

Current Trends in Sterile Manufacturing

by Sterling Kline, RA
Director of Project Development
Integrated Project Services (IPS)

Executive Summary

Drug developers go to great lengths to assure that their products are safe as well as efficacious. For injectable drugs, in particular, a sterile manufacturing and filling environment is necessary to minimize the risk of product contamination. Historically, manufacturers have used “clean rooms” to achieve this. For decades, the clean room approach was sufficient, and the risk/reward ratio did not justify change. In recent years, however, the emergence of expensive biologics and a changing regulatory environment have made other options, including sterile isolators, increasingly viable. As today’s manufacturers look at new products and aging facilities, they have an opportunity to re-evaluate their manufacturing processes, their risks and their options.

In selecting a solution, the manufacturer must weigh a number of factors. This paper addresses the evolution of sterile manufacturing, looks in detail at currently available options and considerations, and provides a glimpse at how sterile manufacturing might continue to progress.

History

Hippocrates said, “First, do no harm.” In their role as health care providers, drug developers go to great lengths to assure that their products are as safe as possible as well as efficacious. For injectable drugs, in particular, a sterile manufacturing and filling environment is a necessary part of providing a safe product to the patient. With injectable drugs, product contamination is of utmost concern, because the product is introduced systemically. Potential contaminants must be controlled, not only during product manufacturing, but also during the process of filling the vials, ampules or syringes.

In the 1970s, pharmaceutical manufacturers began to use clean rooms to control contamination. Clean room technology uses filtered, high-pressure air to push particles down to the floor in order to keep them from contaminating the vial. Theoretically, recirculating the filtered air eventually should remove all particles; however, the presence of operators means potential for particle generation.

By keeping the operator outside the sterile field, isolation chambers, or isolators, significantly reduce the potential for contamination. Introduced in the 1990s, the technology provides a barrier with a Class 100 or better space inside a sealed isolator, which can be located in a Class 10,000 room. Although isolators were rather quickly embraced in Europe, it is only recently garnering real attention in the United States—for several reasons. First, the capital cost is high compared to a clean room. Second, one company had patented Vapor Hydrogen Peroxide (VHP) cleaning, but the decontamination cycle initially was 18 hours. That was not an issue for vaccine manufacturers running long production cycles, but it represented an unacceptable level of downtime for many others. A handful of companies, most notably the LUMS Group (Lilly, Upjohn and Merck) deployed it in the ‘90s with limited success, and others were reluctant to follow.

Today, the business drivers are different. Decades-old clean rooms are aging; wall systems built with inferior materials are breaking down and beginning to particulate. In addition, the emergence of high-value APIs has upped the ante in sterile manufacturing, and few, if any, facilities are available to manufacture them. The cost of these products has reduced manufacturers’ risk tolerance. Generic products produced by chemistry cost a few dollars per vial. Today’s biologics can cost \$100, \$1,000 or more. Investing the capital in a new facility is a less difficult decision than it was a decade or more ago. What’s more, the VHP cycle has been cut to three hours, and the U.S. Food and Drug Administration (FDA) is recognizing the isolator technology process as validatable and reproducible.

Clean rooms

Traditional clean room technology uses laminar flow motion—high-velocity air forced down vertically—to drive particulate past the filling process line, ideally to the floor. By doing this, it is possible to achieve Grade A or Class 100 space—that is, 100 particles per 1 cubic foot of air.

In semiconductor manufacturing, the air is forced down through perforations in the floor and then recirculated. In pharmaceutical manufacturing, however, the perforations in the floor provide a potential breeding ground for bacteria, particularly if fluids become trapped beneath the floor. Instead, return registers around the walls are



used to recirculate the air. This approach makes it difficult to obtain unidirectional laminar flow motion, as the air tends to seek corners instead of flowing straight down. Over the years, the technology has been refined. Making rooms narrower with no more than four inside corners makes it easier to optimize airflow. Air is pushed through HEPA filters at higher velocities, exceeding 90 feet per minute, to drive the particles downward. Horizontal surface that could collect dust can be minimized. For example, fire extinguisher boxes and electrical outlets should be flush with the wall to eliminate any ledges.

