

Aseptic Processing Guidelines and Innovative Engineering Boost Appeal of Barrier Isolators

Maribel Rios

initial costs of operation, and confusion about validation. Two developments, however, may now change the industry's collective mindset: an increase in innovative, customized designs that make it possible to use barrier isolators in applications such as tableting and containment of highly potent compounds and, most important, the release of FDA's long-awaited revised CGMP Draft Guidance "Sterile Drug Products Produced by Aseptic Processing," in September 2003.

Big technology in smaller packages

A fully integrated barrier isolation system is more than just a barrier separating the process from the operator. As explained by Patrice Cloué, director of corporate technology at la Calhène (Rush City, MN), "The barrier itself isn't enough. You need

to have a means to go in and out, a means to manipulate inside it, and a means to create the internal environment. If you miss one of these items, you have an incomplete system." Successful design requires consideration of all the parts unique to the system, including the equipment being enclosed, glove system, air handling, and transfer ports.

Design. Although construction materials are generally standard, isolator design often is customized according to the equipment and the application. Says Brian Smith, applications engineering manager at Carlisle Life Sciences (New Lisbon, WI), "About 90% of my personal experience with engineering these systems has been in custom applications. Every piece of equipment is different, and every customer has different ideas about how to handle containment or the aseptic isolation of a process."

Most equipment is not designed for operation within barrier isolators. The equipment manufacturer, isolator engineer, and pharmaceutical manufacturer must col-

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FDA's aseptic processing draft guidance and the industry's state-of-the-art isolator technologies **prepare manufacturers for the next generation** of contamination control solutions.

Today, some of the industry's top pharmaceutical researchers are controlling, micromanaging, and tenaciously refusing to think "outside the box." And that is exactly how it should be.

In fact, these traits are essential to developing state-of-the-art barrier isolation systems because what is controlled is contamination, what is managed is micro-particulates, and what is in the "box" is valuable product.

Barrier isolators are not new. They've been used for some time to conduct specific tasks such as sterility testing. However, only in the past 10–15 years has the pharmaceutical industry begun using them to enclose processing equipment and to build entire operations as stand-alone, integrated systems, typically for aseptic processes such as the filling and closing of vials, ampuls, and cartridges.

Still, manufacturers have been slow to implement the technology, in part, because of concerns about regulatory acceptance,



Contained potent tableting process (from Carlisle Life Sciences; photo shows Fette model 1090 WIP tablet press).



Tablet press with barrier isolation technology (EnGuard Systems).

laborate to develop a long-term design solution. “One can’t simply place a box around existing equipment,” says John Kirk, vice-president of sales at Bosch Packaging Technology (Minneapolis, MN). “When the technology started,” he says, “people were taking filling machines designed for cleanrooms and then just putting isolators around them. That was not a very good solution because those fillers were not designed for isolation. They were not designed to be sterilized, and they were not designed to have access through glove ports.”

Yet, by modifying existing equipment, successful integration of an isolation system is possible. “The key to isolation,” says Smith, “is knowing the piece of equipment that you are isolating and the process—not just how it runs, but how the customer wants to use it.” In addition, he recommends that manufacturers become aware of what possibly could come up as a maintenance issue when the system is in process. Moreover, a company should inquire about the cleaning of the equipment, including any parts that must be removed for this process. “That is half the battle,” says Smith, “to understand how it disassembles and how you can clean it.”

An example of the successful integration of barrier isolators with existing equipment is their use in nonaseptic (containment) applications. Engineers at Carlisle Life Sciences designed an isolation system for an existing tablet compression process for potent compounds. In this case, the system comprised three separate isolation modules: an isolated tablet press, a deduster–metal-check isolator, and a tablet-testing isolator that are connected using rapid transfer ports. “Although we could have made hard connections between the modules,” says Smith, “the customer wanted two of the units (the tablet check isolator and the deduster–metal detector isolator) to be mobile and the other unit (the tablet press) to be stationary.”

In some cases, the ideal solution is to design an equipment line specifically for operation inside of a barrier isolator. One example of such a system is Bosch Packaging’s MAFS and FLM series of vial fillers. The company designed the filler equipment from scratch for use within barrier isolators.

