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**Barrier and
isolation systems**

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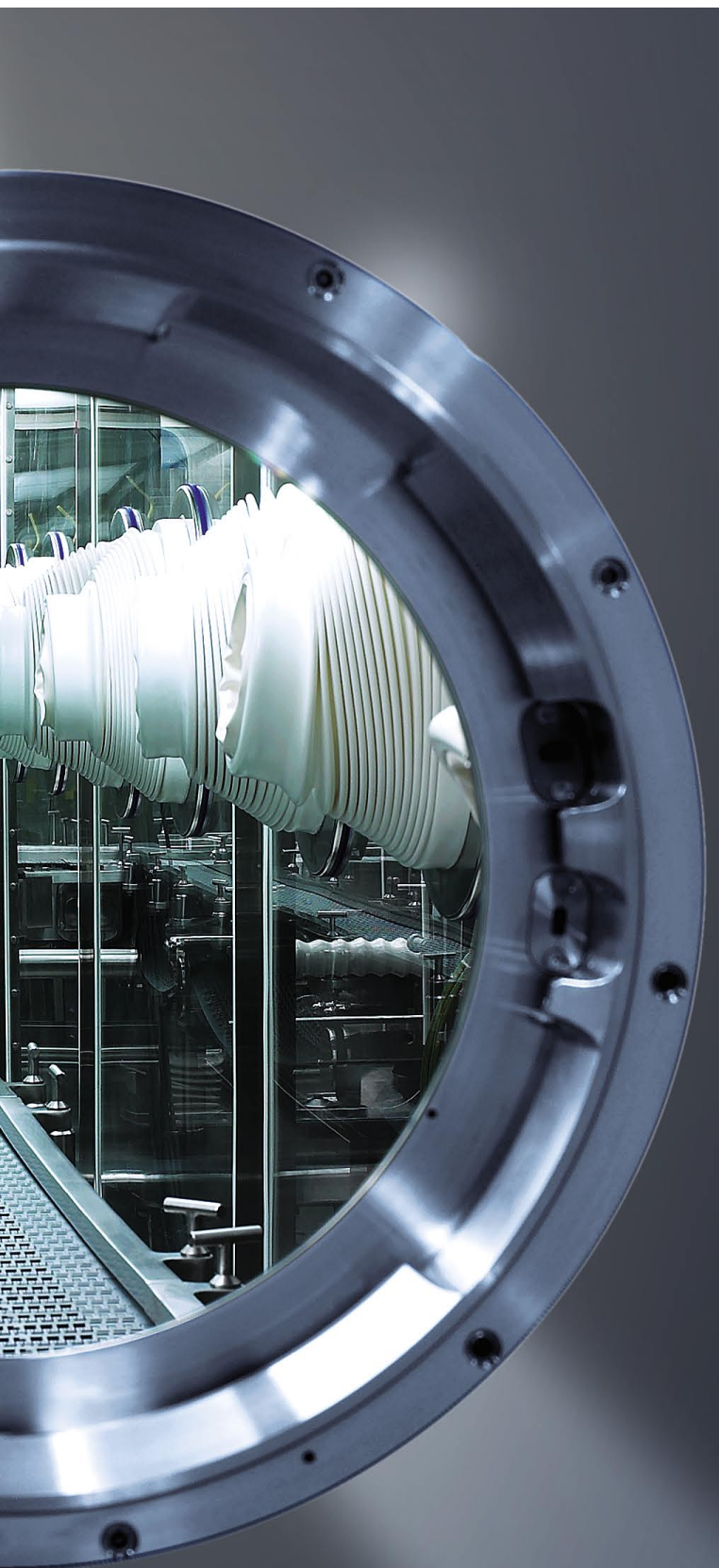
**Clean-in-place
equipment**

Barrier and isolation systems: Technology in transition

New medicines bring new concerns for product and personnel protection, and the cleanroom industry is evolving to cope with these challenges in two key areas: pharmaceutical manufacturing and the compounding of sterile preparations (CSP) within hospitals and pharmacies.

By John Williamson





The life sciences industry, from manufacturers to compounders to the various regulatory and standards agencies involved, is in the midst of extraordinary changes, the end of which may never be in sight. Underlying this is the fact that drugs are becoming more complex.

“New treatments call for more aseptic potent or aseptic cytotoxic drugs, which can have an extremely adverse affect on personnel should they become exposed,” says Bill Friedheim, technical sales representative for Skan US, Inc. (Broomfield, CO). “At the same time, these drugs must be protected from contamination, the largest source of which is people.”

