ASEPTIC TECHNOLOGY TRENDS SERIES:
Advanced Aseptic Processing

By: Hite Baker, Principal Process Engineer
Introduction

This Series of White Papers, entitled Aseptic Technology Trends, is part of DME’s overall Facility Focus Program.

DME Facility Focus was designed to create a dialog within the industry regarding how we are going to meet the challenges presented by aging facilities, evolving regulatory requirements, new technology solutions and market changes in the pharmaceutical industry. It creates an opportunity to take good concepts and turn them into practical facility designs.

DME’s surveys were designed to touch on areas of both pain and opportunity—areas being transformed by technologies into the future facilities for cGMP manufacturing. They were also developed to help DME and other facility design professionals understand what manufacturers value most in the design of their facilities.
Aseptic Technology Trends: Advanced Aseptic Processing

Manufacturing sterile products using aseptic processing is conceivably the most critical process in the pharmaceutical industry. Aseptic processing has seen continual improvements over the last several decades, with new approaches that are transforming traditional aseptic production methods.

In this Aseptic Technology Trends paper, sterile manufacturer stakeholders will discover:

- Emerging technologies and regulatory guidance for implementing Advanced Aseptic Processing
- What the industry is saying about their challenges, priorities, and solutions in advanced aseptic technology adoption
- Considerations in choosing an engineering partner firm

What is Advanced Aseptic Processing?

In its simplest description, Advanced Aseptic Processing, or Advanced Aseptic Technology, protects product manufacturing using separation technologies (isolators, RABS, and closed system processing) and automation (robots, automated lyo loading, etc.)

According to a 2006 article by James Agalloco, James Akers, and Russell Madsen in Pharmaceutical Manufacturing magazine, the term “Advanced Aseptic Technology” emerged in industry forums discussing isolators and blow-fill-seal:
“Over the last few years, the term “advanced” has been applied to a number of aseptic manufacturing technologies. The 2002 Open Conference on Sterile Products, co-sponsored by USP and PDA, made advanced aseptic processing a discussion point, representing, we believe, the first such discussion in a public forum.

At that time, only two advanced aseptic technologies were discussed: isolators and blow-fill-seal. Recently, an advanced technology that fills product into a sealed sterile container has been introduced, and restricted access barrier systems (RABS) have been termed ‘advanced aseptic technology’. “

The same article offered the following definition of Advanced Aseptic Technology and justification, which has largely passed the test of time since the early 2000’s:

“An advanced aseptic process is one in which direct intervention with open product containers or exposed product contact surfaces by operators wearing conventional cleanroom garments is not required and never permitted.

We believe that this distinction is critical, because studies have shown that gowned operators—even when using the best garments and technique—may release several thousand colony-forming units into the surrounding environment during each hour of work. Any technology that allows this level of interventional activity, and the potential for contamination associated with it, is too risky to be considered advanced.”

Mitigating Risk with Advanced Aseptic Processing

Advanced Aseptic Processing mandates that sterile product and critical processing zones should never have immediate contact with gowned operators or the surrounding background environment. Good engineering design can achieve this goal by using automation, single-use/disposables, closed system processing, RABS and Isolators, plus a well-designed facility with nested cleanliness zones.

“The primary risk associated with conventional aseptic processing in staffed clean rooms is microbial contamination introduced by gowned personnel during normal operations and particularly during “interventions,” i.e., activities performed to correct problems that require breaching the critical zone in which product, product-contact surfaces, and containers and closures are exposed.

No reasonable amount of environmental monitoring is likely to detect every viable microorganism that might be released into the aseptic processing environment, and sterility testing is not sensitive enough to ensure the sterility of every unit of finished product.
Real control of risk, however, can only be achieved by removing people from the aseptic processing environment, which can be achieved most effectively by using new technologies that do not rely on gowned personnel and do not expose sterilized product, containers, or closures to the aseptic manufacturing environment.

Such technologies include isolators and barrier systems, blow-fill-seal and form-fill-seal machines, and closed-vial systems. These systems, which exclude personnel from the critical aseptic manufacturing environments, are designed with automated sterilization, monitoring, and control features that detect and react to abnormal conditions that could compromise product sterility.

In the case of aseptic processing, however, no finished product test is available to confirm the sterility of each manufactured unit.”