As Bosch’s Kirk explains, “Whereas a traditional filler has a horizontal tabletop with the mechanics such as the electric motors and the servo drives below the tabletop, the FLM and MAFS systems have vertical walls. The mechanics are on the side, and all of the conveyers and filling systems are ‘hung off’ the wall.” This design made the filler more compact than a traditional style, allowing access through glove ports and eliminating the need to reach over the open vials. In addition, the system includes a drain at the bottom for wash down capability. “The wash down capability has only been applied a few times,” says Kirk, “but we see it as a potential future enhancement for the isolators—to have in a sense a clean-in place capability inside the isolator. The vertical wall is more conducive to that.”

Glove systems. Hank Rahe, technical advisor for Containment Technologies Group and EnGuard Systems (Indianapolis, IN), says that an essential part of any well-designed barrier isolator is the ergonomics or functionality of the system. “To be functional you have to be able to reach things, manipulate things, and get things in and out,” says Rahe, “and that has to do with the design, as well as the location, of the gloves.”

Rahe points out that when companies started integrating equipment inside the isolators, the ergonomics of interacting inside the box became a much more important issue. “There’s been a lot more attention to detail in this area, and it continues to be an area people are working on especially as designs get more and more complex,” says Rahe.

From a regulatory standpoint, poor glove integrity poses a great contamination risk. In fact, FDA considers a faulty glove assembly to be “a critical breach of isolator integrity” that can be “of serious consequence.” Current recommendations call for visual inspection of the gloves for macroscopic physical defects and the performance of routine mechanical integrity tests.

Airflow and ventilation. Airflow requirements inside barrier isolators have traditionally been a source of confusion and debate among isolator manufacturers and end users. Currently, FDA recommends that the interior of an isolator being used for aseptic processing meet a minimum of Class 100 (ISO 5) standards.

FDA does not include the term *barrier isolator* in the aseptic processing guidelines, opting in-



Left: front view of a sterilization module. Right: sterilization module with a DPTE system (la Calhène).



stead to include the more-precise terms *barrier* and *isolator*. FDA also clearly distinguishes between open and closed aseptic processing isolators, with one of the main differences being the type of airflow allowed. Explains Richard Friedman, Team Leader, Guidance and Policy Team, Division of Manufacturing and Product Quality at FDA, "You can describe an isolator as a type of barrier. In other words, it is a full barrier." Turbulent flow is normally acceptable within closed aseptic processing isolators; that is, isolators that use connections with auxiliary equipment for material transfer. This differs from unidirectional airflow, which, according to the draft guidance, is designed to "sweep over and away from exposed sterile materials, product, and container closures" to prevent turbulence or stagnant airflow. Open aseptic processing isolators include openings to the outside environment (such as for material transfer), with overpressure conditions and local HEPA-filtered, unidirectional airflow.

Isolator manufacturers are increasingly receiving requests to provide "enhanced" air-handling conditions to meet custom applications. According to Carlisle's Smith, "HEPA-filtered ventilation systems are typical, but sometimes we receive requests for ULPA filters as well as unidirectional airflow and turbulent airflow." Smith has also seen an increase in requests for special environmental conditions such as low-oxygen environments and temperature and humidity control capabilities. "All of these features are now routine requests," says Smith.

Air pressure differential. Isolation systems are used for two purposes: to protect the product from the operator and to protect the operator from the product. In aseptic operations, isolators are designed mainly to protect the product from the operator. These systems maintain the required sterility assurance level not only by physically separating an operator from the process and reducing the volume of space around the equipment but also by providing a positive pressure environment around openings.

Positive pressure conditions are necessary to meet Class 100 standards and reduce the risk of product

contamination. Contamination remains a top concern for good reason: FDA has stated that nearly all drugs recalled because of nonsterility or lack of sterility assurance between 1980 and 2000 were produced under aseptic processing conditions. In fact, la Calhène's Cloué estimates that currently 99% of barrier isolation applications for sterile production are positive pressure.

