BioPhorum

CLOSED SINGLE-USE SYSTEM INTEGRITY ASSURANCE

Key considerations on mandatory post-use testing of closed single-use systems: an industry position

CONNECT
COLLABORATE
ACCELERATE™

Contents

About BioPhorum

We enable the global biopharmaceutical industry to connect, collaborate and accelerate progress for the benefit of all.

Since its inception in 2004, BioPhorum has become the open and trusted environment where senior leaders of the biopharmaceutical industry come together to openly share and discuss the emerging trends and challenges facing their industry.

Growing from an end-user group in 2008, BioPhorum's membership now comprises top leaders and subject matter experts from global biopharmaceutical manufacturers and suppliers, working in both long-established and new Phorums. They articulate the industry's technology roadmap, define the supply partner practices of the future, and develop and adopt best practices in drug substance, fill finish, process development and manufacturing IT.

In each of these Phorums, BioPhorum facilitators bring leaders together to create future visions, mobilize teams of experts on the opportunities, create partnerships that enable change and provide the quickest route to implementation, so that the industry shares, learns and builds the best solutions together.

1.0

Introduction

During aseptic manufacturing of sterile pharmaceuticals, the sterility of the drug product depends on preventing environmental contamination from entering the product or product contact surfaces. For processing steps where the product and product contact surfaces are exposed to the environment, this is typically achieved by maintaining aseptic environmental conditions such as grade A air. Alternatively, when the product and sterilized critical surfaces (interior of pipes, tubing, vessels, etc.) are closed and isolated from the environment, environmental control may be reduced (e.g. grade C) provided that the integrity of this closure can be assured.

Exactly how this 'integrity assurance' of closed systems can be achieved is a topic of recent debate: what controls and qualifications are minimally necessary to provide this assurance to such an extent that the surrounding environment can be reduced below grade A?

The BioPhorum closed single-use system integrity assurance workstream is finalizing a forthcoming publication covering a deep investigation of these topics, with special attention to single-use systems. Meanwhile, this position statement serves as an introductory analysis of a 'maximalist' opinion occasionally expressed on this topic:

> *"To justify background environments below grade A, assurance of system closure can only be provided by **post-use integrity testing** the entirety of every closed system used."*

The consensus position of the workstream members is that this maximalist position:

- Does not follow directly from a common-language interpretation of Annex 1 text and excludes other approaches capable of providing a similar level of integrity assurance
- Overlooks critical differences between 'integrity testing' and more general 'leak testing'
- Overlooks well-documented risks and limitations associated with post-use leak testing.

Each of these points is described below at a high level.

The upcoming publication from BioPhorum will elaborate on how integrity assurance of single-use systems can be achieved through a combination of lifecycle controls rather than reliance on any single test.

Annex 1 interpretation

Annex 1 emphasizes the importance of risk-based decision-making and introduces the framework of Quality-Risk-Management. Further, the explicit Annex 1 section on the topic of closed system integrity (Section 8.130[1]) states only that the closed system "must be shown to remain integral at every usage" to permit usage in background environments below grade A. It provides some *examples* of how this can be done ("e.g. via pressure testing and/or monitoring") but does **not**:

- Require ***post-use*** leak testing
- Require integrity testing, i.e. a test correlated to the physical microbial ingress probability, in lieu of other leak-detection mechanisms
- Preclude alternative approaches to "show the system remains integral at every usage".

Alternative approaches might include controls such as:

1. Prevention of leaks: quality-by-design, supplier qualification of single-use systems as integral, transport validation, end-user qualifications, training, inspections and controls during routine manufacturing, etc.
2. Detection of leaks: visual monitoring and, based on risk and as appropriate, specific testing (e.g. supplier leak/integrity testing, end-user pre-use leak testing)
3. Ongoing verification: such as demonstration of sterility during periodic aseptic process simulation.

These controls can be embedded within a holistic single-use system integrity control strategy, which is a critical part of the broader contamination control strategy (CCS).

Integrity testing vs leak testing

In the relevant literature (Bio-Process Systems Alliance (BPSA), American Society for Testing and Materials (ASTM)[2, 3, 4]), 'integrity testing' is a precise term used to refer specifically to qualified leak testing with a sensitivity sufficient to detect sterile-barrier breaches equivalent to the smallest hole a microorganism could theoretically enter.

