Aseptic Formulation and Filling Using Isolator Technology

Frank DeSantis, Kent Amsberry, Jeff L. Folks,* Atsushi Yamamori, and James Akers

Isolator technology can be used in clinical product formulation and filling facilities to ensure environmental control and reduce contamination risk during aseptic processing. Key features of the filling system include mass flow technology and a filtration skid that can be cleaned and sterilized in place. The process can accommodate vials and ampuls and can provide lyophilization capability.

Frank DeSantis, PhD, is executive director, pharmaceutics, Kent Amsberry PhD, is group leader, pharmaceutics, and Jeff L. Folks is director of business development at Quintiles (Kansas City, MO), tel. 816.767.3836, fax 816.767.3950, jeff.folks@quintiles.com. Atsushi Yamamori is general manager of the international marketing division of Shibuya Kogyo Co. Ltd. (Kanazawa, Japan), and James Akers, PhD, is president of Akers, Kennedy and Associates (Kansas City, MO).

*To whom all correspondence should be addressed.

The number of parenteral products entering development and reaching the market has increased significantly during the past decade. By some estimates as many as half of all investigational new drug applications consist of biopharmaceuticals, the vast majority of which are manufactured aseptically. Most of these products are proteins and therefore highly susceptible to microbial contamination. In addition, regulatory agencies around the world are devising and enforcing increasingly stringent requirements for environmental and process control in aseptic processing. These factors are creating interest in advanced aseptic technologies that provide superior contamination control.

Historically, the construction of an aseptic processing suite for small-scale or clinical-size batches has been a time consuming and expensive venture. Depending upon a facility's starting point, construction can take 18–36 months. If an existing room or suite of rooms is to be remodeled, it may be possible to have a fully validated and functional facility in 18–24 months, depending upon the scope and complexity of the manufacturing requirements. However, if a facility must be built in a "green field," or if a new construction is attached to an existing structure, the time to completion may be much longer, frequently on the order of 30–36 months. Validation of even a small-scale aseptic processing facility can take 3–6 months or more, depending on the size of the facility and the type of equipment required. It is not uncommon for a project that consists of building and validating a clinical or small-scale aseptic processing facility to cost more than $10 million, which does not include ancillary costs such as staffing and training a highly specialized cadre of operational, quality assurance, and compliance personnel.

After completion, such facilities can be costly to operate because of several factors, not the least of which are high energy costs as a result of extensive air-handling requirements. Even though small-scale facilities are generally not in continuous use, most firms find that running air-handling systems continuously is necessary to maintain the exacting level of contamination control required by the regulations. In addition, monitoring the environment generally is required at all times, which requires expensive gowning supplies and consumables even when the facility is not in production.

A technology that has gained acceptance during the past decade is isolator technology, although this technological solution has not frequently been applied to small-scale or clinical manufacturing. Isolator technology can reduce project timelines, increase environmental quality, and reduce operating costs. Of course, for these benefits to be realized, some important conditions must exist. First, the firm undertaking the project must be willing to move into new technology. Second, the project team must establish clear objectives and logical, well-defined user-requirement specifications based on current regulatory expectations and technological feasibility. Third, equipment vendors must be selected that can provide isolator-compatible equipment in a timely manner.

Facility design and construction costs generally are considerably lower in aseptic processing facilities that are designed around isolator technology. Aseptic processing in conventional staffed cleanrooms requires large, human-scale rooms with cleanliness zones, each of which must be operated and controlled to a specific pressure differential. These facilities also require three-stage gowning facilities for staff entry as well as exit rooms for removing gowns. Air locks with air-handling systems are required for materials entry and the removal of waste and quality-control samples. Human-scale facilities generally consist of ISO Class 6 or 7 filling rooms in which a Class 5 aseptic critical zone is located and used for all aseptic filling, stoppering, and sealing operations. (ISO 14644 1–3 has replaced US Federal Standard 209E. ISO Classes 5, 6, 7, and 8 are equivalent to Federal Standard 209E Classes 100, 1000, 10,000, and 100,000, respectively) (1). Fill rooms are supported by component entry rooms, employee entry corridors, and other support areas as required (e.g., lyophilizer rooms). These facilities are expensive to design, build, and maintain.

