Hospital Pharmacy–Compounding Sterile Preparations

Environmental Requirements for USP Chapter <797> Compliance

This technology report summarizes the environmental requirements for Compounding Sterile Preparations (CSPs). Compounding of sterile preparations occur in the following settings: hospitals, community pharmacies, home infusion services, physician offices, and nursing homes. 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–National Formulary (USP–NF) General Chapter <797>, Pharmaceutical Compounding–Sterile Preparations, dated January 1, 2004 and is subject to change as requirements change.

Proposed changes to USP <797> were approved by the Sterile Compounding Committee (SCC) on November 2004. The next official USP <797> will appear in the annual USP revision in 2006.1

Current Industry Guidelines

- On July 1, 2004, JCAHO began including USP <797> in their accreditation audits.
- In September 2004, the CDC and NIOSH issued NIOSH ALERT Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings

Critical JCAHO Compliance Dates

- July 1, 2004–Process of compliance evaluation and formulation of action plan should have begun.
- January 1, 2005–Completed risk assessment (or gap analysis) of compliance and established a written plan with specific timeframes and funding approvals.
- July 1, 2005–Implementation of interim safety measures to mitigate the impact of non-compliance.
- January 1, 2008–Must complete action plans for full compliance.

CSP Microbial Contamination Risk Levels

Proposed USP <797> changes to Cleanroom. The proposed changes to USP <797> for cleanroom environments will change from ISO Class 8 to ISO Class 7.

USP <797> has described the characteristics of appropriate risk-level for low, medium, or high for CSP environments2 and are summarized as follows:

Low-Risk Level

- CSPs occur in ISO Class 5 or better hood in an ISO Class 8 cleanroom using only sterile ingredients, products, components, and devices.
- Example low-risk environment compounding procedures involve only a few closed systems, manual measurement, simple aseptic transfers, and manipulations of no more than three manufactured products into drugs or nutritional solutions.
- Quality assurance practices include; routine disinfection and air quality testing of CSP environment to minimize microbial surface contamination and maintain ISO Class 5 air quality.

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Medium-Risk Level

- CSPs occur in ISO Class 5 or better hood in an ISO Class 8 cleanroom using only sterile ingredients, products, components, and devices.
- Example medium-risk environment compounding procedures involve multiple pooled sterile commercial products for multiple patients or one patient multiple times (for example, batched antibiotics).
- Quality assurance program is the same as low-risk level CSPs, in addition to having each authorized person annually prepare medium-risk CSPs in order to pass a more challenging Media-Fill Test annually or more frequently.\(^3\)

High-Risk Level

- CSPs occur in ISO Class 5 or better hood in an ISO Class 8 cleanroom using only sterile ingredients, products, components, and devices.
- A wall must separate the cleanroom from the anteroom (gown room). The anteroom may have a demarcation line separating clean and supply cart area.
- Example high-risk environment compounding procedures involve reconstitution of a single vial of lyophilized powder for transferring to a small-volume minibag or large-volume parental solution.
- Quality assurance program is the same as low-risk level CSPs, in addition to having each authorized person annually prepare high-risk CSPs in order to pass Media-Fill Test semi-annually.\(^4\)

Equipment (Primary Controls)

Although the ventilation system designer does not normally select the type of ventilated cabinets that are used within the CSP environment, the designer must know the type of protection (personnel, product, and/or environment) provided by the units. This 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, by maintaining a constant flow inside the cabinet as well.

ISO Class 5 Environment\(^5\)–USP <797> requires the CSP work environment to take place in an ISO Class 5 (1,000 Level) workbench. This means that airflow within the workbench uses HEPA filters to remove any particles or infectious agents. While HEPA filters are effective at trapping particles and infectious agents, they are not effective at capturing volatile chemicals or gases. The NIOSH Alert requires Biosafety Cabinets (BSCs) or barrier isolators to be exhausted to the outside when working with volatile toxic chemicals.\(^6\)

<table>
<thead>
<tr>
<th>Personnel</th>
<th>Product</th>
<th>Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laminar Airflow Workbench</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>Barrier Isolator (+)</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Barrier Isolator (-)</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Class II BSC Type A2</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Class II BSC Type B1</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Class II BSC Type B2</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>

Failure of Cabinet–The impact that a cabinet failure will have on the room environment must be considered during the design process. For example, you have 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 the exhaust ducted to the outside.

Continuous Monitoring–Typically, cabinet manufacturers provide a Magnehelic Gauge to provide visual confirmation of cabinet operation.

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3. This test is completed without interruption in ISO Class 5 hood and simulates CSP conditions. Persons preparing CSPs demonstrate aseptic technique in preparation of CSP.
4. Ibid.