Maintaining a stable positive pressure environment inside an isolator can be a challenge. Differences in pressure may result from simple changes such as reducing the inside volume. As observed by Cloué, "In a closed system, simply putting your hands in the gloves reduces the interior volume, which changes the pressure. The same is true when you remove your hands. You're going to increase the volume of the isolator, so the pressure is going to drop." One way to compensate for these fluctuations is through the use of pressure sensors configured to automatically modulate the speed of airflow fans. Says Cloué, "If you're decreasing the volume inside the isolator, you want the system to automatically send less air inside in order to stabilize the pressure."

Transfer systems. One of the main differences between different types of isolators is the method by which items are introduced and removed. Says Cloué, "An isolator is always approximately the same, but as opposed to just a stainless steel box with windows, the real talent in isolator design can be seen in the transfer system, the ergonomics, and the ventilation."

Of the three aspects, however, the transfer system is perhaps the greatest threat to a potential breach in the sterility of the interior. Various configurations of rapid transfer ports are now commercially available, but companies are continuously working on and offering new designs.

For example, la Calhène's current technology, the "BetaBag" system, incorporates the company's DPTE dock (for *dispositif pour transfert étanche*, French for "leaktight transfer system"). The system is designed to eliminate the need for sterilization of the components at the transfer site and can be used to introduce materials in the same condition as the inside of the isolator. The system also can be used to remove samples and waste. "It's basically the workhorse of an isolator," explains Cloué, "the system allows the operator to make the transfer without having to sterilize in between."

New systems for sterilizing components at the point of transfer also have been developed. For example, Millipore (Billerica, MA) recently com-



Transfer systems are designed to provide fast, easy, and reliable transfer of sterile components or liquids into pharmaceutical filling environments, including new or existing barrier isolators (shown above: "SafePass" sterile transfer system, Millipore).

pleted its "SafePass" technology that consists of a transfer port with the company's patented UV sterilizing source. Says Jim Furey, product manager for disposable technologies at Millipore, "The UV light creates a 'validatable sterile condition' at the barrier-transfer interface."

SafePass containers are filled with components required for transfer and then sterilized. After use, the containers can be discarded, thereby eliminating the need for cleaning and handling. "The goal was to provide a system that provided not only the advantage of a secure sterile transfer," says Furey, "but also a cost-effective, flexible, and convenient alternative to other methods of transferring components into a barrier isolator."

Other point-of-transfer sterilization systems use alternative technology. For example, Central Research Laboratories's "Sterilizable Transfer Port" uses the company's patented dry-heat technology for sterilizing process items.

An "unprecedented" draft guidance

The rapid pace of isolation technology advancement appears to have paid off. Two months ago, in FDA's newly drafted aseptic processing guidelines, the industry received not only formal approval from the agency but also the words that manufacturers and end users had hoped to see: "A well-designed positive pressure isolator, supported by adequate procedures for its maintenance, monitoring, and control offers tangible advantages over classical aseptic processing, including fewer opportunities for microbial contamination during processing."

"FDA doesn't usually make this kind of statement," says FDA's Friedman. "The central tangible advantage is lower contamination risk by greatly removing the direct interaction of a gowned operator with the Class 100 environ-

ment. By essentially setting a wall between them, there is a pronounced enhancement of product protection, as long as the design is a sound one and the isolator is maintained and controlled appropriately."

The fact that the statement was included in the draft guidance is especially meaningful considering the extensive process that was used to reach a consensus. The draft guidance was in part the result of FDA's work with the Product Quality Research Institute (PQRI). PQRI consists of 11 industry organizations, including PhRMA, which is the main lobbying organization of the pharmaceutical industry. Says Friedman, "The outreach is unprecedented for a CGMP document and very exciting to me because the industry and the public have had a chance to preview our current thinking and to provide us with a significant amount of early input. The FDA Advisory Committee meeting and PQRI Aseptic Processing Workgroup inputs were of tremendous assistance in facilitating resolution of many often-discussed but, until now, unsettled technical issues."

Friedman explains that the group thought the draft guidance "provided enough of a broad overview of issues that we consider most important. It also seems to provide enough detail in areas where there has been confusion. There is hopefully sufficient detail here that further guidance on isolators may not be necessary at this time. If public comments tell us that more detail is needed or we see a need at some point in the future, we will certainly consider enhancing the degree of guidance written for isolators."