Russell E. Madsen, President of The Williamsburg Group, LLC

**Regulatory Guidance**

By the mid-2000’s, product protection by better contamination control using Advanced Aseptic Technology—primarily meaning isolators, plus a risk-based design approach—became central to the FDA initiative for Pharmaceutical GMPs for the 21st Century.

In September 2004, the FDA re-issued *Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice* ³. This landmark guidance document contained an entire appendix defining FDA expectations regarding isolators:

Through this guidance, FDA hopes to facilitate the application of good science and modern technology, and thus lessen or eliminate avoidable risks from aseptic operations. The adoption of better contamination prevention practices and a higher assurance of process consistency is expected to reduce the incidence of sterile drug manufacturing problems, thus facilitating the ongoing availability of these often therapeutically significant pharmaceuticals.

Consistent with the objectives of the initiative, the guidance encourages the adoption of new technological advances by the pharmaceutical industry. In particular, the guidance underscores the advantages that automation and isolation concepts offer in protecting the exposed sterile drug product during its aseptic manufacture.
Similarly, explicit statements of the incentives to modernize are stated in the FDA’s Compliance Program Guidance Manual, Sterile Drug Product Inspections document:

Some types of aseptic processing involve manual manipulations of sterile components, containers, and closures, in addition to routine operator interventions in the critical area. Humans are a significant source of contamination in traditional aseptic processing, especially in production lines that require operators to routinely enter critical areas (Class 100, ISO 5, or Grade A) of the filling line.

Aseptic processing systems based on more advanced control-based technologies, such as Restricted Access Barrier Systems (RABS) and Blow-Fill-Seal systems, are designed to reduce human interventions in the critical areas of the fill line, while an isolator system completely separates the aseptic filling line from the external environment and minimizes employee interaction with the critical area.

Regarding what strategy the pharmaceutical industry chooses to formulate and fill sterile products in the future, the FDA rarely prescribes specific solutions, but rather lends principled guidance.

The FDA’s guidance for sterile manufacturing is clear: sterile manufacturers should 1) separate sterile operations from humans and from the external environment, and 2) automate to eliminate human intervention.

FDA’s guidance toward modernization has been quite consistent since the early 2000’s, with the biggest milestone being the re-issue of the 1987 Aseptic Processing Guideline in 2004.

Another useful document showing the FDA’s roadmap since the early 2000’s is Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach.

An excerpt from the roadmap states:

On February 20, 2003, the Food and Drug Administration (FDA) released its first progress report on a major initiative concerning the regulation of drug product quality. The 2-year initiative, Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach (the Pharmaceutical cGMP initiative), which was launched on August 21, 2002, applies to human drug and biological drug products and veterinary drugs and has several objectives:

- Encourage the early adoption of new technological advances by the pharmaceutical industry
- Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance
• Encourage implementation of risk-based approaches that focus both industry and Agency attention on critical areas

• Ensure that regulatory review and inspection policies are based on state-of-the-art pharmaceutical science

• Enhance the consistency and coordination of FDA’s drug quality regulatory programs, in part, by integrating enhanced quality systems approaches into the Agency’s business processes and regulatory policies concerning review and inspection activities
Adoption of Advanced Aseptic Processing Technologies

To gauge adoption rates for the various aseptic technologies, DME invited engineers, manufacturers, and other life sciences professionals to participate in their 2015 Facility Focus survey on the latest trends and technologies affecting the pharmaceutical manufacturing industry.  

Survey participants were asked if/when their company modernizes their legacy sterile manufacturing facility, which advanced aseptic technologies they were most likely to use (See figure 1).

<table>
<thead>
<tr>
<th>Technology</th>
<th>Percentage</th>
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<tr>
<td>Single use/disposables</td>
<td>62%</td>
</tr>
<tr>
<td>Closed system processing</td>
<td>46%</td>
</tr>
<tr>
<td>RABS</td>
<td>26%</td>
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<tr>
<td>Isolators</td>
<td>49%</td>
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<tr>
<td>Automation (including robots)</td>
<td>28%</td>
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<tr>
<td>Other</td>
<td>10%</td>
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Figure 1 - Most Likely Adopted Advanced Aseptic Technologies

The number one choice for advanced aseptic technologies was single-use/disposables (62%), followed by isolators (49%), closed system processing (46%), automation (including robots) (28%), and RABS (26%).

