Engineering Controls

USP <800> Requirements for Engineering Controls

The risks to health care workers handling hazardous drugs (HDs) under non-USP compliant conditions are often underappreciated. NIOSH’s landmark 2004 alert underscored the importance of preventing occupational exposure to HDs and played a key role in the development of USP Chapter <800> Hazardous Drugs—Handling in Healthcare Settings. This new chapter provides a framework of 18 sections that guide HD compounding practices to ensure the safety not only of patients, but also of the health care workers who prepare and administer these products.

A keen understanding of compounding personnel responsibilities is not sufficient to ensure safe HD preparation. Rather, pharmacy must develop expertise in facility design and engineering controls that encompasses the dynamics of airflow and air quality. Specifically, a comprehensive understanding of USP <800> requirements for engineering controls is critical to safe HD compounding. Nevertheless, it is important to note that USP chapters describe the minimal requirements for compounding, and are not intended to be all-inclusive; other references, including peer-reviewed literature, must be considered when developing a comprehensive HD safety program.

Until the advent of USP <797> and the 2004 NIOSH alert, information describing the engineering controls required for sterile compounding was not included in most didactic educational programs for pharmacists. USP <800> was developed to provide guidance pertaining to the proper engineering controls for safely handling and preparing HDs. Specific engineering controls detailed in USP <800> include:

- Primary Engineering Controls (PECs): The Hoods
- Secondary Engineering Controls (SECs): The Room
- Supplemental Engineering Controls: The Tools

The Hoods

Some PECs, such as laminar airflow cabinets, simply facilitate product protection, while others, such as containment primary engineering controls (C-PECs), are designed to use ventilation to protect the product, the operator, and the environment. C-PECs include biological safety cabinets (BSCs) and compounding aseptic containment isolators (CACIs), which are designed to ensure safe HD compounding. These systems mitigate exposure to HDs while protecting the product by integrating the required air management systems and controls, ISO 5 compounding environment, containment/enclosure, and HEPA filtration and specialized exhaust systems designed for the attributes of the HDs, such as vaporization, spills, and sprays. C-PECs required for compounding HDs are broadly classified into ducted cabinets, such as BSCs and CACIs.

It is critical to note that horizontal laminar flow hoods/laminar airflow workbenches (LAFWs) and containment aseptic isolators (CAIs) must never be used for compounding HDs due to their lack of safety controls necessary for operator protection.

Considerations for Choosing C-PECs

USP <800> does not specify whether to use a BSC or a CACI for compounding HDs. Many conditions for use are identical for both devices, including personal protective equipment (PPE) garbing, the recommended facility design, air quality requirements, negative pressure requirement, use of a closed system drug-transfer device (CSTD), cleaning protocols, and USP <797> beyond-use dating (BUD). Considerations when choosing a PEC include:

- Costs: Measure device acquisition cost, maintenance, power, and specialized supplies for the PEC (ie, sleeves for CACIs)
- Methods for product ingress into the workspace and preparation egress into the SEC
- Ergonomics for low-volume compounding (eg, <10 doses per week) and high-volume compounding (eg, >100 doses per day)
- Ease of batching multiple doses
- Ease of certification
- Cost of certification
- Product labeling requirements
- Cleaning needs

The PEC should be constructed with materials that can withstand multiple cleanings with harsh chemicals (ie, stainless steel, high-grade plastics) and yet maintain protective integrity under constant pressure.

SIDEBAR 1
Contamination in the Plenum

The plenum represents a separate space between the PEC and a building’s heating, ventilation, and air-conditioning (HVAC system), and usually is in the space between the structural ceiling and a drop-down ceiling. The plenum can be the interface into a common space where both ducts meet, or it can be hard ducting between the PEC and the building’s exhaust system. In either case, wherever HD compounding occurs, the ductwork and plenum should be considered contaminated with HD residue.

### TABLE 1

<table>
<thead>
<tr>
<th>Classification</th>
<th>Biosafety Level</th>
<th>Primary Protection Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>1, 2, 3</td>
<td>Personnel and Environmental</td>
</tr>
<tr>
<td>Class II</td>
<td>1, 2, 3</td>
<td>Product, Personnel, and Environmental</td>
</tr>
<tr>
<td>Class III</td>
<td>4</td>
<td>Product, Personnel, and Environmental through complete isolation.</td>
</tr>
</tbody>
</table>

Table modified from reference 6.
highly volatile, toxic HDs, including cyclophosphamide.

