Special Report

Pharma Industry Drives Innovation in Barrier/Isolation Design

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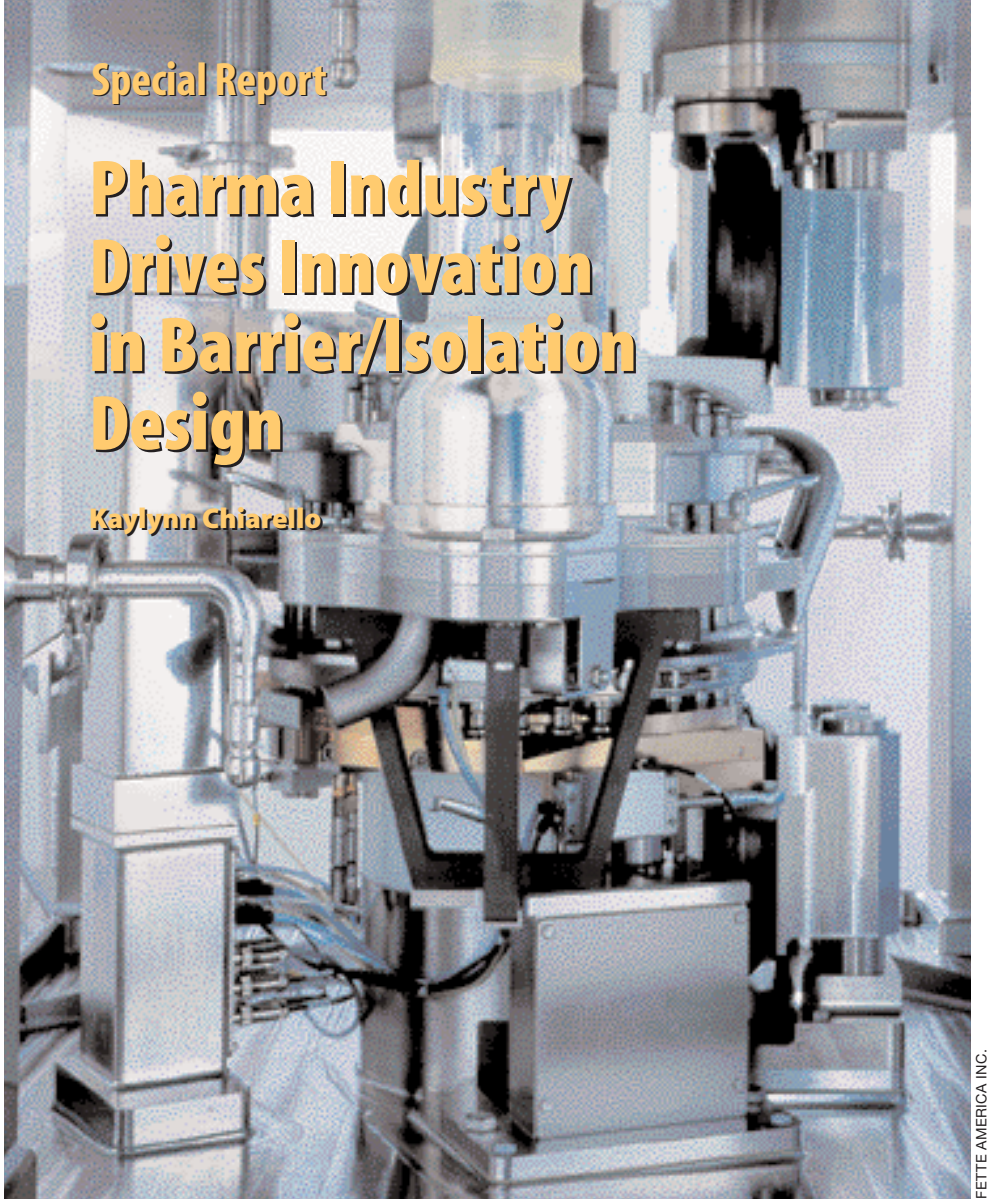


FETTE AMERICA INC.

Each piece of barrier/isolation equipment has a different purpose, and should be designed to meet not only the specialized requirements of the industry, but also those of the product being produced.

It's unlikely that the engineers who designed and built the first gloveboxes for the pharmaceutical industry anticipated the level of complexity to which the requirements for barrier/isolation equipment would evolve and grow. But pharmaceutical applications have regularly posed both challenging and conflicting demands. Today, companies are producing fragile, nanogram-sized, and in many cases, highly-potent compounds. Containment systems must therefore provide a reliable "barrier" between the hazardous substance and technicians, while at the same time, "isolating" the product from environmental and human-borne contaminants.

