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Continuous Quality Verification as a Control Strategy for Biocontainers

An integrated quality/manufacturing approach to ensure the integrity of single-use biocontainers

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Integrity testing of single-use systems, such as biocontainer and tubing assemblies used in the processing of biopharmaceutical solutions, continues to emerge as one of the most sought after means to ensure "integrity" at the point of use. Some will attest that this quest has become increasingly prominent among users and suppliers alike in a desire to deal with the high prevalence of leaks. However, this reactive approach which attempts to test quality in at the end of biocontainer manufacturing, or post assembly operations, is unlikely to become the panacea when it comes to ensuring robust single-use process solutions. Some have suggested that integrity testing should be adopted as standard practice to mitigate potential process risks and promote a more proactive approach toward robust operations. Whatever the motivation may be, can "integrity" testing of single-use assemblies deliver on its premise and does it truly accomplish what it claims to accomplish?

Meissner's biocontainer manufacturing processes employ CQV to ensure fluid integrity.

A SURPRISING ANSWER

Filter manufacturers typically perform integrity testing of sterilizing-grade membrane filters. The results are correlated to bacterial retention per ASTM F838-05, as a means of substantiating the claim of a sterilizing-grade filter. However, the concept of applying the same practices used for integrity testing of membrane filters to single-use systems is inherently flawed. There are two main reasons that these practices are not transferable: single-use assemblies are very rarely compatible with significant pressure; and many single-use components are not only flexible in nature but also gas permeable. Although knowledge accrued during the adoption of filter integrity testing practices is valuable within the context of a broader discussion regarding system integrity, its relevance is restricted to general guidance. This is because established industry filter integrity processes do not lend themselves to immediate adoption with respect to single-use assemblies. Is the concept of "integrity" as it relates to a single-use system truly analogous to that of filter integrity? Is it intended to be the same? Filter integrity testing verifies bacterial retention; however, from a single-use perceptive, one needs to differentiate between leak testing and closure integrity testing. The latter being the ability of a system to provide a barrier to microbial ingress between the general environment and the fluid contact area thus ensuring the sterility of the fluid contained therein. Not all "integrity" tests, which have been implemented for single-use systems, can or are intended to be correlated to microbial ingress. Tests methods that are not intended to be correlated to microbial ingress would be better referred to as leak testing to distinguish them from integrity tests that have historically been associated with bacterial retention and closure integrity claims.

INTEGRITY TESTING

Filter manufacturers routinely provide pre-sterilization (pre-deployment) integrity testing for their sterilizing-grade membrane filters as part of their value proposition. Post-sterilization and/or on site (post-deployment), pre-use integrity testing of filter(s), which are included in a single-use assembly and sterilized by gamma irradiation, can be readily performed by the end user, provided the single-use assembly incorporates the necessary high pressure con-

nectivity and effluent collection functionality in the design. Single-use assemblies that have been designed to accommodate post deployment, pre-use filter integrity testing will also have to provide functionality for wetting the filter with, for example, water, process solution, or product depending on the application at hand. Finally, post-use integrity testing is easily accommodated by removing the filter from the fluid path and testing in a "stand-alone" configuration, although in situ test methods can also be accommodated by more complex designs.

Meissner 2D end-ported TepoFlex® biocontainer with FlexCessory™ hanger and stand.

LEAK TESTING

Pressure Hold. Single-use manufacturers that elect to integrate pre-sterilization (pre-deployment) leak testing of biocontainers and/or single-use assemblies to the degree feasible, often do so by resorting to in situ pressure hold or decay test methods. These tests would have to account for the numerous limitations imposed by the single-use components and the biocontainer itself. For example, biocontainer assemblies, or the unassembled biocontainers (bags) themselves, are often restrained during such testing using fixtures. These fixtures allow for slightly higher test pressures by preventing the biocontainer film from enduring stresses beyond its elastic limit, which would cause deformation, effectively altering the material and theoretically weakening the biocontainer assembly prior to use. Other methods do not incorporate such fixtures because they can theoretically cause damage to the single-use assembly. However, the lack of such restraints imposes strict limits on the test pressures that can be used. In both cases the achievable test pressures are typically so low that the associated testing is known to lack the sensitivity necessary to be correlated to microbial ingress. This limits the applicability of such procedures to leak testing, as opposed to closure integrity testing, and is often only able to detect flaws that could be classified as large defects, which can also be assessed using other techniques such as visual inspection systems.