Shrinking spaces

It is an environment where laminar flow air benches and cabinets are becoming less relevant and where constructing traditional ISO Class 100 cleanrooms also often proves financially impractical.

“Cleanrooms can be expensive places, ranging from \$200 to \$2,500 per square foot in the life sciences industry,” says Richard Matthews, chairman of Filtration Technology, Inc. (Greensboro, NC). “Such expense is driving industry to look for better ways to enclose critical process areas into smaller spaces. Instead of classifying an entire room as a cleanroom, concentrate on those spaces where a controlled environment is critical. Self-contained, controlled clean environment enclosures around a critical core process are an economical alternative.”

The changing paradigm is causing new thinking in containment technology and how cleanrooms and cleanroom processes are incorporated into manufacturing and compounding sterile preparations.

“While all agree that protection is paramount, there is disagreement on terminology used to describe equipment involved,” says James Agalloco, president of Agalloco & Associates (Belle Mead, NJ). “For example, definitions of an isolator or a barrier can differ within the life sciences industry, across national borders, within applications such as hospitals and labs and even within a single organization.”

Among the life sciences terms used for containment devices are enhanced clean devices, barriers, isolation systems and restrictive access barrier systems (RABS) as distinguished from “cleanrooms” as covered under ISO 14644 standards.

The IEST, which serves as the secretariat to ISO Technical Committee 209, Cleanrooms and associated controlled environments, went through several iterations in developing ISO 14644-7, Cleanrooms and associated controlled environments—Part 7, which is the standard relating to these devices. The working group wrestled with a number of terms to describe what the standard covers and how the products differ from conventional cleanrooms. It settled upon the term separative devices, defined in the standard title as clean air hoods, gloveboxes, isolators and minienvironments.

“The standard purposely stayed away from being industry-specific,” Agalloco explains. “It was left to the users and equipment providers to iron out the details of just what is needed—while hoping they speak the same language.

“For example,” he says, “there is a difference between a barrier and an isolation system, although the isolation system can have a barrier. Barriers can be breached, like jumping the line for playoff

tickets. But isolation systems are like Fort Knox, which can, but should not be, breached without very strict procedures. The weakness of a true isolation system is generally the use of gloves, also known as access devices. Thus, we compare the use of RABS to the 'perfect' isolator that, via total automation, functions independently of human intervention."

RABS and isolators: An ISPE definition

In August 2006, the International Society for Pharmaceutical Engineering (ISPE) issued a definition describing RABS. Jack Lysfjord, vice president of consulting for the Valicare Division of Bosch Packaging Technology (Brooklyn Park, MN), chaired the ISPE definition committee and provides commentary on the differences between RABS and isolators.

"Both RABS and isolators serve as barriers between operators and the ISO Class 5 critical zones where fill-finish operations take place," he says. "Both use rigid walls, glove ports and transfer ports for components. RABS are typically open on the bottom and provide product protection by airflow. In contrast, isolators provide product protection by overpressure or perhaps negative pressure for containment applications. RABS operate in an ISO Class 7 surrounding room and isolators in an ISO Class 8 surrounding room."

Lysfjord notes that before beginning batch manufacture in a RABS there must be thorough high-level manual disinfection procedures for all non-product contact surfaces using an appropriate sporicidal agent. Isolators typically use an automated vapor high-level disinfection.

"While the design intent for RABS is to operate as closed at all times, operator intervention is permitted with product protection provided through the use of HEPA or other filters, a controlled unidirectional airflow and an upgraded local surrounding classification to ISO 5," he says. "The intent is to always maintain ISO 5 in the critical zone."

"Some firms are using RABS that are never opened during operations and are achieving very good results," Lysfjord says. "Others have RABS that, while operating closed, may have rare exceptional events that require opening of the enclosure. Such interventions create product risk and are considered deviations that

must be documented so that any risk to the exposed sterile product can be assessed."

Operators must be properly attired. System design and process control are as much a matter of how you do it as how you defend your position to the FDA during an inspection.

"It is important to view RABS as a concept for enhancing conventional equipment and tightening up procedures instead of making excessive equipment investments," Lysfjord explains. "Although they are not as robust as isolators, they can provide initial capital cost savings and are certainly more advanced than traditional conventional cleanroom operations."

Isolator process equipment systems are experiencing a paradigm shift in cost perception, Lysfjord says. "The system does much more to protect the product while saving other capital and operational costs. With isolators, the facility footprint is smaller, and multiple-line operation results in reduced personnel, reduced HVAC and utility costs and reduced gowning and environmental monitoring costs."

