STANDARDS FOR COMPOUNDING PHARMACIES

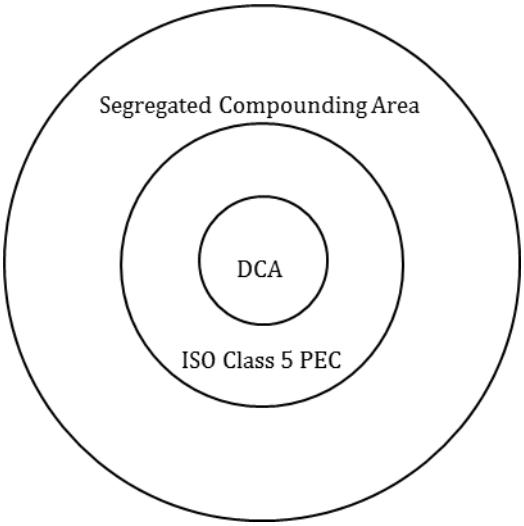
APPLICATION NOTE LC-139 (US)

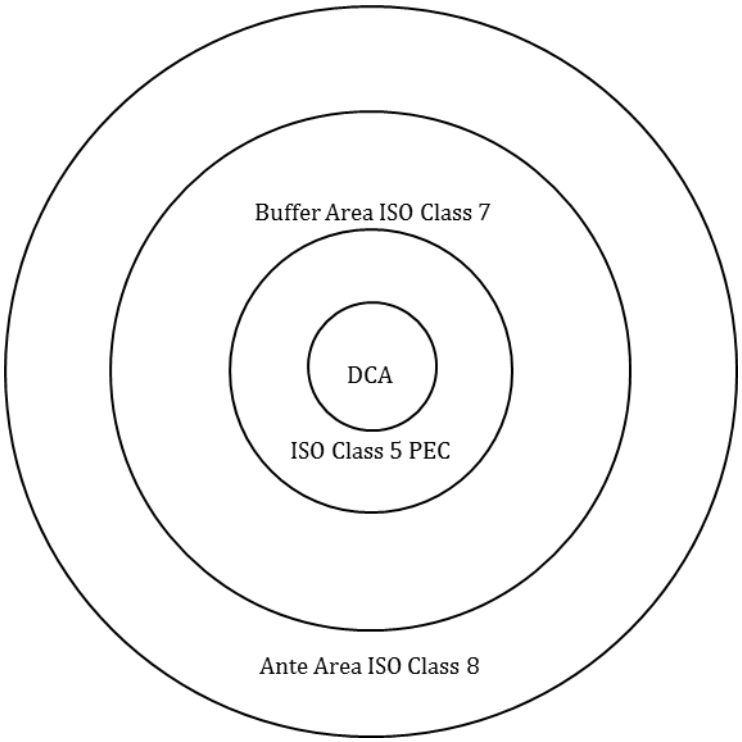
Introduction

This publication provides excerpts from some of the many guidelines and standards that pertain to compounding pharmacies. The intent of the publication is to provide owners, engineers, and consultants an overview of the standards and guidelines that pertain to the design and operation of compounding pharmacies.

This document is arranged by topic. Effort has been made to present the statements that best summarize the documents as they pertain to contamination levels and testing.

The excerpts in most cases are worded as they appear in the standard or guideline, though in some instances may be out of context. Please review the actual guideline or standard for more detailed information and to make the best interpretation of each statement.

Topic	Standard
Architectural Layout	**USP: Guidebook to Pharmaceutical Compounding: Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention, 2008. Print.**  **Figure 1.** Conceptual representation of the placement of an ISO Class 5 PEC in a segregated compounding area used for low-risk level CSP{s with a 12-hour or less BUD.

