



Sterile Compounding with Barrier Isolation Technology

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Sterile compounding in hospital, home care, and ambulatory care settings is undergoing changes. Barrier-isolation technology for the preparation of sterile compounding is becoming available. The regulatory influence of state boards of pharmacy and the Food and Drug Administration (FDA) on maintaining the sterility of parenteral products and that of the Occupational Safety and Health Administration (OSHA) on the preparation and handling of the hazardous drugs may result in changes in pharmacies throughout the country.¹ These regulatory agencies focus on the facilities and practices used in the preparation of sterile drug products.

Barrier-isolation technology ensures the integrity of sterile products and the safety of the personnel who prepare them. Properly designed barrier-isolation workstations that provide class 100 internal environments and personnel protection are now available. This type of technology was developed to protect workers who handle radioactive materials from the hazards of exposure to radiation. The electronics industry advanced the technology to reduce losses of chips as a result of airborne contamination. In the 1980's pharmaceutical manufacturers began using this technique to protect both drug products and the personnel. Barrier isolators contain the process of drug manufacturing, prevent cross contamination by airborne materials in the manufacturing area, and protect personnel by reducing exposure to the drugs produced.

Barrier-Isolation Technology Use in the Pharmacy

Barrier isolators for use in pharmacies were first available in Europe in the 1980s. By the early 1990s, they were the preferred enclosure for use in hospitals in the United Kingdom and Ireland. Pharmacies in the United States began to use the technology in the mid-1990s for the preparation of intravenously administered admixtures and cytotoxic medications. In 1999, the New Jersey State Board of Pharmacy introduced the first regulations requiring that either a pharmaceutical-quality cleanroom or a barrier isolator be used for the preparation of sterile products. Several states have since followed with similar regulations.

The transformation of barrier isolators from "glove boxes" to more sophisticated technology involved creating an ergonomically integrated system that contained the



activities required to prepare a product for patient use. The focus on this attention to detail in producing a user-friendly workstation varies greatly from manufacturer to manufacturer. The manufacturer's understanding of the substances that must be placed into the internal environment and how they should be manipulated is reflected in the quality of the barrier isolators produced.

Laminar flow technology, which has been used in the pharmacy for a number of years in devices such as horizontal and vertical enclosures and class II biological safety cabinets, has defined the space available for the performance of aseptic manipulations in the pharmacy. The laminar flow units are usually 18 to 24 inches deep and range from 2 to 12 feet long. The setback from the front face of these devices and internal placement restrictions significantly reduce the internal usable space. Properly designed barrier isolators have been developed to accommodate the space requirements, ergonomics, and equipment necessary to perform required procedures.

Factors to consider in selection of a system include the quantity and type of products to be produced and the physical layout of the pharmacy. Personnel at the University of Cincinnati Hospital Pharmacy used time-and-motion studies to determine throughput capabilities for the mobile isolation chamber (MIC) workstations (Table 1).³ Table 1 should be used only as a guide and should be verified by the manufacturer of the barrier isolator of interest.

Other design factors to consider include ergonomics, flexibility, ease of installation, and ease with which the barrier isolator can be cleaned and sanitized. Each of these factors is important and can make the difference between a successful project and one that will limit the capabilities of your pharmacy. Ergonomic factors include an easily adjusted working height that can accommodate both sitting and standing at the workstation, as well as the different heights of personnel. Evaluations of the reaches required for operation, the disposal of trash and sharps, and configuration of the hanger bar are important. The adaptability of use of the barrier isolator when the preparation area for intravenously administered drugs must be relocated or reconfigured should be considered. Ease of installation is a major consideration, because the hospital depends on the rapid response of the pharmacy around the clock. The ease with which the barrier isolator can be cleaned and sanitized is critical to the sterility assurance program of any pharmacy. Important design considerations that affect the cleaning and sanitizing of the barrier isolator are presented in the specifications section of this article.

TYPES AND USES OF BARRIER ISOLATORS



Types of Barrier Isolators

Two criteria can be used to identify the type of barrier isolator: 1) the physical structure of the workspace typically described as "hard shell" (constructed from a solid material such as stainless steel [Figures 1 and 2]), or "soft shell" (constructed from a soft plastic material), and 2) the internal pressure scheme of positive or negative pressure. Usually, the pressure scheme is a function of use; positive pressure is used for preparation of sterile products, and negative pressure is used to contain hazardous compounds. Recommendations about the pressurization scheme of cytotoxic materials, which are subject to regulations for both sterile and hazardous materials, differ according to regulatory agency. OSHA recommends negative pressure and the FDA prefers positive pressure, which protects the product. Usually, the FDA wins this argument.

