Barrier isolators as an alternative to a cleanroom

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Abstract: The use of barrier isolators as an alternative to a cleanroom for the preparation of sterile products at ASHP-defined risk levels 2 and 3 and cytotoxic and hazardous drugs is described.

The two isolators selected provide enclosed microenvironments. The isolator used for preparing products of risk level 2 has white acrylic and polycarbonate rigid walls that isolate the sterile product from the operator. The isolator used for preparing level 3 products and cytotoxic and hazardous drugs has epoxy-painted steel walls, a front window, and a pair of glove ports; its design theoretically prevents cross contamination between the operator and the product under preparation and between the product and the external environment. An independent contractor familiar with barrier isolators certifies the equipment every six months. A random microbiological sampling is periodically compared with a control. The isolators have been in operation since July 1998 without microbial growth in any sample tested. The barrier isolators cost more than traditional laminar-airflow hoods, but the hospital considers the barrier isolators to be more cost-effective than a cleanroom. A cost saving in supplies for cytotoxic and hazardous drug preparation as a result of a reduction in overall gown and glove use was observed.

Barrier isolators offer an alternative to a cleanroom for the preparation of products at risk levels 2 and 3 and offer an aseptic, safe environment for preparing cytotoxic and hazardous agents.

Index terms: Antineoplastic agents; Aseptic areas; Compounding; Economics; Equipment; Hazardous substances; Toxicity, environmental

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The "ASHP Technical Assistance Bulletin on Quality Assurance for Pharmacy-Prepared Sterile Products" outlines three levels of risk to the patient who receives such sterile products.1 The levels increase from the least risk (level 1) to the greatest risk (level 3) and recognize a subsequent need to meet or exceed quality assurance recommendations to ensure product integrity and patient safety. A barrier isolator provides a class 100 environment for the preparation of sterile products.2,3 This article describes the implementation of barrier isolators as an alternative to a cleanroom.

Background

St. Joseph’s Hospital in Atlanta is a 346-bed tertiary care hospital. The hospital pharmacy department provides computerized medication profiles, centralized and decentralized unit dose distribution, centralized and decentralized preparation of i.v. admixtures and other injectable products, and other services. The i.v. pharmacy service mixes sterile products in all three ASHP-defined risk levels: small-volume i.v. admixtures, i.v. primary solutions, epidural solutions, and total parenteral nutrient solutions (risk level 1); syringes and small-volume i.v. admixtures of anesthesia agents, syringses for patient-controlled analgesia, and cardioplegia solutions (risk level 2); and injectable solutions of methacholine and phenol from nonsterile ingredients (risk level 3). Also, the i.v. pharmacy service mixes cytotoxic and hazardous drugs for inpatients and outpatients; ASHP recommends that these drugs be prepared in a class II biological safety cabinet (BSC).4 The i.v. pharmacy service prepares 20 batches of nonpreserved products intended for use by multiple patients and 10 cytotoxic admixtures daily. Batch preparations include narcotic syringes (30), cardioplegia solutions (10), anesthesia syringes (300) and minibags (30), and cardiac catheterization laboratory syringes (50) and vials (25). The main i.v. pharmacy operates 24 hours a day, seven days a week.

The i.v. pharmacy is equipped with two horizontal-laminar-airflow hoods and two barrier isolators. The two standard laminar-airflow hoods are used to prepare products of risk level 1. One of the barrier isolators is designated for level 2 products, and the other for level 3 products and cytotoxic and hazardous drugs. The core staffing pattern for the i.v. pharmacy is a pharmacist and an i.v. technician on the day and evening shifts. A night-shift pharmacist is in charge of the medication and i.v. pharmacies and is supported by two technicians (one in each area). The cleaning of the barrier isolators occurs in the early morning hours before our outpatient oncology unit opens at 0800.