Isolator-based aseptic processing facilities are less complex and easier to design and build. Generally, all isolators are located in an ISO Class 8 environment (2). This obviates the need for three-stage gowning because full aseptic suits are not needed. All aseptic activities are conducted in the locally controlled ISO Class 5 environments provided by stationary and mobile (transfer) isolators. Therefore, the background environments can all be considered equivalent from an air-quality perspective, and pressure-differential cascades are not required. These facilities also can make greater use of available space because internal partitioning requirements are reduced.

Depending on the starting point, a small-scale aseptic processing facility based on isolator technology can be up and running in 12–18 months at a cost of $3–5 million. This of course requires that facility design and construction be done in parallel with equipment selection and construction. Careful coordination among vendors is required, and a great deal of attention must be paid to ergonomics and equipment interaction. However, the benefits are lower cost, a shorter path to return-on-investment, and a higher-quality manufacturing environment that is more likely to meet increasingly stringent aseptic processing regulations.

For small batch sizes and early development of sterile products, the use of isolator technology offers benefits over the use of a sterile room. With only the isolators at an ISO Class 5 level, the daily costs to maintain the facility are greatly reduced. Maintaining the aseptic atmosphere during the manufacture of clinical supplies is more efficient with the use of isolator technology because the chief source of contamination, the human operator, is more effectively separated from the production environment than is possible in a conventional human-scale cleanroom. In addition, the isolator can be decontaminated with a sporicide such as vapor hydrogen peroxide (VHP) to ensure that the bioburden within isolator enclosures is maintained at levels that would be unattainable in a conventional cleanroom. Components and other manufacturing supplies are transferred into isolators using reliable transfer ports and are maintained in clean environments within the isolator units.

The following is a description of a new isolator-based aseptic facility being installed at Quintiles, Inc.'s Kansas City, Missouri site. This facility was designed to comply with PDA T/R34, the guidance on isolators provided by FDA's 2002 concept paper on aseptic processing. Other international guidance and standards such as that produced by PIC/S, ISO, and USP were considered. The result is a facility designed to operate in compliance with all current and anticipated international requirements for aseptic processing.

The process

Filling. The isolator and the filling system enclosed within it were manufactured by Shibuya Kogyo Co. Ltd. (Kanazawa, Japan). The isolator has a rigid-wall construction (model PRLF20710) and is equipped with HEPA-filtered, recirculated, unidirectional airflow to provide an ISO Class 5 (EU Class A) environment under dynamic conditions and an ISO Class 4 environment under static conditions.

The isolator will be decontaminated using vapor hydrogen peroxide (VHP) generated by a Steris VHP–1000ED–C. The effectiveness of the decontamination process will be validated to produce complete kill of biological indicators (BIs) containing a population of $\sim 10^6$ *Geobacillus stearothermophilus* spores, providing a total spore log-reduction value of at least 8 logs (3). The BI substrate is stainless steel, and a sufficient number of BIs will be placed throughout the filling isolator to ensure the complete elimination of bioburden with a high margin of safety. The isolator and filling system were designed to exacting hygienic standards to ensure the absence of biofilm and a consistently low bioburden before decontamination. In the event that potent drugs are manufactured within the filling isolator, the isolator is equipped with easily changed HEPA filters to facilitate the replacement of the filters.

The filling system (model Perflac 9001S) is a single-head system capable of filling 600–1500 units/h depending on the type and volume of the container. The filling system will process vials and ampuls and will contain stations to stopper (fully or partially) and cap (aluminum with plastic flip-off) vials and heat-seal ampuls. For oxygen-sensitive products, an inert-gas purge system can be used with both vials and ampuls. Purging can be done both before and after filling so that a low level of residual oxygen can be ensured immediately before stopper placement in vials or heat-sealing of ampuls.