Uses of Barrier Isolators in Hospital and Community Pharmacies

Barrier isolators are used in the pharmacy primarily for the preparation of three categories of parenteral products: intravenously administered admixtures, total parenteral nutrition (TPN), and hazardous drugs such as cytotoxic medications. In the preparation of intravenously administered admixtures, syringes and piggybacks are used for solutions that are prepared by removing the active drug substance from a vial or ampoule and placing it into the delivery system. Dispensing machines are sometimes used to fill syringes from larger containers of the product. Some barrier isolations offer aseptic transfer via a system in which the pump is outside the barrier isolator, which offers economics of space and time. In those units, the aseptic manipulations are performed in class 100 conditions internal to the barrier isolator.

TPN products are nutritional solutions usually administered from 1- to 3- liter plastic bags. The preparation of TPN solutions may involve the use of dispensing machines that much be positioned inside the barrier isolator. The use of a barrier isolator protects the sterility assurance level of the pharmacy by eliminating direct personnel contact in the critical zone and minimizing the number of particulates and microorganisms in the environment.

Barrier isolators are also used in the preparation of hazardous drugs such as antineoplastics agents, those required for gene therapy, and any experimental drug that has not been completely profiled with respect to the hazards of exposure. Any product in the categories described above should be prepared in a properly designed barrier isolator. Studies have identified gross contamination from antineoplastics agents in cancer centers in which traditional class II biological safety cabinets are used. Additional studies that



will soon be published have identified the process by which contamination takes place when those types of safety cabinets are used. That information demonstrated the need for creating the higher level of protection provided by barrier-isolation technology.

Barrier isolators save both time and money when they are used in a home care pharmacy. A major chain store pharmacy is currently evaluating the use of the barrier isolator as a means of providing intravenously administered preparations for home care customers across the United States.

SPECIFICATIONS FOR BARRIER ISOLATORS

Pharmacists who plan to add a barrier isolator should consider the following three factors:

1. **The proper size of the barrier isolator required and the number of workstations necessary.** The determination of the number and size of workstations should be based on both current and projected pharmacy activities in three categories: intravenously administered admixtures, TPN's, and cytotoxic drugs. The use of special delivery devices such as cassettes should be noted. Given the number of daily doses that must be prepared, the required number of barrier isolators (by type) can be determined. Some barrier isolator manufacturers will assist with this analysis.
2. **The most functional layout for the area in which the barrier isolator will be located.** Design a plan for that layout. In the plan, the movement of pharmacist and technicians, compounding materials that will be used, and the quantity of supplies that must be stored should be considered. The plan should include a step-by-step sequence describing how the transition from the current layout to the desired plan will occur. Develop a budget based on the action plan. Some manufacturers of barrier isolators will provide data supporting the justification of the project in terms of return on investment. Reduced capital and operating costs are examples of areas in which savings can be achieved when barrier isolators are installed.
3. **A specification sheet describing the barrier isolator.** The specifications should include the four components common to all barrier isolator systems; physical structure, the internal environment, transfer and interaction technologies, and monitoring systems.

Physical Structure



The physical structure of the barrier isolator refers to the materials of construction used, such as type 316 stainless steel with seal and gasketing materials that have been approved by the FDA or the United States Department of Agriculture (USDA). Those construction materials must be chemical resistant so that the barrier isolator is protected from cleaning and sanitizing agents.

- Interior surfaces must be smooth and cleanable and must have coved junctions of walls, ceilings, and floors. All welds must be ground smooth.
- Lights must be mounted exterior to the class 100 environment.
- A factory acceptance test must indicate that the structure of the barrier isolator is gas tight and capable of maintaining a class 100 environment during normal operation of the workstation.
- The entrance or egress of material from the workstation should not compromise the aseptic quality of the working chamber.
- Ergonomic considerations, such as easy adjustment to accommodate the different heights of personnel and the ease with which work can be performed by a technician who is sitting or standing, should be noted.
- Viewing ports should be constructed at the proper angle, so that personnel can see all interior areas of the barrier isolator. The viewing posts should be constructed of engineered plastic or safety glass.

Internal Environment

- A high-efficiency particulate air (HEPA) filter that has an efficiency rating of 99.97% or greater should be used to filter the air that enters and exits the barrier isolator.
- It must be possible to clean the internal surface area of the HEPA filter or to cover it during cleaning and to sanitize the surface of the filter.
- The barrier isolator must be capable of operating with positive pressure and must maintain a range of air pressures of 0.25 to 1.0 inches of water pressure.
- Documentation of methods used in certification to meet regulations should be provided.

