White Paper: The Benefits of Isolator and Aseptic Processing

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With the need to formulate and fill more potent products aseptically, the use of isolators will continue to grow.

Isolators have been around the Pharmaceutical Industry since the early 1980s and in the Nuclear Industry (glovebox technology) since the 1950s. The intent of isolators is to create an airtight barrier or enclosure around a piece of equipment or process which provides absolute separation between the operator and product. The operator can perform tasks through half-suits or glove ports. Isolators provide a specific environment inside the isolator using HEPA filters. The environment can be positive pressure or negative, can have humidity control, oxygen control, use unidirectional airflow, and can either protect the product from the operator as with aseptic processes, or protect the operator from the product as with potent product handling. The earliest uses of aseptic isolators were for sterility testing. Sterility test isolators make up most of the aseptic isolators in 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. Additional uses for aseptic isolators include component transfers, charging of sterile powders, and interface isolators for filling machines, depyrogenation ovens, and lyophilizers.

Figure 1: Six Glove Sterility Test Isolator

DESIGN GUIDELINES

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 as the process requires. Isolators need to be periodically leak tested to ensure their integrity and prevent escape of the decontamination agent. Leak testing can be done by various methods including pressure decay or chemical detection

Sterility testing isolators have successfully used nonunidirectional or turbulent air flow passing through inlet and outlet HEPA filters for over 20 years. Certain interface isolators also use non-unidirectional airflow. Unidirectional (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. Regardless,

particle monitoring systems may be integrated into the isolator to detect both viable and nonviable particles as part of an environmental monitoring program

Aseptic isolators can be constructed using both flexible materials as well as 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. Decontamination agents are absorbed into the flexible enclosure which results in long decontamination cycles while the agent "outgases" from the enclosure during aeration. Also, great care must be exercised when using sharp instruments in and around the isolator or when using cleaning agents or solvents as the flexible enclosure can be compromised.

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 result in fast decontamination cycles, resist chemical agents, lend themselves to unidirectional 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.

Handling inside of isolators is done via glove ports or half-suits. For aseptic applications, glove assemblies are generally comprised of two pieces. This means the sleeve and glove are separated by a wrist connector. This allows the glove to be changed in-situ. Glove ports can be round or oval and are made from widely ranging materials depending on the manufacturer. A molded port with insert cover presents a crevice free sleeve inside the isolator and is highly cleanable.

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. Half-suits utilize an independent ventilation/filtration system which delivers HEPA filtered air between the two layers of the half-suit. The use of glove ports or half-suits allows the operator to be physically within the system, but "biologically" removed from it.

Transfer systems include: hinged doors, hatchback windows, airlocks, RTP systems, and utility panels. Many isolators include hatchback windows that open for entry of large items or staging of multiple items prior to decontamination. Airlocks are typically small chambers attached to the end of the main enclosure.

Airlocks use pairs of simple 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 opened. Before the airlock door is opened to the outside room it must be decontaminated with a sporicidal agent.

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 which may contain triclamp connections, bulkhead fittings, quick connects, hose barbs, compression fittings, etcetera.

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.

The beta flange is rotated 60° clockwise which engages both door halves together. The operator will open 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 "mated" together.

CONTROLS

A simple isolator can be operated with a single loop control system, the integration with decontamination generators and other special process requirements such as humidity control and oxygen control make PLC

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 which can be operated overnight or at any other time, which will free up the operator to perform other tasks.

DECONTAMINATION

Today's isolators are decontaminated primarily with hydrogen peroxide delivered as either a gas or a condensing vapor depending on the type of generator selected. Chlorine dioxide is also used, but is not that common. Generators can be portable, which can service multiple isolators or be integrated within the isolator. Cycle times depend on the volume of the isolator, materials of construction of 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 106 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 must document the level of sterilant residue that will not negatively affect the process.

Figure 2:
Transfer Isolator

Figure 3: Filling Machine Isolator

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. 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 the RTP system discussed earlier. 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.

Filling machine isolators can be designed to incorporate bench top fillers or to interface directly with a large fill machine table top. These isolators are highly customized and work with batch filling or continuous filling systems. Unidirectional 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 often employed.

COSTS

While the initial purchase of an isolator system is a large capital expense, isolators are less expensive to operate versus a cleanroom. Areas in which isolators save money versus cleanroom technology include:

- No gowning/de-gowning requirements save time and gown costs.
- Smaller HVAC system saves in utility costs.
- Less filtration saves in filter change costs.
- Small volume results in shorter decontamination times saving labor costs.
- Elimination of false positives results in no investigation costs.

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 installation, correct materials of construction, calibration status of instruments, utility connections, filter certificates, and computer software.

Typical OQ checks include verifying that set points and alarms comply with functional specifications and isolator leak test verification.

Typical PQ checks include BI Dvalue Determination Study, Cycle Development/PQ Studies, Sterilant Intrusion Study, and Residue Effects Study—Total System Challenge.

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. Sporicidal agents delivered into the isolator as part of a validated system provide a much higher sterility assurance than in a cleanroom, which is typically disinfected manually. Data has been taken since 1998 on the use of isolators for aseptic filling. Steady growth can be seen for filling machine isolator use worldwide. Sterility test isolator use continues to be one of the more frequent uses of isolators. 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.