For most closed, single-use systems, this sensitivity is only achievable by complex tracer-gas detection methods, not suitable for use in the drug manufacturing operations environment. Simpler leak-test methods such as pressure-decay or airflow rate tests may be possible in the operations environment but often have more limited sensitivity (given pressure limitations) and would not qualify as integrity tests.

Risks associated with post-use leak testing of single-use systems

Current literature (BPSA, ASTM[2, 3, 4]) generally recommends against post-use leak testing, particularly when it is expected as a mandatory requirement rather than applied through a risk-based approach. This position is based on limitations in test reliability, method capability and operator safety:

1. **Reliability of the test**

   Post-use leak testing does not reliably reflect the integrity of the system during processing. The manipulations required for a post-use leak test reduce confidence in results as meaningful indicators of system integrity during manufacture.

They can result in either a false PASS leading to undetected leaks and risks to patient safety, or a false FAIL that does not indicate actual loss of integrity during processing and could lead to increased batch failures and supply risks:

- **Set-up modifications:** Post-use testing often requires manipulation and partial disassembly of the used system. These changes alter the original configuration present during filling and therefore the test is not representative of the system during use. Additional handling can also introduce new defects or failure points.
- **Removal of liquids and product residuals:** To avoid masked defects (e.g. caused by product), removal of process liquid or product residuals would often be required before testing. This typically increases the system complexity (e.g. through additional junctions, clamps, etc.), which raises the risk of introducing new defects and reduces the relevance of the test.

2. **Lack of a suitable high-sensitivity point-of-use leak detection test method**

   There is currently no practical, highly sensitive test method that can guarantee integrity at the point of use. Available post-use test methods have limited sensitivity and cannot reliably correlate detected defects with microbial ingress risk. Highly sensitive techniques, such as helium leak testing, are not feasible for routine point-of-use application due to equipment needs, system modification and logistical constraints. As a result, mandatory post-use testing may create an expectation of assurance that current methods cannot support.

3. **Operator safety considerations**

   Post-use leak testing can increase risks to operators, since additional handling, pressurization and disconnection of used systems may expose operators to potentially hazardous materials.

In summary, post-use leak testing cannot be relied on to detect leaks that occur during processing and are missed by visual inspections, pre-use testing or other risk-based controls. Therefore, post-use leak testing does not provide additional meaningful assurance of system integrity. The quality and reliability of the data generated by post-use leak testing do not justify its use as a mandatory assurance measure.

2.0

Conclusion

For aseptic processing with closed systems, the maximalist position (that background environments below grade A must always be accompanied by *post-use integrity testing of all closed systems*) places disproportionate emphasis on post-use *detectability* rather than lifecycle-based risk reduction and control. It does not account for key practical, technical and scientific limitations of post-use integrity testing approaches (e.g. product masking effects, sensitivity limitations).

Integrity assurance ("showing the system remains integral at every usage" in Annex 1 language) is the conclusion that emerges from a comprehensive system of overlapping measures and controls, not a narrow requirement for post-use integrity testing. The necessity for physical leak testing as part of this suite of controls must be determined by a complete evaluation of the advantages and drawbacks specific to each drug product manufacturing situation and condition, with the primary goal of ensuring patient safety founded on uncompromised, accurate, representative and reliable data.

References

1 European Commission. *EudraLex Volume 4: EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use – Annex 1: Manufacture of Sterile Medicinal Products.* 2022. Section 8.130.

2 Bio-Process Systems Alliance. *Design, Control and Monitoring of Single Use Systems for Integrity Assurance.* Arlington, VA: BPSA; 2017.

3 Bio-Process Systems Alliance. *Design, Control and Monitoring of SUS for Integrity Assurance. Volume 2.* Arlington, VA: BPSA; 2023.

4 ASTM International. *ASTM E324423: Standard Practice for Integrity Assurance and Testing of Single Use Systems.* West Conshohocken, PA: ASTM International; 2023.

https://doi.org/10.46220/2026FF007