All parts within the filling system's fluid delivery pathway are

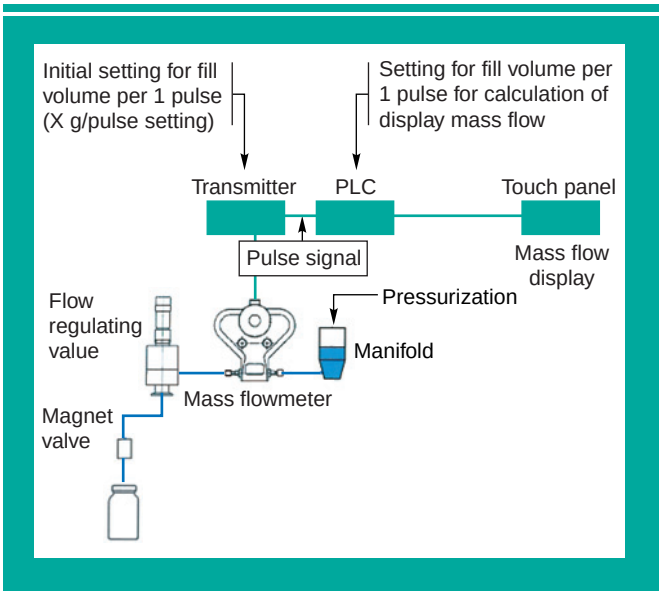

Figure 1: Mass flow rate filling–system structure.

cleaned and sterilized in place. This provides quick and efficient changeover from one lot to the next and may obviate the need for VHP decontamination between the filling of different products that use the same component configuration. Changeover from one component configuration to the other can be accomplished in <1 h. In such cases VHP decontamination and aeration of the filling system and isolator are required.

Compounded liquid product is sterilized by a filter skid that is capable of accommodating various types of standard filter cartridges and therefore is adaptable to the needs of almost all liquid products. The filter skid is sterilized in place along with the fluid path of the filling system. The filter skid has an integrated Millipore Integritest system, which allows the sterilizing grade filter to be integrity tested in situ after steam sterilization. For additional assurance of system integrity, the filter can be retested after filling. The filling system is connected with PTFE tube piping to the flow-metering unit, which houses a small manifold and mass flowmeter (MFM) that regulates the liquid volume delivery. The entire system, including the filtration skid, flowmetering unit, and filling nozzle, can be dried with filtered compressed air or nitrogen to minimize product loss as a result of initial dilution with residual water for injection (WFI).

For loading clean, sterilized stoppers and aluminum flip-off caps onto hoppers within the isolator, the wall of the isolator is fitted with two 190–alpha rapid transfer ports (RTPs), manufactured by la Calhène (Rush City, MN), directly above each hopper. The stoppers and flip-off caps will have been previously sterilized in an autoclave by placing them in nonwoven high-density polyethylene bags attached to a 190–beta flange (la Calhène). The aseptic transfer is accomplished by mating the alpha and beta halves of the RTP and opening the RTP from inside the isolator using an attached glove port. The stoppers or flip-off seals are then pushed into the hopper using the nonwoven high-density polyethylene material of the bag to maintain a sterile component-feed pathway and to reduce the need for intervention with gloved hands.

Previously washed and depyrogenated ampuls or vials are transferred into the filling isolator using a larger (350–alpha) RTP that is attached just above an accumulation platform located inside the isolator. Trays of vials or ampuls will have been previously placed in a transfer isolator (TI) (la Calhène) through an oven-interface isolator (la Calhène) after being washed and depyrogenated in a Despatch (Lakeville, MN) batch oven equipped with Class 5 quality HEPA-filtered air. The TI is fitted with a 350–beta flange through which it will be docked to the corresponding 350–alpha RTP on the filling isolator. With the use of glove ports on the TI and filling isolator, trays of glassware will be transferred onto the accumulation platform. Then with the use of glove ports attached to the isolator, the vials or ampuls will be removed from the trays and loaded onto a conveyer that will feed the vials or ampuls into the supply screw feeder of the filler.

The filling system can accurately fill volumes from 0.5 mL to 25 mL with a standard deviation of less than ± 0.02 g in filling <1 g and ± 1% in filling >1 g (n = 30, using water). The fill-volume range is accomplished with the use of four nozzles of various sizes. Fill volume is measured by a mass flowmeter (Micro Motion, St. Louis, MO), which is described later in this article. The fill volume of each unit can be recorded and stored electronically. Liquid-filled vials that are outside the set fill range will be automatically rejected onto a reject conveyor and removed from the isolator at the end of the run. Another mechanism will automatically reject improperly capped vials. If an ampul fill is outside of its fill range, then the machine will stop feeding ampuls and the out-of-specification ampul will be manually removed as it exits the isolator. An operator will then restart the filling process. Both the isolator and filling machine are completely controlled (including the setting of filling parameters) by an external control panel, thereby minimizing the need for manual intervention during the filling process.

