ASEPTIC TECHNOLOGY TRENDS SERIES:

Sterile Product Facility Design

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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: Sterile Facility Design

The ultimate goal of designing Advanced Aseptic Processing facilities is to eliminate open processing or aseptic manipulations where sterile product, containers, or components are exposed to gowned operators or to the external background environment.

This goal is more easily achieved with new greenfield facilities, where closed processing can become the new norm for optimum product protection. However, for legacy sterile facilities, modernization is a big challenge and has been considered to be the “elephant in the room” for at least a decade for owners with inconsistent quality, as well as for regulators who closely scrutinize aging, unreliable legacy facilities as the possible cause for drug shortages and quality issues.

The complex interplay of challenges, risks, and drivers affecting the design, or re-design, of sterile manufacturing facilities is staggering: from contamination issues to inadequate process control and testing capabilities to evolving, complex regulations and increased inspection scrutiny to escalating costs of reactive modernization projects.

There is both good news and a bright future for the industry: there are more proven technologies and vendors than at any other time that offer facility design solutions. These solutions include Advanced Aseptic Processing technologies, Process Analytical Technology (PAT), automated CIP, and advanced testing and monitoring capabilities.
In this *Aseptic Technology Trends* paper on *Sterile Product Facility Design*, manufacturer stakeholders will further their understanding of:

- Regulatory guidance and best practices for designing and modernizing compliant sterile product manufacturing facilities
- Trending technologies, capabilities, and strategies for sterile facility design
- What the industry is saying about their challenges, priorities, and solutions in sterile product facility design

**Sterile Facility Design Considerations**

To begin thinking about sterile facility design, the *ISPE Baseline Pharmaceutical Engineering Guide (Volume 3)* provides a useful list of high-level considerations for a successful facility design plan:

- The need to understand product and process requirements
- The use of risk-based approaches
- The concept of “Good Engineering Practice”
- The role of terminal sterilization and aseptic processing as mechanisms for producing sterile products
- The protection of the product and the importance of understanding the most critical process steps
- The management of flow and movement of people and materials through the facility
- The importance of an integrated facility design approach
- Understanding the principles of Open and Closed processes and how they affect the specification of the surrounding controlled environment
- The role of barrier and isolator technology
- The role of automation and robotics
- The use of consistent clean room classification terminology
- The principles and understanding of “in operation” and “at rest” conditions for HVAC systems
- The selection of appropriate materials and finishes
- The science-based approach to risk assessment and risk management
Modernizing Legacy Facilities

When it comes to understanding the challenges and best practices of sterile facility design, the “elephant in the room” is the obvious place to start: what do owners of aging, noncompliant facilities with fundamental design deficiencies need to know?

Ultimately, the regulatory compliance issues associated with not modernizing will only become more painful in the future. Starting in the 2000’s, the FDA began stating candidly that risk-based inspections would place more scrutiny on legacy facilities than on modern isolator/RABS-based facilities that incorporate automation and closed-system processing. Within the industry, this “FDA-speak” was commonly understood to mean: “You get a pass from FDA if you modernize, but you will be sorry if you don’t...eventually.”

Manufacturers’ Plans to Modernize Their Legacy Facilities

To learn how the industry is reacting to this regulatory landscape, DME invited engineers, manufacturers, and other life sciences professionals to participate in their 2015 Facility Focus survey.  

When cGMP manufacturers were asked about their modernization plans, the results were mixed from a product protection perspective. The good news is that 27% of the respondents plan to modernize proactively.

The troubling news is that almost half (44%) of respondents do not plan to pull the trigger on modernization unless driven by FDA scrutiny or product quality problems. Another 17% simply do not plan to modernize at all.

For those manufacturers who are planning to upgrade a legacy facility, the majority stated it would occur sometime in the next 5 years (66%). The remaining owners who were planning to upgrade stated they would be undertaking it within 5-10 years (12%).

Advantages of Facility Modernization Planning

Modernization is a positive decision to ensure that products of the highest quality are consistently manufactured. Therefore, the goal of a modernization project should be focused on facility engineering issues and how to provide cost-effective facilities that make best use of available modern technologies.

The optimum circumstance is to plan ahead to modernize before there is a crisis, so as to avoid regulatory action (483’s or warning letter) or quality issues.
**Avoiding a Crisis**

Planning ahead begins with investigating the feasibility of modernizing through a feasibility study, whether by way of a facility renovation or a new greenfield facility.

Performing a modernization feasibility study prior to a crisis allows for a paced and phased approach, where there is plenty of time for risk analysis and risk mitigation, ensuring efficient design and implementation.

Once a crisis arrives, a phased approach can be compromised, an owner’s control is diminished, some options disappear, and risks and costs frequently escalate.

