Helium integrity test

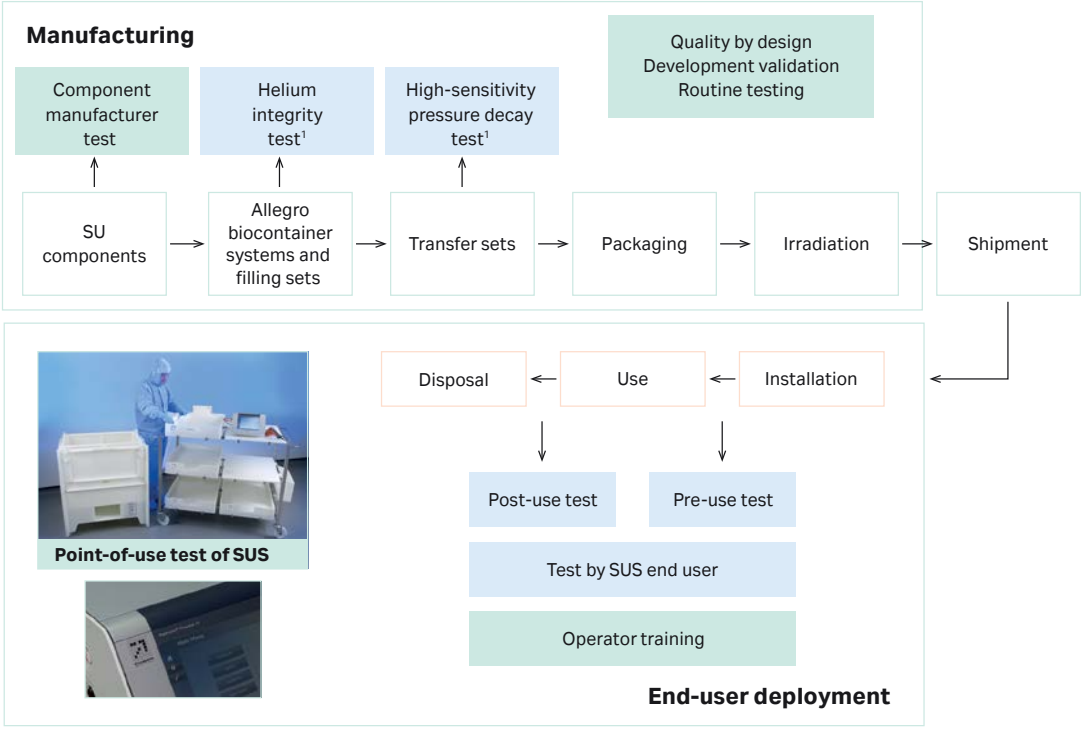
FOR ALLEGRO™ SINGLE-USE SYSTEMS

A high-sensitivity integrity test at the point of manufacture for enhanced quality risk management of single-use systems (SUS)

Single-use technologies have gained strong market acceptance in both clinical and manufacturing operations. A suitable strategy to assure the integrity of the SUS during the life cycle is essential. This strategy includes the manufacturing process and the supply chain.

The helium integrity test (using HIT™ technology) provides a higher level of assurance that the SUS leaving the factory is leak-free. The size of detectable defects is correlated to microbial ingress. The test can be requested for Allegro™ biocontainer systems, Allegro mixer biocontainer systems, and single-use filling sets.

Fig 1. Example of a single-use system which can be helium integrity tested before leaving the factory.



[1]Performed upon customer request

Fig 2. SUS life cycle with Cytiva and end-user steps.

As single-use systems are delivered as ready-to-use systems, the SUS supplier has an increased responsibility in the design, manufacture, and validation of SUS. That is different compared to conventional reusable stainless steel systems, where the end user is responsible for their life cycle, from design to maintenance, including validation, routine operation tests, etc. With SUS, the responsibility is shared between the supplier and the end-user.

To develop a suitable strategy for the assurance of integrity of SUS, in addition to the SUS application specific requirements, all the steps in the life cycle of the SUS should be considered, from its design and manufacture at the supplier to its disposal by the end-user. A proper risk assessment should be performed to define the most appropriate risk mitigation strategy. This risk-based approach is recommended in the Bio-Process Systems Alliance (BPSA) guide on "Design, Control, and Monitoring of Single-Use Systems for Integrity Assurance" (http://bpsalliance.org/technical-guides).

