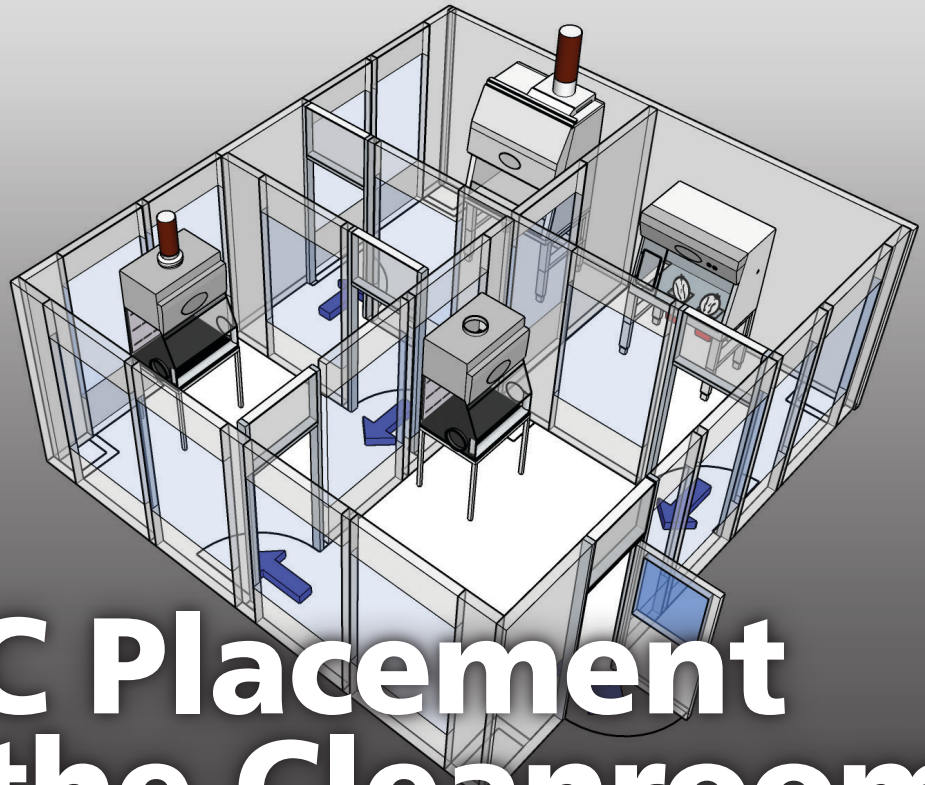
PART 2



PEC Placement in the Cleanroom

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Primary engineering controls (PECs) are an integral tool in hospital and compounding pharmacy cleanrooms. A compliant sterile cleanroom must be designed with consideration of the appropriate PEC per the guidelines in USP chapters <797> and <800>. USP <797> defines the *primary engineering control* as "A device or zone that provides an ISO Class 5 air quality environment for sterile compounding."[1] The two chapters, USP <797> and USP <800>,[2] define the types of PECs designated for use in nonhazardous and hazardous cleanrooms, but beyond that, the important task of determining proper placement of the PEC remains with pharmacy.

Choosing the Appropriate PEC

PECs for compounding in a cleanroom are available in many different models and serve various purposes, so each facility must choose the PEC that will best suit its needs. All PECs fall under the term *containment*, and when establishing the goals for the cleanroom, the main purpose of the facility's containment strategy must be defined. There are three strategies to choose from:

1. Product protection
2. Personnel and environmental protection
3. Product, personnel, and environmental protection

Product protection is an important focus of USP <797> in guaranteeing product quality and sterility for patient safety through aseptic technique.[1] The PEC's role in this process is to provide positively pressured, HEPA-filtered ISO Class 5 first air over the compounded sterile preparation (CSP) in the direct compounding area. PECs utilized for product protection also typically recirculate HEPA filtered air back into the secondary engineering control (SEC), which comprises the anteroom and buffer room of the cleanroom suite. Examples of PECs for product protection include laminar airflow workbenches (LAFWs), either vertical or horizontal models; and containment aseptic isolators (CAIs).