5. Classification of air cleanliness; ISO Class 5 is equivalent to 100 particles per ft\(^3\) or 3520 particles per m\(^3\) of 0.5 \(\mu\)m per m\(^3\) or larger.
Failure of the building exhaust system will not be apparent to the user, since the cabinet supply blower will continue to operate. A pressure-independent monitor should be installed to sound an audible alarm and shut off the BSC supply fan. It is recommended that a sensor be installed in the exhaust system to monitor cabinet airflow. For operator safety purposes, NIOSH recommends that, regardless of cabinet type, each cabinet is equipped with a continuous monitoring device to confirm adequate airflow before each use.

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 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 airflow in the cabinet, allowing contaminants to either escape the cabinet, or 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) to allow historical data, alarms and alarm acknowledgement to be collected and archived to document compliance with JCAHO and NIOSH requirements.

Barrier isolators (glove boxes) are usually connected to a dedicated exhaust system.

Environmental Monitoring

To maintain environmental quality of the CSP environment, USP <797> requires the evaluation and verification of personnel aseptic techniques, processes and procedures, assessment and verification of the CSP environment. A written plan and schedule for environmental monitoring procedures must be developed and followed.

Evaluation of the environmental quality is done by:

- Certification that each cabinet (LAFW, BSC or barrier isolator) is functioning properly and meets the air quality requirement of ISO Class 5.
- Certification that the air quality of the buffer or clean area and anteroom area meet the ISO Class 8 requirements.
- Qualified Operator(s) must certify both cabinets and room environments at least every six months and when renovations occur. Theses records should be maintained and reviewed by the supervising pharmacist or other designated employee.
- Evaluation of airborne microorganisms in the controlled air environments (ventilated cabinets) by either measuring the total number of particles using electronic air samplers or exposing sterile nutrient agar plates for a suitable time frame.

### Proposed USP <797> changes to Air Quality

<table>
<thead>
<tr>
<th>CSPs per Week</th>
<th>Min. Sample Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low/Med Risk</td>
<td>High Risk</td>
</tr>
<tr>
<td>ISO 5 Surfaces</td>
<td>Fingertips of Gloves</td>
</tr>
<tr>
<td>&lt;=100</td>
<td>0</td>
</tr>
<tr>
<td>101 to 300</td>
<td>1-2</td>
</tr>
<tr>
<td>+300</td>
<td>+3</td>
</tr>
</tbody>
</table>

### Monitoring Controlled Storage Areas

USP <797>, JCAHO EC6.20.14 and MM2.20 require documentation that medications are stored under necessary conditions to ensure stability (monitoring controlled storage areas).

Controlled storage areas in the pharmacy (refrigerators, 2° through 8°C; freezers, -20° through -10°C; and incubators, 30° through 35°C, etc.) should be monitored at least once per day and the results documented on a temperature log. Additionally, pharmacy personnel should note the

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7. Ibid.

8. The results from testing each cleanroom or clean zone shall be recorded and submitted as a comprehensive report along with statement of compliance or noncompliance with specified designation of airborne particulate cleanliness classification. ISO 14644-1:1999

9. The National Environmental Balancing Bureau (NEBB) provides a Cleanroom Performance Testing Certification Program to certify firms that test cleanrooms and clean zones. There are no published guidelines for testing barrier Isolators (for example, gloveboxes). The product manufacturer should provide specific procedures for testing equipment.
storage temperature when placing products into or removing products from the storage unit in order to monitor temperature deviations.

During a recent JCAHO survey at one hospital, refrigerator checks were identified as a concern because of missing entries and findings that temperatures were outside the required range without evidence of action.

Audible and visual indication of controlled storage temperature alarms should be provided for healthcare workers as well as recording the time of alarm. Integration of controlled storage area monitoring into the building automation system (BAS) allows historical data, alarms and alarm acknowledgement to be collected and archived to document compliance with JCAHO and USP <797> requirements.

**Design Requirements for CSP Pharmacies**

USP <797> requires the compounding area (buffer or clean area) to be certified to ISO Class 8 (Class 100,000). For all industries using cleanrooms, the ISO 14644-x series provides a more comprehensive family of standards than the standards of FS 209E.

The compounding area must be separate from the general pharmacy with a controlled (particle count, temperature, humidity and air changes) environment.

**Cleanroom Layout**

The cleanroom environment is designed to have the primary work environment (for example, laminar airflow workstations, biological safety cabinets, or isolators) 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 cleanroom attire.

The buffer room must be cleaner than the anteroom to reduce the risk of air particles being blown, dragged, or introduced into the clean room environment. The buffer area or clean area in which workbenches are located must provide at least ISO Class 8 air quality.

