Pharmacies**

USP <797> requires that CSP preparation must be performed in a PEC that meets ISO Class 5.

- **Category 1 CSPs:** The PEC may be located in an SCA (unclassified space) without a buffer or ante-area.
- **Category 2 CSPs:** The PEC must be located within an ISO Class 7 Buffer area with an ISO Class 8 ante-room.

If facilities are designed with ante-areas and buffer areas, the areas must be separate from the general pharmacy and must control for these environmental conditions:

- Particle count
- Temperature
- Humidity
- Differential pressure (D/P)
- Air changes

**Buffer and Ante-Area Requirements**

The environment is designed to have the PEC located in the buffer area or clean area. An anteroom adjacent to the buffer area provides a clean area for donning personnel barriers, such as hair covers, gloves, gowns, shoe coverings, or other cleanroom attire.

The compounding area must be designed to facilitate safe movement of personnel, equipment, and components without disruption of the air flow or air quality.

The temperature must not exceed 68°F (20°C) and humidity must not exceed 60% in the compounding area.

Access to the area must be controlled.
The PEC must be located so that it is not affected by air currents or streams from heating, ventilation, and air conditioning (HVAC), personnel, or doors.

ISO 7 and ISO 8 rooms must be physically separated, with walls and doors between them and with controls to prevent the flow of lower-quality air into the controlled area.

ISO 7 areas must have at least 30 air changes per hour (ACPH), and at least 15 ACPH must be HEPA-filtered fresh air.

ISO 8 areas must have a minimum of 20 ACPH.

There must be a D/P of at least 0.02 inches water column (wc) between the ISO 7 area and the ISO 8 area. There must be a D/P of at least 0.02 inches wc between the ISO 8 area and the pharmacy or unclassified area.

Must have a differential pressure monitoring system in place that continuously monitors differential pressure.

Surfaces must be smooth, impervious, free of cracks and crevices, and non-shedding. Walls must be constructed of durable material.

Supply Air
Supply air is provided to the space through HEPA filters which make the supply air virtually free from contaminants. While HEPA filters are effective in removing most particulate contamination, they are not effective in removing gases and vapors. For this reason, the National Institute for Occupational Safety and Health (NIOSH) requires that BSCs and isolators used for volatile drugs be externally vented.

Room Exhaust
Return openings from the room should be low on the walls to promote a downward flow of air from the supply to return, sweeping contaminants to the floor and away from the product. Perforated floors are not recommended due to the difficulty in cleaning them.

The room exhaust should be sized to handle both the room and all containment devices vented through the system.

Room Pressurization
A pressure gradient is used to minimize particle migration into the clean space from a less clean space. The pressure gradient causes the air pressure in the buffer zone space to be higher than that of the ante area, so air cascades or flows from the cleaner area into the dirtier area.

Typically, the pressure differential between two adjoining areas (ISO Class 7 and ISO Class 8) is +0.02 inches wc.

To ensure minimum air changes, the supply airflow volume must be compensated for filter loading.

Differential Pressure (D/P) Monitoring - A differential monitoring system must be used to continuously monitor the pressure differential or airflow between the ante-area and the buffer area and between the ante-area and the general environment (corridor or pharmacy). This system is used by the healthcare workers to verify that the required room pressurization is being maintained and warns them of any loss of the required D/P. A momentary loss in D/P occurs when a door is opened and then closed. Therefore, D/P alarms should have an adjustable delay period to prevent nuisance alarms during the time needed for normal passage through the doorway and for the ventilation system to restore the required D/P.

Temperature and Humidity
Maintain the temperature below 68°F (20°C) and the humidity below 60% in the CSP compounding area. Maintain humidity and temperature at a level necessary for operator comfort in the compounding area designated for the preparation of CNSPs.

Temperature and humidity must be controlled through an HVAC system.

3. ASHRAE Handbook 2003, Chapter 16 Clean Spaces
Air Changes

The required rate of air changes is dictated by the internal generation of particles from operators and building elements such as walls, ceiling, floor, and so on.

The ISO 7 buffer room must maintain an ACPH value of not less than 30. The ACPH of 30 can include re-circulated HEPA-filtered air, but at least half of the ACPH must be HEPA-filtered fresh air.

The ISO 8 ante-room must maintain an ACPH value of not less than 20.

Monitoring and Alarms—The International Society for Pharmaceutical Engineering (ISPE) Good Practice Guide\(^4\) states that critical parameters that can affect end product quality must remain within process limits and should have alerts and alarms. USP <1079> Good Storage and Distribution states that alarms should be used to reveal environmental excursions during operations. The following critical room conditions should be monitored to document cleanroom environmental conditions:

- Room temperature
- Room humidity
- Room D/P
- (Optional) Particle count

Audible and visual indication of cleanroom alarms should be provided for healthcare workers, and the time of the alarm should be recorded. Integration of HVAC controls into the BAS allows historical data, alarms, and alarm acknowledgements to be collected and archived to document compliance with regulatory requirements.

### Building Exhaust Design Considerations

Care must be exercised in the system design and particularly in the location of the exhaust air inlets. The following list describes important design criteria for healthcare exhaust systems\(^5\).

- Consult with the facility engineer before adding a new cabinet to the building exhaust system.
- Exhaust air should be discharged away from supply air intakes to prevent entrainment of exhausted laboratory air back into the building air supply system.
- Exhaust air discharge outlets should be placed as high as practical and typically are located on the building roof.
- The exhaust air discharge outlet must not have a rain cap or other elements that could disrupt the upward direction of the exhaust air stream.
- Exhaust stacks or outlets must be located at least 25 feet (7.62 meters) from fresh air intakes. Plumbing and vacuum vents that terminate at a level above the top of the air intake may be located as close as 10 feet (3.05 meters).