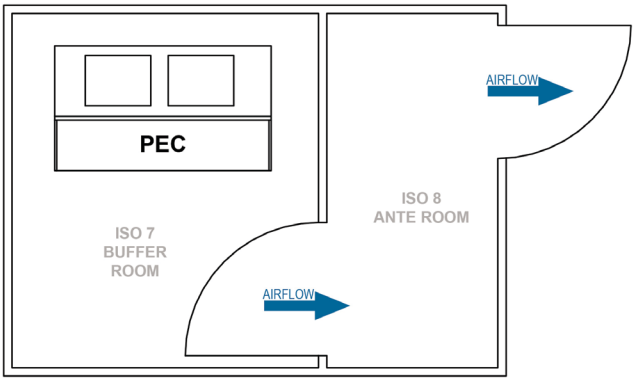
Personnel protection focuses on protecting the PEC user and environment against exposure to the drug during the compounding process. PECs serving this purpose pull a negative pressure through the face opening, sweeping across the work surface as one-pass air, and usually exhaust through a HEPA filter, which either recirculates into the SEC or is connected externally to an exhaust blower that pulls the air out of the facility. It is important to understand that these PEC types do not provide any level of product protection, so they are not permitted for final preparation of CSPs. These

Part 1, Design Tips for Creating a USP <800> Compliant Cleanroom, ran previously and can be accessed at **pppmag.com/white_papers**.

PEC Placement in the Cleanroom

FIGURE 1

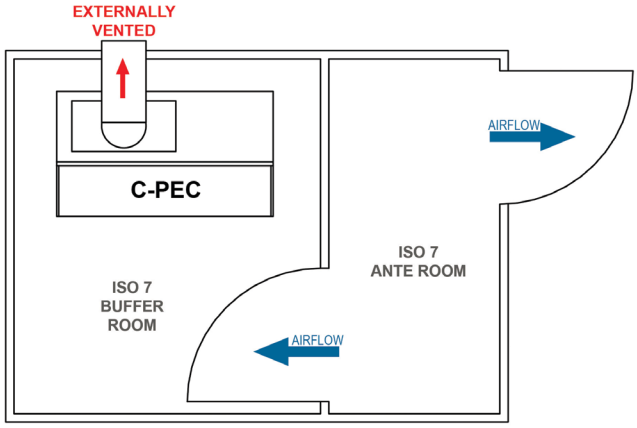
Example of a Two-Room Positive Pressure Cleanroom for Nonhazardous Compounding



Common PEC Types:
1. Laminar Airflow Workbench: Horizontal or Vertical
2. Compounding Aseptic Isolator
3. Biological Safety Cabinets - Class II

FIGURE 2

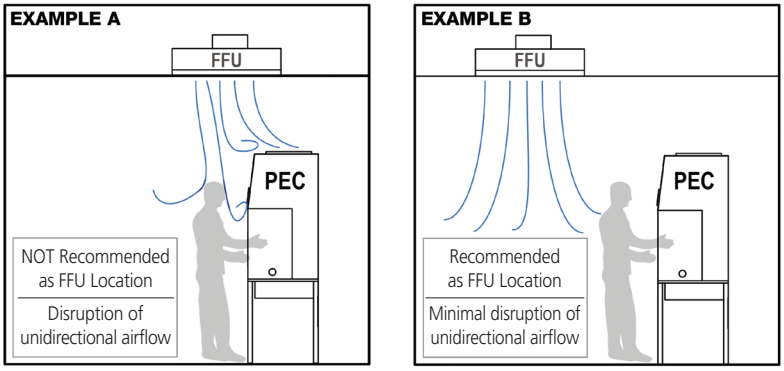
Example of a Two-Room Negative Pressure Cleanroom for Hazardous Compounding



Common PEC Types:
1. Biological Safety Cabinet - Class II (A2, B1, B2)
2. Compounding Aseptic Containment Isolator

FIGURE 3

Examples of Fan Filter Unit (FFU) Ceiling Locations in the Cleanroom



PECs can be used during nonsterile presterilization processes such as weighing active pharmaceutical ingredients (APIs) and tablet crushing, according to both USP <797> and <800>.[1,2] Examples of PECs for personnel protection include: Class-I biological safety cabinets (BSCs) and containment ventilated enclosures (CVEs).

