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Container Closure Integrity Testing

A critical step in understanding the safety and suitability of primary packaging is the ability to evaluate the potential of the container closure system to maintain a sterile barrier or to prevent leakage resulting in contamination or loss of the drug product.

As the driving forces behind safety evaluation of materials and container closure systems in the US, the United States Pharmacopeia (USP) and Food and Drug Administration (FDA) enforce stringent requirements for Container Closure Integrity Testing (CCIT).

Historically, Dye Immersion and Microbial Immersion (both probabilistic tests) were the two leading methods for Container Closure Integrity Testing. In 2016, USP issued guidance that deterministic methods are preferred over probablistic methods because they are able to achieve reproducible and predictable results at low detection limits for CCIT. While we do offer the traditional Dye Immersion and Microbial Challenge Testing for container-closure systems, these methodologies are considered to be probabilistic, as per USP. These tests are also destructive to the samples under test, and typically require a significant number of units for method development and validation.

Eurofins BioPharma Product Testing is committed to offering the most up-to-date methods for testing container-closure systems for final drug product packaging. We have invested in state-of-the-art instrumentation to meet these regulatory guidelines and verify the safety of your container-closure system. In addition to the probabilistic methods, such as Dye Ingress, Microbial Immersion and Microbial Aerosol Challenge Testing, we also offer deterministic methods, such as Vacuum Decay, Pressure Decay, High Voltage Leak Detection, Oxygen Headspace and Helium Leak Detection. Each of these methods offers unique capabilities with product-package specific applications. We can help you determine which method is most suitable for your product-package configuration.

Why Choose Eurofins BioPharma Product Testing?

- We have vast experience developing and executing methods for hundreds of container closure testing projects utilizing various container types.

- We offer eight techniques for CCI testing.
- Our techniques accommodate various packaging configurations.
- Our methods can minimize the number of samples required for testing.

Deterministic Methods

Vacuum Decay

Instrumentation: VeriPac 455-M5 Vacuum Decay
Description: Measures leaks by vacuum decay based upon ASTM F2338. This system can detect leaks down to approximately 5 microns by measuring a change in vacuum pressure over time. Pressure transducers detect changes in vacuum pressure resulting from gas flow through leaks for both gross and micron sized leaks during two consecutive test cycles.
Best Application: This technology is suitable for leak testing on container/closure systems such as syringes and vials. Because this method is non- destructive to the sample under test, it is a great option for leak testing both before and during stability studies.

Pressure Decay

Instrumentation: TM Electronics BT Integra-Pack Burst, Creep and Leak Tester
Description: Measures leaks by pressure decay based upon ASTM F2095.
Best Application: This technology accommodates both



seal and package integrity testing for flexible packaging, such as bags and pouches. This is a destructive test.

High Voltage Leak Detection

Instrumentation: E-Scan 655 MicroCurrent High Voltage Leak Detector (HVLD)
Description: Detects package defects using an electrical current.
Best Application: This technology is suitable for use with liquid-filled parenteral drug product glass vials and syringes, where the packaging is far less conductive than the liquid inside.

Oxygen Headspace

Instrumentation: FMS-760 Oxygen Headspace Analyzer
Description: Uses Frequency Modulation Spectroscopy (FMS) to detect oxygen in the headspace of transparent rigid containers and measures rise or fall in the oxygen levels in the container's headspace to identify a potential leak. It can also be used to determine the rate of oxygen permeation into a sealed container over time, as well as oxygen reactivity with a drug product.
Best Application: Because this method is non-destructive to the sample under test, it is a great option for leak testing parenteral containers both before and during stability studies. This technology is also used during package development to verify inherent package integrity and maximum allowable leakage limit (MALL) through leak rate modeling.

Helium Leak Detection

Instrumentation: SIMS 1284+ Helium Mass Spectrometer – Tracer, Gas Detection, Vacuum Mode and Sniffer Mode
Description: Measures leaks based upon ASTM F2391 and E499. Quantitates the flow rate of helium from leaks in packaging after having been charged with helium as a tracer gas. If a defect is present, the helium is then drawn out of the packaging through the defect by vacuum and detected using a mass spectrometer. This method is the most sensitive option, allowing for the detection of defects as small as 0.2 microns in a matter of seconds.
Best Application: This technology is suitable for package development to verify inherent package integrity and maximum allowable leakage limit (MALL). This technique is applicable to a wide variety, of package types, can isolate and identify leak location, and can directly measure leak flow rates.

Probabilistic Methods

Dye Ingress Testing

Sample and positive control packages are fully submerged in a dye bath. A vacuum pressure of about 0.5 atmospheres is applied for a specific amount of time, samples are returned to atmospheric pressure, and then a positive pressure of about 2 atmospheres may be applied for a specific amount of time. The packages are then visually compared to a sensitivity solution of a known concentration of dye to evaluate the samples for the presence of dye inside the packages. Alternatively, the solutions inside the packages can be tested for the presence of dye using a UV/Vis spectrophotometer.

Microbial Immersion Testing

Generic in-house methods are available and may be customized based on individual testing requirements. Techniques offered include Vacuum, Static, or Challenge Organism.

Microbial Aerosol Challenge Testing

Generic in-house methods are available and may be customized based on individual testing requirements. Techniques offered include Vacuum, Static, or Challenge Organism. Vacuum or Static techniques utilize a 0.4 m^3 air-tight test room connected with thermo-stated aerosol delivery system.