Access to the buffer area should be restricted to minimize contamination, while allowing the delivery of essential materials for CSPs. Supplies are uncartoned and disinfected in the anteroom area, which is physically isolated from the buffer area.

Air turbulence within the cleanroom is influenced by the location of supply and return configurations, foot traffic and the location of process equipment such as LAFWs, BSCs, and barrier isolators. Non-unidirectional airflow can provide satisfactory contamination control for cleanliness levels of ISO 14644-1 Class 6 through 8.

**Supply Air**

Supply air is provided to the space through high-efficiency particulate air (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. This is why NIOSH requires that biological safety cabinets (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**

Pressure gradient is used to minimize particle migration into the clean space from a less clean space. This means the air pressure in the buffer zone space is higher than that of the ante area, so

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10. *FacilityCare Email Report*, May 24, 2005 a newsletter from FacilityCare magazine

11. IEST-RP-CC001.3, defines a HEPA filter as: “A thruway, extended-medium, dry-type filter in a rigid frame, having the minimum particle collection efficiency of 99.97% (that is a maximum particle penetration of 0.03%) for 0.3 microns particles in diameter”.


13. ASHRAE Handbook 2003, Chapter 16 Clean Spaces
air is said to *cascade* or flow from the cleanest area into the dirtier area.

Typically, the pressure differentials between two adjoining areas (Class 10,000 area to Class 100,000 area) are +0.05 in. WC.

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Between areas of different classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO 14644-1</td>
<td>0.02 in. WC (5 Pa) through 0.08 in. WC (20 Pa)</td>
</tr>
<tr>
<td>FDA Aseptic Process Guide</td>
<td>0.04 in. WC (9.95 Pa) through 0.06 in. WC (14.93 Pa) Minimum of 0.05 in. WC (12.5 Pa) from aseptic processing room to unclassified space</td>
</tr>
</tbody>
</table>

To ensure minimum air changes, the room pressure may be maintained by static balancing the supply airflow volume to compensate for filter loading. Airflow tracking is the recommended method of controlling room differential pressure. The pressure differences are passively controlled, via proportional air volume balancing and room pressure relief dampers. Active control of differential pressure differences using actuated dampers is not recommended per ISPE Pharmaceutical Engineering Guide, Volume 3.¹⁴

**Low/Medium-Risk**—These applications use *Displacement Concept (low pressure differential, high airflow)* to maintain separation of clean-area from the *ante-area*. A demarcation line identifies the separation of the clean-area from the ante-area. The use of low-pressure differential and high airflow is difficult to measure since typical minimum air velocity is 40 fpm (0.2 mps)¹⁵.

**High-Risk**—These applications use *Pressure Differential Concept (high pressure differential, low airflow)* to maintain separation of clean-area from the *ante-area*. A wall must separate the clean-area from the ante-area (gown room). The ante room may have a demarcation line separating clean and supply cart area. The pressure differential between cleanroom cleanliness levels from 0.02 in. WC (5 Pa) through 0.08 in. WC (20 Pa) allows doors to be opened and prevents unintended cross-flows due to turbulence.

**Differential Pressure Monitoring**—To verify that the required level of pressure difference is maintained between the cleanroom, anteroom and corridor, visual indication of the direction of airflow is recommended at the entry to the anteroom and cleanroom. This allows the pressurization to be constantly monitored and provides visual indication of the direction of airflow to the healthcare workers. It lets them know that the required room pressurization is being maintained and also warns them of any loss of the required differential pressure. A momentary loss in differential pressure occurs as the door is opened, and then closed. Therefore, differential pressure alarms 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 differential pressure.

**Temperature and Humidity**

Maintain the temperature in the compounding pharmacy from 68°F through 75°F (20°C through 24°C) with relative humidity from 40% through 60%.¹⁶

Pharmacy compounding personnel are required to wear garments to reduce the generation of airborne contaminants. Where full-coverage garments are used, cleanroom temperatures of 68°F or less may be required to provide occupant comfort.

**Air Changes**

Air changes are the biggest single factor that affects cleanroom sizing, building configuration and energy costs. Recent articles in the ASHRAE Journal and Cleanroom Magazine have identified air changes for various cleanroom classes based on common practice. FDA Guidelines identifies 20 air changes per hour as being acceptable for ISO Class 8 (100,000). Other sources recommend 40 to 60 air changes per hour for ISO Class 8. The amount of air changes is dictated by the internal generation of particles from operators and building elements such as walls, ceiling, floor, etc.

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The most effective way to control cleanroom quality is to minimize the internal generation and to supply HEPA filtered air to limit actual particle counts under the ISO standard-specified limit\(^{17}\).