Product, personnel, and environmental protection accomplishes all of the goals mentioned previously and is referred to as a *containment primary engineering control* (C-PEC), as defined in USP <800> in section 5.3.2, Sterile Compounding.[2] Like the previously mentioned PEC, the C-PEC provides a HEPA filtered ISO Class 5 air quality for the CSPs being reconstituted or compounded. The negatively pressured C-PEC provides a barrier with appropriate airflow control that protects the user and environment from harmful exposure to hazardous drugs (HDs). Examples include: BSCs (Class II, Types A2, B1, and B2) and compounding aseptic containment isolators (CACIs).[2]

Sterile Nonhazardous PEC Placement

In the framework of choosing PECs for nonhazardous CSPs, USP <797> is referenced, with a primary focus on product protection. **FIGURE 1** shows a two-room, positively pressured cleanroom for compounding nonhazardous CSPs.

So important is the issue of PECs in sterile compounding that USP <797> references PECs over 100 times in the 37-page chapter. The most granular purpose for PECs appears in section 4.2, Facility Design and Environmental Controls, with key statements such as:

The PEC must be located in the buffer room of the cleanroom suite or the SCA in a manner that minimizes conditions that could increase the risk of microbial contamination. For example, strong air currents from opened doors, personnel traffic, or air streams from the HVAC system(s) can disrupt the unidirectional airflow of an open-faced PEC such as a laminar airflow workbench (LAFW).[1]

Sterile Hazardous PEC Placement

FIGURE 2 shows an example of a two-room, negatively pressured cleanroom for compounding hazardous CSPs. USP <800> defines the C-PEC as "a ventilated device designed and operated to minimize worker and environmental exposures to HDs by controlling emissions of airborne contaminants…"[2] which encompasses both sterile HD

and nonsterile HD PECs. Further into the chapter, the C-PEC is described for sterile HD compounding as "…an ISO Class 5 or better air quality, such as a Class II or III BSC or CACI. Class II BSC types A2, B1, or B2 are acceptable. For most known HDs, type A2 cabinets offer a simple and reliable integration with the ventilation and pressurization requirements of the C-SEC. Class II Type B2 BSCs are typically reserved for use with volatile components."[2]

PEC Placement

No two cleanroom suites are designed alike. Effective PEC placement will differ for sterile nonhazardous compounding versus sterile hazardous compounding, for example. Further, some cleanrooms may have space constraints, presenting challenges for placing PECs, fan filter units (FFUs), lights, carts, and other equipment to support optimal performance. Conversely, some cleanrooms are quite spacious and allow for multiple PECs and multiple users, with increased foot and cart traffic in these controlled spaces. In any situation, the placement of the PECs inside the cleanroom (and all compounding areas) must accommodate workflow design considerations in an effort to optimize performance, product protection, and personnel protection.

A key consideration for PEC placement and workflow design is ensuring that the face opening of the PECs be protected from unnecessary cross drafts from staff, processes, doors, and sheer from ceiling FFUs. As infinite design variations exist, an underlying rule is that traffic and door activity should be kept to a minimum in controlled environments, especially while active compounding is occurring in front of a PEC or C-PEC.

FIGURE 3 demonstrates strategies for FFU placement in the cleanroom, depicting what is ***not*** recommended (Example A) and what is recommended (Example B). The downward airflow from the FFU creates sheer directly over the PEC's face opening, which causes disruption of unidirectional airflow for both the PEC and FFU. The FFU location shown in Example A, directly over the PEC, is not recommended because unnecessary turbulence could occur in the direct compounding area, which in turn, negatively influences the ISO 5 first air. Example B shows the recommended alternative ceiling placement, which allows both the FFU and PEC to function as engineered.