The filling process involves applying filtered compressed air or nitrogen at a specified pressure to the upstream side of the filtration skid. This forces the compounded product through the sterilizing-grade filter into the small manifold located in the flowmetering unit, which is located upstream of the MFM (see Figure 1). The programmable logic controller (PLC) of the filling machine uses an electronically controlled valve to regulate the volume of filtered sterilized product in the manifold. The MFM measures and controls fill volume using an electronic transmitter that interfaces with the filling system PLC.

The MFM measures fill weight using the Coriolis principle. The unit measures mass flow and density of the liquid being filled to convert mass flow (g/s) to fill volume (mL/unit). The mass flow unit is depicted in Figure 2. Liquid entering the sensor is split into two flow tubes, each of which has the same total volumetric capacity. The flow tubes oscillate up and down in opposite directions, and this movement is detected and transmitted to the PLC using "pickoffs" consisting of a magnet and coil assembly mounted on the flow tubes on both the inlet and outlet sides. The oscillation of both the inlet and outlet side is recorded as a sine wave by a sensor–transmitter. When there is no movement, the sine waves from the inlet and outlet pick-off are superimposed or in phase. When there is movement of fluid, Coriolis forces are induced. These forces cause the flow

tubes to twist in opposition to each other. As a result of the twist of the flow tubes, the sine waves generated by the pick-offs are now out of phase because the inlet side is lagging behind the outlet side. The magnitude of the out-of-phase force is measured as the time difference (Δt), in microseconds, between the height of the inlet sine wave and that of the outlet sine wave. The magnitude of Δt is proportional to mass flow (g/s). Mass flow is calculated by multiplying Δt by the instrument's specific flow calibration factor, which is determined during factory calibration of the mass flow unit. The density of the liquid is inversely proportional to the period of the sine waves. Each transmitter–sensor pair is factory calibrated before shipment for flow and density calibration. Flow and density calibration factors are stored in the transmitter's memory to automatically perform the necessary calculations to determine mass flow and volume fill.

Capped vials (liquid or freeze-dried) and sealed ampuls will be discharged from the filling isolator through separate openings. Air pressure at each opening is positive to the ISO Class 8 room to maintain the aseptic environment of the isolator and validated to demonstrate environmental integrity. The openings will be kept closed when not in use. Partially stoppered vials for lyophilization will exit the isolator through a different 350–alpha RTP. Another TI, fitted with a corresponding 350–beta RTP, will be docked to the exit. Using the glove ports of the isolator and TI, the partially stoppered vials will be loaded onto freeze-drying trays in the isolator and then passed through to the TI for transport to the freeze dryer. The vials containing freeze-dried product are fully stoppered in the lyophilizer and then transported back into the filling isolator for capping as described previously for transferring empty vials into the filling isolator. Particles generated in the ampul sealing and vial-capping sections of the isolator are prevented from entering the filling section by differential pressure and airflow management (the pressure in the filling section is greater).

Lyophilization. Lyophilization, or freeze-drying, is an important pharmaceutical process because it enables the removal of water, through the sublimation of ice, at low temperatures. Lyophilization has several advantages over other methods of product drying. Because lyophilization occurs at low temperatures, chemical decomposition of heat-sensitive products such as biologicals is minimized. The resulting product has a very large specific surface area, which promotes rapid and complete dissolution upon reconstitution. Lyophilization is highly compatible with aseptic operations because the product solution can be sterilized by filtration before lyophilization. This type of process allows for more precise liquid filling and less particulate contamination in the aseptic environment than a comparable powder filling operation.

