Integrating Single-Use Disposable Processes into Critical Aseptic Processing Operations

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Disposable technologies are nothing new to the biopharmaceutical industry. Drug manufacturers have adopted preassembled, plastic-based process components to perform various upstream and downstream processing purification and separation steps. Considering the benefits already demonstrated, such as improved process security, increased process flexibility, and enhanced process economics, what company wouldn't be eager to embrace or expand the use of such technologies (Photo 1)?

However, integrating presterile disposable components into critical and highly regulated manufacturing steps, such as aseptic processing and sterile fill-and-finish operations, shifts the validation and operation burden from drug manufacturers to suppliers. To increase the use of disposable technologies in these critical manufacturing operations, the stigma of outsourcing the sterilization process must be overcome.

Thorough validation and robust controls must be in place at supplier facilities for the biopharmaceutical industry to adopt outsourced presterile disposable process components into aseptic processing operations. Suppliers can ensure the same high level of process validation and sterility assurance as currently provided by in-house cGMP practices. Suppliers can achieve this through best-in-class supply chain management processes including

- evaluation, selection, and validation of individual components
- qualification of the assembly process
- a well-controlled manufacturing environment
- a validated sterilization process
- well characterized component extractables
- and appropriate quality control systems.

Critical Components of a Validation Master Plan

There are several critical considerations when validating a presterilized disposable assembly for use in an aseptic manufacturing operation.

Fundamentally, the strategy for validating and qualifying a disposable assembly for use in aseptic processing is no different from that of a traditional stainless steel operation. However, it is likely to include a high level of participation from suppliers of presterilized disposable process components. Once a drug manufacturer clearly defines application and performance requirements, a supplier can design an appropriate disposable solution and formulate a validation protocol.

Photo 1: Presterilized, preassembled, and validated disposable systems are increasingly being used in drug manufacturing processes. (Millipore Corporation)

Despite overall consistency in validation approaches, there are distinct requirements for implementing a new disposable aseptic process (see the "Traditional or Disposable?" box). The following section highlights some critical considerations for creating a new validation master plan for disposable aseptic processing.

Extractables: As with traditional stainless steel filter holders and filter assemblies, filters must be validated for extractables. This usually involves validation under worst-case conditions using a model solvent approach for both static, total extraction volume and dynamic, extractable extinction operating modes. These protocols simulate

both the holding (static) and filling operations for a drug product subject to aseptic processing. However, in the case of an entire disposable system, extractables have to be measured and validated for the entire system, not just the filter. All product contact surfaces (previously stainless steel) are now validated based on the materials of the disposable components.

For disposables, the worst-case extractable conditions include

- a maximum gamma sterilization dose of 45 kGy;
- the smallest possible surface-area-to-volume ratio;
- the longest filtration, holding, and filling times; and
- the highest temperature.

Components are typically tested using WFI (water for injection), NaCl, NaOH, and ethanol to mimic leaching properties of various drug products. Analysis, which typically includes NVR (hydrocarbon nonvolatile residue), TOC (total organic carbon), HPLC (high-performance liquid chromatography), and FTIR (Fourier-transform infrared spectroscopy) is then performed on samples from both the extract solutions and the controls.

Quantifying and identifying all extractables discovered during analysis that might affect the manufacturer's drug product requires suppliers of disposable assemblies to understand the physicochemical characteristics of materials that make up each subcomponent. Suppliers of disposable assemblies and processes must therefore have strong relationships with the component vendors. With those relationships, and using data collected during years of testing and qualification, equipment can be accurately designed and validated to acceptable extractable levels for an entire disposable unit process operation or a single disposable component.

Filter Retention: The FDA and GMPs require specific validation processes for a current drug manufacturing process with any intended filter, and filter retention requirements do not change when an entire system is switched to a disposable basis. Using scale-down parameters, the actual process must be simulated, including pressure, volume, and temperature.

Sterilization: The most common end-user methods for process and primary packaging component sterilization are moist-heat autoclaving or steam-in-place (SIP) and dry heat sterilization. Autoclaving is used for all dry and porous goods, filters, hardware process components, and tubing. SIP is used primarily for closed process equipment in the formulation and filtration areas and less frequently in filling areas.

The biopharmaceutical industry has acquired years of experience in validating and routinely running autoclave and SIP sterilization cycles. The key inhibitor for presterilized materials in aseptic processing is outsourcing the sterilization of process components to aseptic disposable assembly suppliers.