Topic	Standard
Architectural Layout *(continued)*	**USP: Guidebook to Pharmaceutical Compounding: Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention, 2008. Print.**  **Figure 2.** Conceptual representation of the arrangement of a facility for preparation of CSPs categorized as low-, medium-, and high-risk level.
	USP: Guidebook to Pharmaceutical Compounding: Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention, 2008. Print. *Facility Design and Environmental Controls* …The CSP work environment is designed to have the cleanest work surfaces (PEC) located in a buffer area…
Primary Engineering Control Locations	**USP: Guidebook to Pharmaceutical Compounding: Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention, 2008. Print.** *Placement of Primary Engineering Controls* PECs (LAFWs, BSCs, CAIs, and CACIs) shall be located with a restricted access ISO Class 7 … buffer area, … with the following CAI/CACI exceptions below: • Presterilization procedures for high risk-level CSPs such as weighing and mixing, shall be completed in no worse than an ISO Class 8 … environment. • PECs shall be located out of traffic patterns and away from room air currents that could disrupt the intended airflow patterns…

Topic	Standard
Primary Engineering Control Locations *(continued)*	CAIs and CACIs shall be placed in an ISO Class 7 … buffer area *unless* they meet all of the following conditions: • The isolator shall … meet ISO Class 5 … during dynamic operating conditions, including transferring ingredients, components, and devices into and out of the isolator and during preparation of CSPs. • Particle counts sampled approximately 6 to 12 inches upstream of the critical exposure site shall maintain ISO Class 5 … levels during compounding operations. • Not more than 3520 particles (0.5 μm and larger) per m^3 shall be counted during material transfer, with the particle counter probe located as near to the transfer door as possible without obstructing the transfer.
Compounding Hazardous Drugs —Storage	**USP: Guidebook to Pharmaceutical Compounding: Hazardous Drugs. Rockville, MD: United States Pharmacopeia Convention, 2015. Print.** *5. Facilities* 5.2 Storage …HDs *[Hazardous Drugs]* must be stored in a negative-pressure room with at least 12 air changes per hour (ACPH)… … Depending upon facility design, HDs may be stored within a negative pressure buffer room with at least 12 ACPH. However, only HDs used for sterile compounding may be stored in the negative pressure buffer room. Refrigerated antineoplastic HDs must be stored in a dedicated refrigerator in a negative pressure area with at least 12 ACPH…
Compounding Hazardous Drugs —Compounding	**USP: Guidebook to Pharmaceutical Compounding: Hazardous Drugs. Rockville, MD: United States Pharmacopeia Convention, 2015. Print.** *5. Facilities* 5.2 Storage …Sterile and nonsterile HDs must be compounded within a C-PEC located in a C-SEC. The C-SEC used for sterile and nonsterile compounding must: • Be externally ventilated through high-efficiency particulate air (HEPA) filtration • Be physically separated (i.e., a different room from other preparation areas)…

Topic	Standard
Room Pressure Differential	**USP: Guidebook to Pharmaceutical Compounding: Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention, 2008. Print.** *Facility Design and Environmental Controls* The *(buffer)* room shall be segregated from surrounding unclassified spaces to reduce the risk of contaminants being blown, dragged, or otherwise introduced…. For rooms providing a physical separation … a minimum differential positive pressure of 0.02 to 0.05 inch water column is required.
	USP: Guidebook to Pharmaceutical Compounding: Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention, 2008. Print. *Room Pressure Differential Monitoring* …The pressure between the ISO Class 7 … and the general pharmacy area shall not be less than 5 Pa (0.02 inch water column)…
	USP: Guidebook to Pharmaceutical Compounding: Hazardous Drugs. Rockville, MD: United States Pharmacopeia Convention, 2015. Print. *5. Facilities* 5.2 Storage …Sterile and nonsterile HDs must be compounded within a C-PEC located in a C-SEC. The C-SEC used for sterile and nonsterile compounding must: • …Have a negative pressure between 0.01 and 0.03 inches of water column
Displacement Airflow	**USP: Guidebook to Pharmaceutical Compounding: Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention, 2008. Print.** *Facility Design and Environmental Controls* …For buffer areas not physically separated from ante-areas, the principle of displacement airflow shall be employed. This concept utilizes a low pressure differential, high airflow principle. Using displacement airflow typically requires an air velocity of 40 ft per minute or more from the buffer area across the line of demarcation into the ante-area…
	USP: Guidebook to Pharmaceutical Compounding: Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention, 2008. Print. *Room Pressure Differential Monitoring* ...In facilities where low- and medium-risk level CSPs are prepared, differential airflow shall maintain a minimum velocity of 0.2 meters per second (40 feet per minute) between buffer area and ante area…