Tracer Gas. A more sensitive method is tracer gas testing, with Helium often being the gas of choice. This has been practiced for many years by filter manufacturers and has earned considerable adoption in container closure integrity validation. Tracer gas testing can be correlated to microbial ingress provided it is validated as such. Given the vast number of combinations and permutations which single-use systems can be assembled in, the correlation of a permeation/leak rate to the ability of a given assembly to provide a barrier to microbial ingress can be very challenging. Further, certain gas permeable single-use components often render the method unsuitable, or at the very least, limit its application to certain sections or subassemblies. While multilayer films commonly used in the manufacture of biocontainers are engineered to contain significant gas barrier properties, other components used in the single-use assembly at large, e.g. platinum-cured silicone tubing, thermoplastic elastomeric tubing, aseptic connectors which rely on peel away porous membranes as microbial barriers, etc., are all gas permeable. This inherent permeability of many components effectively relegates tracer gas efforts to leak testing. Only in certain cases, it may be possible to design single-use assemblies for in situ tracer gas testing, allowing pre-use leak testing at the point of use (post-deployment) with a high degree of sensitivity. This technique, however, has to be considered invasive, hence the required design provisions for proper sterile gas admittance and subsequent flushing which adds yet another layer of design complexity and process risk.

QUALITY-BY-DESIGN AND QUALITY-BY INSPECTION CONTROL STRATEGIES

With the advent of the ICH Q8 guidance and ASTM E2500 much has been written about its fundamental premise of building quality into a system, i.e. Quality by Design (QbD), versus testing or inspecting it in, commonly referred to as Quality by Inspection (QbI). QbD concepts are not new and have seen tangible implementations in other process industries that require a high level of product robustness. We can easily expand the QbD/QbI discussion to the manufacture of single-use products and draw parallels between the control strategies utilized by single-use manufacturers and those applied by drug manufacturers. For a single-use manufacturer, a simple QbI control strategy could include in-process and lot release visual inspections with additional leak testing instilling a certain level of quality. Given the ever-increasing complexity of single-use designs and the virtually unlimited design configurations, some suppliers understand the limitations of relying solely on a QbI control strategy. On the other side of the quality spectrum is a modern QbD approach, which as a term, appears to have been readily adopted by single-use manufacturers. However, it may find its highest application only in operational excellence strat-

egies ranging from lean manufacturing to Six Sigma and Statistical Process Control (SPC). QbD goes beyond establishing parameters that define the operational bounds included in a process validation used to implement, for example, a welding process for biocontainers. Skilled automation and manufacturing engineers are familiar with QbD concepts. In fact, many have successfully implemented multi-parameter control strategies, often based on the outcome of elaborate Design of Experiments (DOE) testing schemes, to ensure robust manufacturing processes. Those suppliers who have invested in automation and process control technologies will attest that highly robust biocontainer manufacturing processes can be achieved and that the product quality associated with these processes exceeds that accomplished by those which follow QbI control strategies, even those harboring in situ leak testing. This is because in situ leak testing only implements a pass/fail quality metric within the limitations of the method itself, which adds little to process capability and may even provide for a false sense of comfort.

CONTINUOUS QUALITY VERIFICATION (CQV)

The most modern variant of process validation is Continuous Quality Verification (CQV), which promises the best of PAT (Process Analytical Technology) and QbD in an integrated control strategy as portrayed by ASTM E2537. For example, the application of such principles in the manufacturing of biocontainers was conceived by Meissner more than five years ago, and has progressed to an integrated manufacturing/quality control strategy that has proven its effectiveness. Early industry adopters of single-use assemblies who have gained insight with regards to the failure modes of biocontainers are quick to point out that the weakest link is often the seams, or welds, which define a biocontainers perimeter and provide for the addition of porting. Intuitively that may not seem all that surprising, but upon closer examination it does not have to be that way. Correct film design, advanced control strategies, and error proofing provide for an altogether different process outcome. All thermoplastic film welding processes are achieved by the application of heat and pressure to the respective plies and/or porting fitments with time, temperature, and pressure serving as the typical process control variables. It is however possible to conceive a CQV welding process that uses a fourth process parameter, i.e. energy input, as a control variable and as an in-line diagnostic parameter. Meissner implemented such a control strategy to further enhance the robustness of biocontainer manufacturing, which combined with the in-line serialization of every biocontainer, ensures a high level of fluid integrity for every biocontainer manufactured and effectively mitigates the risks of leaks.

While no single control strategy on its own may be able to effectively ensure 100% fluid integrity, an integrated manufacturing/quality approach borrowing from QbD principles and integrating CQV may be suitable to ensure fluid integrity of biocontainers and negate the need to rely on factory leak testing as a release test. ■