Validating Autoclave and Gamma Irradiation: Validation of autoclaves and gamma irradiation chambers proceeds along parallel lines. Both must be qualified and are validated using well-documented standards. Autoclaves focus on temperature mapping, cycle times, and load patterns, and gamma irradiators use radiation dose mapping, product density, and load patterns. Routine sterilization conditions must be established for both to obtain the required sterility assurance level (SAL), generally 10^{-6}. Minimum time and temperature for autoclaving and minimum absorbed dose for irradiation must be validated.

Validating Steam Sterilization or Radiation Sterilization: Similar to the steps above, temperature mapping is used to identify the slowest heating points in an autoclave, and radiation dose mapping is used to identify the minimum dose locations in an irradiator. Those identified critical locations will then be used for the routine monitoring of sterilization cycles.

Requalification Guidelines: The validation of autoclave cycles for process components currently involves the use of biological indicators. Their concentration (10^6) and resistance (a D-value at 121 of two minutes) represent a large degree of worst-case conditions during validation. Hence, a yearly requalification is usually necessary for an autoclave.

The validation of irradiation cycles is based on the actual bioburden in the assembled disposable process components. A quarterly audit procedure for an irradiation sterilizing process is required to

TRADITIONAL OR DISPOSABLE?

The following compares elements of a traditional and a disposable validation master plan for aseptic processing.

TRADITIONAL ASEPTIC PROCESSING	DISPOSABLE ASEPTIC PROCESSING
Filter retention	Filter retention
Filter extractables	Disposable assembly extractables
Integrity testing Preuse Postuse	Integrity testing Preuse may require new SOP Postuse
Steam sterilization	Gamma irradiation sterilization
Adsorption	Adsorption
Media fills	Media fills
Fills accuracy	Fills accuracy
Bioburden and sterility testing	Bioburden and sterility testing
Stability testing	Stability testing
Others	Others (elimination by incineration)

account for potential seasonal change in the actual bioburden.

Validating Gamma Sterilization

Validating the gamma sterilization of disposable assemblies includes four key steps:

- Determining presterilization bioburden
- Establishing the verification dose
- Performing the verification dose experiment
- Interpreting the verification dose experiment.

Determining Presterilization Bioburden: The first step in gamma sterilization validation is to determine the actual bioburden in all materials submitted to radiation, using methods such as those contained in ANSI/AAMI/ISO 11737-1 (1). The average bioburden estimate per product unit is established for at least 10 random samples from a minimum of three production batches, as well as for all product units sampled for exposure to gamma radiation.

For this method, the maximum bioburden allowed per unit is 1000 cfu. The calculated absorbed dose to attain SAL = 10^{-6} for a bioburden of 1000 cfu per unit is 24.9 kGy. Therefore, the substantiation of a 25-kGy dosimetric release is overkill for all units with bioburden of ≤1000 cfu.

Establishing the Verification Dose: Once the bioburden has been evaluated, the verification dose can be established. Based on the average unit bioburden, the verification dose is statistically calculated to provide an SAL = 10^{-2} in accordance with AAMI TIR27:2001 (2). The verification dose experiment states that for an SAL = 10^{-2}, there should be no more than one positive out of 10 samples. If the 10^{-2} test is successful, then the substantiation of 25 kGy as a sterilization dose for SAL = 10^{-6} is verified (Table 1) (3).

Performing the Verification Dose Experiment: As described in AAMI TIR27:2001 (2), 10 units from the three production lots used for the bioburden estimate or from a new batch manufactured under conditions representative of normal production are randomly sampled and irradiated at the appropriate verification dose (±10%). Dosimeters are placed in predetermined locations throughout the equipment to check for absorbed doses to be ±10% of the verification dose. This step is also used to identify zones receiving minimal doses and define the worst-case locations during routine sterilization cycles. During product runs, dosimeters should be placed in first, middle, and last product containers (2).

Interpreting the Verification Dose Experiment: Each sample is tested for sterility after exposure to the verification dose. If no more than one (0 or 1) positive test of sterility is obtained in the 10 tests, then a sterilization dose of 25 kGy (to provide an SAL = 10^{-6}) is substantiated. If two positives are found, the verification dose experiment can be repeated. If zero positives are found (a maximum total of two out of 20), then a sterilization dose of 25kGy (to provide an SAL = 10^{-6}) is substantiated. If three or more positives are found in the first 10–20 tests, then the sterilization dose of 25 kGy is not substantiated, and alternative dose setting methods will be required (2).