An excellent tool for determining the effectiveness of the cleanroom layout is the results of the dynamic airflow smoke pattern tests conducted in both the C-PEC and the SEC; these results should be included in your certification report. USP <797> states that "a dynamic airflow smoke pattern test must be performed in the PEC initially and at least every 6 months to ensure that 1) the pharmaceutical isolator is properly placed into the facility and 2) compounders understand how to utilize the unidirectional airflow to maintain first air in the DCA."[1] Dynamic airflow is not reflected by the certifier mimicking movement in the cleanroom while performing the smoke studies. Rather, dynamic airflow testing should be performed with real users/technicians under actual (and ideally, the most strenuous) working conditions.

The PEC and the Compliant Cleanroom

To assist with visualizing a compliant cleanroom, **FIGURE 4** shows one example of the many combination options for placement of PECs and C-PECs in the SEC cleanroom suite. In this design, the ISO 8 anteroom also serves as a preparation space for the sterile nonhazardous compounding process. This is a recommended setup wherein a Class-I BSC or CVE is required for weighing or otherwise manipulating nonhazardous APIs before introducing them into the ISO 5 PEC located inside the ISO 7 SEC for final sterilization processes. This combined anteroom and preparation space requires air quality of ISO 8 or better, per USP <797>.[1] This anteroom is a positively pressured space to the outside unclassified areas of the facility, as reflected in the blue arrows, signifying airflow pressure mapping.

The ISO 7 sterile nonhazardous buffer room is positively pressured to the anteroom since it is not acceptable to introduce lesser quality air (eg, ISO 8 or unclassified) into an ISO 7 buffer room. The PEC in this room is drawn as a compounding aseptic isolator (CAI) (ie, a positively pressured glovebox). The CAI will recirculate HEPA filtered air back into the room as connection to an external exhaust is not required. The CAI could also be replaced with an LAFW (horizontal or vertical airflow), or a recirculating BSC.[1] The user's choice of PEC is oftentimes a matter of personal preference or may be defined in the facility's SOPs as acceptable for the task. USP <797>'s Table 3, Summary of Minimum Requirements for Placement of PEC for Compounding Non-HD CSPs, defines acceptable PEC types and placement.

The positively pressured ISO 8 anteroom also allows access into the negatively pressured ISO 8 hazardous anteroom. Both the nonhazardous and the hazardous anterooms must be rated with ISO 8 air quality because the two rooms share air. The negatively pressured HD prep room is necessary for compounding facilities that weigh or manipulate hazardous nonsterile APIs before final sterilization in the ISO 7 hazardous buffer room; USP <800> does not explicitly state guidance on presterilization weighing, so it can be deduced that the HD APIs must be handled in a negatively pressured room

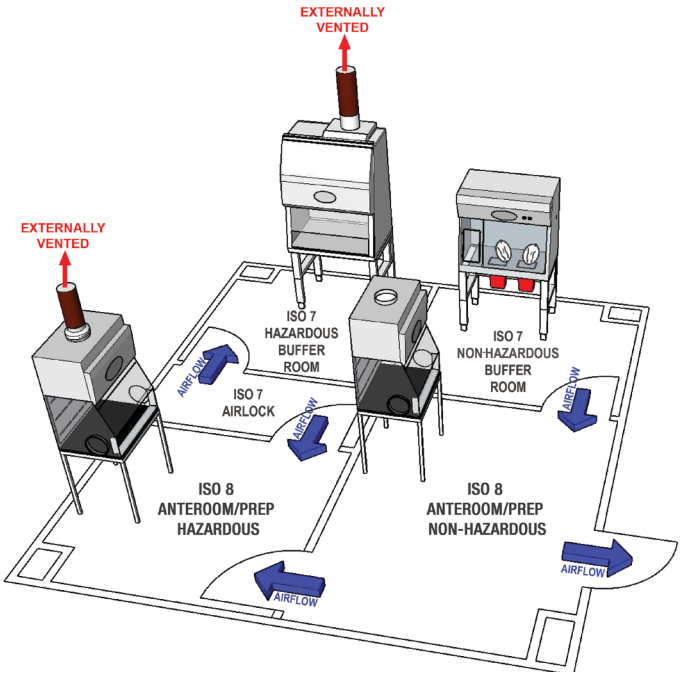
SIDEBAR

What is "Externally Vented," per USP <800>?

