PART 3 OF A 3-PART SERIES

Understanding Compounding Isolation Systems

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Safety for staff and patients is the primary goal when handling and compounding drugs in the pharmacy. Conducting aseptic processing with isolation systems separates the cleanroom environment from the aseptic processing line and minimizes exposure to personnel. Per US FDA's current good manufacturing practice (cGMP) guidance documents, a well-designed positive pressure isolator, supported by proper maintenance and monitoring, increases safety by preventing opportunities for microbial contamination during compounding.[1]

PEC Isolating System Terminology

In 2015, USP published the first proposed revision to USP <797> (2008) for comment. Therein was the introduction of new terminology defining a primary engineering control (PEC) for compounding: restricted access barrier systems (RABS). In the latest proposed revision to USP <797> (2019), the terminology is clearly defined:[2]

- **Compounding aseptic containment isolator (CACI):** A type of RABS that uses HEPA filtration to provide an ISO Class 5 unidirectional air environment designed for the compounding of sterile hazardous drugs (HDs)
- **Compounding aseptic isolator (CAI):** A type of RABS that uses HEPA filtration to provide an ISO Class 5 unidirectional air environment designed for compounding of sterile non-HDs

USP clearly notes that CAIs and CACIs are *not* pharmaceutical isolators; although in the world of acute care practices, these units will likely continue to be referred to as *isolators* as the general term.

Evolution of USP Guidance on Isolating Systems

The 2004 version of USP <797> states: "A well-designed positive pressure barrier isolator...may offer an acceptable alternative to the use of conventional LAFWs in cleanrooms for aseptic processing." The document continues: "It is preferred, but not necessary, to locate barrier isolators within such a buffer air quality area." A garb component exemption is also noted: "When preparing compounded sterile products (CSPs)... using an isolator, wearing a face mask is optional, but head and facial hair must be covered."[3]

The noted exemptions of the physical location of the isolator in relation to the establishment of the beyond use date (BUD) of sterile preparations and of garb component exemptions have since been synchronized in the proposed revisions to USP <797> (2021) to traditional PECs. The proposed revision requires all garb components noted for ISO 5 laminar airflow workbenches, including sterile gloves over the RABS/isolator gloves/gauntlets, and the isolator must be located (like the traditional PECs) either in a defined segregated compounding area or ISO 7 buffer room with an adjoining ISO 7 anteroom (note: the anteroom can be ISO 8 if there is not an adjoining negative pressure room).[2] The synchronization of the surrounding compounding environment in which the isolating system resides now establishes the BUD of sterile preparations versus the type of PEC, whereas RABS and isolating systems no longer have exemptions for all the requirements for PECs related to the assignment of BUDs of compounded sterile products.

USP does specify which general classification of PECs are appropriate for compounding sterile preparations and does not specify which of the noted classifications are preferred.

FIGURE 1

Waste Safety

Isolators can improve waste management processes, as some units offer a port for trash, which keeps potentially contaminated waste off of the work surface.

Key Operational Differences

PECs should be constructed with materials that can withstand regular cleaning with harsh chemicals (ie, stainless steel, nonporous high-grade plastics), yet must maintain protective integrity under constant pressure. The ISO 5 airflow within all PECs, including isolating systems, must be unidirectional and confirmed via a visual smoke study.

The key difference between isolating systems and traditional PECs is the attribute of isolation. Air flow direction for isolating systems is primarily vertical, from the top to the bottom over the work surface, which may differ from a traditional horizontal flow PEC. RABS can offer operational benefits in terms of compliance, noise reduction, waste management, ergonomics, and the transfer of materials.

Compliance Enhancement

RABS are designed to minimize staff exposure to the materials being compounded within the PEC, as these units are self-contained and act as a physical barrier between the environment and the operator. The aseptic process of moving sterile gloved hands from lower classified air (ie, ISO 7) to a higher classification of air suitable for aseptic manipulations (ie, ISO 5) requires a disinfecting step with a sterile disinfectant (ie, sterile 70% isopropyl alcohol). Thus, the use of isolators can assist in preventing improper disinfection protocols from occurring (or being observed during a state board of pharmacy inspection). Because the gloved portion of the gauntlets constantly remains in the ISO 5 environment, the user can take their hands in and out of the gauntlets to perform any necessary manipulations, as many times as needed, and the process remains secure. Furthermore, the use of isolators does not require sterile garbing, so these systems help when garbing components are limited.