The need to accomplish both conflicting tasks while developing more efficient containment strategies overall has initiated a wave of innovative solutions in barrier/isolation equipment design and implementation. Systems are now being redesigned, reconfigured, and integrated into manufacturing lines in ways that were virtually unheard of as recently as 2–3 years ago.

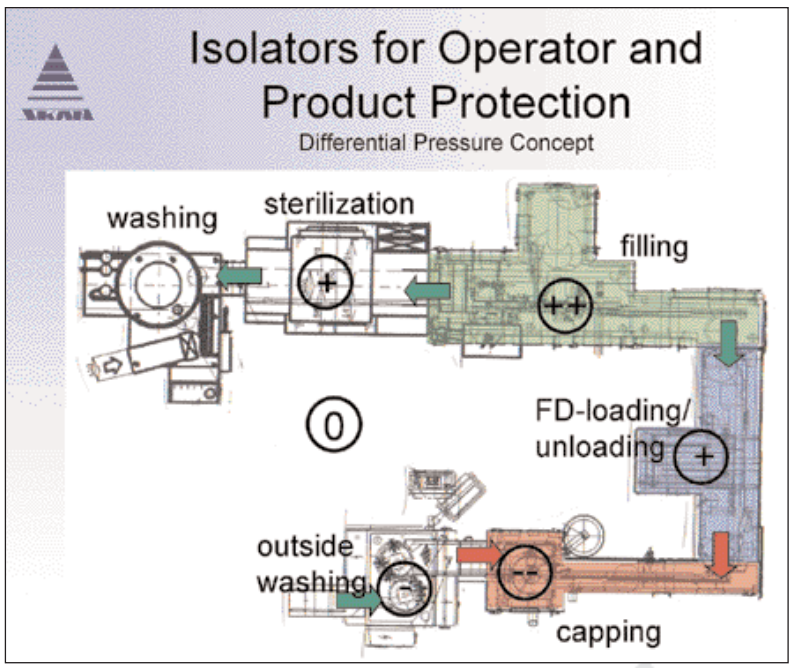
In their efforts to meet the demands of pharmaceutical barrier/isolation systems, one common principle has emerged among manufacturers: no two barrier/isolators should be exactly the same. Manufacturers are now recognizing that each piece of equipment has a different purpose, and therefore should be designed to not only meet the specialized requirements of the industry, but also those of the product being produced, the handling system used, and the skill level of the technicians managing the process.

Balancing quality and safety issues

The need to ensure both product quality and operator safety has long been a challenge for the pharmaceutical industry. To protect operators from hazardous substances, the Office of Health and Safety recommends the use of negative pressure within containment systems to prevent the escape of toxic substances. In contrast, FDA is concerned with protecting the product from the environment and recommends using positive pressure to prevent anything from infiltrating the system. "It's a big challenge to accommodate both requirements," remarks James J. Spolyar, principal of Aseptic Barrier Systems and a US agent for SKAN AG (Las Vegas, NV). "There are a lot of issues to resolve in terms of product handling, potential aerosols on the liquid side, and what to do if your process requires a freeze dryer."

For high-speed filling lines, SKAN is approaching the problem by building systems based on a differential pressure concept. Since one manufacturing line is often used to produce different types of products, SKAN's isolation systems allow for the adjustment of air pressure differentials to accommodate both toxic and nontoxic compounds.

The technique involves a two-zone air pressure system in which the entire manufacturing line from filling to unloading is run with gradations of positive and negative air flow depending on FDA recom-



Top: SKAN AG's (Basel, Switzerland) two-zone air pressure differential concept runs a manufacturing line with gradations of positive and negative air flow for product and operation protection.

Bottom: A barrier/isolation system designed by SKAN AG.

mendation or the client's specifications. For example, if a facility was filling a cytotoxic product in which a lyophilizer, or freeze-dryer, was needed, the accumulator would run at air pressure more positive than the tunnel and filler to eliminate the potential of any contamination migrating back into the tunnel.

Because FDA requires product protection during filling operations, the filling area is run with equal or more positive air pressure differentials in comparison to the lyophilizer. Unloading functions such as capping and exterior vial washing are always run with negative pressure to prevent powders from escaping into the air.