In this facility, filled and partially stoppered vials will be lyophilized using a BOC Edwards Lyoflex 1.3 lyophilizer. The lyophilizer will have a monoblock design with all components mounted to a single frame. The lyophilizer chamber door extends through the wall into the sterilized interface isolator while the remainder of the unit is located in a nonsterile utility room. The product is loaded onto the shelves from the interface isolator by an operator in a half suit. The product is loaded in trays with removable bottoms to facilitate good thermal contact between the vials and the shelves. The lyophilizer will have five usable shelves located in a single chamber with a total surface area of 1.3 m^2. With full loading, the unit will be able to process ~1400–5200 vials per batch, depending upon vial size. The unit will have one horizontal ice condenser separated from the chamber by a pneumatically operated butterfly valve. The chamber will be evacuated by an oil-sealed, two-stage vacuum pump. The vacuum level of the chamber will be monitored and controlled using an MKS capacitance manometer. The chamber is cleaned in place (CIP) by filling the chamber with WFI and is steamed in place (SIP) by flooding the chamber with clean steam. A liquid ring pump is used to dry the chamber following a CIP or SIP cycle. Two independent single-purpose refrigeration circuits or compressors are provided for shelf and condenser coil cooling. The shelves can be cooled to −55 °C and heated to +70 °C. Shelf heating and cooling is achieved using an immersible electrical heater and the shelf refrigeration circuit. The chamber normally operates under a high vacuum achieved using the two-stage vacuum pump. During the sublimation process, large quantities of vapor are released from the product and these are condensed on the chilled condenser coils. Condensing the vapor on the condenser coils prevents contamination of the vacuum pump. The condenser coils are chilled to an ultimate minimum temperature of −70 °C. Filtered nitrogen is bled into the chamber during processing to control the vacuum level in the chamber. Nitrogen also is used to release the vacuum in the chamber at the end of the lyophilization process. A hydraulic pump is used to operate the shelf-positioning hydraulic ram to seat the stoppers at the end of the process. The lyophilization cycle is controlled using a Lyomaster personal computer using Windows XP and Intellution iFIX software with a lower level of control provided by a PLC.

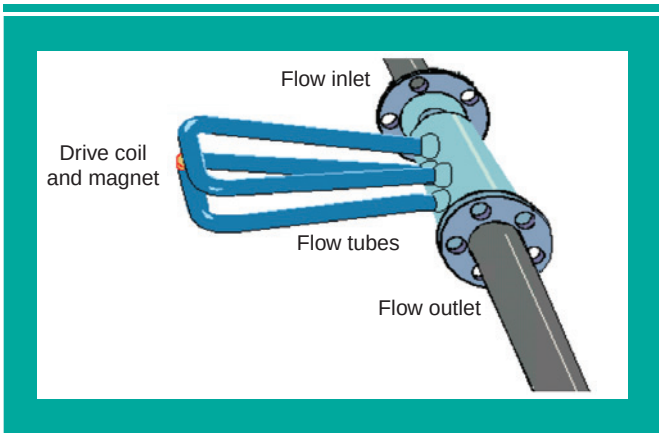

Figure 2: Mass flow device.

Validation and process control

Isolators. The clinical filling system described in this article operates using an "islands of isolation" strategy consisting of a network of stationary isolators, each of which serves a single piece of equipment. Two TIs serve as shuttles to move sterilized components to the filling isolator, partially stoppered vials to the lyophilizer, and fully stoppered lyophilized vials back to the fill isolator for sealing.

There are two interface isolators, one attached to a Despatch batch depyrogenation/sterilization oven and the other attached to the Edwards lyophilizer. Both interface isolators are flexible-wall, engineered, turbulent-flow, closed isolator units equipped with half suits. Each of the interface isolators will be decontaminated using a Steris VHP–1000ED–C vapor hydrogen peroxide generator. The cycles will be developed by evaluating temperature conditions in the isolator during decontamination and an injection rate will be chosen to provide the optimal concentration of vapor hydrogen peroxide relative to the dew point. The decontamination cycles will be demonstrated to achieve a complete kill of a sufficient number of BIs of *G. stearothermophilus* with a population of $\sim 10^6$ spores/indicator. Three full tests with BIs will be conducted to verify decontamination cycle efficacy.

The TIs are flexible-wall turbulent-flow closed isolators equipped with three glove–sleeve assemblies. The flexible wall design was selected because of its reliability and because its relatively light weight enhances maneuverability. Transfer bridges custom built and ergonomically tested will facilitate movement of container trays into and out of the TIs. An identical decontamination strategy will be used for the isolators. Because these isolators will be used only to transfer sterilized materials, the TIs will be decontaminated without removing shelves or materials handling tools. A sufficient number of BIs will be placed throughout the isolators to verify the effectiveness of the decontamination process.

The TIs and interface isolators also will provide an environment that is consistently free of microbiological contamination throughout the designated use period. This will be validated by a comprehensive microbiological monitoring program using both surface and active air-sampling methods. It is expected that all microbial samples will be free of contamination. The isolator air-handling system will be verified to comply with ISO Class 5 conditions and the ability of the isolators to control to the required overpressure set point also will be verified.