Table 1: Verification (or dose kGy) required to achieve a given sterility assurance level for various bioburdens

Bioburden	Verification Dose (kGy)
10	7.1
75	9.1
240	8.6
750	8.2
1000	8.1

Selecting the Right Supplier

A preestablished set of criteria for assessment of the processes, skills, and services of your suppliers should be part of your strategy. Below is an example of criteria you may want to include in your evaluation process.

Does your supplier have:

- ☐ Experienced, dedicated individuals to support your company's needs?
- ☐ Financial strength illustrating long-term viability?
- ☐ Consistent quality control during handling, storage, packaging, preservation, and delivery of the product?
- ☐ A quality management system (QMS) to ensure compliance with good manufacturing practices (GMPs)?
- ☐ Scheduled reviews of the QMS by top management and internal audits executed regularly?
- ☐ Procedures identifying training needs for all quality-related personnel?
- ☐ Existing validation documentation for device, packaging, and process specifications?
- ☐ Established corrective/preventative action plans?
- ☐ Suitable facilities and quality equipment (proper cleaning, sufficient space for clean rooms, manufacturing, labs, warehouse, and safety areas)?
- ☐ Information technology for ongoing procurement and 21 CFR part 11?
- ☐ Sufficient resources to support any possible issues?
- ☐ No environmental discrepancies or regulatory findings?
- ☐ No trace of animal derivatives in the manufacturing process, material used, or product itself?
- ☐ Proof that all documentation is properly maintained and analyzed?

Presterilized, Disposable Aseptic Filling Technology

The benefits of using self-contained,

presterilized disposable assemblies in aseptic processing can be seen through the example of using such technology in a final filling operation. Today, conventional biopharmaceutical filling operations involve sterilizing separate components. Those filling-pump components must be disassembled, cleaned, and autoclaved as separate components, then reassembled in a cleanroom. This is time consuming and expensive, and it requires a high level of expertise to avoid cross-contamination and compromised accuracy.

A presterilized disposable system offers many advantages over that type of conventional filling operation. Because the system is presterilized and all contact surfaces are single-use, the need for SIP and clean-in-place (CIP) operations is eliminated.

An example of this type of filling system is the Millipore Acerta® DS1 dispensing system. It incorporates both an automated system and a single-use disposable module to create a volumetric–gravimetric dispensing process. The system fills reproducibly, and set-up takes only 15 minutes. All product contact parts are disposable and USP Class VI. The entire disposable module is presterilized by gamma radiation up to 45 kGy, and an operation using such a system is streamlined substantially. Operator intervention and potential cross-contamination risks are greatly reduced, as are requirements for dismantling, cleaning, and maintenance.

Extending the Process

Presterilized, preassembled disposable systems comprising such components as flexible tubing, bioprocess containers, capsule filters, and connecting devices are increasingly being used in drug manufacturing processes (Photo 1). These disposable technologies can be a safe, economical alternative to conventional stainless steel systems for aseptic processing and sterile fill-and-finish operations. Adoption of these technologies is not only helping the biotechnology industry improve the efficiency and economics of process development and production through the elimination of cleaning, sterilization, and aseptic assembly; it is improving process safety and quality by lowering the risk of cross contamination and human error, and it is reducing the number of aseptic connections needed.

A shift in mind-set is required because the use of disposable technologies continues to migrate toward more critical aseptic processes, resulting in the transfer of a portion of the validation burden from drug product manufacturers to the suppliers. However, the assembly, sterilization, and validation of a disposable assembly is in reality an extension of the drug manufacturing process. The responsibility for quality and validation ultimately rests with the manufacturers. This makes strong supplier validation expertise, processes, and relationships the most critical aspect of successful implementation of disposables into the manufacturing process.

References

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2 Association for the Advancement of Medical Instrumentation. Procedure. *Sterilization of Health Care Products — Radiation Sterilization — Substantiation of 25kGy as a Sterilization Dose – Method VD_{max}.* AAMI TIR27:2001, Sections 5.3, 5.3.4, 5.3.5, March 2001.

3 Association for the Advancement of Medical Instrumentation. Table 2. *Sterilization of Health Care Products — Radiation Sterilization — Substantiation of 25kGy as a Sterilization Dose — Method VD_{max}.* AAMI TIR27:2001, www/aami.org (the document must be purchased).

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