Monitoring air pressure differentials within a facility can itself be challenging. To address this issue, EaglePicher Pharmaceutical Services LLC's (Lenexa, KS) three-suite manufacturing facility has a computer-controlled air handling system that measures the air flow in each room. Sensors between suites measure and adjust the air pressure in the rooms so that it gets progressively more negative as you approach the hazardous product. "Basically, it's moving more air out of the room as you're heading in towards the production area," says Steve Greenwald, PhD, project manager at EaglePicher.

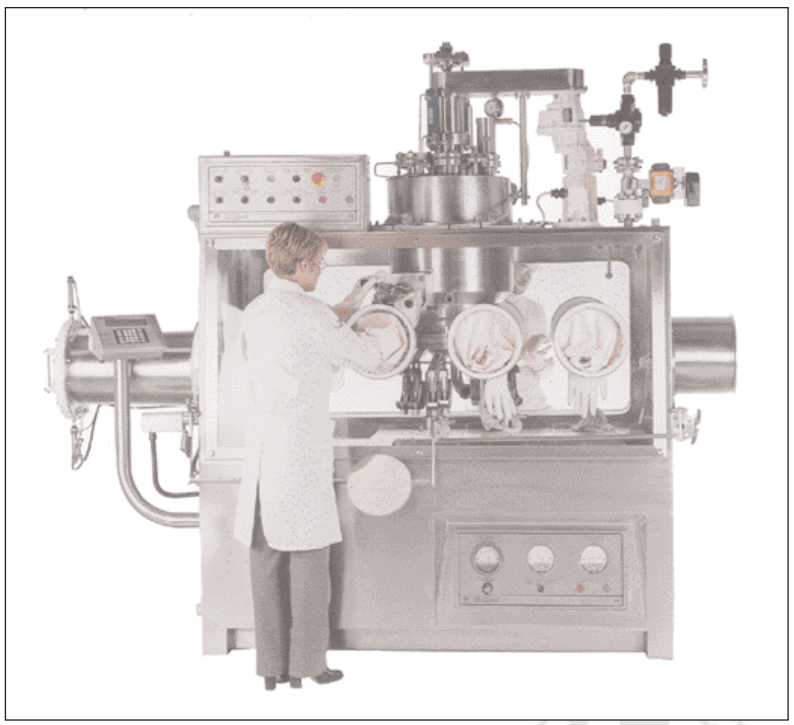
The most hazardous parts of the manufacturing process are conducted in containment. For example, a vacuum drying oven was integrated into a custom glovebox to prevent airborne materials from entering the air stream. "We're not using workers in protective gear as the primary form of containment," says Greenwald. "We designed the system so that the primary form of containment is carried out inside the barrier/isolation system."

Determining the containment plan

Gloveboxes may have roots in the nuclear industry, but manufacturers of barrier/isolation equipment now recognize that isolators must be refined to suit the needs of the pharmaceutical industry. For example, JetPharma Group's (Balerna, Switzerland) approach to barrier/isolation equipment design involves an examination of the entire process to determine which sections require isolation and how much is needed. Says Serge Lewithin, JetPharma's group commercial director, "Pharmaceutical products must be approached in a different way. Containment of pharmaceutical materials must be designed for the whole process."

Robert Piccirillo, containment technology director at Process Facilities, Inc. (Boston, MA), agrees. "You have to look at the complete manufacturing process and supply chain. Factors such as how you're bringing the product in and how you're packaging the product for the customer are also important to the isolation system's design and in choosing the right containment technology."

One approach in designing a total isolation plan may be based on operator risk potential. For example, if a company was manufacturing active pharmaceutical ingredients in powder form, the most potentially hazardous part of the process might be the filtering and drying stage in which substances have the potential to become airborne. According to Michelle Frisch, manager of US Technical Systems at Powder Systems Limited (US Office, Boise, ID), "If during a filtration and drying process system there wasn't a glovebox or bar-



Left and right: Powder Systems Limited (Liverpool, UK) has developed a barrier/isolation system in which slurries are filtered and dried under containment using a specially designed filter dryer system.

rier present, operators would risk exposure when the discharge hatch is opened and the powder is sampled or removed." For this reason, Powder Systems Limited has developed a barrier/isolation system in which slurries are filtered and dried in containment.

Although the drying process is performed in containment, the only part of the equipment that's inside the glovebox is where the product is discharged. Most of the mechanical drives, such as the agitator, are external to the glovebox, where they can be easily cleaned without posing a contamination risk.