After the completion of validation, routine environmental monitoring for both viable and total particulate will ensure that the isolators continue to provide a suitable environment for aseptic processing. The target contamination levels for the flexible wall isolators will be zero. Should viable counts be found, a thorough investigation will be conducted and appropriate action taken to ensure that the environment is free of microbial contamination (4).

The filling isolator is a rigid-wall, unidirectional airflow, open isolator. This isolator has openings to allow for the removal of sealed vials or ampuls. The isolator will be validated to demonstrate that ISO Class 5 air-quality conditions can be maintained during operation and to demonstrate that the openings are effectively sealed by air overpressure.

The filling isolator will be decontaminated using the same methods and to the same specification as previously described for the interface and transfer isolators. To ensure safety, the isolator will be decontaminated with the exit doors closed.

The ability of the isolator air-handling control PLC to control air pressure in the isolator to set point will be verified. The integrity of the isolator will be demonstrated in validation, and standard operating procedures (SOPs) will be developed to define in-process integrity test conditions. A full environmental monitoring performance qualification will be done to demonstrate the ability of the isolator to maintain aseptic conditions for the unit's defined operational period. As is the case for all isolators in the network, we expect that the filling isolator will remain free of detectable bioburden.

Preparation of containers and closures. The filling system can accommodate various vials and ampuls. Each vial and ampul system will be washed using a Cozzoli glassware washer. The efficacy of the washer will be verified by particulate removal studies on glass containers. After washing, the trayed glassware will be sterilized and depyrogenated in a Despatch batch oven equipped with high-temperature HEPA filters so that ISO Class 5 conditions can be maintained during operation. The ability of the oven to maintain this particulate air quality and to achieve targeted temperature will be verified. The depyrogenation process will be validated to provide a minimum 3–log reduction of reference standard endotoxin inoculated onto test glass (5).

Rubber closures for vials will be purchased prewashed from vendors and sterilized in nonwoven high-density polyethylene beta-bags as previously described. The mass of stoppers placed in each bag will be verified to ensure load uniformity. The stoppers will be sterilized in a Fedgari autoclave which will be validated in the conventional manner. Temperature penetration and distribution studies will be conducted and the delivery of lethality sufficient to achieve a 10^6 probability of nonsterility will be verified by BI challenges.

Cleaning and sterilization of the fluid path. The sterilization of the Shibuya product filter skid and mass-flow filling system will be validated to demonstrate a 10^6 probability of nonsterility. Temperature distribution throughout the fluid path will be assessed, and BIs will be used to confirm lethality. From the sterility assurance perspective it is advantageous that the fluid path is sterilized fully assembled and ready to operate and no aseptic connections are required.

The entire fluid path will be cleaned in place and temperatures and flow rates will be verified against the system's user requirement specifications. Cleaning acceptance criteria will be developed for each clinical material filled on the system considering the toxicological characteristics of the product. The acceptable carryover value will be determined using a starting point of either 1/1000 of the minimum therapeutic dose or a no-observable-effect-level model. The safest approach to determining carryover will always be chosen (6).

Filling accuracy. The ability of the filling system to deliver accurate volumes will be verified over the specified volume delivery range. The filling control loop will be verified as well. After validation, the system will be checked for accuracy during setup and will be calibrated on a regularly scheduled basis. Because the Shibuya filler provides weight control data on each container, there will be no need for manual in-process weight checking.

Stopper and seal feeding system. The parts hoppers for both the rubber stopper and aluminum seals are located inside the Class 5 decontaminated isolator environment and will be decontaminated in situ using VHP. The parts hoppers and feed tracks will

be cleaned after each use to remove process-related dust and lubricants. This system has two substantial advantages over typical cleanroom installations. First, there is no aseptic assembly required, and second, the capping machine is within a section of the isolator. The design provides separation so that particulate generated during sealing can not affect product, but it also ensures that sealing is performed in the same high-quality environment as filling and stoppering. This ensures complete protection of the entire container assembly process from microbial contamination for optimum assurance of safety.

The stopper-placement system will be validated to reliably fill and half-stopper vials. The system will be shown to meet a consistent process capability requirement. The capper will be validated to demonstrate the application of consistent seal-force pressure. The total container closure integrity of each container will be verified by microbial immersion testing. The filler is capable of inert-gas overlay, and this system will be validated to demonstrate that it can achieve suitable levels of residual oxygen on a product-by-product basis.

