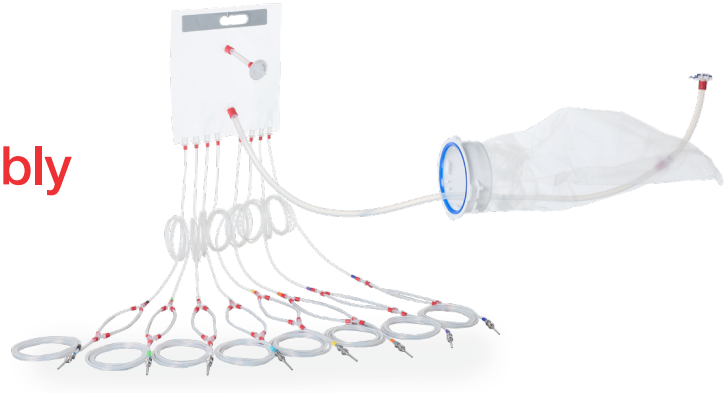
Fill finish

Advanced aseptic filling assembly helium integrity testing



Keywords: Fill finish, helium integrity testing, aseptic manufacturing, sterility

Introduction

Ensuring the integrity of single-use systems in fill finish operations is essential for maintaining the quality, sterility, and efficacy of a final drug product throughout the aseptic filling process. Integrity testing evaluates the confined barriers of the aseptic filling assembly for potential leaks and contamination. Helium leak tests are particularly effective due to their high sensitivity, which is crucial for detecting minute leaks and facilitating product sterility for single-use assemblies.

Thermo Fisher Scientific offers comprehensive aseptic filling assemblies with a robust and reliable design aimed at maximizing drug product recovery while upholding the highest standards of product integrity. Although many end users consider a standard leak size of 15 µm acceptable, Thermo Scientific™ Fill Finish Solution aseptic filling assemblies are helium integrity–tested to pass the leak test at an even lower threshold of 10 µm.

The data presented in this application note reflect the trusted standard for helium integrity testing of these assemblies, which surpasses the ASTM F2338 standard for other products that provide data for leak sizes ranging from 10 µm to 30 µm [3].

Helium integrity testing equipment

The Q010 assembly leak check station (third party–sourced) is a helium leak testing instrument equipped with a vacuum chamber and mass spectrometer, and it is designed to detect leak rates equivalent to what would be caused by a 10 µm hole in a single-use aseptic filling assembly with up to 13 hoses. The instrument fills the assembly with a consistent test helium concentration inside the vacuum chamber, and measures the helium leak rate via the mass spectrometer. The test result indicates a pass or fail based on whether the measured leak rate exceeds the reject limit. The standard leak rate for a 10 µm hole is 1.15 x 10^{-3} mbar·L/sec based on pure helium at 71°F (22°C) and 2.5 pounds per square inch absolute (PSIA) pressure relative to vacuum. The reject limit for each filling assembly is adjusted from this standard leak rate, taking into account the test helium concentration, testing time, background helium gas in the chamber, bag volume, number of hoses, and hose size.

Testing procedure

The Q010 instrument performs several tests and preparation steps before introducing helium into the filling assembly:

1. The Q010 instrument performs a pressure test to verify that all components are sealed and connected.
2. The vacuum pump gradually removes the air from the chamber until the mass spectrometer no longer detects a significant amount of helium in the background and the pressure in the chamber reaches a vacuum state.
3. Once the chamber is free of helium, a test helium concentration is introduced into the main fill line connected to the filling assembly until pressure and time thresholds are met.
4. Helium fills the dosing lines until the assembly is at system pressure.
5. The mass spectrometer begins the test by measuring the helium leak rate in the vacuum chamber. Any change from the background helium leak rate can now be attributed to the filling assembly either leaking or not leaking.
6. The filling assembly passes the integrity test if the measured leak rate is below the reject limit within the testing time. If the measured leak rate is above the reject limit, the filling assembly fails the integrity test.

