Isolator Technology For Aseptic Processing

Sterility testing, component transfer, and filling applications are typical isolator uses. Read more here to determine which one is best suited for your next upgrade.

by Gary Partington

Uses of isolators for aseptic processing are far reaching. The earliest use of aseptic isolators were for sterility testing. Sterility test isolators make up most of aseptic isolator use and are available in many different sizes and configurations. Sterility test isolators do not need to be installed in a classified area. No formal requirement exists for a Grade D environment, but the area should be controlled to allow only trained personnel. The room should also have temperature and humidity control.

Autoclaves (steam sterilizers) used to prepare media for sterility testing were interfaced with isolators to keep the entire sterility test process under isolator conditions. Other uses for aseptic isolators include interface isolators for depyrogenation ovens, lyophilizers, filling machines, component transfers, and charging of sterile powders.

Test isolator with airlock.

Design Guidelines

Primary guidelines to consider when designing an aseptic isolator system are:

- Materials of construction
- UAF or non-UAF
- Glove ports/half-suits
- Decontamination
- Controls
- Pressurization
- Transfer systems

Aseptic isolators can be made from flexible or rigid materials. Flexible wall isolators use clear plastic film (usually PVC) at a variety of thicknesses. These isolators are lighter weight, offer good visibility, and are easy to set up. However, great care must be exercised when using sharp instruments in and around the isolator or when using cleaning agents and solvents as the flexible enclosure can be compromised. Also, decontamination agents are absorbed into the flexible enclosure which results in long decontamination cycles while the agent "outgases" from the enclosure during aeration.

Rigid wall isolators are generally made from 316L stainless steel for the enclosure and laminated safety glass for viewing windows. While these isolators are heavier and take more time to install, they are more durable, do not absorb decontamination agents which results in fast decontamination cycles, resist chemical agents, lend themselves to uni-directional airflow, and are easier to leak check than flexible wall isolators. Rigid wall isolators can be used for any isolator system, especially filling machine systems where a mock up of the design is preferred.

Aseptic isolators need to keep microorganisms out of the environment and therefore need to operate under positive pressure air delivered through HEPA filters. Generally this pressure is 0.25 inches of water column, but can be raised or lowered when multiple isolators are linked together (in the case of a filling line) and cascading pressures are needed. At times, a negative pressure system may be added as an emergency system when potent materials are being filled or charged aseptically. Periodically, isolators need to be leak tested to ensure integrity and prevent escape of the decontamination agent. Leak testing can be done by various methods including pressure decay or chemical detection.

Uni-directional (sometimes called laminar) air flow through HEPA filters is required for particle-generating operations such as filling and capping or with the manufacture of sterile medicinal products. Other operations such as sterility testing have successfully used non uni-directional or turbulent air flow for more than 20 years. Certain interface isolators may use non uni-directional airflow as well. Regardless, particle monitoring systems may be integrated into the isolator to detect both viable and non-viable particles as part of an environmental monitoring program.

Transfer systems are a function of the size of the items that need to enter/exit the isolator and at what point in the process. Transfer systems include hinged doors, hatchback windows, airlocks, RTP (rapid transfer port) systems, and utility panels. Many isolators include hatchback windows for entry of large items or staging of multiple items prior to decontamination. Airlocks are small chambers attached to the

end of the main enclosure.

Airlocks use pairs of hinged doors that are located between the airlock and the main isolator and the airlock and the room. These doors can be interlocked so one cannot be opened if the other is open. This prevents exposure from/to the main chamber and the room. Airlocks can be any size and often are equipped with a view window and a glove port.

The future may include automated or robotic systems to perform testing or handling of extremely potent or radioactive products.

Airlocks can be equipped with a pressure equilibration HEPA filter or its own ventilation/HEPA filtration system. Airlocks are used to enter or exit materials from the main chamber. These materials are generally larger than those that can fit within an RTP system. Before the airlock door is opened to the outside room it must be decontaminated.

Often electrical cords for scales, mixers, stir plates, and other equipment can be passed out of the isolator through a utility panel. Similarly vacuum, liquid, air, or other process utilities need to be brought inside the isolator. This can be done using a utility panel built into the body of the isolator. The panel is customized for the process being performed inside the isolator. The custom-made utility panel can contain triclamp connections, bulkhead fittings, quick connects, hose barbs, compression fittings, and etc.

RTP systems (double door transfers) are used to enter into the isolator or remove items from the isolator without breaking the "sterility" of the isolator. The RTP system is made of the two parts typically called the alpha flange and beta flange. Diameters of the most popular RTPs range from 105mm to 460mm. Materials used in construction are polyethylene or polypropylene and stainless steel.

The beta flange is rotated 60^0 clockwise which engages both door halves together. The operator opens the combined flanges inside the enclosure via the glove ports or half-suit. The gaskets on the flanges seal the two door halves together and the beta flange to the alpha flange. Microbes can neither get in/out of the chamber or in/out of the two door halves when they are "sandwiched" together.

Handling inside of isolators is done via glove ports or half-suits. For aseptic applications, glove assemblies are comprised of two pieces. The sleeve and glove are separated by a wrist connector. This allows the glove to be changed in-situ. Glove and sleeve materials are available in neoprene, butyl, and Hypalon. Glove sizes range from size 8 to 10 and come in left hand, right hand, or ambidextrous configurations. Glove sleeve diameters range from 8" to 10", with 10" being most commonly used. Glove ports can be round or oval and are made from widely different materials depending on the manufacturer. A molded port with insert cover presents a crevice-free sleeve inside the isolator and is cleanable.

Transfer isolator with RTP.