Lyophilizer sterilization. The Edwards lyophilizer is designed to be sterilized in place by moist heat. Temperature distribution will be verified using thermocouples and an appropriate sterilization process cycle developed from these data. Sterilization of the lyophilizer chamber and condenser will be demonstrated using BIs to confirm a 10^6 probability of nonsterility. The lyophilizer is cleaned in place and the efficacy of the cleaning procedure will be verified.

Utilities services validation. The new aseptic facility will have a full complement of pharmaceutical utilities. These include water for injection, clean steam, pharmaceutical compressed air, instrument air, and compressed gasses. Each of these utility services and their related generation, storage, and distribution systems will be validated to industry and compendial standards. Testing will be conducted over a suitable time duration to demonstrate the long-term reliability of each utility system. In addition, a concurrent validation program that will require more intensive testing and monitoring during the first 30 days of operation will be implemented. Ongoing testing and monitoring programs will be designed to demonstrate ongoing control and to ensure continuous compliance with industry and compendial quality requirements.

Validation of the background environment. The isolator network will be located in an ISO Class 8 surrounding environment as required by current worldwide regulatory guidance. The surrounding environment will be certified to comply with ISO Class 8 conditions under dynamic conditions. The room environment will be the subject of an environmental monitoring performance qualification, and temperature and humidity will be controlled in the range of 17–25 °C and 50 ± 10%, respectively (7).

Process simulation media fills. We anticipate that the typical lot sizes filled in this system will range from a few hundred to ~5000 vials. Media fills will be conducted to verify aseptic processing performance over a representative range of container-closure systems. Media fills will simulate ampul, vial, and lyophilized vial filling processes. The media fills will consider all line interventions and adjustments required during normal processing. Trypticase soy broth media will be used for all media-fill tests, and the containers will be incubated for 7 days at 20–25 °C followed by 7 days at 30–35 °C. It is expected that all media fills will be completely free of microbial growth (8).

Regulatory compliance

Care has been taken in the design of the aseptic processing facility to ensure that it will comply with all global regulatory requirements. Current regulatory guidelines require clinical product to have the same sterility assurance as commercial product. Therefore, the facility was designed to provide contamination control superior to that of any staffed cleanroom and to achieve near-zero contamination results in environmental monitoring and media-fill testing. The validation and process control programs are of the same standard as would be applied to a commercial aseptic processing facility.

Summary and conclusions

The scientists and engineers involved in this project have endeavored to design and equip a facility that will manufacture safe and contamination-free clinical products. The timeline is ambitious and the company plans to have the facility fully functional in early 2004. The use of consultants who have experience working with key equipment suppliers on complex large-scale projects should allow the project to be completed as scheduled.

References

1. *Cleanrooms and Associated Controlled Environments. Part 1: Classification of Air Cleanliness (*International Standards Organization, May 1999).
2. D. Meyer, "Developing a Barrier/Isolator Implementation Plan," in *Isolator Technology*, C.M. Wagner and J.E. Akers, Eds. (Interpharm Press, Buffalo Grove, IL. 1995), pp. 97–121.
3. "PDA Technical Report No. 34: Design and Validation of Isolator Systems for the Manufacturing and Testing of Health Care Products," *J. Pharm. Sci. Technol.* supplement to volume **55** (5) (2001).
4. J.M. Khoury, "Successfully Meeting FDA and Industry Expectations in the Use of a High Speed Isolator—A Case Study," in *Proceedings of the PDA Isolation Technology Conference* (PDA, Irvine, California, 2000).
5. L.B. Coleman and G.D. Heffernan, "Dry-Heat Sterilization and Depyrogenation," in *Validation of Pharmaceutical Processes—Sterile Products,* F.J. Carleton and J.P. Agalloco, Eds. (Marcel Dekker, New York, 1999), pp. 483–526.
6. J.P. Agalloco, "Steam Sterilization-in-Place," in *Validation of Pharmaceutical Processes—Sterile Products,* F.J. Carleton and J.P. Agalloco, Eds. (Marcel Dekker, New York, 1999), pp. 451–482.
7. J. Akers, "PDA Technical Report No. 34: Harmonization and Key Technical Discussion Points," in *Proceedings of the PDA Isolator Technology Conference* (PDA, New Brunswick, New Jersey, May 2002).
8. "PDA Technical Report No. 22: Process Simulation Testing for Aseptically Filled Products, " *J. Pharm. Sci. Technol.* **50** (S1) (1996). **PT**