Operators remain the weak link in the clean room system. Effective training on gowning, degowning and other procedures can help reduce the risk that an operator will introduce contamination, but some risk always remains. Conversely, a clean room does not provide a barrier to protect the operators from exposure to potent products, which could contaminate a gown and expose the operator during de-gowning. Clean rooms are also expensive to operate. Energy costs to operate an air system at 90 fpm are significant. Additionally, the time operators must spend gowning and de-gowning is not productive. The economics vary by project; however, several confidential client studies have shown an approximately six-month payback when comparing capital expenditures to operational savings.

Isolation technology

Isolation technology has matured to the point where it can be reliably deployed. One factor that makes isolation more attractive than it was in the '90s is a shorter decontamination cycle. Steris's patent on VHP expired, leaving the door open for innovations from other vendors. Both SKAN and Bosch put engineers to work on the challenge. As a result of their changes to isolator designs and air handling systems, VHP cycles are as short as three to four hours. What's more, the process can be validated and reproduced reliably, and as a result, the FDA is increasingly more comfortable with the technology.

Advantages: Parenteral manufacturing center

A recently expanded parenteral manufacturing center demonstrates many of the advantages of today's isolation technology. The 20-year-old facility required additional capacity for both liquid and lyophilized products. The goal was to have four independent product cells, each with capabilities for formulation, primary packaging and ancillary support services, such as autoclaves, parts washers, etc. When evaluating technologies for the new aseptic facilities, a multidisciplinary team considered industry benchmarking, quality and regulatory expectations. It made facility visits and assessed technologies. Based on its findings, the team decided to pursue isolation technology rather than convention clean rooms.

Next, the team looked at isolator technology versus restricted access barrier (RABS) technology, a relatively new approach that places an aseptic filler in a Class 10,000 room. RABS are appealing due to lower capital costs, but the technology has several problems. RABS are not pressurized the way isolators are; when the door is opened, it creates an opportunity for contamination. RABS do not use VHP decontamination, but must be opened up and cleaned manually, thereby increasing the environmental monitoring burden. The problems might be addressed by using laminar flow with Grade A air over the door, but in order for this approach to be effective, the space must be small, the returns must be close to the HEPA filter, and the HEPA filters must be larger than four feet. Eventually, the space becomes a Grade A room—which defeats the purpose. With a true isolator, it is possible to leverage Grade C support spaces. A study conducted by Johnson & Johnson found that lifecycle costs for RABS are higher than for clean rooms or for isolators.

Ultimately, the team recommended isolator technology. It offers an improved compliance profile and protected both the product and personnel. It eliminates the need for Class A support space and gowning rooms, and reduced expected operating costs. Finally, its validated VHP cycle provides more effective and reproducible decontamination than manual sanitization.

The process called for a continuous line for liquid and lyophilized products and fixed, automatic loading into four lyophilizers. A number of different configurations were possible; computer modeling was used to optimize the line configuration select the number of cappers. Based on the operating rules, production scheduling,



equipment and facility design, and quality assurance concerns, the model suggested that a “T” configuration would offer a 50-percent increase in capacity and justify the added cost of a third capper.

Vendors were selected early in the design phase. Bosch manufactured the filling line; SKAN manufactured the isolators, and BOC Edwards manufactured the freeze driers and loading system. The addition was adapted to the equipment; a three-story design allows use of a two-story lyophilizer and improves maintenance access. The production cells are Grade C throughout for efficient personnel and material flows and to reduce the need for airlocks and gowning rooms. Like the addition, rooms were designed around optimized manufacturing process flows, rather than the opposite. Corridors to the cells are Pharmaceutical Unclassified, with controlled access.

Advantages: Clinical supplies operation (CSO)

An isolator also was the technology of choice for a recently completed CSO expansion facility for both oral solid dosages and parenteral liquid fill batches. The goal was to create a flexible facility with the ability to perform multi-product clinical scale manufacturing that handles solvent-based and potent compound operations—formulation and finishing—while adhering to current good manufacturing practice (cGMP) and European guidelines. The project represents the first FDA-approved clinical sterile continuous process isolation facility in the United States. It utilizes state-of-the-art isolation/containment technologies, including closed system processing equipment, contained material transfer systems and isolated equipment and operations.

