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**In Search
of a
Sterile
Fill**



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In Search of a Sterile Fill

Erik Greb

Technological developments make it easier to manufacture sterile parenterals.

More than any other dosage form, injectable drugs require a manufacturing process that ensures sterility. Problems discovered at Genzyme's (Cambridge, MA) Allston Landing, Massachusetts, facility last fall illustrated how contamination can play havoc with a drugmaker's operations. But recent developments in disposable components and isolators are helping companies protect their products and the patients who depend on them.

Fill the drug, toss the system

Disposable components are gaining currency in pharmaceutical fill operations because they can help ensure sterility and save companies time, effort, and money. "The most evolved disposable design is a complete, disposable fill set from the connection to the tank, to a filter, to the lines and hoses that go directly to the fill needle," says Jim Agalloco, president of Agalloco and Associates, lecturer about sterile processing, and member of *Pharmaceutical Technology's* Editorial Advisory Board. "The dream is to get something that's inexpensive enough to use once and throw away," he adds.

Until recently, pharmaceutical manufacturers had to integrate single-use elements such as tubing and fittings into reusable equipment. But in 2008, Bosch Packaging Technology North America introduced the PreVAS filling system, which is completely disposable. The system includes a supply connector, tubing, fittings, rolling-diaphragm pumps, and needles. One available version includes an eight-head filling machine, which is common in production-scale operations, and a manifold that feeds all eight pumps and needles. The PreVAS system is assembled in a cleanroom, gamma-irradiated, and double-bagged for sterility. It fills vials, cartridges,

syringes, and ampuls at clinical and production scales.

The PreVAS system is the first to include a disposable positive-displacement pump, according to Jeff Jackson, North American pharmaceutical sales director at Bosch. The pump is made of polycarbonate, rather than stainless steel or ceramic, which enables it to be gamma sterilized and discarded. Because it is hard to use liquid product as a seal in plastic pumps, Bosch chose a diaphragm pump with

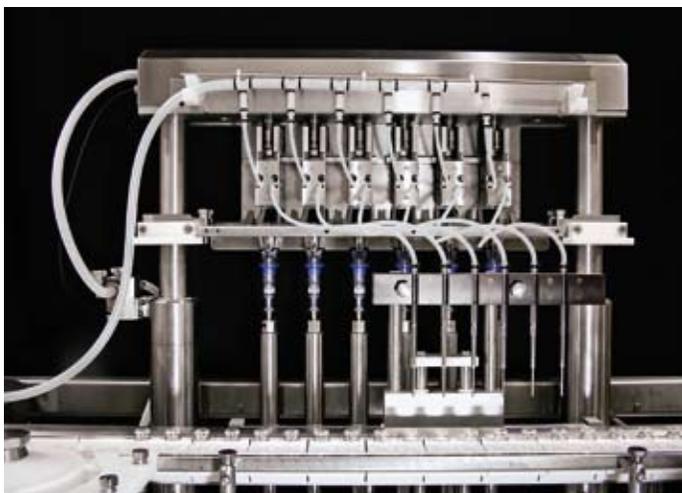
a platinum-cured silicone seal for the PreVAS system. The pump's design and performance are the same as those of Bosch's stainless-steel diaphragm pump, which the company debuted 30 years ago. The PreVAS pump can complete 400,000 cycles with no reduction in performance, says Jackson.

The PreVAS system can perform positive-displacement filling with either a rolling-diaphragm pump or a peristaltic pump, two devices familiar to

the drug industry. The PreVAS pump also can perform optical filling (i.e., using a vision sensor) and fill-by-weight, but these less-common techniques generally are used for specific applications such as cartridges. One common technique that the system cannot perform is time-pressure filling, says Jackson.

Because the pump is disposable, it does not need to be disassembled for cleaning and sterilization. The PreVAS system thus spares manufacturers much labor, reduces utility consumption, and eliminates an opportunity for operators to be exposed to hazardous materials. Like individual single-use components, the system can be dedicated to one product, thus eliminating the risk of cross contamination.