Automation

As compounds become increasingly more potent and hazardous, there is growing pressure to remove human operators from the manufacturing environment entirely. "In an ideal scenario, the process would be so automated that human interaction would be minimized or eliminated," remarks John Kirk, vice-president of Liquid Pharmaceutical Packaging at Bosch Packaging Technology (Minneapolis, MN). However, as Hank Rahe, technical advisor for Containment Technologies Group and EnGuard Systems (Indianapolis, IN), points out, "It's not clear whether robotics will be able to handle the sophisticated manipulation required to handle fragile compounds."

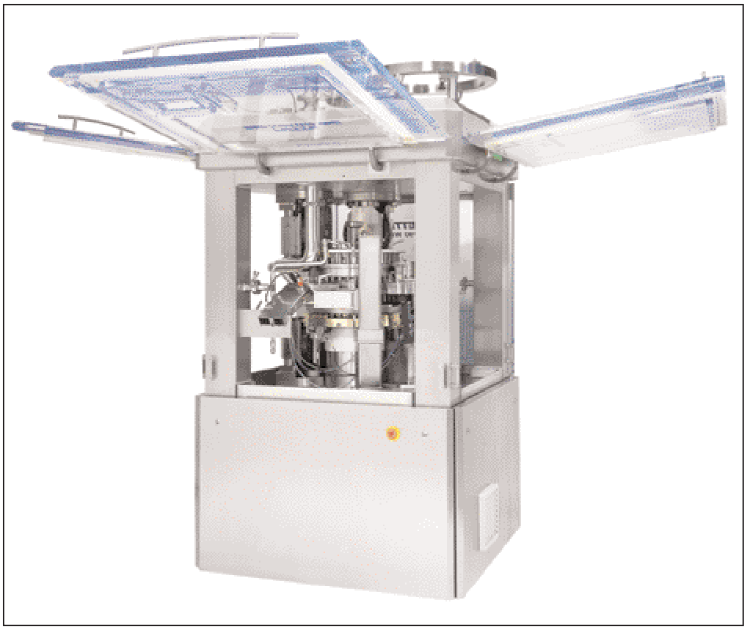
Though the pharmaceutical industry may not see perfected automated systems for several years, many companies are already experimenting with integrating robotics into isolation systems. For example, Bosch Packaging applies an automated "checkweigh" technology to vial filling lines. A robotic system removes vials from the line and weighs them before and after filling to measure whether the correct fill volume of the liquid is used. The entire process is performed in a barrier/isolation system to minimize operator involvement.

At the Achema 2003 conference in Frankfurt, Germany, Fette (Rockaway, NJ) debuted a completely contained system with an integrated robotics system for tableting highly potent material. The "driverless" transport system automatically removes and replaces turrets without operator intervention. Driven by electrical motors, the system works with a robotic arm that pulls out the tablet press after wash, puts it on an automated guided vehicle, and brings it back to a central station. "In systems that don't have wash-in-place (WIP) technology, mechanics have to manually clean and disassemble systems," notes Erik Barman, manager of Special Projects at Fette America Inc. "This system is completely unmanned so it can be cleaned and maintained without any operator intervention." Currently in trials, the system is capable of 24-h operation.

Understanding operator needs

Ergonomics. Although barrier/isolators have the capacity to achieve extremely low leakage levels, technicians must also use them properly if they are to provide full protection. Simple design changes in the shape of glove ports or the height of a machine can have a significant impact on whether isolators are used correctly and effectively. Observes Thomas M. Vorbach, managing director at JetPharma USA Inc., "If you make equipment more ergonomic and easier to handle, you get much greater productivity. I've seen sites that aren't user-friendly and the equipment doesn't get used."

A simple example of this, Rahe points out, is the redesign of gloves fitted to gloveboxes. The



Left: A positive/negative pressure glovebox isolation system from Isolation Systems, Inc. (Dearborn, MI).

Right: Fette's (Rockaway, NJ) tablet press with an automated guided vehicle for turret changes.

gloves used in early glovebox designs were too bulky for handling the fragile compounds used in the pharmaceutical industry. "What the pharmaceutical industry is doing is exacting. You need the feel and tactility," Rahe stresses. Improvements on gloves include the use of slimmer, 20–25-mL single-piece glove sleeves.

Another example can be seen in glove port design. Because operators often use gloveboxes for long periods of time, companies are making elliptical glove ports to offer technicians freer movement. "Glove ports are now larger and oval-shaped to be more comfortable for the user," says Rob Weber, engineering manager at Central Research Laboratories (Red Wing, MN). Elliptical glove ports assist the technician with reachability, another key element in the design of gloveboxes. "Operators must be able to reach all surfaces inside the glovebox," says Frisch. "If an operator dropped something inside a glovebox and couldn't reach it, containment would have to be breached to recover it."