Control helium leak profiles

A control helium leak profile serves as a reference for the leak rate associated with a 10 µm hole in an assembly. The control leak rate is measured by attaching a standard capillary tube with a 10 µm equivalent leak rate (1.15×10^{-3} mbar·L/sec) to the filling assembly.

Figure 1 shows line graphs of control leak rates associated with 10 µm equivalent leak rate holes in three aseptic filling assemblies: a 1 L bag with 2 hoses, a 5 L bag (wide) with 12 hoses, and a 10 L bag with 12 hoses. The starting point (0) on each graph represents the moment helium was introduced. The larger assemblies and those with more hoses took longer to fill and reach system pressure. Each test was conducted with the test helium concentration and varying background helium concentrations, which were accounted for in the adjusted reject limits. Consequently, each standard produced a different slope for the reject limit signal and initial strength.

Helium leak test profiles of aseptic filling assemblies

The helium leak test profiles indicated that all seven aseptic filling assemblies tested for leaks passed (Table 1). The line graphs in Figure 2 show that the three examples with sealed components passed the leak test without exceeding the reject limits. Note: not all tested configurations are shown. The adjusted leak rates plotted on the *y*-axes were measured based on the configuration of each assembly. In the absence of a leak, the graph will show the background helium level gradually decreasing as the test progresses. A continuous decrease in the leak rate was observed with the 1 L bag and 10 L bag with 12 hoses as the vacuum pump extracted air from the chamber (Figure 2A, 2C). The 5 L bag (wide) with 12 hoses and thin dosing lines exhibited helium permeation with a slight upward trend in the leak rate towards the end of the test (Figure 2B).

Table 1. Testing configurations and leak test results.

Aseptic filling assembly configurations	Result
1 L bag with 2 hoses	Pass
5 L bag with 6 hoses	Pass
5 L bag with 8 hoses	Pass
5 L bag (wide) with 10 hoses	Pass
5 L bag (wide) with 12 hoses	Pass
10 L bag (wide) with 10 hoses	Pass
10 L bag with 12 hoses	Pass

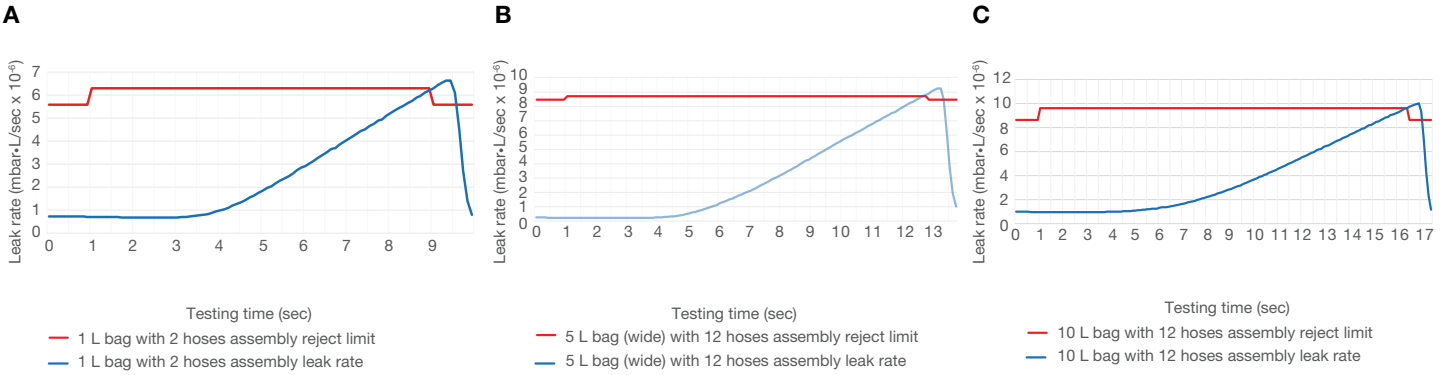


Figure 1. Control helium leak profiles of aseptic filling assemblies with 10 µm equivalent leak rates. (A) 1 L bag with 2 hoses, **(B)** 5 L wide bag with 12 hoses, and **(C)** 10 L bag with 12 hoses.

