Validation Strategies for Disposables

The adoption of disposable manufacturing in conventional biopharmaceutical processes has already demonstrated tremendous benefits for the industry in terms of process flexibility, economics and security. However, the regulatory and validation requirements for disposable technologies are not well-characterized. As the biopharmaceutical industry continues to integrate disposable components and systems into their manufacturing operations, and these technologies migrate toward more critical unit operations, it is essential to develop a practical application-based validation strategy.

The Strategy

Acceptable validation, qualification and implementation of new disposable technologies requires that the manufacturer assess the application and define the desired performance, design appropriate validation approaches in the form of a protocol, and then execute, report and measure the effectiveness of the protocol and the new process step. Fundamentally, these steps are no different for a disposable system than for a traditional, rigid biopharmaceutical operation.

The approach to the development of this qualification and validation master plan should not only be both scientific and practical, but should also consider certain application-based factors:

- Risk and criticality of the operation
- Validation requirements (vis-à-vis current system)
- Current or emerging regulatory considerations

A scientifically sound plan should be protocol driven and utilize an experimental design based on solid assays, analyses and statistical methods. It should also be practical, based on a full understanding of the intended application, the standard of validation/qualification associated with it and any related regulatory considerations.

Application Example

Consider a large scale bioprocess container system which could be used for storage and transfer of sterile bulk material. These container systems would be used typically as storage vessels for product campaign hold or transport of sterile bulk material to a contract manufacturing site.

Based on this application, some of the regulatory and validation considerations include;

- Chemistry
- Container Robustness
- Integrity
- Sterility

Chemistry

- The impact, if any, of extractables and leechables on the product or solution being stored or transported should be well understood. This question is routine in other areas of biopharmaceutical processing, e.g. filtration. For disposable systems which are being used for storage or transport of sterile bulk materials, answers to the following questions should be readily available.

What is the extractables or leechable profile of the disposable system?
Under what conditions could they be extracted?
What are the potential levels for these extractables?
What is the toxicity profile (e.g. USP Class VI) of the extracted material?
Are there any adsorptive interactions between container and product?
Is there a need based on the materials of the disposable system to evaluated product stability?

Container Robustness

- The reliability and durability of fluid-filled disposable containers as well as shipping conditions must be well understood. Wave action during shipping conveys energy into the plastic film, which may lead to the cyclic fatigue of the container material causing integrity failures and leaks.
- The tensile properties of the container must be evaluated in order to predict its mechanical ability to withstand the rigors of a particular application. Five of the tensile properties that may be used as part of the study are secant modulus, yield strength, ultimate tensile strength, maximum percent elongation and toughness.
- Puncture resistance of fluid filled large surface containers must also be characterized due to the increased susceptibility for damage from impact with other objects.

Disposable assemblies, such as the one shown here from Millipore, can shift some of the validation burden to the supplier.

Integrity

• A high level of integrity assurance and robustness must be ensured through the design, validation, qualification, quality procedures and overall process control to quickly correct any deviations from process parameters.

Sterilization

• Sterilization data should be available to support the level of sterility assurance required for the application.

Disposable Technologies Today...and Tomorrow

The range of disposable technologies now being developed varies from individual components such as filters, bags, and connectors, to integrated disposable assemblies-preassembled, sterilized, and validated assemblies. Validation/qualification approaches will vary, as described above, from one application to another.

In addition, moving from traditional stainless steel process operations to disposable technologies may require a shift in mind-set. For example, purchase of a preassembled, sterilized, and validated system shifts the validation burden from the drug product manufacturer to the supplier. However, it remains the ultimate responsibility of the user to ensure quality, validation, qualification and reliability of the technology being implemented.

Traditionally restricted to dedicated equipment and facilities, biopharmaceutical manufacturers have an opportunity to dramatically increase production efficiency through the use of disposable systems. Some industry experts predict completely disposable facilities in the near future.

Defining a scientifically sound, practical validation strategy for disposable technologies is imperative as they migrate from upstream process steps to more critical aseptic operations. The industry has the opportunity now to step forward, share what it has learned and meet emerging regulatory trends which apply to these technologies.

— Neil B.T. Holman, Global Group Product Manager for Disposable Technologies, and Maurice G. Phelan, Director of Regulatory Affairs, BioPharmaceutical Division, Millipore Corporation

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