Topic	Standard
Displacement Airflow ***(****continued)*	**USP: Guidebook to Pharmaceutical Compounding: Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention, 2008. Print.** *Facility Design and Environmental Controls* **…The displacement concept shall not be used for high-risk compounding…**
Environmental Conditions	**USP: Guidebook to Pharmaceutical Compounding: Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention, 2008. Print.** *Facility Design and Environmental Controls* …Compounding facilities … shall provide a comfortable … working environment, which typically includes a temperature of 20° or cooler… …Room air exchanges are typically expressed as ACHPHs. Adequate HEPA-filtered airflow supplied to the buffer area and ante-area is required to maintain cleanliness classification during operational activity through the number of ACPHs. Factors that should be considered when determining air-change requirements include number of personnel working in the room and compounding processes, as well as temperature effects. An ISO Class 7 … buffer area and ante-area supplied with HEPA-filtered air shall receive an ACPH of not less than 30… …If the area has an ISO Class 5 … recirculating device, a minimum of 15 ACPHs through the area supply HEPA filters is adequate, providing the combined ACPH is not less than 30… …More air changes may be required, depending on the number of personnel and processes…
Exposure of Critical Sites	**USP: Guidebook to Pharmaceutical Compounding: Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention, 2008. Print.** *Environmental Quality and Control* Maintaining the sterility and cleanliness … of critical sites is a primary safeguard for CSPs…The risk of, or potential for, critical sites to be contaminated with microorganisms and foreign matter increases with increasing exposed area of the critical sites, the density of concentration of contaminants, and exposure duration to worse than ISO Class 5 … air… Protection of critical sites by precluding physical contact and airborne contamination shall be given the highest priority in sterile compounding practice. Airborne contaminants, especially those generated by sterile compounding personnel, are much more likely to reach critical sites than are contaminants that are adhering to the floor or other surfaces below work level. Furthermore, large and high-density particles that are generated and introduced by compounding manipulations and personnel have the potential to settle on critical sites even when those critical sites are exposed within ISO Class 5 … air.

Topic	Standard
Particle Concentration Limits	**USP: Guidebook to Pharmaceutical Compounding: Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention, 2008. Print.** *Facility Design and Environmental Controls* …PECs shall maintain ISO Class 5 … or better conditions for 0.5-μm particles (dynamic operating conditions) while compounding CSPs… …Buffer areas are designed to maintain at last ISO Class 7 … conditions for 0.5-μm particles under dynamic conditions and ISO Class 8 … conditions for 0.5-μm and larger particles under dynamic conditions for the ante-areas.
Testing Primary Engineering Controls	**USP: Guidebook to Pharmaceutical Compounding: Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention, 2008. Print.** *Placement of Primary Engineering Controls* …When isolators are used for sterile compounding, the recovery time to achieve ISO Class 5 … air quality shall be documented and internal procedures developed to ensure that adequate recovery time is allowed after material transfer before and during compounding operations.
Environmental Sampling —Program	**USP: Guidebook to Pharmaceutical Compounding: Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention, 2008. Print.** *Viable and Nonviable Environmental Sampling (ES) Testing* The ES program should … demonstrate that the PEC is maintaining an environment within the compounding area that consistently ensures acceptable low viable and nonviable particle levels. The compounding area includes the ISO Class 5 PEC …, buffer areas, ante-areas and segregated compounding areas.
Environmental Sampling —Test Frequency	**USP: Guidebook to Pharmaceutical Compounding: Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention, 2008. Print.** *Viable and Nonviable Environmental Sampling (ES) Testing* Environmental sampling shall occur as part a comprehensive quality management program and shall occur minimally under any of the following conditions: • As part of the commissioning and certification of new facilities and equipment. • Following any servicing of facilities and equipment • As part of the re-certification of facilities and equipment (i.e., every 6 months) • In response to identified problems with end products or staff technique • In response to issues with CSPs, observed compounding personnel work practices, or patient-related infections (where the CSP is being considered as a potential source of the infection).

