Using Barrier Isolators for Sterile Compounding

By James T. Wagner

Photo courtesy of NuAire

The PharmaGard 797 is a positive pressure barrier isolator.

EARLIER THIS YEAR, TWO DOCUMENTS WERE PUBLISHED THAT DRAMATICALLY affect every compounding facility throughout the United States. In January, the United States Pharmacopeia published USP Chapter <797>, *Pharmaceutical Compounding—Sterile Preparations*, which details regulations for almost every aspect of operations that compound sterile preparations. In September, the National Institute for Occupational Safety and Health (NIOSH) published an Alert for *Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings*. Both of these documents contain excellent guiding principles, but they do not contain the specifics that would be necessary for pharmacists, technicians, and administrators who do not have extensive experience in such matters to fully comply with them. The barrier isolator is mentioned in both documents as a viable engineering control for the compounding of sterile preparations. In order to provide pharmacy professionals with the knowledge they need to comply with these new regulations, this article will discuss barrier isolators in more depth than Chapter <797> or the NIOSH Alert.

While barrier isolators have been used for some time in the United Kingdom, they have only recently begun to see more widespread use here in the United States. Currently, there are no formal industry standards or federal regulations concerning isolators. The guidelines that do exist were written for the pharmaceutical manufacturing and microelectronics industries, and do not translate to the pharmaceutical compounding industry very well. In an effort to give some guidance to the compounding industry, the Controlled Environment Testing Association (CETA) recently posted a document *(CETA Applications Guide for the Use of Barrier Isolators in Compounding Sterile Preparations in Healthcare Facilities)* that is available on their website. Although the document offers guidance for complying with USP Chapter <797>, it does not discuss measures for handling the hazardous drugs that would fall under the scope of the NIOSH Alert.

In some cases, barrier isolators offer tangible advantages over traditional methods.

Barrier isolators differ from traditional Laminar Air-Flow Workbenches (LAFWs) or Biological Safety Cabinets (BSCs) in many ways. The most obvious difference is that the work area in a barrier isolator is physically separated from the surrounding environment; compounders perform their tasks via gloves that are integrated into a clear view screen. In some cases, barrier isolators offer tangible advantages over traditional methods. In other cases, the advantages are outweighed by the disadvantages. A common concern expressed by those considering isolators is the potential impact on productivity. There is no doubt that working in an isolator is cumbersome compared to working in a LAFW. Low-output facilities will probably find the inconvenience minimal, but high-volume users should include the potential impact on productivity in their decision-making process. I do believe that the forced discipline of working through the gloves of an isolator, along with the process of inserting and removing product via the pass-through, will have a very positive effect on aseptic technique. It is important to consider such issues before using barrier isolators; they should not be thought of as an "easy way out" or a cheap alternative to a Cleanroom.

Material Transfer

When planning your environmental controls, the first thing you should decide is how you are going to move the materials in and the product out of the isolator. Traditionally, there have been two types of aseptic processing isolators: *open* and *closed*. Closed isolators employ connections with auxiliary equipment for material transfer. These sealed transfer devices have several classifications based upon their design, degree of containment, adaptability to sterilization, and general protective features. They are typically used in a manufacturing setting. Open isolators have openings to the surrounding environment that are carefully engineered to segregate the inner isolator environment from the surrounding room via overpressure.

Most isolators used for sterile compounding are closer in design to open isolators in that they bring product in and out through pass-throughs instead of through sealed, sterile aseptic transfer devices. The purpose of a pass-through chamber is to isolate the inside of the isolator from the room to maintain the integrity of the isolator interior. The pass-through chamber design allows the higher air pressure in the isolator interior to cascade through the pass-through chamber and then out to the surrounding room. Product is placed into the pass-through chamber from the room through the outer door, which is then sealed. With product in the pass-through, the pass-through space is now "contaminated"

Photo courtesy of Germfree Laboratories

Laminar Flow Glovebox/Isolator

by the ambient room air and by the outside of the packages that have been introduced. Wiping down the packages and purging the pass-through prior to opening the interior door will help reduce the particulate load that is transferred into the isolator. Isolator manufacturers should provide documentation regarding the procedures and purge times needed for safe material transfer.

Pass-throughs can utilize unidirectional air, turbulent air, or stagnant airflow. Because the pass-through can impact overall product contamination, pharmacists should consider the quality of room air where the isolator is located, how the materials will be wiped down in the pass-through, and how effective the purge cycle will be. Unidirectional pass-through designs offer the shortest purge times, afforded by the single pass of HEPA filtered air. Longer purge times are required for the turbulent flow pass-throughs because contaminants are removed through dilution rather than washed away in a flow of filtered air. Stagnant air pass-throughs offer no purging of contamination prior to transferring products to the isolator.