Selection of barrier isolation over cleanroom

Barrier isolation hoods were selected instead of a cleanroom1 to meet our institution’s need to properly prepare sterile products at risk levels 2 and 3. A clean-
room consists of a class 100 work area enclosed in a class 10,000 environment. Personnel working in a cleanroom must wear a gown, gloves, a cap, a mask, and shoe covers to inhibit particle shedding. The cleanroom is constructed with special ceiling, wall, and floor tiles to prevent contamination. It also uses an air filtration and pressure system to prevent particle entry into the environment. A cleanroom is restricted to trained personnel.

The projected capital requirement for a cleanroom, according to outside contractors, was $50,000; projected annual operating costs were $10,000. This capital requirement did not include horizontal-laminar-airflow hoods because we were able to use our existing ones (if purchased separately, an additional $15,000 was required for two). The capital requirement for barrier isolators, as estimated by the manufacturers, was $35,000; projected annual operating costs were $2,000.

Cleaning time for the barrier isolators is 15 minutes longer than for standard laminar-airflow hoods but much less than would be required for cleaning a cleanroom. Preparation planning time is also longer as a result of using the barrier isolators but is less than the time spent properly preparing to enter or exit a cleanroom. Another consideration was the downtime for change to the new system: 2 days for setup of the barrier isolators versus 10 days for construction of a cleanroom. Also, we knew we could move the barrier isolators if future needs dictated a change in location.

Design of barrier isolators

The two barrier isolators we selected (IsoTech Design, Montreal, Quebec, Canada) provide “enclosed microenvironments.”

**Isolator for preparation of products at risk level 2.** The barrier isolator used for preparing products at risk level 2 has white acrylic and polycarbonate rigid walls that isolate the sterile product from the operator. The internal dimensions of the barrier isolator are 24 × 36 inches (0.61 × 0.91 m); the external dimensions are 57.25 × 86.75 × 27 inches (1.45 × 2.20 × 0.69 m). The product is handled through a pair of glove ports, so there is no direct contact between the operator and the product. The rigid enclosure theoretically eliminates the risk of contamination from disturbances in the background air. An airtight, transparent, acrylic door between the work chamber and the transfer chamber (on the side) enables input and output of materials. The ventilation system provides an average airflow of 540 cubic feet per minute (cfm) (90 feet per minute [fpm]) through the microenvironment. Air flows vertically in the work chamber through a terminal down-flow high-efficiency particulate air (HEPA) filter that spans the entire width of the stainless steel work surface. Once through the work chamber, the air exits through two air outlets located in the work surface of the unit.

The greater air pressure in the work chamber (0.15-0.20 inches of water) compared with the transfer chamber (0.01 inches of water greater than ambient room-air pressure) ensures that outside contaminants introduced into the transfer chamber cannot freely enter the work chamber. Air flows horizontally into the transfer chamber through a HEPA filter. A ventilated front door allows for continuous airflow. A static differential mini-helic pressure-indicator gauge, located on the left side of the front panel of the isolator, indicates the difference in pressure between the work chamber and the transfer chamber; the work chamber should have greater pressure to prevent air in the transfer chamber from entering when the door between the two chambers is open. When not in use, the work chamber is a class 10 environment and the transfer chamber is a class 100 environment. A 40-watt fluorescent light behind the front panel illuminates the work surface.

The glove-port handling system is composed of a pair of vinyl, cotton-backed sleeves; cuff rings; and gloves. Retainer rings (O-rings) hold the components together. Each sleeve is attached to the work chamber’s flexible-film front by a shoulder ring and an elastic gasket. Different types of gloves (e.g., latex, vinyl, nitrile) are used to meet the requirements of the application and the handler.