Accomplishing compliance with USP <800> may seem overwhelming for facilities handling HDs, because "all C-PECs used for manipulation of sterile HDs must be externally vented."[2] To achieve this engineering standard, external exhaust connections from the C-PEC must be routed outside of the facility as noted with the red arrow in **FIGURE 2**.

FIGURE 4

Example of a Cleanroom Suite for Both Non-Hazardous and Hazardous Compounding



This is one example of the many combination options for placement of PECs and C-PECs in the SEC cleanroom suite.

under minimum standards of ISO 8 air quality as defined by USP <797>. The C-PEC in this room contributes to the C-SEC's negative pressure because it is externally vented, as represented by the red arrows in **FIGURE 4**.

Just like the ISO 8 hazardous anteroom, the ISO 7 hazardous buffer room also is required to be under negative pressure, per USP <800>.[2] The C-PEC in the ISO 7 buffer room is drawn as a BSC, either an A2 or B2 cabinet. The externally vented BSC will contribute to the hazardous buffer room's negative pressure. An A2 or B2 BSC produces a significantly different percentage of exhaust air (expressed in cubic feet per minute [CFM]). A BSC A2 type cabinet typically recirculates around 70% internally and exhausts the other 30% via a canopy connection. This type of BSC facilitates less externally exhausted CFM out of the facility, resulting in a lower energy cost. The B2 cabinet does not recirculate air inside the cabinet, meaning it is a fully exhausted one-pass air system; it can exhaust sometimes up to twice as much CFM as the A2, which creates increased energy cost and consumption. For facilities handling volatile HDs, the B2 cabinet is the recommended C-PEC choice. For further guidance on choosing the appropriate C-PEC for HD compounding, see Appendix 3 in USP <800>.[2]

Not common to most cleanroom suite designs, **FIGURE 4** includes an ISO 7 airlock that breaks up the airflow before entering the ISO 7 hazardous buffer room from the ISO 8 HD anteroom. It is important to understand that if the airlock did not exist in this scenario, then the entire five-room suite would have to be rated as an ISO 7, because all of the rooms share the same air quality.

The overall engineering principle of the airlock room is outside the scope of this paper because its functionality to regulate air pressure gradients between rooms has no direct effect on the PECs or C-PECs. However, the airlock room offers a beneficial utility, especially for facilities working on the design of a multiroom cleanroom suite: when a cleanroom suite has multiple negative pressure rooms, cascading pressure from one negative room into another negative room can prove problematic, especially with the strict design parameters as defined in USP <800>. From an engineering perspective, the airlock room serves as a necessary positive pressure break between the multiple negative pressure rooms, and, as previously mentioned, keeps the entire cleanroom suite from being ISO 7 rated.

Proper PEC Use

As a final point, the importance of proper use and aseptic practices associated with PECs cannot be overemphasized. USP <797> and USP <800> state that personnel engaging in compounding must demonstrate competency annually in various aspects of their job roles.[1,2] User interaction within an ISO 5 PEC should be part of the competency assessment list in order to ensure aseptic technique while compounding CSPs. While reconstituting, compounding, cleaning, or performing any other sterile operations inside of the PEC, the user should operate with controlled and intentional movements so as not to disrupt the unidirectional ISO 5 airflow over the critical site. Staff members should not breach containment by removing their gloved hands from the front face of the PEC or C-PEC during these CSP operations. Product protection, personnel protection, and environmental protection can only be achieved through proper use of the PEC. It is of the utmost importance that consistent training and competency assessments of aseptic technique be established by the facility's designated person.

References

1. USP General Chapter <797>. Pharmaceutical Compounding – Sterile Preparations. Second Supplement to *United States Pharmacopeia and National Formulary* (USP 42-NF37). June 3, 2019. www.usp.org/compounding/general-chapter-797. Accessed June 19, 2020.
2. USP General Chapter <800>. Hazardous Drugs – Handling in Healthcare Settings. www.usp.org/compounding/general-chapter-hazardous-drugs-handling-healthcare. Accessed June 19, 2020.