BSCs are designed to provide three types of protection: operator protection, product protection to avoid contamination, and environmental protection from contaminants contained within the cabinet (see TABLE 1 on page 16). 6

NSF International provides minimum standards for cabinet classifications and certification, as defined by NSF within NSF/ANSI 49-2008, Biosafety Cabinets: Design, Construction, Performance, and Field Certification. 7

Class II, Type B2 BSC (see FIGURE 2). A Class II, Type B2 BSC, which is open to the operator, requires proper use to deliver protection. Given the design of the movable front glass damper and the protective-airflow curtain, caution must be taken to not block the intake grills located in the front (next to the operator) and back of the BSC. Blocking these grills can create turbulence, which may lead to inadvertent exposure of the operator and the environment to HD vapors and/or particles. Class II BSCs have an inflow velocity of 100 ft/min, HEPA-filtered, vertical descending air, which is a portion of the mixed vertical descending and inflow air from a common exhaust plenum. Thus, Class II, Type A2 BSCs cannot be hard ducted to the building’s exhaust system and should inter-

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1. NSF International provides minimum standards for cabinet classifications and certification, as defined by NSF within NSF/ANSI 49-2008, Biosafety Cabinets: Design, Construction, Performance, and Field Certification.

2. Class II, Type A2 BSC (see FIGURE 1). A Class II, Type A2 BSC, which is open to the operator, requires proper use to deliver protection. Given the design of the movable front glass damper and the protective-airflow curtain, caution must be taken to not block the intake grills located in the front (next to the operator) and back of the BSC. Blocking these grills can create turbulence, which may lead to inadvertent exposure of the operator and the environment to HD vapors and/or particles. Class II BSCs have an inflow velocity of 100 ft/min, HEPA-filtered, vertical descending air, which is a portion of the mixed vertical descending and inflow air from a common exhaust plenum. Thus, Class II, Type A2 BSCs cannot be hard ducted to the building’s exhaust system and should inter-

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**FIGURE 1**

Class II, Type A2 BSC

(A) front opening; (B) sash; (C) exhaust HEPA filter; (D) supply HEPA filter; (E) positive pressure common plenum; (F) negative pressure plenum.


**FIGURE 2**

Class II, Type B2 BSC

(A) front opening; (B) sash; (C) exhaust HEPA filter; (D) supply HEPA filter; (E) negative pressure exhaust plenum.

Class III BSC

(A) glove ports; (B) sash; (C) exhaust HEPA filter; (D) supply HEPA filter; (E) double-ended autoclave or pass-through box.

Class II, Type B2 BSC (see FIGURE 2). A Class II, Type B2 BSC is open to the operator and has the same airflow characteristics as a Class II, Type A2 BSC. As such, operators must heed the same warnings to avoid blocking intake grills as discussed above to ensure the proper use of Class II, Type A2 BSCs. The primary differences between the two BSCs is that the B2 does not recirculate the potentially contaminated air within the workspace, and must be hard ducted to the building’s exhaust system. Refer to the manufacturer’s specifications for the correct ducting procedure. All ducts must be under negative pressure, and the cabinet ducting must be exhausted externally from the building and away from any fresh air intakes.

Class III BSC (see FIGURE 3). A Class III BSC, which is totally enclosed, is designed for work with infectious microbiological agents and for handling hazardous materials. This system is rarely used in pharmacy practice sites due to its expense, the costs of maintenance, and the complexity of use. All operations are performed through a glove system. Ingress and egress of materials occurs through a dunk tank or a double-door, pass-through box that can be cleaned. Operations and manipulations are observed through a fixed view window. The internal environment of the cabinet is maintained under negative pressure of at least 0.50 inches water gauge. Air from the environment is taken in through a HEPA filter. The cabinet space and 30% is exhausted. All air going through the ducts should be considered contaminated and must be under negative pressure. The cabinet ducts must be exhausted externally from the building and away from any fresh air intakes.

Attributes and Unique Features of CACIs

The term isolator is frequently used in the industry to describe enclosures used to compound sterile hazardous or non-HDs (see SIDEBAR 2). Such enclosures cover a wide range of configurations, sizes, features, and performance. Below is a list of the requirements that define an enclosure as a CACI (see FIGURE 4).

An advantage of a CACI is that this primary C-PEC isolates the operator from potential exposure to HDs during preparation. In addition, a CACI, compared with a Class II BSC, minimizes the potential for contamination of the room’s air during product preparation, as there is no chance of an operator’s contaminated gloves or arm covers moving into and out of the containment device.

There are strong similarities between Class III BSCs, which are primarily used for handling highly infectious microbiological agents such as viruses, and CACIs. Class III BSCs and CACIs share similar construction, features, operational requirements, and functional performance. Moreover, Class III BSCs include additional HEPA filtration of the exhaust and higher air velocity.