Isolator Airflow

The traditional turbulent flow isolator is basically a sealed, ventilated box with a view screen that provides access to the inside through gloves. Both inlet and recirculated air are HEPA filtered, diluting interior air with clean, particulate-free air. The amount of dilution that takes place is dictated by the quantity of air that is recirculated. This is usually expressed as Air Changes per Hour (ACH). Turbulent flow isolators have been designed with as few as 40 ACH to well over 150 ACH.

In addition to considering how to prevent contamination of the isolator from the outside, a fundamental decision needs to be made about how the contamination inside the isolator will be managed. An isolator needs to be open from time to time for maintenance and cleaning. At that time, the air inside the isolator is as dirty as the surrounding environment. The isolator must be able to eliminate this contamination. Additionally, particulate build-up and cross-contamination that will occur during compounding needs to be controlled. Reliance on dilution control to manage these tasks is somewhat risky but the chances for success can be improved with higher air exchange rates. Increasing the amount of HEPA-filtered recirculated air increases the amount of particle-laden air that is removed by the air return. Eventually, the particulate burden can be reduced to acceptable levels. How long it stays that way is dependent on how long it is until more products are brought into the isolator and how well the product is cleaned prior to entry.

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Because of a turbulent flow isolator's unpredictable particle removal characteristics, the pharmaceutical manufacturing industry requires a validated decontamination procedure, typically Vapor Phase Hydrogen Peroxide (VHP) or some other gaseous process, to be in place when using isolators for sterile production. While sterile compounding isolators typically do not employ this type of system, some validated method for disinfection must be in place.

The USFDA has shown some support for the turbulent-flow-controlled isolator design concept; however, concerns have been raised about aspects of the design. In their recently released industry guide (*Guidance for*

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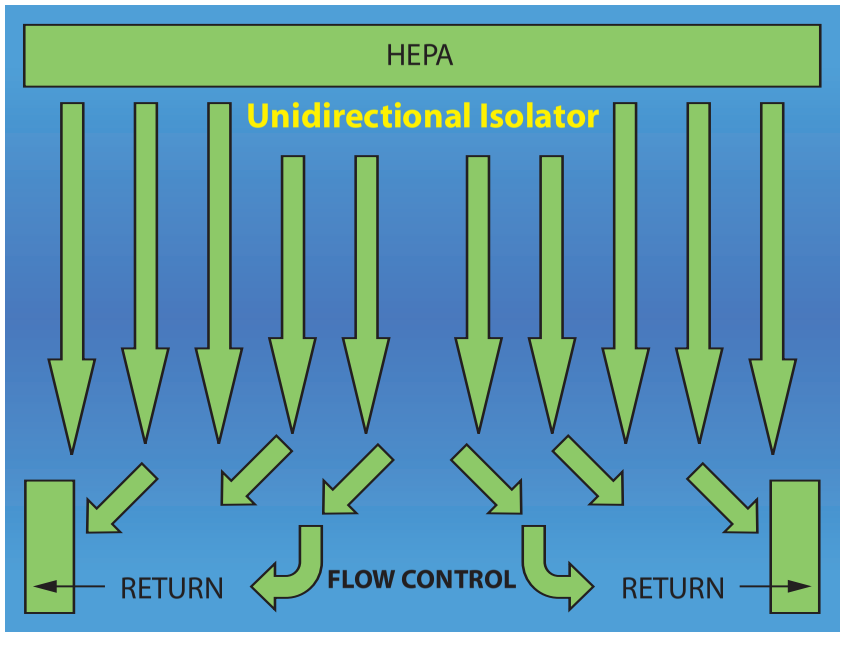
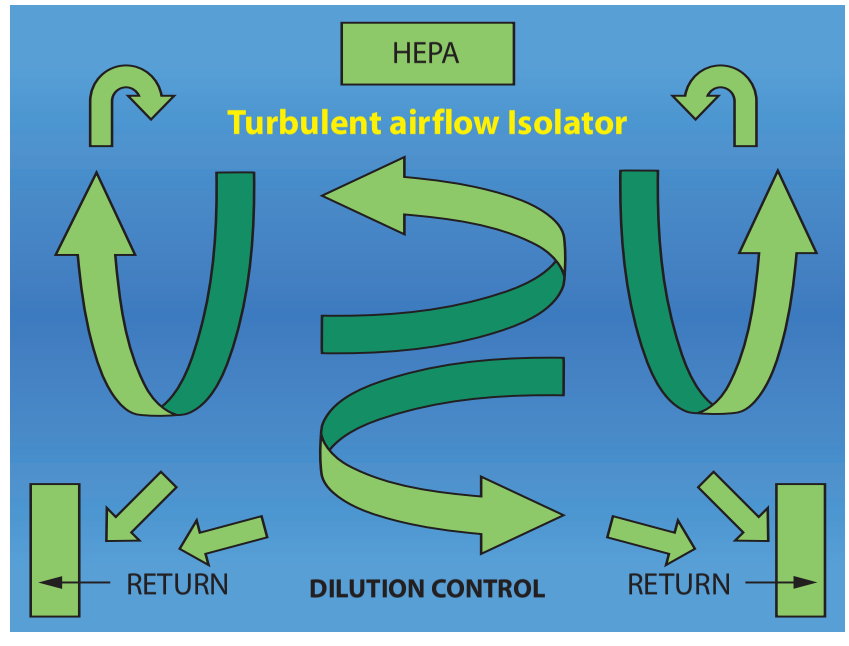