Noise Levels

Certain RABS offer quieter operations than biological safety cabinets (BSCs) and LAFWs. The high-velocity HEPA filtered air and associated noise are contained within the cabinet, thus reducing the overall decibel levels. This is important when considering the limits noted for hazardous noise level exposure, as defined by NIOSH.[4]

Waste Management

RABS can enable proper waste management, as some units offer ports for trash within the workspace, which is a better alternative to keeping waste on the work surface while compounding (see **Figure 1**). Further, some RABS offer specialized sharps containers that integrate with the work surface to allow for safe disposal of sharps and hazardous materials without leaving the confines of the cabinet structure. Hazardous waste can be secured within the negative pressure environment, thereby protecting against off-gassing through exhausting to the outside.

Ergonomics

Ergonomics is another consideration, and operating an isolator can produce

an unexpected advantage, as it prevents poor work habits such as leaning onto the deck in garb that may not have been disinfected or cleaned properly. Staff input on functional use and workflow is important, as employees work in these units regularly and can share valuable perspectives.

Transfer of Materials

The transfer of materials into and out of an isolator can affect workflow efficiency. Most RABS are designed with an antechamber to move materials from the ISO 7 environment into the ISO 5 work surface. The transfer system must be secured, for example, with a double door pass-through hatch with a mechanical or electromechanical interlocking of the opposing doors.

Some manufacturers require a purge time when materials are placed into the antechamber; this allows contaminated air to exit while the materials are bathed with ISO 5 air prior to moving them into the main chamber. Purge times are equal for the movement of materials into as well as out of the system. While they may vary by manufacturer, purge time requirements must be followed to minimize the loss of compounding environment integrity. To assist with the movement of materials within the RABS, units may have 2 to 6 arm ports with secured gauntlet/sleeve to glove systems.

Cleaning Considerations

Cleaning is a critical aspect of successful PEC utilization. For all staff, especially those who may not be accustomed to isolator system use, education and training are essential to ensure best results with cleaning and maintenance. Consider the amount of time it will take to complete a cleaning, because all surfaces, including the top, the back, the sides, and the deck will need to be addressed, as well as the inside of the front panel, gauntlets, and gloves.

The cleaning procedure for the gauntlets—the sleeve housings that adhere to the front panel—is an important part of training and should be addressed in the policies and procedures (P&Ps) related to isolator system maintenance.

Within isolator systems used for compounding non-HDs, the front portion of the cabinet may be opened to clean the ISO 5 work surfaces. However, a risk assessment should be conducted to determine the safety of frequently opening the front of a CACI where HDs are compounded. The four-step process as defined by USP <800>—deactivate, decontaminate, clean, and disinfect—will take more time versus the standard cleaning requirements for isolating systems used for non-HDs.[5] An additional focus area for cleaning is the underdeck of the work surface, which must be cleaned monthly by opening the front panel and lifting the surface for access.

Maintenance

Maintenance of PECs is the responsibility of the pharmacy. It is critical to read the manufacturer's maintenance manual and clearly understand that these devices require general maintenance beyond certification.

Gauntlets/sleeves should be inspected daily for breaches and must be replaced regularly, based on the level of use. Changing of gloves from the sleeves should be reviewed to effectively ensure that both systems are sealed and meet performance expectations. Manufacturers may offer guidelines on the inspection and replacement time for gauntlets/sleeves and gloves for specific systems, but a reasonable guideline is to change them monthly, regardless of the presence of any holes or penetrations. To ensure the maximal safety of the isolator's operation, usage levels must be considered. Systems in heavy use will necessitate more frequent replacement. To maintain a consistent schedule, the next targeted replacement date may be written on the sleeve at the time of changing (see **Figure 2**).