**Recovery Time**—Another consideration in designing the cleanroom HVAC system is the recovery time. Recovery time is the amount of time it takes the cleanroom to recover from a change in ISO classes. For example, it takes approximately 5 minutes for an ISO Class 7 room to recover from shutdown condition of ISO Class 8 (100,000) to an operational 10,000 level (ISO Class 7), using 30 air changes per hour\(^{18}\).

**Monitoring and Alarms**—ISPE guidelines state that, *critical parameters* that can affect CSP quality are required to remain within process limits and should have alerts and alarms. The following critical room conditions should be monitored to document cleanroom environmental conditions: Room Temperature, Room Humidity, Room Differential Pressure, and Particle Count (optional).

Audible and visual indication of cleanroom alarms should be provided for healthcare workers, as well as recording the time of alarm. Integration of HVAC controls into the building automation system (BAS) allows historical data, alarms and alarm acknowledgement to be collected and archived to document compliance with JCAHO Environment of Care, 2004 performance elements:

- EC 9.10: Organization monitors conditions in the environment.

**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\(^{19}\).

- Consult with the facility engineer before the 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 as high as practical and, therefore, most typically 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 ft (7.62 m) 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 ft (3.05 m).

**Cleanroom Design Considerations**

The following list describes important design criteria for cleanrooms\(^{20}\):

- Walls, floors, ceilings, fixtures, shelving, counters, and cabinets should be constructed so that the surfaces are accessible for cleaning.
- 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 minimize spaces where microorganisms and other contaminants may 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.
- Ceilings with inlaid panels should be impregnated with a polymer to render them impervious and hydrophobic. They should be caulked around each perimeter to seal them to the frame.
- Ceilings may be panels locked together and sealed or be made of epoxy-coated gypsum board.
- Floors should be overlaid with wide sheet vinyl flooring with heat-welded seams and coving to the sidewall.
- Avoid dust-collecting overhangs, such as ceiling utility pipes, or ledges, such as windowsills.
- Exterior lens of ceiling light fixtures should be smooth, mounted flush, and sealed.

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18. Ibid
• 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 buffer area. Faucet handles should be designed to be hands-free.
• The ventilation system used to support the hospital pharmacy CSP cleanroom should be on the essential electrical system since the loss of ventilation will have direct impact on CSP quality. The loss of electrical service to the CSP environment will cause loss of room pressurization and disrupt the operation of ventilated cabinets (BSCs, LAFWs, and isolators).

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 (MBtus) to be able to meet the cooling requirements for the cleanroom?
• Does the air handler serving the pharmacy have enough static pressure to meet the static pressure to requirements of the HEPA filtered diffusers diffusers?
• Can the HVAC terminal equipment be located in an area adjacent to the pharmacy to facilitate good maintenance practices?
• How does ICRA impact the type of HVAC system?

Construction and Renovation Procedures

Healthcare facilities are almost continually undergoing some construction, either for expansion or facility upgrades. Construction activities can pose a significant challenge to maintaining the proper level of infection control in existing, functioning parts of the facility. The following recommended measures minimize the adverse affects of construction activities:

• Establish a multidisciplinary team that includes architect, contractor, consultant(s) and infection control personnel to plan the necessary preventive measures during demolition, construction, or renovation activities. The Infection Control Risk Assessment (ICRA) will determine the location and construction of construction barriers to prevent dust from construction areas from entering any part of the facility. In addition, construction areas must be maintained at a negative pressure relative to the adjoining part of the facility.
• Educate the project design firms (architects and engineers) on the special needs of the ICRA to prevent airborne infection due to construction. These requirements must then be properly documented and added to or referred to by the project documents and contract documents (plans, specifications, instructions to bidders, etc.). This is necessary to ensure that during the negotiation or bidding process, contractors can include these measures in their cost estimates and in establishing their construction schedule. In addition, including these requirements in the contract documents, or referring to them, will ensure that they can be enforced.
• During construction, it is important to monitor the integrity of the construction barriers and to ensure proper directional airflow. Establish and maintain a surveillance program for airborne particulate. That particulate may include mold spores, bacteria, microbes, etc.) within the active part of the facility during construction to ensure the health and safety of immunocompromised patients and continued maintenance of indoor air quality goals.
• During the entire construction period, ensure that signs and other provisions remain in place to direct persons away from the construction zone and minimize the dispersion of dust and contaminants. When construction personnel require access to the interior of the existing facility, entrances and elevators should be designated specifically for those workers. When the work mainly involves an area within the interior of an existing facility, separate washrooms and break areas should also be designated for the workers and, when practical, these areas should be separated from the other parts of the facility by adequate barriers.

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21. Immune suppressed patients are particularly susceptible to infections caused by airborne mold spores, particularly Aspergillus (which is often fatal and tends to multiply rapidly in the high moisture situations as associated with new masonry and rainwater penetration in areas without finished roofs).