Quality by design (QbD) principles, junction tests, visual inspection, quality control tests, and validated processes are used for all our manufacturing procedures to ensure robustness and integrity of manufactured SUS. Additionally, we can perform the helium integrity test (using Cytiva HIT technology) upon request for Allegro SU assemblies. The HIT method provides a higher level of integrity assurance for SUS incorporated into the most critical steps of drug substance or drug product bulk storage.

The helium integrity test occurs at the Cytiva site during the manufacturing of Allegro SUS. Figure 2 shows the life cycle of an Allegro SUS with our manufacturing steps in the upper region, and the SUS deployment steps at the end-user site in the lower region of the figure.

When dealing with complex SUS, additional tests using a high sensitivity pressure decay test may be required on the SUS fluid transfer parts. We can also offer these tests on request.

Working principle of the HIT method

We have developed a highly sensitive integrity test system using helium as a tracer gas.

The tracer gas detection method, in vacuum mode, is the method of choice recommended by USP <1207.2> on package integrity leak test technologies (1). Helium is used as a tracer gas, due to its favorable properties (inertness and small atomic size), in an inside-out test method, whereby helium will be collected in the test chamber should there be a defect (Figure 3).

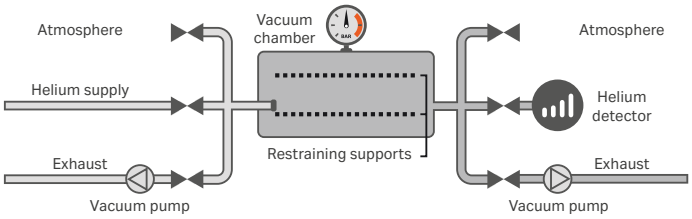


Fig 3. Test chamber schematic.

A highly sensitive mass spectrometer (MS) connected to the test chamber quantifies helium gas concentration. A leak rate calculated from the helium concentration in the test chamber is compared to an acceptance criteria (threshold value) to determine whether the tested SUS assembly passes or fails the test (Figure 4).

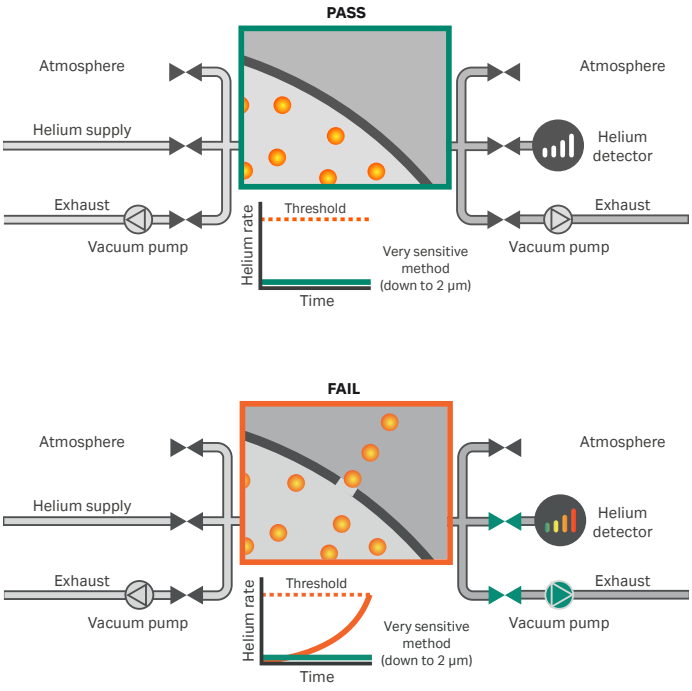


Fig 4. Leak rate measurement.

The HIT method is a nondestructive test method. The method and acceptance criteria have been fully validated to detect down to a 2 µm defect with assemblies including Allegro biocontainers ranging in size from 50 mL to 200 L and Allegro mixer biocontainers in sizes up to 200 L.

For filling set assemblies, the method is validated to detect down to a 10 µm defect.