Making room for future technologies

As important as the draft guidance is for clarifying relevant issues, equally important for researchers is the fact that the document welcomes alternative approaches to meeting regulatory requirements. As Friedman explains, "The goal of this guidance and of the Pharmaceutical CGMPs in the 21st Century Initiative is to encourage better manufacturing facilities and processes. We feel we are fostering through this guidance an environment in which new technologies and different CGMP approaches can flourish."

According to Friedman, "Coming to a consensus was a challenging task because it's still a somewhat new manufacturing technology and there are still things to learn." Examples of areas that still may need to be resolved include biological indicators and the lack of an accepted method for D-value determination. The D-value method determines the time of exposure at a given temperature that causes a one-log or 90% reduction in the population of a specific microorganism. In-



Photo and sketch of FLM 4080 liquid filler with barrier isolator (introduced in 2002 by Bosch Packaging Technology).

coming lot D-value and microbiological count define the quality of a biological indicator. The challenge microorganism then is used to analyze the efficiency of the sterilization cycle.

Explains Friedman, "A better definition of the specific type or types of equipment that can accommodate D-value determination is needed. Another issue relates to the resistance of the biological indicator on a given substrate and the influences of material composition, quality, and porosity. It is an area that should be considered for further basic science studies."

Friedman considers a measuring technology for H_2O_2 , or other chemical sporicidal agents, to be another issue for discussion because vapor-phase hydrogen peroxide (VHP) is currently the most common sanitizing agent. "There are a number of areas that can be enhanced or tweaked," says Friedman, "and we generally aim to avoid making any pronouncements on areas that haven't been well-enough studied and articulated in the literature." Friedman stresses that the agency can't

write comprehensive guidance without sufficient data about specific topics. "In those cases where there is no empirical or scientific evidence available to answer certain questions, we've remained silent. In cases where some information exists and it was demanded of us that we say something, we prepared limited language summarizing the current science."

Biodecontamination alternatives

While some researchers work on issues related to the operation of isolation systems such as the transfer mechanisms and the airflow systems, others are turning their attention to finding alternative methods for their decontamination. Although VHP is by far the most popular biodecontamination agent in the industry, the potential for using chlorine dioxide gas has gained some attention as an alternative.

The selection of the method depends on several factors, including cost, application, turnaround time, and risk of residual by-products. As observed by Cloué, "The use of chlorine dioxide, for example, is very efficient. A big advantage is that it is a gas as opposed to a vapor. That means you have much better diffusion and the system is easier to purge out after sterilization."

However, as Cloué observes, the use of chlorine dioxide gas also has some disadvantages: "It's more difficult to enclose. For a hydrogen peroxide vapor, you have an operational exposure limit (OEL) of 1 ppm, that means you can't have more than 1 ppm of the vapor outside of the isolator, while for the gas [the OEL] is 0.1 ppm outside of the isolator, which means that the isolator must be 10 times better in terms of gas tightness." Another negative aspect of chlorine dioxide gas is its high corrosivity, which means that any piece of machinery and any tools inside the isolator will need to be resistant to corrosion.

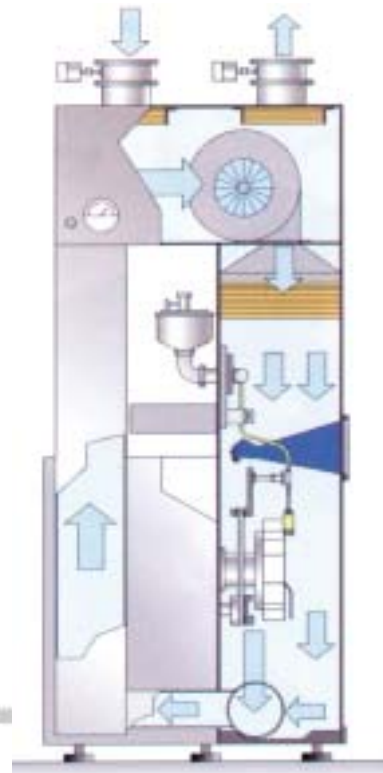
VHP methods also have patent protection, which can make their use an expensive process. Jim Wagner, president and CEO of Micro-Clean (Bethlehem, PA) believes that fact may motivate some manufacturers to seek more-affordable alternatives. Says Wagner, "People are looking for much more flexibility, especially when it comes to cost, and a lot of people are rooting that chlorine dioxide can be developed into a method that works well." Still, Wagner doesn't see chlorine dioxide as a commercially viable alternative yet, although he believes it will be. "Competition is always good," he says, "Even if all that chlorine dioxide ever does is make VHP more cost effective, then it's a good thing."