Pharmaceutical manufacturers try to minimize the number of aseptic connections they must make in their produc-



The Bosch PreVAS filling system is completely disposable.

tion systems. The PreVAS system requires only one aseptic connection: a link to the bulk supply. Personnel can use many different types of connectors (e.g., traditional tri-clamps, quick-connects, closed connectors) with the PreVAS system, including disposable connectors. The connectors can be made of the same materials as the PreVAS system, or they can be made of different materials, depending on the drugmaker's needs.

The PreVAS system's disposability and capacity can simplify scale-up. Many drugmakers use a single-use product path during clinical-trial fills, partly to reduce costs, and partly because they don't know what the cleaning requirements at production scale will be. Manufacturers can use the PreVAS dosing-pump system as a one-pump station for clinical fills and laboratory work. "You have the exact same fluid path all the way to production with the same performance, accuracy, and materials. Nothing needs to be changed," says Jackson.

Agalloco acknowledges that disposable technology eliminates the need for cleaning and sterilization, and so makes product changeovers quicker, which is especially important for multiproduct facilities. Single-use systems also maximize uptime, which is a goal shared by drugmakers and contract manufacturers alike. But, he cautions, companies must verify that their products are compatible with disposable materials. He adds that normal wear could affect the components' extractables-leachables profiles.

Fill in splendid isolation

Pharmaceutical manufacturers have recently begun to evaluate how they could incorporate isolators into their filling operations. Isolators incorporate sealed environments that are supplied with filtered air, and are decontaminated through reproducible means. The industry took particular notice when Richard

Friedman, director of the Division of Manufacturing and Product Quality at the Center for Drug Evaluation and Research, and Robert Sausville, supervisory consumer-safety officer at the Center for Biologics Evaluation and Research, both of the US Food and Drug Administration, stated at the International Society for Pharmaceutical Engineering's 2009 Washington Barrier Isolator conference that isolator technology is the new standard in aseptic processing. Isolators constitute one of

Lysfjord. These machines include automation with sensors that detect faults (e.g., missing stoppers) and eject unsuitable containers.

Vendors such as VanRX are developing integrated robotic isolator systems for sterile-manufacturing applications. The company's Raptor Aseptic Workcell uses a multiarm robotic architecture that performs clinical-scale aseptic filling of potent and nonpotent products. With its digital vision-guided system, the Raptor targets containers inside the isolator, according to Chris Procyshyn, the

company's chief executive officer. After containers are transferred into the system on a tray, sensors scan them to identify their type (e.g., vials or syringes), verify that they are the correct containers, determine their locations, and complete the fill-finish process.

Vials or syringes are transferred from a sterilizer to an interface isolator, and then directly into the system. This transfer removes the largest source of product contamination, human intervention. For example, one of the system's advantages is that it does not require any part changes other than simple fill-tubing sets. Operators can fill a batch of 5-mL vials in the morning and, after changing the per-

istaltic tubing and decontaminating the system, can fill 50-mL vials in the afternoon with no other adjustments. "The average company might spend \$25,000–50,000 on change parts for a new vial set on an automated filler, and it can take as long as 20 weeks to get it ordered, installed, and ready. In this case, for a manufacturer, it's as simple as installing a new set of tubing and going," says Procyshyn.

Robotics traditionally have not been used in isolator systems because of concerns about hermetic sealing, particle generation, and vapor-phase decontamination systems. The Raptor system incorporates hermetically sealed, peroxide-compatible, stainless



VanRX's Raptor system performs isolated filling.

the largest leaps in aseptic technology, according to Jack Lysfjord, principal consultant for Lysfjord Consulting. This technology improves sterility assurance by at least 1000, if not 10,000 times, says Lysfjord, who has more than 29 years of experience in aseptic fill-finish equipment design and application.

The trend towards isolation is influencing equipment vendors, who increasingly are designing processing equipment to run more reliably with fewer interventions so that it is suitable for installation inside an isolator. Some new aseptic fill-finish equipment can operate for as long as 28 days without interventions, says

steel robotics to enable the first gloveless isolated filling system, according to Procyshyn.