**Isolator for preparation of products at risk level 3 and cytotoxic agents.** The barrier isolator used for preparing products at risk level 3 and cytotoxic and hazardous drugs has epoxy-painted steel walls, a front window, and a pair of glove ports. Its design—three HEPA filters, a transfer chamber, a work chamber, and an exhaust duct—therefore prevents cross contamination between the operator and the product under preparation and between the product and the external environment. The front window is inclined for operator comfort and is removable for easy access and cleaning. The internal dimensions of the barrier isolator are 24 × 48 inches (0.61 × 1.22 m); the external dimensions are 68.875 × 99 × 33.125 inches (1.75 × 2.51 × 0.84 m). Two fan motors allow for 1950 total air changes per hour, 544 cfm airflow in the work chamber, and 147 cfm of fresh replacement air at the intake. The airflow inside the work chamber is vertical laminar. To extend the life of the filter and minimize temperature rise inside the work chamber, 80% of the air is recirculated.

The air pressure in the work chamber (approximately −70 Pa) is lower than the ambient room-air pressure, while the pressure in the transfer chamber (approximately −95 Pa) is lower than that in both the work chamber and the outside environment. These differences in air pressure ensure that, when the unit is in perfect working order, no toxic product particles can escape from the work chamber to the environment and no outside contaminant can enter the work chamber from the transfer chamber. A pressure gauge indicates the work chamber’s internal air pressure. The glove-port handling system and the transfer chamber are
similar to the barrier isolator we use to prepare products of risk level 2. An additional pair of gloves is worn during preparation of cytotoxic and hazardous drugs. These gloves are powder free and nonlatex.

Built-in safety features include gaskets and components under positive pressure that are surrounded by a negative pressure plenum, welding of most unit components, and high- and low-pressure alarms that prevent accidental simultaneous opening of the inner door and the front window. A drip tray under the work surface of the work chamber retains liquid spills and isolates the prefilter. This prefilter can be replaced through the glove ports by simply raising the work surface with the special tool provided. Gloves and sleeves can be changed without asepsis and safety being compromised.

This barrier isolator offers safety advantages over a BSC, which is typically pharmacy’s choice for preparing cytotoxic and hazardous drugs. The BSC has a partial opening at the front to allow products, supplies, and the operator’s arms to enter so that the final products can be prepared. This opening increases the risk of worker exposure by potentially allowing cytotoxic and hazardous drug residue to escape into the environment. The barrier isolator eliminates this opening to reduce the risk by enclosing the work area. The barrier isolator also uses negative pressure to reduce the risk of exposure.

**Maintenance**

Daily cleaning of the barrier isolators is completed with lint-free wipes and diluted disinfectant (glutaraldehyde solution) or detergent and hot water. It is recommended that not too much alcohol be used for cleaning these units. Decontamination and cleaning include cleaning of gloves, sleeves, the work surface, interior-wall surfaces of work and transfer chambers, doors, and the exterior surface of the front wall of work chambers. The prefilters are changed monthly; the HEPA filters are changed at least every two years.

Gloves are replaced in each isolator daily. This process takes five minutes for a pair. Surgical gloves are worn during this procedure, and only one isolator glove is changed at a time. A glove change may be more frequent if a different size is needed, because of the size of the operator’s hands, or if a breach, such as a tear or a pinhole, in the glove is detected. Before use in the isolator, we test each glove for leaks by filling the glove with water, holding the glove (keeping it closed), examining the glove and looking for water leaks, disposing of any glove that leaks, and cleaning and using gloves that do not leak. Because the air pressure in the work chamber is less than that in the room, any breach in glove or sleeve integrity can introduce bacterially contaminated room air into the work chamber.

When required, we can change a sleeve without opening the unit to the outside environment. We use the following procedure, one sleeve at a time: Disinfect the inside of the work chamber and the sleeve from the inside, paying special attention to the shoulder-ring area; remove the outside O-ring from the sleeve; move the sleeve edge onto the first groove of the shoulder ring; from the outside, install a complete sleeve-and-glove assembly over the sleeve to be changed, making sure that the replacement sleeve fits tightly inside the shoulder groove; with the other glove and from the inside, carefully pull the old sleeve; and reinstall the O-ring. The old sleeve is removed through the transfer chamber and properly disposed.