TRANSFER AND INTERACTION TECHNOLOGIES

The term "transfer technology" refers to the means by which materials are moved into and out of workstations.



- An air lock of appropriate size offers the most versatile means of entering and exiting the work space.
- Closed system transfers of sharps and trash that improve efficiency are desirable.
- Ergonomic reaches in the transfer of materials should be within acceptable limits.

"Interaction technology" refers to methods of working inside the workstation. The most common methods of accessing the interior of the workstation involve the use of glove ports or half suits. Sleeves with attached gloves are secured to the barrier isolator⁴ at the glove ports. The sleeves provide access to the interior of the barrier isolator. Glove ports are usually used unless extreme reaches are required. The half suit encases the upper half of the torso in a "diving suit."

- Gloves, sleeves, and half suits must be latex free.
- Two-piece sleeves and gloves are preferable because the hand size of the operators varies.
- Ergonomic arm supports are desirable in the glove ports.

MONITORING SYSTEMS

- Monitoring systems are used to verify that the workstation is operating within design parameters. Gauges with visual readouts should be included and checked regularly.
- The workstation can be monitored by a pressure-calibrated pressure differential gauge that has easily readable gradation indicators and is located in the front control panel of the workstation.

COST

The cost of a barrier isolator system varies according to its function, size, complexity, and manufacturer. Installing a workstation that meets both regulatory and functional requirements for the preparation of sterile products will require an investment that ranges from \$25,000 to \$45,000. Beware of bargains in either cleanroom or barrier isolators!

The cost of a barrier isolator is usually less than 70% of the cost of a properly designed cleanroom that has smooth, easy-to-clean hard wall surfaces and a defined pressure differential with the outside environment. In addition, the cost of operating a barrier isolator is less than 20% of the cost of cleanroom operation. A barrier isolator requires less total floor space than the necessary for a cleanroom and eliminates the need for gowning. A barrier isolator is also much easier to relocate than a cleanroom.



STERILITY ASSURANCE LEVELS AND THE EFFECT OF BARRIER ISOLATORS

The quality of pharmacy-prepared sterile products is defined by the level of sterility achieved during product preparation.⁷ The sterility assurance level is the number of contaminated products that could be delivered to a patient. A sterility assurance level of 10^{-7} , which indicates that 1 in 1 million containers could be contaminated, indicates a sterile product. Most parenteral products are prepared via aseptic techniques that, in most cases, result in a sterility assurance level of 10^{-3} (1 in 1000 containers might be contaminated). Additional handling of the product after its manufacture reduces the level of sterility assurance, so it is critical that the best environment and techniques be used for sterile-product preparation in the pharmacy.

The sterility assurance level of a product is a function of the quality of the environment (the number of particles and the degree of sanitization) to which the product is exposed during manipulation. The use of barrier-isolator technology in the pharmacy eliminates the direct contact of personnel with the critical zone in which products are exposed, and this eliminates the major source of contamination. Properly designed barrier isolations also provide an environment that is easily sanitized. As a result of those factors, the FDA has recognized that the use of barrier-isolator technology is superior to that of conventional laminar flow techniques in maintaining the sterility assurance level of products of parenteral administration.

CONTAINMENT OF HAZARDOUS DRUGS

The containment of hazardous drugs begins with an understanding of the level of acceptable exposure. All pharmaceuticals are hazardous by definition, because their purpose is to produce an effect such as lowering blood pressure or killing viruses or cancer cells in the human body. Exposure to certain pharmaceutical can help the individual who needs treatment but can be very harmful to others, especially pharmacy staff who handle those substances daily.

Data indicate that cytotoxic compounds have been detected outside class II biological safety cabinets, but the sources of such contamination have not been identified. Contamination observed in the pharmacy can be caused by contaminated vials, transfer from hands and gown sleeves, improper protection of materials during their removal from the containment of the cabinets, minimal quantities of microaerosols that escape through HEPA filters, or small airborne particles that escape the front face of open cabinets. Barrier isolators that are supported by proper transfer devices reduce the 8-hour, time-



weighted exposure level of airborne contamination to below 2.0 ng. Table 2 is a summary of the study conducted by SafeBridge Consultants (Mountain View, California) that led to the development of these data. This exposure level is more than 400 times lower than that of paclitaxel, which is currently the most widely used cytotoxin compound. Paclitaxel has an occupational exposure limit of 800 ng/m³.

CONCLUSION

Barrier-isolation technology is the most cost-effective system for maintaining the sterility assurance levels of parenteral products and for protecting pharmacists and technicians from hazardous drugs. To implement this technology in the pharmacy, it is important to understand the basic components of barrier isolators and to determine the correct questions to ask the vendors of those systems before a purchase is made.