Smart pharma design

Julian Wilkins, vice president and senior consultant for PharmaConsultUS, Inc. (Bridgewater, NJ), says factors reshaping the life sciences industry include trends toward live vaccines, small molecules, larger molecule combination and small-volume, high-value, highly targeted drugs.

"This means high-throughput manufacturing churning out millions and millions of dosages is becoming impractical," Wilkins believes. "Constructing cleanrooms under the old operating standard to meet new market realities would cost and waste billions. Instead, we're moving to highly flexible facilities that meet stringent standards while being tailored to small product runs."

Put another way, the trend in pharmaceutical manufacturing is toward continuous small-scale production in facilities that will minimize the need for conventional cleanrooms.

The mini-cleanroom is geared to produce small-volume, high-value drugs as opposed to mass-produced products. "This is lean manufacturing," Wilkins says. "It uses continuously running, closed-production equipment that is easy to monitor from the

outside." Major added benefits are substantial cuts in labor, gowning and other costs.

According to Wilkins, smart pharma design includes several continuous-output, isolator-based production lines that allow a stepwise increase to suit demand and a stepwise decrease as demand falls. "Such a scenario allows downtime without significant impact on throughput," he says. "The lines are adaptable, so that they can be reconfigured for other products. Product-contact parts can be used for other compounds where science-based risk assessment is made, or can be product dedicated. With multiple mini-lines available, maintenance can be scheduled. The plant gains production flexibility because it does not rely on a single process system."

"Pharmaceutical production equipment must go through a design revolution," Wilkins says. "For instance, little has been done in the oral solid dosage (OSD) area. OSD design would move away from the unit operations that our grandfathers would recognize. Closed systems would be used to provide a product environment, while the operator would be in a separate environment tailored to meet human comfort. The result would be a cleanroom-in-a-box using a fraction of the energy currently used in conventional cleanrooms."

Wilkins says that the biotech industry—the architects, engineers, safety, compliance, R&D, QC, production, packaging and other personnel—must get on board with this thinking.

What's the holdup?

Despite the apparent benefits of new aseptic processing systems, the industry has been slow to respond, especially in the United States. Sterling Kline, R.A., senior director of project development for Integrated Project Systems (Lafayette Hill, PA), says one of the reasons is that pharma failed to take ownership of the challenge.

"There's an obligation in the pharma industry to achieve aseptic processing, and the reason is patient protection," he says. "That is the position of the Food and Drug Administration (FDA), and it's up to the manufacturers and compounders to prove that their processes achieve that end. It's not up to the FDA to tell them how to make it happen."

"This was a hurdle," Kline continues. "Although isolator technology was proven in Europe, the attitude of the FDA was 'show me.'"



Figure 1. An isolator system showing (from left to right) a rotary washer, a sterilization tunnel, an isolator with an accumulation area, filler and stopper insertion station, and a RABS hood with a capping station. Photo courtesy of Bosch Packaging Technology.

This involved companies making financial and other resource commitments to prove the process. Today, however, there has been positive progress. For example, three pharma companies, the 'LUM' group (Lilly, Upjohn, Merck), stepped up to the challenge and made investments to prove the process, without a guarantee that the FDA would accept the findings. Today the FDA considers isolators, specialized barriers and robotic systems as among the advances in aseptic processing technology.

Another key aseptic operating issue was resolved with the reduction of vaporized hydrogen peroxide (VHP) cleaning cycles from eighteen hours to three. This provided a positive impact on system flexibility.

Internal struggles have also often impeded progress. "Decisions on achieving advanced aseptic processing can be hampered due to conflicting objectives within a company," Kline says. "Management looks at financial performance and sees investment in a process it might not understand as a risk to that performance. This can lead to the position, 'If conventional cleanrooms work, why change?' Conversely, however, with the unit cost of some of today's formulations reaching astronomic levels, the risk of losing a batch of drugs due to contamination can likewise be extreme.

"Summing up," says Kline, "the challenge is to get people on board. The FDA accepts isolators as a means of achieving reproducible performance. Operating issues are being addressed. It comes down to the mindset of corporations and the people within; their attitudes, prejudices, being 'risk averse' and other notions of changing the way things are done."

There's no question that companies

thinking about advanced aseptic processing face important decisions. Fortunately, more data is available to help them. Valicare's Lysfjord says, "Looking at the big picture, designing and installing an advanced aseptic processing system must be well-thought-out, with the ultimate goal being validation by FDA and/or other agencies. We believe the best approach is a design of isolators and fillers where components work together while being fully integrated into the building power, HVAC and plumbing systems (see Fig. 1). System



Figure 2. SterilchemGARD® III Advance° Class II, Type B2 total exhaust cabinet. Typical applications include toxicology laboratories and similar facilities where microbiology, cell culture and pharmaceutical procedures are common. Photo courtesy of The Baker Company.

monitoring must be continuous. Similarly, personnel training is crucial in order to raise knowledge of cGMP aseptic processing to protect the product as well as containment of potent products to protect themselves."