**Managing Costs**

During an ISPE (International Society for Pharmaceutical Engineering) Q&A session with a panel of regulators, FDA’s Richard L. Friedman shared an anecdote that he calls “the 10X rule”: If a legacy owner fixes a problem before it becomes a crisis, then it costs 1x to fix; after a crisis arrives (e.g., product recall, discard, 483, warning letter, injunction, etc.), the remediation will then cost 10x to fix.

It’s important to remember that today’s decisions will impact the manufacturer for 15 to 25 years. Capital equipment technology and the accompanying depreciation expense last a long time. Look at what is in the pipeline for R&D to make a decision that will cover future products. Many product candidates will have the need of aseptic processing and containment in order to protect both operators and product. ³

**Adhering to Regulatory Guidance**

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. ⁴

**Elements, Risks, and Incentives of Modernization**

FDA spokesman Friedman provided further advice in 2010, in the Informa Healthcare textbook *Advanced Aseptic Processing*, in which he defined the following elements and risks of modernization:
Elements of Modernization

Three elements are vital to a modernized approach to aseptic processing:

1. *Separation* of the aseptic processing line from the surrounding room environment, including the direct contamination risks posed by people.

2. Use of *automation* and integration to replace manual operations (interventions and other activities conducted by human operators) and transfers that still exist in legacy operations and are well-known sources of contamination risk.

3. Robust *advanced testing and monitoring* approaches to increase the amount of information on the state of process control.  

Risks of Avoiding Modernization

These older, open aseptic processing systems will continue to receive extra regulatory attention because so many variables must be properly controlled to ensure consistent contamination prevention.

FDA inspectors have found noncompliant facilities that allow a major and persistent risk of sporadic contamination. These systems lacked the inherent process capability needed to substantially and robustly protect exposed sterile materials from external risks.

Ultimately, these firms realized the need for very extensive corrective actions to eliminate fundamental design flaws.

Benefits of Modernization

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.

When conducting inspections of sterile drug manufacturers, it is important to cover systems and areas within systems that present the greatest risk of product contamination and/or require strict control of processing parameters. For example,
if a firm has several aseptic processing lines, cover the line(s) that require the most manual manipulations in the Class 100 (ISO 5) areas\textsuperscript{7}.

**Design Priorities for Facility Modernization Projects**

The key to a successful facility design effort is a well-defined manufacturing process that is seamlessly integrated with the facility. When defining the manufacturing process, there are a number of drivers that will have a significant impact on the facility design. The synergy between product–process–facility will become apparent.\textsuperscript{8}

According to the DME survey results, primary design efforts should be placed on the process equipment first, then facility programming, HVAC design, and room classifications (including nested cleanliness zones)\textsuperscript{2}.

Given that process equipment normally has the highest cost and complexity in a project—and receives the greatest regulatory scrutiny because it is closest to sterile product—the criticality of creating equipment User Requirement Specifications (URS) cannot be over-emphasized.

**User Requirements Specifications**

Comprehensive User Requirement Specifications (URS) are the foundation for all subsequent specification documents. A URS provides a high-level description of the user’s expectation of the project scope, with emphasis on product parameters and process performance parameters.

The successful compilation and execution of the Installation Qualification (IQ) (for installation), Operational Qualification (OQ) (for functionality) and the Performance/Product Qualification (PQ) (for operability), is dependent on a URS containing clear, concise, and testable requirements.

**Criticality of Heating, Ventilation, and Air Conditioning (HVAC) and Other Utilities**

Heating, Ventilation, and Air Conditioning (HVAC) can be a critical system that affects the ability of a pharmaceutical facility to meet its objective of providing safe and effective product to the patient. Environmental control systems that are appropriately designed, built, commissioned, operated, and maintained can help ensure the quality of product manufactured in a facility, improve reliability, and reduce both initial costs and ongoing operating costs for a facility.

The design of HVAC systems for the pharmaceutical industry requires special considerations, particularly with regard to providing a clean and safe space environment. HVAC can consume a major portion of the energy used by a facility, and
requires a blend of Good Engineering Practice (GEP) and Good Manufacturing Practice (GMP).  

Clean cGMP utilities that are normally needed to support the aseptic fill/finish operation include Water for Injection (WFI), oil-less compressed air, nitrogen gas, sterile steam and vacuum. The compressed air and nitrogen gas will have point-of-use sterile filters inside the aseptic core, and the vacuum system should have one-way check valves. The WFI is predominately used in the preparations for the rinsing of vials, stoppers, and equipment change parts.  

**Regulatory Guidance for Facility Design**

FDA guidance for facility design is well known at a high-level view, but can be quite challenging and critical at the detailed design level, because design know-how includes both formal and tacit knowledge of a facility’s products, process and equipment, and regulations: 

21 CFR 211.42(b) states, in part, that “The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination.”

21 CFR 211.42(c) states, in part, that “Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm’s operations as are necessary to prevent contamination or mix-ups during the course of the following procedures: * * * (10) Aseptic processing, which includes as appropriate: (i) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable; (ii) Temperature and humidity controls; (iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or non-laminar; (iv) A system for monitoring environmental conditions; (v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions; (vi) A system for maintaining any equipment used to control the aseptic conditions.”