Use of isolation technology made it possible to create a multipurpose sterile line to manufacture chemical, biologic, flammable and explosive potent compounds up to Band 5 while protecting personnel from exposure and product from contamination. In addition, cutting-edge wireless Process and Analytical Technology (PAT) also helped minimize human interface by reducing the frequency of entry and exit from the process rooms. Single-pot processors further reduced contamination risk. Finally, IPS developed a formal integrated program and practices for conducting a risk-based assessment approach to commissioning/qualification. This innovative approach helped minimize the project schedule and eliminate delays when evaluating the impact of system conditions or components on product quality. The approach also resulted in a Facility of the Year award from ISPE, INTERPHEX and *Pharmaceutical Processing* magazine. The CSO/DPTC (Drug Product Technology Center) expansion project was selected from a group of nineteen nominees from six countries as 2008 Category Winner in Equipment Innovation award.

Options and considerations

Today, manufacturers can select equipment from a number of vendors, as listed below:

- | | | |
|---------------------|----------------------|--------------------|
| • Isolators | • Lyophilizers and | • Beta bags |
| - SKAN | loading devices | - La Calhene |
| - Bosch | - BOC Edwards | - Central Research |
| - Steris | | |
| • Filling equipment | • Stopper processing | |
| - Bosch | systems | |
| - Groninger | - Steritect | |
| - Inova | - Gettinge | |

Isolator facilities can be laid out in a number of ways, depending on process requirements and other considerations. The isolator can be located in a traditional suite, or it can be located in an isolator cell with a Grade C corridor, as it was for the CSO facility. It can be located in a process cell ballroom, as was done for the parenteral manufacturing site, or it can be added to an existing traditional suite. The choice of layout is based on consideration of several variables, including the number of products, the number of cells and the overall building layout. Another advantage of isolator technology is that it makes it possible to segregate functions and locate all aseptic processing in a single zone. For example, all process mechanical equipment



can be located on the first floor, product manufacturing on the second and HVAC on the third. Each zone has its own distinct set of procedures. Color-coding the zones can help facilitate compliance.

From the outset, the company's operating philosophy will drive the decision-making process. To minimize risk, the optimal approach is to select the best equipment available for the task and to have it sized, and then design the space around the equipment. This approach saves time. It is not necessary to specify every detail of the equipment, as long as the specifications include any necessary options and indicate that the equipment meet all applicable regulations.

In today's pharmaceutical manufacturing environment, isolators clearly offer an advantage. The primary obstacle to widespread acceptance is the relative lack of experience with the technology. This lack of confidence is a barrier, but it is not insurmountable, as long as the organization is open to developing and training on new SOPs that ensure a well-defined and defensible flow of material.

Looking ahead

With the growing importance of biologics in the pharmaceutical industry, and the continued aging of the existing manufacturing infrastructure, the need for new sterile manufacturing capacity can only increase. Isolator technology is already widely accepted in Europe and is beginning to make inroads in the United States. As the base of experience builds, so will confidence in the technology on the part of manufacturers and regulators alike, and isolators will become an increasingly clear choice for sterile manufacturing.

Sterling G. Kline, R.A., has more than 35 years of experience in strategic planning, master planning, programming, design, construction management and facilities management for the health care, pharmaceutical and biotech industries. He has held senior management positions at engineering and construction service firms and has also served as director of engineering for several major pharmaceutical manufacturers. Mr. Kline has completed pharmaceutical projects ranging from major R&D facilities including discovery, development and kilo labs; clinical manufacturing pilot plants for sterile and oral solid dosage, including potent compounds; to manufacturing facilities for sterile products using vials, syringes and devices incorporating both traditional and isolation technology, and oral solid dosage products utilizing traditional and isolation technology. He has also completed pharmaceutical support facilities including office, warehouse, quality lab, utility, parking, and hazardous material holding buildings. A member of ISPE, he holds a degree in Civil Engineering from Northeastern University.