Both comply to the MALL (maximum allowable leakage limit defined in USP <1207>) approach and are correlated to microbial ingress (1, 2).

Features	Benefits
50 mL to 200 L Allegro biocontainer systems integrity tested to detect defects down to 2 µm	Assurance of single-use systems integrity
50 to 200 L 3D LevMixer™ biocontainer systems and Magnetic Mixer biocontainer systems with top hat,integrity-tested to detect defects down to 2 µm	Enhanced risk control your contamination control strategy
Filling sets are integrity tested to detect defects down to 10 µm	Less risk of batch losses due to leakage or sterility breach

Applications

Single-use systems for the clinical and commercial production of drugs

- Aseptic processes in vaccines, gene and cell therapy applications
- Bulk storage of mAbs, vaccines, r-proteins, etc.
- Aseptic filling processes

Key elements of SUS integrity

We have very high standards with regards to the design (QbD) and validation of the manufacturing process for Allegro SUS. Additional key elements of our approach for assurance of integrity are the HIT test and pressure decay test at the supplier as well as a SUS leak test at the end-user (Figure 5).

Should there be a need to confirm the absence of leaks prior to use from a risk management perspective, an easy and reliable point-of-use leak test can demonstrate that the SUS has not been damaged during installation. This point-of-use test at the end-user complements our manufacturing tests and provides an additional level of assurance of integrity.

The Palltronic® Flowstar LGR test instrument enables *in situ*, post-installation point-of-use leak testing of single-use systems up to 200 L nominal volume and provides the ability to test filter integrity. It allows end users to test endless configurations of single-use systems and filters with one device, without compromising system sterility. It is more specifically designed for use in the vaccines, biotech, and pharmaceutical applications with a specific focus on formulation and filling operations.

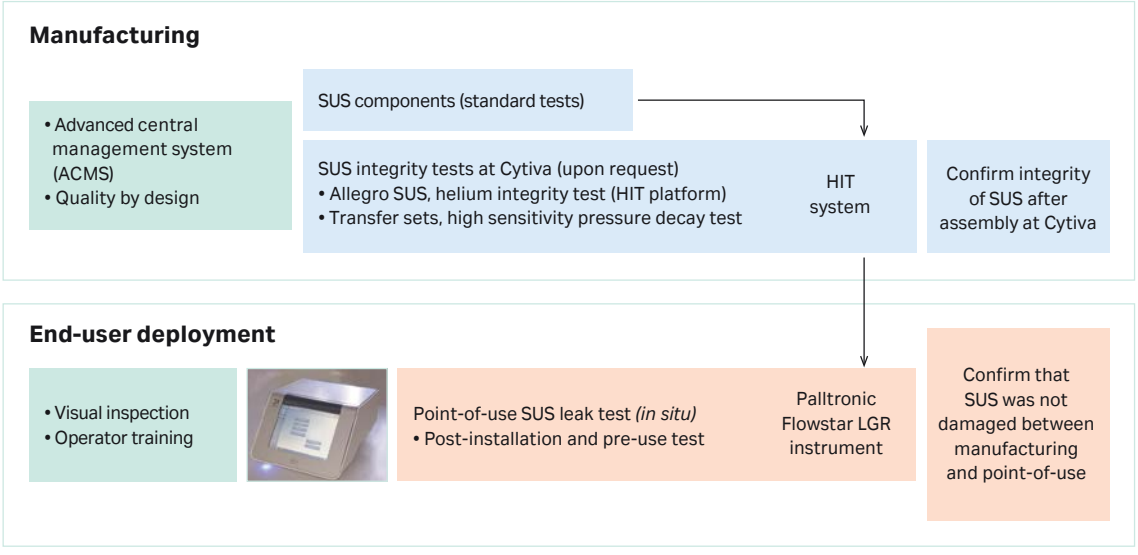


Fig 5. Supplier/end-user steps for assurance of integrity.

References

1. United States Pharmacopiea <1207.2> General Chapter, Package Integrity Evaluation – Sterile Products – Package integrity leak test options
2. Pall Life Sciences data - Design, Control, and Monitoring of Single-Use Systems for Integrity Assurance, BPSA, July 2017

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