

Features

Isolator Quest

Perseverance necessary to find the right fit

BY Robert Guardino and Kevin Jones

The pursuit of a good sterility test isolator is an adventure that involves deciding the rationale for its use, selecting the equipment, justifying the capital expense, and installing and validating the unit.

We embarked on a mission to study isolators for sterility testing, though many of the issues also apply to aseptic processing. We navigated a variety of roadblocks to realize the efficiency these isolators provide.

The risks cannot be completely eliminated. Removing the operator/analyst from the environment and ensuring that exposure of product and test material only occurs within a sealed, decontaminated environment greatly enhance the process, however. Aside from the obvious regulatory expectations and interests, other issues, such as analyst comfort and the cost of disposables for clean room operation (e.g., gowning, preparation time, sanitization, and clean room monitoring) make the use of isolators enticing.

Isolators with automated decontamination cycles allow for unattended preparation of the working space and test materials. Once all test items are loaded, the cycle can be initiated and decontamination and aeration accomplished without further human intervention. This is a clear advantage over clean room sanitization and rinsing, which involve the manual decontamination of materials required during sterility testing in a clean room. Isolators with an automatic decontamination cycle allow you to prepare the chambers for use, run the cycle overnight, and commence testing the following morning. This functionality saves both time and money.

The Equipment

When deciding which vendor to work with, you must choose either glove box or half suit and either hard wall or soft wall isolators. Height restrictions and the taller profile of half suit isolators led us to pick glove box isolators. To shorten the decontamination/aeration cycle, we chose the hard wall models.

In considering which vaporized hydrogen peroxide (VHP) vendor to use, you will immediately get caught up in the wet versus dry process dispute. Both processes work, but they have different cycle times; the dry process requires higher peroxide levels and a longer aeration period. We strongly recommend that you visit sites using the equipment under consideration and talk with users before deciding on the isolator and VHP generator. Of particular importance are the challenges inherent to validation, routine maintenance of the equipment, and associated down time. This research is the best investment of time and resources that you can make during the decision-making process. After evaluating vendors of both the isolator and VHP generator equipment, we became aware of an isolator system manufactured by Skan AG (Allschwil, Switzerland) with a fully integrated VHP generation system. This product offers several advantages:

- Each isolator has its own generator, providing redundancy (if more than one isolator is purchased) that can minimize down time;
- It costs about 25% as much as the stand-alone models;
- The design is simple;
- The generator is validated as an integral part of the system; and

- There is no need to regenerate desiccant because the process is wet and desiccant is not used.

After additional discussions with Skan AG isolator customers, we decided to purchase their unit.

The Justification

Sterility isolator technology is a significant investment for any company. If you're a project manager or owner, you must be prepared to justify the purchase.

The benefits of sterility test isolator technology can be tangible (efficiency, greater throughput for samples, and use of fewer consumables) or intangible (reduced fatigue and employee burnout).

Key criteria to focus on when preparing the operational justification include:

- Significant reduction in the risk of false-positive results and the corresponding savings for investigations and product release delays;
- Increased capacity for sample analysis;
- Enhancement of compliance with domestic and international guidelines and expectations;
- Reduced employee fatigue and attrition due to harsh conditions in clean room technology environment;
- Decreased expenditures for consumables (about \$20,000 per year, including reduced cost for gowning supplies, disinfectants, and related supplies); and
- Portability (sterility test isolators can be relocated).

In our example, isolators can save 745 work hours, which can be used for other activities such as batch release or testing. You can do more with the same number of employees—or fewer. There will also be greater flexibility in scheduling personnel, which will increase capacity.

Clean room technology may require two employees to work in tandem to pass through needed materials or for safety purposes. The isolator equipment allows the analyst to leave the lab for supplies or other reasons. Carefully planned decontamination cycles in a sterility test isolator can allow for faster turnaround on test scheduling when compared with that required for a clean room environment. Planning allows for greater sample throughput, expedited product release, and greater capacity.

Clean room technology frequently requires annual shutdowns for maintenance, such as repairing epoxy paint and disinfectant-induced corrosion.

Sanitizing and monitoring to recommission the clean room can add two weeks to the down time. Isolators minimize this time, ensuring more efficiency and sample volume for the lab.

Though it is difficult to calculate because it varies with time and conditions, there will be a reduction in the organism isolate identification related to environmental excursions and positive sterility test investigations. Additionally, the costs associated with subcontracted DNA-sequence identification of isolates will be reduced because the isolator technology should reduce or eliminate the environmental effects of clean room technology.

Financial decision-making criteria are weighted differently from company to company

and industry to industry, but key indicators for any investment are net present value, internal rate of return, and return on investment. These will factor into any company's decision to buy sterility test isolators.

The Installation

Perhaps the next biggest hurdle is deciding where to install the isolators. This is especially problematic if you have an older laboratory space that was not designed with isolators in mind.

An isolator may be the largest piece of equipment purchased for a microbiology lab. The footprint must allow ample space on all sides for work and maintenance. When height restrictions are an issue, choose a unit with maintenance access on the front of the unit rather than on the top.

To meet height requirements, we constructed a lab. We installed dedicated HVAC to meet the requirements of an ISO Class 8 clean room. FDA advises that an aseptic processing isolator should not be located in an unclassified room. While no such requirement exists for sterility test isolators, it is prudent to plan for ISO 8 even if the environment is not classified. Providing a clean, controlled-access environment helps to ensure safety.

Isolators are typically custom-built, even when a standard unit is available. Knowing how the isolators will be used and documenting user requirements are vital parts of the process. At AAIPharma, a supplier of product development and support services to the pharmaceutical, biotechnology, and medical device industries, we purchased two Skan ARIS isolators, which are a standard design for sterility testing purposes.