With unidirectional airflow, the speed of contamination removal is very high.



Contamination removal takes longer to achieve with turbulent airflow.

Photo courtesy of The Baker Company

The ChemoSHIELD is a gas-tight negative pressure containment glovebox.

ISOLATORS (Continued from page 5)

Industry—Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice), they state: "Turbulent flow can be acceptable within closed isolators, which are normally compact in size and do not house processing lines. Other aseptic processing isolators employ unidirectional airflow that sweeps over and away from exposed sterile materials, avoiding any turbulence or stagnant airflow in the area of exposed sterilized materials, product, and container closures. In most sound designs, air showers over the critical area once and then is systematically exhausted from the enclosure." Isolators used for compounding sterile products do not bring materials in and out through sealed sterile transfer devices, and are therefore closer to an "open" design. As such, careful planning and strict adherence to decontamination discipline is a must when using an isolator in sterile compounding.

The buffer room and the primary engineering control work together to facilitate good work practice.

Recent interest in isolators, sparked by USP Chapter <797>, has led to the innovative marriage of unidirectional airflow, which has been used in BSCs, with barrier technology. Unidirectional airflow provides protection to the work area with flow instead of dilution. Particulate-laden air is swept from the work area with a wash of HEPA-filtered air. Filtered air washes over the work area into the front and rear grilles. Particles that are generated by the work are immediately washed into the returns and out of the work zone. Aseptic technique is further aided by using the flow of HEPA-filtered air to isolate the work from the gloved hand and to prevent cross-contamination from within the cham-

ber. The pharmacist can rely on this unidirectional airflow to assure that there is an area washed with HEPA-filtered, particle-free air that will reliably yield contamination-free work.

The use of unidirectional airflow makes it possible to use the same isolator to compound different products. Internal cross-contamination can be prevented by employing sound aseptic technique with an understanding of "working upstream." Particles generated by the compounding process and the operator will be carried to the returns and removed from the isolator. No source of contamination should ever be placed between the HEPA filter and the product. With an understanding of unidirectional airflow, products can be placed in an isolator to take advantage of the airflow. This is the basic concept behind working upstream.

Pressurization

Isolators used for sterile compounding are typically under positive pressure relative to the room unless they are used for hazardous drugs. In the event of a leak in the shell of the unit, air will flow out of the isolator, preventing room air from entering it. Devices used for containment of hazards are typically under negative pressure relative to the room. If the unit leaks, room air will flow