**Preparation of products**

Preparation of products is planned in advance after an order for a cytotoxic agent or a request for a batch preparation is received. Upon receiving the initial order for a cytotoxic agent, a pharmacist verifies the order and generates a label for the agent. Another pharmacist checks the order and the label for accuracy. For inpatients, the nursing unit is contacted to schedule mixture of the product. For outpatients, the product is mixed as soon as possible. The i.v. technician is given the label, enters the admixture in the cytotoxic agent log, and gathers the appropriate supplies. The supplies are cleaned, if appropriate, with 70% isopropyl alcohol before being placed in the transfer chamber (a small tray is used for multiple supplies). Disposable covers of i.v. bags and syringes are removed. A final check is made to ensure that all needed supplies are transferred to avoid a time delay for obtaining missing supplies after preparation is under way. The technician takes a seat and places each arm and hand into the sleeves and gloves (approximately 30 seconds).

The product to be mixed and supplies are moved from the transfer chamber to the work chamber through the inner door, which is then closed. Before and after each product is mixed, the gloves are cleaned with 70% isopropyl alcohol. After aseptic preparation of the product is completed, a pharmacist checks the finished product. The inner door is opened, and the product is placed in a product bag in the transfer chamber and left there. Excess agent is retained in its original container until the end of the workday and then discarded. The inner door is closed, and the hands and arms are removed from the gloves and sleeves. The product bag is removed from the transfer chamber via the front door and delivered to the nursing unit. The average time to complete the admixture process is 10 minutes. We saw very little increase in time as a result of using the barrier isolators instead of the open-front BSCs once the process became familiar. This was very important to our outpatient oncology population because these patients are very time sensitive. Our overall oncology turnaround time is 30 minutes.

The preparation of batch products is carried out in a similar manner. The main difference is that batch-prepared products are checked and labeled outside the
barrier isolator. This is appropriate because these products do not pose a risk of cytotoxic effects to the personnel handling them. The label includes product description, batch number, and expiration date. Only one batch at a time is prepared and checked in order to prevent errors. A detailed description of how to prepare each batch is outlined and recorded in a log, including batch number, ingredient manufacturer, lot number, expiration date, and technician and pharmacist initials. A sample product from a randomly selected batch is tested for sterility. The tested batch is quarantined until results are returned. As of April 1999, none of the products sent for testing has had a negative result (i.e., microbial growth).

**Validation**

An independent contractor who does not work for the barrier isolator company but who is familiar with barrier isolators certifies the equipment every six months. This person measures the following operating characteristics: work chamber internal pressure, average air velocity below the HEPA filter face, and at-rest airborne particle count; internal pressure of the transfer chamber with the front door closed and at-rest particle count; and HEPA filter integrity. The limits for these operating characteristics are set by Federal Standard 209E. Also checked are the main power supply, lighting, ventilation, speed control (of the blower that maintains air velocity), and approval by the Canadian Standard Association (similar to Underwriters Laboratories in the United States). A random microbiological sampling from the isolator is periodically compared with a control (zero colony-forming units). Our two isolators have been in operation since July 1998 without a negative result.

**Discussion**

The barrier isolators have a distinct advantage over traditional laminar-airflow hoods. The contained environment is designed to protect the operator from direct exposure to the product during mixture and to protect the product during preparation from contaminants in the external environment. The installation, cleaning, and maintenance of barrier isolators is similar to the procedures for traditional laminar-airflow hoods. There are no special room requirements for the barrier isolators. The barrier isolators cost more than the traditional laminar-airflow hoods, but, given the construction and supply costs of a cleanroom, we consider the barrier isolators to be more cost-effective. In addition, we have noted a cost saving in the supplies for cytotoxic and hazardous drug preparation as a result of a reduction in overall gown and glove use.

**Conclusion**

Barrier isolators offer an alternative to a cleanroom for the preparation of products of risk levels 2 and 3. The isolators offer an aseptic, safe environment for preparing cytotoxic and hazardous agents.

**References**