### Cleanroom Design Considerations

The following list describes important design criteria for cleanrooms\(^6\):

- Construct walls, floors, ceilings, fixtures, shelving, counters, and cabinets so that the surfaces are accessible for cleaning and so that spaces in which microorganisms and other contaminants can accumulate are minimized.
- Select materials that will not deteriorate with use and affect particle control and contribute to contamination.
- Reduce the number of joints, cracks, and crevices to promote cleanliness and to minimize spaces where microorganisms and other contaminants can accumulate.
- Junctures of ceilings to walls should be coved or caulked to avoid cracks and crevices where dirt can accumulate.
- Any penetrations through the walls and ceiling should be sealed.

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Ceilings with inlaid panels should be impregnated with a polymer to render them impervious and hydrophobic. Caulk around each perimeter to seal the panels to the frame.

Walls may be constructed of panels locked together and sealed or can be made of epoxy-coated gypsum board.

Floors should be overlaid with wide sheet vinyl flooring with heat-welded seams and coving at the sidewall.

Avoid dust-collecting overhangs and ledges, such as ceiling utility pipes and windowsills.

The exterior lens of ceiling light fixtures should be smooth, mounted flush, and sealed.

The buffer area should not contain a sink or floor drain. The anteroom should contain a hands-free sink for hand-washing and no floor drain.

Hand-sanitizing and gowning occur in the anteroom area adjacent to the buffer area. Faucet handles should be designed to be hands-free.

**HVAC Design Considerations**

Before developing the project design, assess the pharmacy HVAC system for the following:

- Does the air handler serving the pharmacy have enough cooling capacity to meet the cooling requirements for the cleanroom?
- Does the air handler serving the pharmacy have enough static pressure to meet the static pressure requirements of the HEPA-filtered diffusers?
- Can the HVAC terminal equipment be located in an area adjacent to the pharmacy to facilitate good maintenance practices?

**Certification and Recertification**

**Compounded Nonsterile Preparations**

Before a CVE can be used to prepare CNSPs, it must be certified in accordance with current guidelines from the American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE).

The CVE must be certified regularly thereafter:

- A CVE that is equipped with an exhaust alarm must be certified annually.

**Compounded Sterile Preparations**

Before an area is used to compound either Category 1 or Category 2 CSPs, it must be certified using procedures in the current Controlled Environment Testing Association (CETA) certification guide for Sterile Compounding Facilities or equivalent guideline.

Environmental quality is evaluated as follows:

- Certification that each PEC is functioning properly and meets the air quality requirement of ISO Class 5. Certification must include the following tests:
  - Airflow testing
  - HEPA filter integrity testing
  - Total particle counts testing
  - Smoke studies
- Certification of the buffer area (ISO Class 7) and ante-area (ISO Class 8) must include:
  - Air velocity and volume measurements
  - ACPH verifications
  - Room pressure cascade verification to ensure proper airflow
  - Air quality measurements
- Qualified Operator(s) must certify both PECs and the room environments at least every six months and when renovations occur. These records should be maintained and reviewed by the supervising pharmacist or other designated employee.
- Total (non-viable) particle counts on ISO areas must be conducted during operations every six months.
- Active air sampling (viable) of all ISO-classified areas must be conducted during typical operating conditions at least every 6 months.
• Temperature and Humidity monitoring equipment must be calibrated or verified for accuracy at least every 12 months or as recommended by the manufacturer.

• Differential pressure monitoring equipment must be calibrated or verified for accuracy at least every 6 months.

**Monitoring Controlled Storage Areas**

USP <795> and <797> require documentation that medications are stored under necessary conditions to ensure stability.

Controlled storage areas in the pharmacy should be monitored at least once per day and the results documented on a temperature log. If the facility uses a continuous temperature-monitoring device or system, then personnel must verify at least once daily that the recording device is functioning properly.

<table>
<thead>
<tr>
<th>Component</th>
<th>°F</th>
<th>°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freezer</td>
<td>-13</td>
<td>-25</td>
</tr>
<tr>
<td>Refrigerator</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>Cold</td>
<td>&lt; or = 46</td>
<td>&lt; or = 8</td>
</tr>
<tr>
<td>Cool</td>
<td>46 to 59</td>
<td>8 to 15</td>
</tr>
<tr>
<td>Room Temperature</td>
<td>Prevailing area</td>
<td>Prevailing area</td>
</tr>
<tr>
<td>Controlled Room</td>
<td>68 to 77</td>
<td>20 to 25</td>
</tr>
<tr>
<td>Temperature</td>
<td>Warm</td>
<td>Excessive Heat</td>
</tr>
<tr>
<td></td>
<td>&gt; 104</td>
<td>&gt; 104</td>
</tr>
<tr>
<td>Storage area humidity</td>
<td>Dry Place</td>
<td>Average relative humidity not &gt; 40%</td>
</tr>
</tbody>
</table>

Storage area humidity should be maintained at or below 60%.

Audible and visual indication of controlled storage temperature alarms should be provided for healthcare workers, and the time of the alarm should be recorded. Integration of controlled storage area monitoring into the BAS allows historical data, alarms, and alarm acknowledgements to be collected and archived to document compliance with USP requirements.