Topic	Standard
Environmental Sampling —Test Frequency *(continued)*	**USP: Guidebook to Pharmaceutical Compounding: Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention, 2008. Print.** *Viable and Nonviable Environmental Sampling (ES) Testing* Engineering Control Performance Verification PECs … are essential components of the overall contamination control strategy for aseptic processing …Certification … shall be performed … no less than every 6 months and whenever the device or room is relocated or altered or major service to the facility is performed.
	USP: Guidebook to Pharmaceutical Compounding: Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention, 2008. Print. *Viable and Nonviable Environmental Sampling (ES) Testing* Total Particle Counts Certification that each ISO classified area, for example, ISO 5, 7, and 8, is within established guidelines shall be performed no less than every 6 months and whenever the LAFW, BSC, CAI, or CACI is relocated or the physical structure of the buffer area or ante area has been altered…
Room Pressure Differential Monitoring	**USP: Guidebook to Pharmaceutical Compounding: Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention, 2008. Print.** *Facility Design and Environmental Controls* T The *(buffer)* room shall be segregated from surrounding unclassified spaces to reduce the risk of contaminants being blown, dragged, or otherwise introduced… and this segregation shall be continuously monitored *Room Pressure Differential Monitoring* … A pressure gauge or velocity meter shall be installed to monitor the pressure differential or airflow between the buffer area and the ante area and between the ante area and the general environment outside the compounding area. The results shall be reviewed and documented on a log at least every work shift … or by a continuous recording device.
HEPA Filter Testing	**USP: Guidebook to Pharmaceutical Compounding: Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention, 2008. Print.** *Facility Design and Environmental Control* ... All HEPA filters should be efficiency tested using the most penetrating particle size and should be leak tested at the factory and then leak tested again in situ after installation…

<table>
<tr><th>Topic</th><th>Standard</th></tr>
<tr><td>Compounding Hazardous Drugs —Nonsterile Compounding</td><td>USP: Guidebook to Pharmaceutical Compounding: Hazardous Drugs. Rockville, MD: United States Pharmacopeia Convention, 2015. Print.
5. Facilities
5.3.1 Nonsterile Compounding
Table 2. Engineering Controls for Nonsterile HD Compounding
<table>
<tr><th>C-PEC</th><th>C-SEC</th></tr>
<tr><td>• Externally vented (preferred) or redundant-HEPA filtered in series</td><td>• 12 ACPH
• Externally vented
• Negative pressure between 0.01 and 0.03 inches of water column</td></tr>
</table></td></tr>
<tr><td>Compounding Hazardous Drugs —Sterile Compounding</td><td>USP: Guidebook to Pharmaceutical Compounding: Hazardous Drugs. Rockville, MD: United States Pharmacopeia Convention, 2015. Print.
5. Facilities
5.3.2 Sterile Compounding
Table 3. Engineering Controls for Nonsterile HD Compounding
<table>
<tr><th>Configuration</th><th>C-PEC</th><th>C-SEC</th></tr>
<tr><td>ISO Class 7 Buffer Room</td><td>• Externally Vented</td><td>• 30 ACPH
• Externally vented
• Negative pressure between 0.01 and 0.03 inches of water column</td></tr>
<tr><td>C-SCA</td><td>• Externally Vented</td><td>• 12 ACPH
• Externally vented
• Negative pressure between 0.01 and 0.03 inches of water column</td></tr>
</table></td></tr>
</table>

References

USP: Guidebook to Pharmaceutical Compounding: Hazardous Drugs. Rockville, MD: United States Pharmacopeia Convention, 2015. Print.

USP: Guidebook to Pharmaceutical Compounding: Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention, 2008. Print.

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