Validation and the need for due diligence

The introduction of a new technology in a highly regulated industry always creates a perceived risk, especially when it comes to validation. The many parts of an integrated barrier isolator system means there are more processes to validate. As isolator systems become increasingly complex, the validation and documentation process

becomes even more time-consuming. Some companies simply cannot justify devoting the time or resources to resolving new-technology validation issues.

For example, one source of confusion is the air-handling system. Certifying an isolator requires information about all of the parameters, including what type of air-flow is needed, why that type of airflow is required, the number of air changes, ve-



Cross-section showing unidirectional airflow patterns (FLM 4080, Bosch Packaging Technology).

locities, and how the HEPA filters are challenged. Says Wagner, "Quite often companies don't have this information because they didn't do a very good job at validating it to begin with. To simply say all you need is to get the right pressure in this chamber is not as responsible as it should be." He recommends that users perform due diligence before integrating an isolator system and establish acceptance criteria as part of a "validation master plan" before a certifier is called in.

One way Bosch Packaging is meeting the validation challenge is by changing the skills of its staff. The company traditionally consisted mainly of mechanical and electrical engineers, but it now employs several microbiologists and pharmacists to work on validation issues. "We are no longer just machine builders," says Kirk. "Five or seven years ago people were trying to figure out how to validate isolators. Most of those questions have been answered. There were some big learning curves to go through, and we're not through all of them, but we're up the learning curve quite a ways."

Friedman points out that the newly drafted guidelines "leave significant flex-



ibility” for manufacturers, even though the agency has the option to provide regulations. “By not establishing mandatory standards, alternate approaches can be used other than what we state in our aseptic processing guidance or any other guidance published by FDA,” says Friedman. These other approaches, he says, “will be considered in an open-minded fashion. No two processes or isolators are alike, and

the product requirements are not always the same. We would entertain different approaches in these and other cases.” Ultimately, Friedman emphasizes, the Pharmaceutical CGMPs in the 21st Century Initiative is “meant to encourage more consistent and predictable processes.”

Future applications

For as much as technical advancements and

regulatory acceptance help increase the adoption of isolator technology, perhaps the final and most challenging hurdle is convincing the industry itself about its potential opportunities. Toward this effort, isolator manufacturers are trying to show how barrier isolators can be used in areas other than aseptic filling and closing of parenteral products.

For example, Carlisle Life Sciences is working on synthesis isolators that enclose pressure filter and tray-drying processes all in one isolator. These systems have been designed mainly for contract bulk chemical manufacturers. On the aseptic side, the company also is working on the aseptic filling of potent pharmaceuticals. The project will handle medium-speed vial filling of liquids, the lyophilizing of the liquid, and various solvent filling.

One hot-button issue right now is the use of “containment” isolators for the manufacture of highly potent compounds (e.g., cancer therapies). Rising consumer demands for once-a-day or even once-a-week dosings is leading to a new class of drugs that are much more chemically active. Very small amounts of these substances can affect a person. To protect operators from these products, isolators must operate under negative pressure differentials. However, if the isolator is in an environment that is less stringent than Class 100 conditions, negative-pressure systems may pull lower quality air into the isolator’s interior.

Currently, there is no industry consensus or accepted guidance on the use of containment isolators for this application (FDA’s purview is the protection of drug quality, whereas the protection of the worker falls within OSHA jurisdiction). However, a few companies, including Carlisle Life Sciences, are currently working on containment isolators for tableting. Says Rahe, “One company had a multi-barrier system such that the inside barrier was negative pressure, and a second small barrier around it was positive pressure. That’s probably the most exotic one I’ve seen.”

Regardless of the solution, the manufacture of highly potent or cytotoxic compounds is likely to involve barrier isolator systems, further driving the demand for this technology. Says Rahe, “It keeps us happily busy.” **PT**