Because technicians are of different height and strength, companies also are developing ways to allow gloveboxes to be vertically adjusted. For example, Isolation Systems, Inc. (Dearborn, MI) installs manual or automatic lifting devices on the frames of its systems. Operators can raise or lower the equipment as much as 4 in.

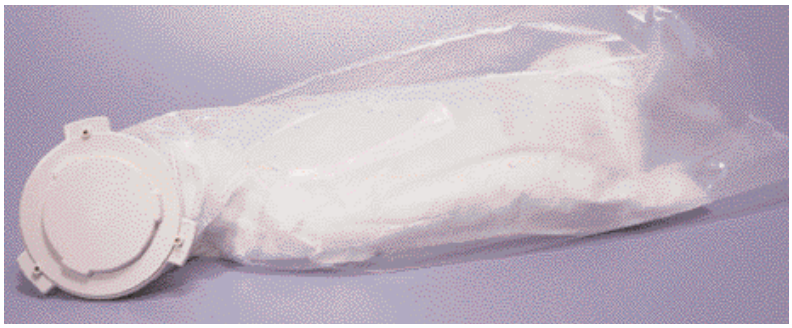
Operator involvement. Of course the best way to determine whether a system design is user-friendly is to go straight to the source. As Rahe points out, "Many engineers have never run an isolation system and therefore, engineer–operator interaction is absolutely critical." John Farris, president and managing principal of Safebridge Consultants, Inc. (Mountain View, CA), agrees. "Engineers should never sit back and design the equipment. They need to involve the operators who will be running the systems," he says.

Because of this necessary involvement, many companies have made a standard practice of manufacturing cardboard, wooden, or plastic mockups of gloveboxes to send to clients for a "test drive." Often, surrogate powders with similar physical properties to the active pharmaceutical ingredients that will be used in the actual process are used to evaluate the equipment.

According to Powder Systems Limited's Frisch, not all companies accept mock ups when they're offered. However, she warns, engineering barrier/isolation systems without such interaction will only spell trouble in the future. Operators who aren't involved in the development process and don't understand the system may even try to override the isolation system without realizing that they could risk exposure to toxic or explosive materials. "If operators have a say in the design, they'll be more apt to take care of the equipment and use the machine properly," she stresses. "And don't just get the first shift involved. Get operators for every shift involved."

Putting the pieces together

Integrating process equipment. Marrying the various parts of a manufacturing line while still maintaining a consistent level of barrier/isolation performance can be a complicated puzzle. Manufacturers need to overcome issues of cleanability, the requirements of good manufacturing practices (GMP) standards, ergonomics, and operator safety.



The "SteamPac" from West Pharmaceutical Services (Lionville, PA) transports sterile stoppers into a barrier isolation system.

Although an individual piece of equipment may have the capacity to contain nanogram-sized particles, its performance may not be as effective when married to other systems. As Sean Scully, director of operations at Fette America Inc., stresses, "We could develop a tablet press for the microgram level, but if it's then put in a room with a different isolation or feeder system, you'll never achieve that level. It has to be balanced."

Although it's usually possible to develop an isolator for a company's existing equipment, it's also often more expensive and time consuming to integrate an older piece of equipment into a barrier/isolation system than to buy updated machines. Some older generations of equipment weren't intended to meet today's high GMP standards or even be configured for use in a glovebox. And, as Kirk notes, many older generations of process equipment, such as filling machines, weren't designed with the stringent biodecontamination mechanisms that FDA requires of new handling process. "Your equipment has to start with the right materials and design to update the process with an isolator," he says.

To address this problem, process equipment vendors are developing products to be more compatible with barrier/isolation systems. According to Frisch, "It's a really big change. Manufacturers are bringing their products up to GMP standards and configurations so that they can be more readily adapted to use in gloveboxes." Fette's Scully agrees. "Containment isn't new, but process equipment manufacturers are now also challenged to help integrate their equipment," he notes.

Absolut Filter Systems (Germany) and Fette are currently collaborating to develop a new WIP product line that combines Fette's tablet presses, Absolut's dust collection systems, and containment technology. The new systems will be designed and integrated by Fette so that customers won't have to approach several different vendors for equipment and then find a way to integrate them.