VanRx had to select the robots for its system carefully. Other systems have used six-axis robots, which are highly configurable and move much like human arms. These robots, however, require large and complex sealing to be enclosed in an isolator. "If you add more robots and keep your motion planar, that allows you to use a simpler, more reliable seal design," Procyshyn explains. The Raptor system's design is similar to that of robots long used in the semiconductor industry.

While the robotics and vision system are unique to the Raptor system, VanRx chose not to develop new filling technology for the system, relying instead on conventional peristaltic filing. "This means that the product is only seeing something with a good history of reliability in terms of product-contact materials and processes." Although other isolated systems are compatible with specific products and dosage containers, the Raptor system was designed to work with any product and any dosage container. "We know that, by the time it hits manufacturing, a dosage has been picked, stability has been done, and nobody really wants to change the product at that point, even for a manufacturing efficiency. So you really have to make your system work with what the formulators have worked out if you want your system to have readiness and acceptability," says Procyshyn.

Close the door on open vials

Technology such as disposable components and isolators has improved the degree of sterility assurance possible during the filling of open vials. The vials' own design, however, leaves the product susceptible to airborne contaminants that could be introduced during the filling process.

A closed vial developed by MED-Instill was designed to eliminate the need for filling open containers. The

company used an olefin polymer base to create its Intact closed vials. Robotic arms produce the vials in a closed, aseptic, and controlled environment that protects against viable and nonviable particles until the vials' closures are in place. After the vials are closed, they are sterilized by electron beam, gamma irradiation, or pulsed light, depending on the sensitivity of the formulation to be filled. The closure's primary seal is completely controlled while the vial is empty and the seal cannot trap product. MED-Instill originally closed the vials with a specially formulated thermoplastic elastomer (TPE), but has since developed and validated new materials that provide stability for more formulations.

MEDInstill's closed-vial system is "a game-changer" that has an "extremely low" potential for contamination, according to Agalloco.

MEDInstill also developed a filling machine specifically for its Intact vials. Inside the machine, a noncoring needle pierces each preassembled closed container and fills it with product. After the needle is withdrawn, a laser seal or a novel material-sealing mechanism ensures that a totally hermetic seal is maintained during the container's shelf life. This filling system "is at least 10,000 times safer than most aseptic filling technology," says Daniel Py, founder and chairman of MEDInstill. The technique does not require isolators because the Intact containers themselves act as isolators, he adds.

MEDInstill's closed-vial system is "a game-changer," says Agalloco. "The potential for contamination in that system is extremely low. It's got to be one of the safest containers available for sterile products," he says. The fact that the containers are made sterile completely changes the way manufacturers handle them in their facilities. "You don't have to have a stopper washer, a glass washer,

a steam sterilizer for stoppers, or a dry-heat tunnel for glass depyrogenation," Agalloco says. The containers thus reduce the amount of utilities and equipment that manufacturers need for filling. The closed vials also eliminate the possibility of mishandling and prevent cross contamination.

MEDInstill's filling system also removes the need for human intervention. Validation studies have shown that little or no environmental control is required during filling to protect against viable and nonviable particles and cross contamination, says Py. Even when operators spray microbial contaminants into the Intact filling tunnel, the Intact containers are filled sterile. The system also greatly reduces the amount of quality-

control operations needed, which led FDA agents to remark that MEDInstill had engineered regulatory compliance into the Intact technology, according to Py.

MEDInstill licensed their original system for vaccines and injectables to Aseptic Technologies, a Belgian company owned by GlaxoSmithKline (London).

Conclusion

The high standards for sterility and purity have long challenged makers of injectable drugs. Technological innovations and new process designs promise to reduce operator interventions, shield products and containers from foreign particles, and allow equipment to be dedicated to specific drugs. Although manufacturing parenteral drugs is not easy, these advances allow companies to ensure sterility to a greater extent, and with greater efficiency, than was previously possible. **PT**