These promising technologies are detailed in the following sections.
Automation (including Robots)

A strong trend toward robotics to separate people from sterile processing was recently unveiled at the ISPE Aseptic Conference in Arlington, VA on February 29 – March 1, 2016. At that conference, an industrial panel discussion for this emerging technology was conducted, composed of six industry leaders:

- Jim Nadlonek, Bausch & Stroebel
- Wenzel Novak, Groninger
- Christopher Procyshyn, VanRX
- Joshua Russel, AST
- Klaus Ulherr, Bosch
- Sergio Mauri, Fedegari
- Mathias Poskovski, Optima

The most interesting robotic designs performed aseptic processing inside closed, gloveless isolators; “closed” meaning no mouse holes (See VanRX and Fedegari).

The premise of sterile, robotic equipment suppliers is that pharmaceutical manufacturing leaders must manage smaller batches, shorter runs, greater complexity, more volatile demand, and ever-increasing quality expectations. Machine suppliers are developing advanced compact solutions for filling aseptic cytotoxic drugs; for example, one style is a gloveless isolator in which all operations are handled by a GMP-compliant stainless steel robot.
**Why a Robotic Solution?**
Because an environment free of humans is expected to be cleaner. Furthermore, considering the danger of handling cytotoxic compounds, a robotic solution increases process safety because the operator is never directly involved with the manufacturing process.

Isolators could contain one or more 7-axis GMP robots, with 316L stainless steel construction, Grade A design with low particle shedding, and capable of high pressure and temperature water wash down, fully compatible with H2O2 decontamination, and hollow wrists (no external wires).

Peristaltic filling pump(s) with 100% disposable wetted paths could perform liquid filling. At the end of a campaign, the entire isolator and robot(s) could be washed in place to remove all products’ residual prior to opening the isolator to the background room.

Of all the contributions of automation to Advanced Aseptic Processing, among the most important are automatic washers and depyrogenation tunnels to supply sterile glass vials for filling and automatic lyo loaders to tray partially-stoppered vials and place them inside freeze dryers.

**Takeaway: What This Means for Your Operations**
These are mature automated processes that emerged a generation ago. Manual batch washing, depyrogenation of glass vials, and manual loading of lyo cabinets should be avoided with modern facilities. These manual processes are among the weakest links in the aseptic-chain in legacy sterile manufacturing facilities.
Single-Use/Disposables

The single-use revolution began in upstream processing and has multiplied itself in formulation and filling facilities, especially over the last five years. It is now quite common for high-speed, vial-filling machines to be supplied with 100% disposable wetted paths.

Although originally pioneered by Robert Bosch in partnership with Sartorius, all leading equipment suppliers now supply proven, reliable, single-use wetted paths for automated filling lines, frequently integrated with time-pressure or peristaltic pumps, with feedback controls from Wipotec load cells for 100% weight checks at 400 vpm and higher speeds.

**Takeaway: What This Means for Your Operations**

*Disposable wetted paths with 100% weight checks is one of the most important innovations for product quality in the last decade and should be seriously considered for every modernization project.*
Closed System Processing

Closed system processing has countless applications in sterile manufacturing and has been around for decades. Recent innovations include sterile connectors to complement sterile tubing welding, disposable feed-throughs to make a liquid connection through the wall of an isolator without an aseptic manipulation, and rapid transfer ports for transfers into and out of an isolator or a RABS.

Closed systems have historically been constructed of stainless steel systems, which are rapidly being augmented by flexible plastic systems, frequently disposable, even including disposable closed-system sensors and instrumentation during the past decade.

Takeaway: What This Means for Your Operations

The goal of designing Advanced Aseptic Processing facilities is to have zero open processing and/or aseptic manipulations where sterile product, sterile containers, or sterile components are exposed to gowned operators or to the external background environment. For new green field facilities, “zero” should become the new norm for optimum product protection.
Restricted Access Barriers (RABS)

The first authoritative, peer-reviewed RABS definition was published in ISPE’s *Pharmaceutical Engineering* magazine in 2005. Publishing this definition in 2005 was the start of when the industry began to differentiate between “compliant RABS” and “non-compliant RABS,” a differentiation that is still going on in 2016.

There are a number of “compliant RABS”: either an "Open RABS" or a "Closed RABS," either an “Active RABS” or a “Passive RABS,” which, when properly designed and operated, can be FDA compliant. As such, can all be classified as Advanced Aseptic Processing, i.e., what the FDA expects to protect sterile product.