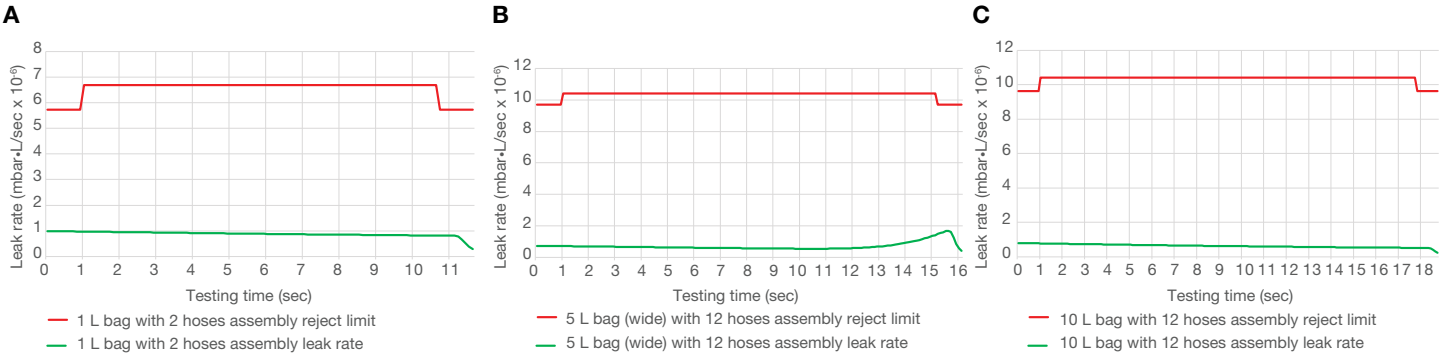


Figure 2. Helium leak test profiles of Fill Finish Solution aseptic filling assemblies. (A) 1 L bag with 2 hoses, **(B)** 5 L wide bag with 12 hoses, and **(C)** 10 L bag with 12 hoses. All 3 assemblies passed the leak test without exceeding the reject limits.

Conclusion

To help ensure the integrity of Fill Finish Solution components, the aseptic filling assemblies are tested in compliance with industry standards and regulatory guidelines set by USP <1207> and another US regulatory agency on container closure systems as well as EMA GMP Annex 1. These guidelines mandate that the testing methods be validated to ensure sensitivity, accuracy, reproducibility, and the capability to detect leaks as small as 15 µm [1,2]. As such, Thermo Fisher tests Fill Finish Solution aseptic filling assemblies for leaks as small as 10 µm using helium, exceeding the industry benchmark of 15 µm. Helium integrity testing with the Q010 Bag Leak Check Station underscores our commitment to the highest standards of product integrity, sterility, and efficacy in aseptic filling processes. The ability to detect leaks as small as 10 µm provides an advantage over the 15 µm leak size benchmark and helps ensure superior protection against contamination and product loss.

The testing procedure, which includes comprehensive preparatory steps and precise control leak profiles, validates the robustness of Fill Finish Solution aseptic filling assemblies. The results of the helium leak tests described here confirmed that all seven filling assemblies tested met stringent integrity requirements. These data support the reliability and effectiveness of Fill Finish Solution aseptic filling assemblies in maintaining drug product quality and sterility.

References

1. United States Pharmacopeia (2024) General chapter: package integrity evaluation—sterile products. SP-NF. Rockville, MD.
2. EMA EU GMP Annex 1: manufacture of sterile medicinal products.
3. ASTM F2338-09 (2020) Standard test method for nondestructive detection of leaks in packages by vacuum decay method.

Learn more at **thermofisher.com/fillfinishsolution**