Key design features of CACIs that differentiate them from Class II, Type A2 BSCs include:

CACI Isolator Chamber Construction. The isolator chamber must create a leak-tight environment, operating at negative pressure, that can be efficiently cleaned to eliminate residues potentially left over from previous compounding processes. Crevices and difficult-to-clean areas should be minimized. The negative pressure of the CACI is not sufficient to meet the USP <800> room requirement for negative pressure; in other words, the negative pressure CACI must be located in a negative pressure room.
Airflow, Filtration, and Pressure Management. The CACI system chamber must include laminar, unidirectional airflow from top to bottom of the chamber. The air movement within the chamber must be free of turbulence and dead zones. Confirm proper airflow patterns with a smoke study as part of the system’s validation process. The air passing through the isolator must be filtered by three separate filters: a pre-filter at the air intake of the isolator, a set of primary HEPA filters that cover the ceiling of the chamber, and an exhaust HEPA filter that prevents potentially hazardous materials from escaping the chamber. The air handling system must be capable of achieving a minimum of 15 air changes per hour (ACPH), and chamber pressure must be maintained at set point at all times; excursions outside of the acceptable limits must be detected by an alarm system.

Monitoring Control System. Ideally, the CACI isolator system should have an integrated, computer-based control system with a touchscreen operator interface device for chamber pressure and airflow monitoring, product entry airlock and door management, and all other basic control functions. However, in most cases, less sophisticated CACI control systems are acceptable for pressure maintenance (magnetic pressure monitor) and alarm capability.

Product Ingress and Egress Airlock. The CACI isolator design must include an airlock chamber that allows the introduction of components into the isolator without the risk of contaminating the chamber. The product entry airlock should include a dedicated HEPA filtration system and dual interlocked doors—one to the outside of the airlock and one between the airlock and the main isolator chamber. The isolator control system must be capable of managing the functionality of the product entry airlock without affecting the pressure maintenance and airflow quality inside the main isolator chamber. A similar airlock chamber can optionally be integrated into the CACI isolator for the purpose of exiting the compounded product out of the isolator chamber. Although not required, separate product entry and egress airlock chambers yield the benefit of creating a continuous product flow through the isolator.

Chamber Configuration and Ergonomics. The chamber must be of ample size to meet the space requirements of the specific application, and the product entry airlock should be large enough to yield a continuous product flow through the isolator. The number of gloves and their position should ensure an ergonomically acceptable setup for the operator(s). Use lighting to enhance the visibility inside the chamber, and incline the front access door toward the rear to ensure better operator comfort and reach.

Waste Material Management. Most compounding operations generate significant amounts of waste materials, including wrappers, bags, wipes, CSTDs, and sharps. To create an optimal compounding process through the isolator, a waste material port should be provided within the isolation chamber and connected to the appropriate waste receptacle. Integrating the waste process allows the operator to maintain a clutter-free workspace within the isolation chamber and enhances the workflow. A reliable, operator-friendly implementation of the waste removal function includes a rapid transfer port (RTP).

SIDEBAR 2
Avoiding C-PEC Isolator Terminology Confusion
In 2015, USP published the proposed revision to USP <797> for comment. Within the proposed document was the introduction of a new cabinet definition for compounding: restricted access barrier systems (RABS). RABS, which are widely used in aseptic pharmaceutical manufacturing, have almost identical design features as CACIs, with the exception that they are normally operated under positive pressure with the primary function of aseptically filling sterile products. USP <800> does not mention RABS, which may lead to confusion with the term isolator for compounding. However, it is important that pharmacists understand the purpose of RABS and how they differ from CACIs.

RTPs. RTP technology, which has been used in the nuclear and pharmaceutical manufacturing industries for decades, permits the transfer of products, tools, and supplies into and out of the isolator system without impacting containment or aseptic integrity. RTPs come in various sizes depending on the application. One half of the port is permanently installed on the isolator and one part can be connected and disconnected as necessary. The part that is disconnected usually consists of a container, called the RTC, within which the components to be transferred are placed. The RTC is usually decontaminated with the isolator system.

Product Egress in a Sealed Container. Protection of the compounding operator and the administering nurse are of utmost importance. Product can be exited out of the isolator system by being inserted directly into a clear film bag and sealed inside. The clear bag is never placed inside the isolator, thus ensuring that its outer surfaces are not contaminated. The technology to achieve such an additional level of protection without affecting the aseptic integrity of the isolator exists, but its integration into the isolator must be such that it does not compromise any of the critical design features described previously.

Gas Decontamination. Gas decontamination removes the uncertainty associated with manual decontamination. All surfaces are automatically decontaminated by virtue of uniform distribution of the gas within the chamber. The most commonly used gas is a vaporized form of hydrogen peroxide ($H_2O_2$). Other gases, although not as widely used, include formaldehyde gas, chlorine dioxide gas, and nitrogen dioxide gas. More specifically in the case of $H_2O_2$, a gas generator injects the gas into the chamber up to a certain concentration level and for the programmed time duration. After this process is complete, the gas is exhausted to the outside of the facility until the concentration inside the isolator reaches a predetermined level, usually less than one part per million. All functions of the gas decontamination process must be managed by the system’s control system. A leak-tight chamber is a critical requirement of the decontamination process.

