The Containment Master

MIKE AUERBACH, Editor in Chief, Pharmaceutical Processing

 Sterling Kline is an expert in aseptic facility design and is considered by many to be a leading authority in state-of-the-art sterile isolator technology. Mr Kline works for Integrated Project Services (IPS), a full-service engineering firm.

Pharmaceutical Processing: Can you briefly describe the history and evolution of containment systems?

Sterling Kline: During the mid-1990s initial efforts were initiated to introduce isolator technology to the aseptic filling process. Stainless steel and glass containment units were constructed to segregate operators from the product to reduce the risk of contamination. H2O2 vapor was introduced as the sanitization agent to ensure all surfaces met regulatory expectations. The initial effort in the US known as the LUMs project was marginally successful with several issues including the lengthy eighteen hour sanitization cycle and unmet forecasts of cleanliness levels. The following decade the H2O2 isolator systems were predominately abandoned in favor of barrier systems that substituted manual sanitization of internal surfaces in lieu of the vaporized hydrogen peroxide (VHP) system. These barrier systems became known as Restricted Access Barrier Systems (RABS) and varied significantly in their level of isolation and containment. The RABS units can be configured to use room air and be open at the top and bottom with closed panels, closed at the top- and open on the bottom or be fully enclosed with internally recirculated air. These RABS units obviously vary dramatically in their success in the primary objective to separate the operator from the product and reduce the risk of contamination.

In 2002, the patent on the H2O2 systems expired and systems with sanitization cycles that were repeatable and were as low as four hours were introduced. Over the next decade these isolators became well accepted and became the preferred option by regulators and manufacturers including Big Pharma, CMO and Generic companies alike. These isolator systems continue to be improved and have cycle times in the range as low as two hours.

Pharmaceutical Processing: What is the FDA’s current thinking regarding containment technologies?

Sterling Kline: The FDA currently strongly prefers isolator technology but will accept closed RABS technology. The advantages of the isolator as seen by the regulators are the isolator technology separates the operators from the product and product contact parts more completely, the sanitization process is automated and repeatable, and continuous processing including automated lyo loading is possible. In addition, numerous studies have shown that isolation technology is less expensive than RABS for both initial total project capital investment and long range operating costs.

Representatives of both CBER and CDER have stated recently that all traditional non-barrier filling suites will be closed within the next five years. Auditors will also scrutinize RABS designs to insure the operators maintain the integrity of the barrier throughout the manufacturing process including refraining opening the RABS doors for interventions.

Pharmaceutical Processing: Who is driving innovation in this segment of the market? Are pharma companies driving equipment vendors or are equipment vendors constantly improving their designs and systems?

Sterling Kline: Innovation in isolation technology has been primarily driven by the equipment vendors over the past fifteen years with pharma companies typically requiring significant encouragement to accept change. Many of the pharma companies are still not willing to invest in the proven technologies that will lower the risk to patients in favor of other business priorities.

The majority of the advances in isolation technology have come from two equipment manufacturers: SKAN and Bosch Packaging. SKAN has lead the way with initial reduction of cycle times, new methods of rapid component transfer boxes and the current cutting edge proprietary aeration process.

Some advances have been driven by biotechnology companies for specific product segment needs such as the requirements for lower residual VHP levels in the range of ppb in lieu of the traditional ppm driven by OSHA requirements to limit or to formulate the product aseptically in isolators.

Pharmaceutical Processing: How important are elements such as system design, facility design and operator training for effective application of containment technologies?

Sterling Kline: Aseptic manufacturing requires a fully integrated process involving the process equipment, the facility and the operators to work in harmony. Barrier technologies reduces the risk of product contamination but still requires an integrated facility design that reduces other risks such as product cross contamination or segregation of raw materials and finished filled containers. Operator knowledge of manufacturing processes and procedures is still critical. Technology can reduce risks and the requirements for human actions and interventions but does not eliminate the risk of human error.

Pharmaceutical Processing: What impact does operator training have on effective containment system operation?

Sterling Kline: Operators are always the greatest compliance risk factor in aseptic manufacturing no matter what technology is used. Properly applied isolation technology effectively eliminates direct operator contact with exposed product, however proper cGMP techniques are still essential. Understanding the technology, product and component set up and transfer procedures and predetermined uniform reactions requiring human interventions are critical to safe products. All of these functions require intensive training that requires constant reinforcement.

Pharmaceutical Processing: What are the top 5 pitfalls or mistakes pharma manufacturers make when specifying, designing and installing/qualifying containment systems? How can they be avoided?

Sterling Kline: In no particular order:

1. Ordering the equipment too late: The filling line equipment is typically on the critical path to manufacture product for sale. In order for the facility and the equipment to come together on parallel schedules, the filling line including isolators should be ordered at the end of the Conceptual Design Phase. Also, knowing the exact layout of the purchased equipment simplifies the detailed facility engineering effort and reduces overall project cost. This process requires a consulting SME that can develop equipment URSs at this early stage in the project, and a capital procurement process that can authorize large expenditures at this stage of a project.

2. Underestimating internal staffing ramp-up: Too often pharmaceutical companies do not hire/assign the operating staff early enough in the project. This can lead to significant delays in start up. The projects are managed by project engineers that control the construction and installation efforts but they require an integrated transfer to the operation staff who should be leading the CQV and start up effort. These folks should be available for the FAT which is typically 18-24 months prior to full scale operation.

3. Choosing consultants without extensive containment experience: Currently a number of design consultants experienced in traditional but not barrier technology design are producing projects that lack current design efficiencies. Since the technology is advancing rapidly and the projects are lengthy, new facilities are typically five years behind current technology when approved. It is therefore critical that the latest technology and process be evaluated for all designs.

4. Choosing second tier quality vendors: Isolation technology vendors that do not fully understand the technology and science of the H2O2 process. There are many cases of isolators with inferior H2O2 systems taking an additional year to validate, extending the cycle time from 2-5 hours to 8-10 hours, and requiring substantial maintenance over time.

5. Overdesigning for isolator technology requirements: Many facilities are being

overdesigned for current technology. Room classifications associated with traditional non-isolated filling lines are being implemented: this adds an additional twenty to thirty percent of additional space due to added airlocks and gowning rooms. This can be resolved by classifying the entire aseptic suite as ISO 8 for the US and grade C for the rest of world.

Pharmaceutical Processing: What do you think the future holds for containment technologies?

Sterling Kline: Based on recent comments from the regulatory agencies, all aseptic manufacturing facilities will be transitioning to containment technology within the next five years. Considering the time required to design, implement and validate an aseptic facility, the conversion to all containment facilities should be complete by 2020.

Design using containment technology continues to improve through the collaboration of industry SMEs and equipment vendors. Current new introductions include single-use filling systems, component rapid transfer VHP devices, and one pass isolator aeration technology continue to simplify and shorten the manufacturing process. New devices and processes will continue to provide safer product at reduced cost to the consumer.

For more information, please visit www.ipsdb.com *[1].*

Links:
[1] http://www.ipsdb.com