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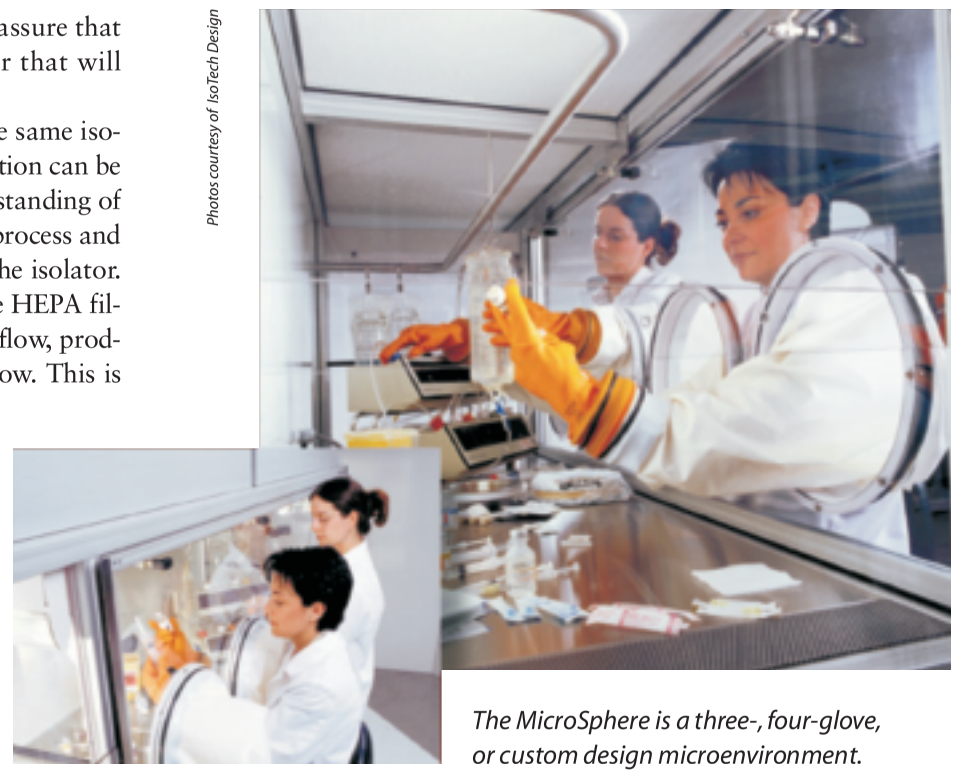
Photos courtesy of IsoTech Design



The MicroSphere is a three-, four-glove, or custom design microenvironment.

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into it, preventing what is inside from leaking out.

Isolators usually operate somewhere between 0.05˝ to 1.0˝ water column (w.c.). Unidirectional units will be near the lower end of the range while dilution control units usually operate closer to the upper end. Airflow in a unidirectional isolator is the primary separator between the product and the outside atmosphere, therefore lower pressure is acceptable. In a turbulent flow unit, the pressure differential between the isolator and the room is the only means of separation should a penetration in the shell occur. Therefore, these units tend to use a higher pressure differential.

The critical nature of sterile compounding requires a commitment to quality that must be embraced by the entire compounding staff.

Is a barrier isolator an alternative to a buffer room?

Much has been made of the USP Chapter <797> statement, "It is preferred, *but not necessary*, to locate barrier isolators within such a buffer air quality area." This loophole was left in the document to allow some flexibility, but not to promote the isolator as an alternative to a well thought-out facility. Hand washing, product flow, and facility cleaning must still be considered if you are using an isolator. The buffer room and the primary engineering control work together to facilitate good work practice. An isolator may allow some concessions in buffer room design, but is not an alternative to a buffer room. The FDA is very clear on this subject in their guide for aseptic processing (*Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*): "A Class 100,000 (ISO 8) background is commonly used based on consideration of isolator design and manufacturing situations. An aseptic processing isolator should not be located in an unclassified room."

Photo courtesy of The Baker Company

The ChemoSHIELD connects to the exhaust system for venting to the outdoors.

Summary

Barrier isolators can be a viable option as the primary engineering control for compounding sterile products. While they should not be used instead of a buffer room, they may allow some concessions in buffer room design. Many different isolator designs are now available. When shopping for an isolator, the most critical decision is whether to use turbulent flow or unidirectional airflow. Compounding of sterile products is most commonly associated with unidirectional airflow.

The critical nature of sterile compounding requires a commitment to quality that must be embraced by the entire compounding staff. Contamination is an unseen enemy that can be controlled with proper facilities and technique. The new environmental requirements called for by USP Chapter <797> promise to have a positive effect on overall quality. Innovative engineering controls are being developed to make the transition to more stringent facility requirements easier. P&P

James T. Wagner, principal of Controlled Environment Consulting, in Bethlehem, Pennsylvania provides expertise in critical environments, with over 25 years experience evaluating facilities used for aseptic processing as well as laboratories and manufacturing facilities handling hazardous substances. He has served on many industry standards writing committees, among them, the NSF std. 49 for Class II Biological Safety Cabinet, and the Institute of Environmental Sciences and Technology for various Cleanroom standards.

Additional Sources for Sterile Compounding Information:

Controlled Environment Consulting ..... jimwagner@fast.net
CETA Applications Guide ..... www.cetainternational.org
NIOSH Alert www.cdc.gov/niosh/docs/2004-HazDrugAlert
USFDA Guidance for Industry ..... www.fda.gov/cder/guidance
USP Chapter <797> ..... www.usp.org

Where to find it:

The Baker Company ..... circle reader service #29
Containment Technologies Group ..... circle reader service #60
Germfree Laboratories ..... circle reader service #70
Innovative Technology ..... circle reader service #80
IsoTech Design ..... circle reader service #90
NuAire ..... circle reader service #100