It is critical to note that horizontal laminar flow hoods/ laminar airflow workbenches and containment aseptic isolators must never be used for compounding HDs due to their lack of safety controls necessary for operator protection.
FDA-Cleared CSTDs

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>FDA Cleared</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhaSeal</td>
<td>Becton, Dickinson and Company; Carmel Pharma, Inc. (original)</td>
<td>1998</td>
</tr>
<tr>
<td>Spiros</td>
<td>ICU Medical, Inc</td>
<td>2005</td>
</tr>
<tr>
<td>Texium with SmartSite</td>
<td>Becton, Dickinson and Company; CareFusion, Inc (original)</td>
<td>2006</td>
</tr>
<tr>
<td>Tevadaptor (OnGuard)</td>
<td>B. Braun Medical Inc (US distributor) TEVA Medical, LTD (manufacturer)</td>
<td>2006</td>
</tr>
<tr>
<td>ChemoClave</td>
<td>ICU Medical, Inc</td>
<td>2008</td>
</tr>
<tr>
<td>Equashield</td>
<td>Equashield, LLC; Plastmed, LTD (original)</td>
<td>2009</td>
</tr>
<tr>
<td>ChemoLock</td>
<td>ICU Medical, Inc</td>
<td>2013</td>
</tr>
<tr>
<td>ChemoSafety</td>
<td>Becton, Dickinson and Company; CareFusion (original)</td>
<td>2013</td>
</tr>
<tr>
<td>Equashield II</td>
<td>Equashield, LLC</td>
<td>2014</td>
</tr>
<tr>
<td>Halo</td>
<td>Corvida Medical</td>
<td>2015</td>
</tr>
</tbody>
</table>


Gas Decontamination of Product Ingress Airlock. Isolators with gas decontamination capability offer the additional benefit of also decontaminating the product entry airflow chamber. Such capability ensures that the materials entering the isolator do not affect the isolator’s asptic integrity. The product entry airlock is decontaminated by H₂O₂ gas independently of the isolator chamber and without affecting the pressure maintenance and airflow quality inside the main isolator chamber.

SEC: The Room
In addition to C-PEC selection, USP <800> describes the proper placement of compounding equipment within the designated rooms, which is important because C-PEC devices depend upon the room in which they operate to function correctly. A Class II BSC or CACI must be placed in an ISO Class 7 area that is physically separated, with a minimum of 12 ACPH, and with a minimum negative pressure of 0.01-inches of water column to the adjacent positive pressure ISO Class 7 (or better) ante-areas. This room setup ensures an inward airflow to contain any airborne drug that may result from spills, broken vials, off-gassing of waste containers with residues, and from residue on vials/packaging. A pressure indicator must be installed and continuously monitored to ensure correct room pressurization. The Class II BSC and CACI should be 100% exhausted to the outside air through HEPA filtration. Note that USP <800> does offer the option to place a C-PEC in a compounding segregated compounding area (CSCA) that does not meet ISO 7 quality air for the compounding of low- and medium-risk HDs; but in this scenario, the guidance for BUD as defined in USP <797> does not apply, rather the BUD may not exceed 12 hours.

For more information regarding the requirements and best practices for setting up the SEC, review USP <800> and visit the CriticalPoint Web site.²³

Supplemental Engineering Controls: The Tools
There are currently nine devices, broadly categorized as closed-system drug-transfer devices (CSTDs), on the US market cleared by the FDA to supplement C-PECs and SECs in the effort to minimize operator exposure to HDs during compounding and administration (see Table 2).¹⁰

USP <800> states that CSTDs should be used in HD drug preparation, regardless of the C-PEC used (ie, Class II BSC or CACI), and CSTDs must be used during drug administration. During drug preparation, CSTDs should be used within the ISO Class 5 environment of a Class II BSC or CACI and not alone. Choosing the right CSTD for your facility should occur with input from nursing and pharmacy; in addition, consider peer-reviewed articles and ease of use as part of the evaluation process.

Conclusion
As the official implementation date of July 1, 2018, for USP <800> compliance is rapidly approaching, organizations must examine their engineering controls and create a plan for achieving compliance with the chapter. Multiple factors must be taken into account when choosing a PEC for use within the SEC, and complementary CSTDs must be considered as supplemental engineering controls to maximize safety when compounding and administering HDs. Input from frontline staff utilizing these devices, as well as continuous monitoring to ensure best practices, are crucial to continued safety.

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References
5. LaBella CJ. Does your pharmacy have a compounding isolator? Am J Health-Syst Pharm. 2007;64:855-858.