21 CFR 211.46(b) states that “Equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.”

Emerging FDA guidance places a clear emphasis upon innovation and modernization of pharmaceutical manufacturing: 

CDER is committed to supporting and enabling the modernization of pharmaceutical manufacturing as part of the Agency’s mission to protect and promote the public
health. These efforts also may be one long-term solution to avoid drug shortages, as noted in FDA’s drug shortage strategic plan.

As part of its commitment to modernizing pharmaceutical manufacturing, in 2002, FDA launched an initiative entitled “Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach,” to encourage the implementation of a modern, risk-based pharmaceutical quality assessment system. The initiative was published with several goals, including encouraging the early adoption of new technological advances by the pharmaceutical industry and ensuring that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science.

In 2004, this was further described in FDA guidance for industry entitled “PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance.” This guidance describes the concept that quality cannot be tested into products; in other words, it should be built-in or should be present by design.

Quality is built into pharmaceutical products through a comprehensive understanding of the intended use of the product, the characteristics of the product, and the design of the product and manufacturing process using principles of engineering, material science, and quality assurance to ensure acceptable and reproducible product quality and performance throughout a product’s lifecycle.

The FDA uses a systems-based approach for regulatory review. The six systems are quality, production, facilities, materials, packaging/labeling, and laboratory controls.

The routine inspection process will either be a full inspection of the quality system and three of the other defined systems, or an abbreviated inspection of the quality system plus one other system. The fact that the facility is considered a critical system defines the importance of the relationship between facility design and validation.

**Responses Divided on Manufacturing Capabilities**

DME survey responses confirmed that the industry is heading in the direction of more flexible, multi-product, small-batch and toxic/high-potency facilities.

A number of promising manufacturing capabilities carry about the same weight with respondents when it comes to upgrading their sterile facilities within the next five years: efficient small batch production with fast changeover was the most favored (53%), serialization and multi-product capabilities were next (43%), primary container flexibility using one filling machine was third ranked (41%), and capability to handle toxic/high potency drug products was least favored (19%).
Advanced Aseptic Processing Technologies

According to DME survey results, 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%) \(^2\).

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 (e.g., VPHP (Vapor Phase Hydrogen Peroxide) pass-through, automated lyo loading, and robots), 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.” \(^{14}\)

Russell E. Madsen, President of The Williamsburg Group, LLC
Trending Technologies for New Form/Fill Facilities

The industry is heading in the direction regarding better product protection and modernization, driven by a clear understanding of the primary risks associated with conventional aseptic processing.

This is confirmed by the DME survey responses regarding building new formulation and filling facilities and which technologies they would implement: isolation technology is the clear leader (66%), followed by single-use mixing equipment (54%), aseptic connectors (53%), single-use filler feed path (47%), and automatic vial/syringe inspection (38%)\(^2\).

Long-Term Strategy for Drug Product Segregation

The legacy approach to drug manufacturing—built around dedicated large-volume filling lines with manual clean-up and changeover—appears to be waning.

Flexible, smaller-batch facilities that achieve product segregation by closed systems (including single-use/disposable components), without manual cleaning procedures are the wave of the future.

According to survey results, the most promising long-term strategy for segregating sterile drug products are multi-product facilities using single-use/disposable components and/or automated CIP of the insides of barriers\(^2\).
Moving Into the Future of Sterile Manufacturing

Historically, our industry evolves slowly and deliberately. Up until the 2000’s, there were inevitable gaps and weak links in the aseptic “chain-of-custody” in our sterile manufacturing facilities. Perhaps now, we will enter an era where a spate of legacy facilities will be forced to modernize during the next ten years.

From DME’s perspective, the future looks very bright. Today, those gaps can be bridged with reliable solutions, including:

- Advanced aseptic filling/packaging systems—i.e., barrier systems, isolators, and closed RABS, BFS (blow-fill-seal), FFS (form-fill-seal), automation and robotics, closed vial filling
- More effective statistical process capability and control metrics
- Quality risk management and assessment techniques
- Process Analytic Technology (PAT)
- Risk-based, scientific lifecycle approaches to process and system validation
- Innovative sterilization techniques—e.g., E-beam surface sterilization
- Single-use drug manufacturing and filling systems with 100% weight checks
- Highly-flexible, small-batch combination filling machines for vials, syringes, cartridges
- Ready-to-use primary containers, components, stoppers, over-seal/caps
- Real-time and rapid microbiological monitoring and testing
- Post-Aseptic Lethal Treatment
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


2 DME Facility Focus Survey, October 14, 2015 to November 18, 2015.