The PEC's HEPA prefilters require regular inspection and replacement, as they serve the important function of preventing larger particles from impacting the HEPA filter and potentially breaking it. If the prefilter becomes clogged, it can increase the pressure inside the RABS, which can in turn put more pressure on

FIGURE 2

Sleeve Maintenance

When CAI sleeves become worn and show holes, it is time to replace them. Pharmacy may date the sleeves to clearly display the next replacement date.

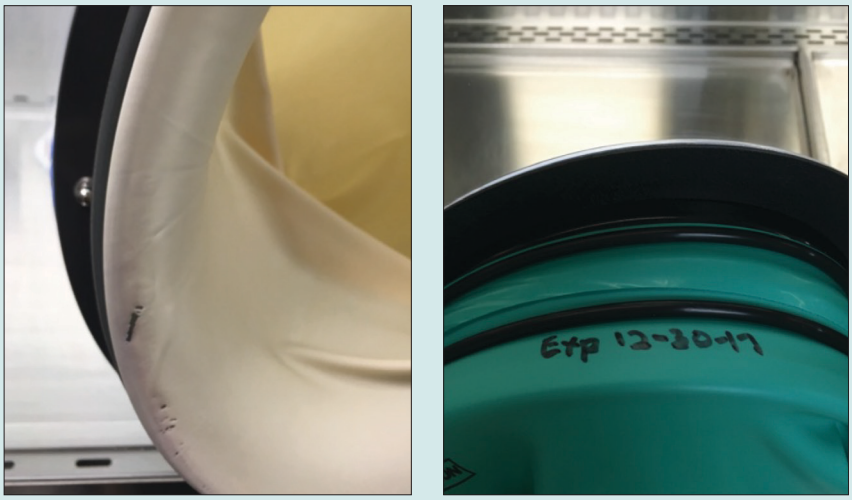

FIGURE 3

Gasket Failure

Gasket failure will negatively affect the safety of a CACI.

FIGURE 4

Rust in a PEC

Rust inside the cabinet is an indication that it may be time for a new unit.

the HEPA filter. The maintenance frequency will depend on the level of particles generated, and while it is usually acceptable for the certifier to do it every 6 months, some manufacturers may recommend changing the prefilter monthly.

Gaskets around the isolator's doors should be evaluated regularly. Cleaning solutions can deteriorate the gaskets over time, especially those located between the antechamber and the outside. If gaskets become worn or loose, they will not seal properly; thus, losing the capacity to isolate (see **Figure 3**). Pharmacy may ask the certifier to inspect the gaskets, but bear in mind that system maintenance remains the responsibility of the pharmacy.

Replacing PECs

PECs are durable, as they function 24 hours a day, 365 days a year to provide an ISO 5 environment for sterile compounding. Nonetheless, PECs should be considered for replacement approximately every 10 years. Older PECs may pass certification, but they likely lack the energy efficiency, adequate lighting (fluorescent bulb vs LED), availability of replacement parts, and other attributes of contemporary cabinets. The age of the isolating system is critical, and physical components such as gantlets, the front plexiglass protective panel, gaskets, and interlocking chamber doors, may indicate the unit's condition.

Signs of wear become obvious with time, such as chipped paint on the outer cabinet surface, scratches, or cracks on the front part of the visual field, or a working surface that is pitted, scratched, or worn in any way that prevents proper cleaning. Caulking of junctions of side walls to the work deck may become worn or disappear completely, and buildup of cleaning solutions or spilled drugs may become visible and pose problems for proper cleaning.

Although units may be constructed with stainless steel, this material does have impurities and can develop rust (see **Figure 4**). If rouging or rusting is apparent anywhere within the cabinet, it may be due for replacement. Rust can indicate microbial growth and is a contaminant; as such, any rust that is noted in any space within the compounding area is classified as an insanitary condition, per the FDA.[6] In any of these scenarios, consider replacing the unit.

Conclusion

Multiple factors must be considered when choosing a PEC for safely compounding sterile preparations for patients. Input from frontline staff utilizing these devices is key, as they will provide critical insight as to workflow, ease of cleaning, and maintenance oversight. For facilities struggling with overall USP compliance for sterile compounding or those simply seeking improved staff safety, isolator systems can provide a solution for the pharmacy when used properly.

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