One benefit of the integrated design is operator convenience. "When you can integrate the control system into the package, the isolator is much easier for the operator to run," Kirk says. Fette's system will allow operators to monitor several functions from one WIP station because the isolators and dust collectors will be interfaced into one unit on the tablet press.

West Pharmaceutical Services Inc. (Lionville, PA) also is developing products that focus on barrier/isolation system compatibility. The "SteamPac" system transports stoppers from the manufacturing area, through an autoclave, and into the barrier isolator. A plastic coupler allows a sterile bag to be docked to a system and introduced into isolation. The polyethermide docking port provides secure closure to withstand dry heat sterilization. A Central Research Laboratories beta port for connection to a corresponding alpha port is designed for the safe transport of stoppers. According to Don McMillan, vice-president of marketing at West Pharmaceutical Services Inc., "Because each barrier/isolation system is different, the sterile bags are custom designed to mate with the customer's system." The company anticipates that the new technology could be ready for use in 2004.

The cleaning of integrated equipment can pose unique challenges. Traditionally, systems are equipped with self-draining clean-in-place systems that can be quickly washed and blown dry through a spray ball system. A new solution under development by Bosch Packaging uses a foam cleaning system instead of water. Whereas a liquid cleaner runs off equipment quickly, foam sticks to the surface and keeps the decontamination agent in contact with the machine longer. Such systems could be ready for use within the next 2–3 years.

Facility considerations. One other important consideration for any barrier/isolation system is the facility in which it will be housed. According to Process Facilities, Inc.'s Piccirillo, "Most people focus on the barrier/isolation equipment, and neglect the fact that it has to be incorporated into, and be operable within, a facility."

Process Facilities, Inc. has developed a "containment strategy" for integrating containment technology into facilities. According to Piccirillo, the integration of the process, the facility design, and the barrier/isolation technology are all key considerations for facilities that will handle hazardous materials. Process Facilities's technique first establishes exposure limits and identifies special factors for design consideration such as cleanability, the isolation of air handling units, and personal protective equipment for technicians. Nonessential support equipment that doesn't need to be isolated such as steam generators, vacuum pumps, and heating/cooling skids are placed outside of the

control zone. "We try to separate the containment side from the support side," notes Piccirillo.

Because isolators aren't completely airtight, a major consideration of the facility design should be the areas where materials are transferred into and out of isolation. It's also important that the physical layout and room adjacencies are designed to minimize travel distances and create levels of separation when handling potent compounds. "This creates a secondary barrier level so that contamination doesn't spread downstream or to the support systems," Piccirillo explains. "Even if there's a breach of containment at a material transfer point, there's a secondary means of containment so that the rest of the facility isn't contaminated." For example, one area where a secondary level of containment might be needed is at the room air exhaust and supply so that contamination won't spread into the ductwork and air handling units.

New demands

During the 1990s, an experimental period in barrier/isolation technology led to a number of overly complex and unreliable designs, and a subsequent lack of confidence in the equipment by many users. In fact, many pharmaceutical companies still have "graveyards" filled with unused barrier/isolation equipment. However, as Les Edwards, partner/principal engineer at Advanced Barrier Concepts Inc. (Cary, NC) points out, customer demand for the new generation of equipment is rising. "Safety concerns are really driving the upsurge in customer demand of barrier/isolators because of the new highly potent products that are coming out," he explains. These concerns have driven down leakage levels to the nanogram-level. "Containment requirements and specifications for this equipment are becoming more and more stringent as time goes on," notes Isolation Systems's Mike Hennessey, vice-president of market development. "Up until two years ago, manufacturers considered Level Three for occupational exposure limits tight. Now we're seeing specifications for gloveboxes with containment Levels 4 and 5." PT

FYI

Courses slated

The United States Pharmacopeia (USP) has released its 2004 Pharmacopeial Education (PE) course schedule. These PE courses, which will be held in Rockville, Maryland, aim to help participants comply with the new requirements of the 2004 *United States Pharmacopeia and National Formulary (USP–NF)*.

The course format is either lecture or a combin- ation of lecture and hands-on laboratory exper- ience. Topics include analytical methods validation, fundamentals of dissolution, fundamentals of microbiological testing, fundamentals of titration, fundamentals of the *USP–NF* and standards-development process, and advanced use of the *USP 27–NF 22*, notices, monographs, and chapters.

For full course descriptions, pricing, and schedules, visit www.usp.org/education or contact Diana Lenahan at dpt@usp.org or tel. 301.816.8530. For on-site training, e-mail Pharmacopeial-Education@usp.org