Reach inside the isolator is limited due to the length of glove sleeves. When more reach or range of motion is required, a half-suit is employed. This is often the case with isolators that interface with autoclaves, ovens, and lyophilizers, but are also used in sterility testing. The half-suit is made from a cloth-like material with a PVC outer layer. A half-suit utilizes an independent ventilation/filtration system which delivers HEPA filtered air between the two layers of the half-suit. Airflow escapes through holes near the helmet. The use of glove ports or half-suits allows the operator to be physically within the system, but "biologically" removed from it.

Controls

While a simple isolator can be operated with a single loop control system, integration with decontamination generators and other special process requirements such as humidity control and oxygen control make PLC (programmable logic controller) systems a better choice. A PLC system will also control blower operation, valve operation, and provide various user access screens and alarm points. Using a PLC allows for automated decontamination cycles that can be operated overnight or at other times, which frees up the operator to perform other tasks.

Decontamination

Today's isolators are decontaminated primarily with hydrogen peroxide delivered as a gas or as a condensing vapor depending on the type of generator selected. Chlorine dioxide is also used, but is not as common. Generators can be portable and can service multiple isolators or be integrated within the isolator. Cycle times depend on the volume of the isolator, materials used in constructing the isolator, materials to be decontaminated within the isolator, and isolator HVAC design. To validate decontamination cycles, multiple biological indicators typically inoculated with a minimum of 10^6 Geobacillus stearothermophilus spores on stainless steel, are placed throughout the isolator for a worst-case load. Three successive, successful cycles resulting in no remaining spores constitute a validated cycle. Aeration of the enclosure should also be validated. Users typically add 20-25% to the validated exposure time to account for potential system variability. The user

documents the level of sterilant residue that will not negatively affect the process.

Applications

Aseptic isolator uses include sterility testing, interface isolators, transfer isolators, filling machine isolators, and powder charging/handling isolators. Sterility test isolators are used to eliminate false positives during the testing process. This is done by separating the operator from the products during testing. The isolator is decontaminated and operates under positive pressure, HEPA filtered air.

Interface isolators attach directly to a flange on the door of the equipment being interfaced to, such as an autoclave, depyrogenation oven, or lyophilizer. Due to the volume of the equipment chamber and the load within, the isolator often utilizes a half-suit so the operator can reach into the equipment and into any loading cart.

Transfer isolators are used to transfer components or product from one isolator to another. This is achieved by using an RTP system. Transfer isolators are mobile and usually contain shelves for storage of materials. Often materials are loaded into the transfer isolator and then decontaminated before transfer. An example would be pre-sterilized vial packs that would be opened inside the transfer isolator, and then transferred to the filling machine isolator.

Filling machine isolators can be designed to incorporate bench top fillers or to interface directly with a table top fill machine. These isolators are customized and work with batch filling or continuous filling systems. Uni-directional flow through HEPA filters is required with a positive overpressure system. For aseptic fill of potent liquids or radiopharmaceuticals, a negative pressure breach system is used.

Validation

Aseptic isolator validation includes installation qualification (IQ), operation qualification (OQ) of the isolator and the performance qualification (PQ) of the system which includes the decontamination generator. Typical IQ checks include:

- Equipment (specified equipment was received and properly installed)
- Construction materials (specified materials were used)
- Instruments (calibration status of instruments is listed)
- Utility specifications (verify and check connections)
- Filter certificates (test data or certificates are available)
- Computer software (software provided is properly listed)

Typical OQ checks include:

- Operational performance check (set points and alarms comply with functional specifications)
- Isolator integrity check (leak test verification)

Typical PQ Checks Include:

- *BI (biological indicator) D-value determination study:* This includes execution of a D-value protocol in triplicate using the isolators and decontamination generator. This testing provides resistance data for the lot of BIs that will be used during validation and provide a detailed procedure for testing new BI lots for future system re-qualification tests.
- *Cycle development/PQ studies:* Developed cycle will be validated in triplicate using TCs (thermocouples) and BIs placed throughout the worst case load to verify temperature and gas characteristics and uniformity within the isolator. Aeration studies will be performed on the worst case load using the normal cycle (BI kill time plus 20%) in triplicate at the end of various generator aerate times and/or external exhaust periods until the gas concentration has been reduced to a level considered acceptable for operations and for operator safety.

Sterilant Intrusion Study

A product container matrix is developed and each type will be bracketed in terms of size and then semi-quantitatively assayed for residual sterilant after a single or back-to-back decontamination cycle. The goal is to show that sterilant penetration does not occur. A representative from each container type will be challenged microbiologically in residual effects testing.

Residue Effects Study – Total System Challenge

This testing, also known as a 'false negative determination test' is performed with triplicate product and environmental monitoring samples in the isolator following a single or back-to-back decontamination cycle to rule out the possibility of false negatives due to sterilant residues in the isolators, in the samples, and/or on the supplies.

Conclusion

There are many benefits to using isolator technology for aseptic processing. Separating the operator from the process/product results in greater product quality and operator safety. In sterility testing, there are virtually no "false positives", which saves investigation time and money. Sporicidal agents delivered into the isolator as part of a validated system provide a much higher sterility assurance than in a clean room, which is typically disinfected manually. Isolators are less expensive to operate and there are no gowning requirements, which saves money and time. Plant utility cost savings are also realized. Data gathered since 1998 on the use of isolators for aseptic filling have shown a steady growth rate worldwide. With the need to formulate and fill more potent products aseptically, the use of isolators will continue to grow. The future may include automated or robotic systems to perform sterility testing or handle extremely potent or radioactive products to eliminate operator interaction through gloves.

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