To reiterate, all these types of RABS can adequately protect product, if designed and operated correctly. The operative word when discussing compliant RABS is "restricted." Unless your RABS is designed and operated to restrict human access, it is not a compliant RABS.

Since 2005, when ISPE published this first RABS definition, PHSS (Pharmaceutical and Healthcare Sciences Society) has developed a more comprehensive RABS definition (PHSS definition is 95 pages, ISPE definition is 3 pages).

The PHSS guidance is excellent and is quite consistent with ISPE’s guidance. The PHSS web site resources and events are worth exploring, especially for understanding MHRA (Medicines and Healthcare Products Regulatory Agency) expectations, since they are a UK organization.

Takeaway: What This Means for Your Operations

When considering modernizing with a RABS enclosure, the most important thing to remember is that FDA (and good aseptic best practice) requires that RABS access be "restricted." Beware of vendors who merely place a box or "machine guard with doors" around a filling machine and call it a “RABS.” That is not a compliant RABS because no RABS can adequately protect product unless you keep the doors closed.
Isolators

Isolators are a mature technology, having been successfully used for decades, more in Europe than the U.S. However, isolators remain challenging projects to manage and keep on-time and on-schedule, especially to start up predictably. Many veteran owners dread isolators due to bad experiences in the 1990’s. Fortunately, times have changed and hundreds of successful isolator projects have now been completed. With such a large installed base in 2016-17, isolators are no longer a pioneering endeavor.

**Takeaway: What This Means for Your Operations**

*When considering modernizing using isolators, make every decision with product protection in mind, applying risk management at each step. The weakest links for isolators are gloves and transfers.*
Moving into the Future of Sterile Manufacturing

Regarding long-term strategies for sterile manufacturing, we have remained an industry that evolves slowly and deliberately. Perhaps now, we will enter an era where a spate of legacy facilities will be forced to modernize during, say, a 10-year period.

From DME’s perspective, the future looks very bright. Currently, there are more proven technologies and vendors to provide Advanced Aseptic Processing solutions than any other period in history.

Up until the 2000’s, there were inevitable gaps and weak links in the aseptic “chain-of-custody” in our sterile manufacturing facilities. Now those gaps have disappeared and are bridged with reliable solutions that include numerous advanced aseptic filling/packaging systems, including:

- Barrier systems
- Isolators
- Closed RABS,
- BFS (blow-fill-seal)
- FFS (form-fill-seal)
- Automation and robotics
- Closed vial filling
About the Author

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An industry innovator in cGMP manufacturing, Hite’s focus is equipment and facility design for parenteral fill-finish operations. He has extensive experience in the regulated life sciences industry, including biopharmaceuticals, vaccine products, cleanroom facility design, and technology transfers. An expert in sterile manufacturing technology, Hite has led engineering design efforts for every stage of the process—from formulation to sterile filling to lyophilization—as well as for the isolation technology and cGMP facilities where drug products are manufactured.

Hite holds dual degrees in Mechanical and Electrical Engineering from Virginia Polytechnic Institute and State University,

He is an active member of ISPE and is a member of the SPP COP Steering Committee where he co-leads their barrier education track. He is a frequent speaker on sterile manufacturing technology.
About DME

Designing a technically complex facility for drug product manufacturing requires both cGMP design expertise and the ability to mitigate risk through facility programming, layout, and technology selection. DME’s engineers, designers and subject-matter experts leverage these capabilities to provide innovative, flexible design solutions for both new facilities and legacy upgrades or renovations.

Risk management is job #1.
We understand the issues associated with quality risk management and product contamination prevention in a cGMP fill/finish facility. Risk-based design is so engrained in our culture that it touches every aspect of our project delivery.

We deliver pragmatic, cost-effective solutions.
At the end of the day, what matters most is that your facility is able to manufacture a high quality product with the capacity, flexibility, and cost of goods that meet your business requirements. DME works with you to design and deliver formulation and filling capabilities—at the appropriate scale to fit your needs and budget.

Aseptic process technology expertise.
DME has unique technical capabilities designing sterile manufacturing facilities. Our experience and expertise in compounding, lyophilization, RABS and isolators for aseptic processing, single-use/disposables technology, and biohazard and potent compound containment are second to none.
References

http://www.pharmamanufacturing.com/articles/2006/018/?show=all