Compounding sterile preparations

IEST 146447-7 addresses "separative devices" from the perspective of pharmaceutical manufacturing. Compounding sterile preparations at the corner pharmacy, in the hospital, in physicians' practice facilities and similar locations is addressed by United States Pharmacopeia Chapter 797 (USP <797>). It covers low, medium and high risk levels.

"Pharmacy compounders work in an environment substantially different from that of pharmaceutical manufacturers," says Henry D. (Hank) Rahe, technical advisor for Containment Technologies Group, Inc. (Indianapolis, IN). "That's because they take components from several sources and then manually sanitize them before compounding. Although the insides of the container are considered sterile, the outside of the container is not, due to touch contamination.

"Within this segment of the industry there are also a number of terms used to identify equipment," Rahe explains. "Examples include isolators, barrier isolators, biological safety cabinets and aseptic compounding isolators. Whatever the name used, however, the objectives are similar to those on the manufacturing side—product and personnel protection."

One firm, The Baker Company (Sanford, ME), uses the term isolators. "These replace open-fronted laminar flow cabinets in the aseptic preparation of drugs—mostly intravenous or parenteral—which are immediately given to patients," explains David Eagleson, vice president of business development. "Positive pressure isolators are used for sterility assurance in instances where drugs do not pose a hazard to the pharmacy worker, whereas negative pressure systems are used where such exposure is hazardous." The most common class of the latter are drugs used in chemotherapy.

"USP <797> provides guidelines for these activities, but changes are in the making," Rahe says. "Since 2006, more stringent proposals have been under review by the industry, attracting hundreds of comments, many of which are not favorable. For example," he

points out, “there is a high level of questioning on the validity and science of proposed revisions. But what is consistent between the original 2004 guidelines and the proposed 2006 revisions is that isolators are not required to be in a cleanroom and that they are recognized as superior tools for compounding because they provide high sterility assurance levels. In short, they are proven in practice because they eliminate touch contamination.”

Although the debate on the proposed revisions is having an impact on investment decisions within organizations impacted by <797>, until such time as the 2006 revisions are adopted, the 2004 recommendations remain in effect. Rahe says, “Organizations expecting a ‘final product’ won’t see it happen. That’s because the final product is the USP process itself, which allows for annual changes.”

Biological safety cabinets

Biological safety cabinets are another member of the barrier and containment system family, sharing many attributes and similarly charged with protecting people, product and the environment from biohazards and cross contamination during routine procedures (see Fig. 2).

“This is becoming increasingly important,” says Baker’s Eagleson. “Protection is provided in Biosafety Levels (BSL) 1, 2, 3 and 4 corresponding to Class I, II and III cabinets, with the latter specified for high-risk (BSL 3 and 4) biological agents. Standards are set and periodic testing is administered by NSF International through NSF/American National Standards Institute (ANSI) Standard 49.

“The highest BSL levels of agents must be handled in a Class III cabinet operating under negative pressure and with gas-tight construction,” Eagleson says. “Supply and exhaust air must also be suitably treated to protect the environment.” Cabinets are fitted with rubber gloves to provide the highest containment reliability consistent with high-risk agents. Some Class III cabinets used in containment laboratories (BSL 3 or 4) provide aseptic conditions within the work area.

Design features

There are many sources for equipment used in advanced aseptic processing and the selection procedure can be extremely complex. Decisions, made with the help of experts, should focus on the processing to be accomplished, maximizing efficiency and flexibility, and complying with

applicable standards. Several features can contribute to achieving these goals.

Equipment should be easy to clean and sanitize inside and out. Stainless steel, glass, high-performance scratch-resistant plastic and rounded corners contribute to this. Accessibility, spray guns, vacuum wands, well-placed drains and quick-drying capability are also pluses.

Conclusion

Choosing between conventional cleanrooms, RABS, isolators and their various configurations is not an easy task. As Kline notes, “Think of what you need to do, then design the process to make it happen.” Kline suggests setting up procedures in advance, focusing less on the building and more on the fact that you are making products. Isolator-based manufacturing can work in a variety of configurations, he says. “It works for vials and pre-filled syringes. Properly designed, it can work for mass production, and because it is easy to validate cleaning between batches, it works for generics and contract manufacturing.” 