For our use, we determined that we wanted the isolators directly linked with pass-through doors. As a contract lab, we see many product formats, ranging from aqueous injectables and ophthalmic and otic solutions to sterile powders and implantable combination products and devices, to name a few. Each format has unique test parameters. Our worst-case scenario, from a material-needs point of view, requires in excess of 80 one-liter bottles of media plus samples, as well as all associated testing materials and controls. To set up one test requires the space available in both isolators; thus, we needed the units to be joined in some fashion. For simplicity, we opted for a pass-through setup rather than a rapid transfer port. The isolators may be used as a single-test environment or as independent clean zones for testing. We have essentially doubled our capacity from a single ISO Class 5 clean room to two side-by-side isolator units.

Other design considerations include the isolator's working height, which affects analyst comfort, and the accommodation of an integral membrane filtration unit. The choice of vendors for the filtration unit was important because a design modification became necessary for the unit chosen. The two most widely marketed devices are the Millipore Steritest Equinox (Millipore, Billerica, Mass.) and the Sartorius Sterisart (Sartorius Stedim Biotech, Aubagne, France). The Equinox has a higher profile inside the isolator, while the Sterisart has a greater profile beneath the isolator chamber, requiring the door to the electrical panel beneath the work surface to be redesigned to accommodate the pump unit.

Once we established our design requirements, we scheduled the manufacture of the isolators. With the exception of the review of design documents, the build process was

rather seamless. Most of the lab's preparation during this time was focused on facilities and utilities issues. This required diligence from all parties involved, including company engineering and facilities maintenance departments, contractors, equipment vendors, and the isolator company. The HVAC system components required perhaps the longest lead times. Each isolator/VHP generator has particular temperature and relative humidity (RH) range requirements.

It's important to ensure that the HVAC unit can deliver the appropriate environment consistently. Ensuring proper ventilation and isolator exhaust required continued discussions. The exhaust component was particularly troublesome. To decrease the aeration time, which is the key to a shorter decontamination cycle, unrestricted exhaust is critical. The ARIS isolators have unidirectional airflow.

No fans are required to disperse the VHP. Exhaust is accomplished through an air return in the back of the unit that is driven, by a blower, through a HEPA filter and up the exhaust flume.

An additional consideration for the location of the isolators is their exhaust needs. A short, straight, unrestricted exhaust flume greatly enhances the aeration rate. No auxiliary exhaust blower is necessary as long as the length of the exhaust duct is less than 10 meters, there are no right angle bends, and the diameter of the HVAC ducts is as large as the exhaust coupling on the isolator.

Because cycle time is critical to turnaround time between testing, we sought to maximize the efficiency of this component of the system. We achieved all parameters necessary to minimize the aeration times by carefully selecting the location of the isolator lab, the location of the isolators within the lab, and the components of the exhaust system, and by ensuring proper installation. The exhaust system was made of surgical welded stainless steel and run straight through the roof.

Prior to construction, we planned the location of the isolators in the room. During construction, lighting fixtures were installed that we later found to be directly in line with the exhaust couplings of the isolators. Once the isolators were installed in the optimal location in the room, we decided that it would be wiser to relocate the lighting fixtures rather than to bend the exhaust system around the lighting fixtures. Though it seems like a simple item—and something that could have been avoided during the lab design phase—it was not obvious, until the isolators were installed, precisely where the exhaust ducts would need to go. The exact location of the isolator exhaust coupling, the angle at which the isolator chamber was mounted on the stand, and the location of the ceiling joists were all important considerations in deciding the final exhaust location.

While installing the isolators in new construction, we became aware that the final electrical inspection was going to be performed after the isolators were installed. The isolators were labeled with European electrical certification rather than a UL-listed one as required in the U.S. This was discovered during the electrical inspection and further delayed implementation of the isolators. The equipment had to be retrofitted on site before the in-field UL labeling could be accomplished. While waiting for the retrofit and UL labeling—roughly a two-month process—we proceeded with installation and operational qualification (IO/Q), some of which had to be repeated after UL labeling.

The Validation

Because we had no experience validating isolators, we contracted with a third party for validation services.

In our travels to visit the users of various isolators, we had learned how time-consuming and difficult validation can be. We spoke to individuals who had been trying to validate their isolators for more than a year. This problem has a lot to do with isolator design and features, but it's also related to the level of experience of those performing the validation. Hiring individuals with a proven track record is money well spent. Though they are few, they are easy to find: Just ask an isolator vendor or most users. Aside from the IO/Q mentioned above, the steps involved include D-value testing of biological indicators in the isolators, decontamination/aeration cycle development, the formal load-dependent performance qualification (PQ) studies, and sterilant intrusion and residue effects (false-negative studies).

Document preparation alone justifies the cost of validation services; the nuances of isolator validation, together with the tricks of the trade, will truly make you glad that you did not "try this at home."

Also, the advice given by validation vendors regarding the materials and supplies needed up front, as well as applicable vendors of the same, may save a great deal of time. Speaking of materials, one critical parameter for validation is the proper selection of test samples for cycle development and PQ loads and for sterilant intrusion studies. Those companies who have one or more products to test with the same format, such as sealed glass vials, have the advantage of simply including all products in validation studies. We already mentioned the variety of product formats that we test as a contract lab. These come in all sizes and shapes—not to mention the various construction materials used for containers and closures. Add to that the particular seal strengths used during processing, and you are left with quite a selection.

Now imagine that you don't have samples available because they all belong to other companies. Careful planning and a good relationship with your clients are both critical to sourcing the samples needed for validation. Fortunately, the benefits for the client companies during sterility testing in an isolator should make most of them willing participants in your validation activities.

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RESOURCES

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