ATC by PFEIFFER VACUUM

Container Closure Integrity testing of IV bags

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Introduction

As a means to ensuring the safety of sterile products, the Food and Drug Administration (FDA) and the United States Pharmacopeia (USP) have provided strict guidelines for the testing of container closure systems. Manufacturers of IV bags are one of the many industries that must meet these test requirements. IV bags may be filled with water, saline, sugar solution or various drugs. Testing these bags for leaks is of the utmost importance since leaks may compromise the sterility of the overall container and hence user safety.

Advanced Test Concepts, (ATC) has been in the business of improving leak testing for over 25 years, providing a straightforward, sensitive and reliable technology to efficiently and thoroughly test various products for leaks, using advanced Micro-Flow & Mass Extraction sensors. In addition, ATC's technology has the capability to test products for pressure leak testing and burst limits, offering further value and expertise to clients who need to perform quality control.

The process of implementing container closure integrity testing (CCIT) for IV bags can be a challenge for manufacturers. ATC has provided solutions for several manufacturers, designed specifically to test IV bags for multiple defects. From concept design, feasibility testing, R&D testing, to production testing, our attention to quality and detail translate to a product that will serve and perform to the highest standard. Here is an example of how ATCs Mass Extraction technology (recognized by USP 1207 and ASTM) has been used to help manufacturers of IV bags to implement CCIT for their sterile product.

Section 1:
Container Closure Integrity Testing with Mass Extraction Technology

A flexible sterile package, such as an IV Bag, needs to be inspected during its product life cycle to ensure sterility. The FDA Guideline for Container and Closure System Integrity[1] maintains that physical tests provide more reliable testing in lieu of microbial sterility testing. CCI testing should be conducted during product design and validation, then continue during clinical testing, and finally end with quality control during the manufacturing phase.

The point of quality control is, as a first step, to test the integrity of a given container or package on a statistical basis. This testing is widely used in the medical and pharmaceutical industries, notably on IV and blood bags as well as other sterile flexible packages. IV bags are vulnerable to leaks around the seams and especially around the ports where tubes or

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drugs could be inserted. The USP <1207> guideline for CCIT published by United States Pharmacopeia, classifies the Mass Extraction test method as a "Deterministic" test method, differentiating it from a dye ingress test, which is a "Probabilistic" test method. "Deterministic" methods are validatable relying on physical measurement technologies where test results are variable and can be compared to pass/fail criteria. Whereas, "Probabilistic" methods, such as dye ingress testing, rely on human interpretation and are prone to error.

ATC's Mass Extraction tests are non-destructive and offer higher measurement sensitivity. The Mass Extraction instruments are efficient, offering short test time, and higher accuracy and repeatability than many of the other non-destructive deterministic methods currently used. These other methods, such as pressure/vacuum decay and high voltage testing, have some drawbacks. They have less sensitivity, heavily rely on bag shape and volume, and require frequent recalibration. The Mass Extraction instruments include an Intelligent Molecular Flow Sensor (IMFS), which is based on the Knudsen micro and molecular flow physical models. These instruments measure the true gas flow (of any gas) extracted from the container while it is inside a custom designed vacuum test chamber. This flow rate is proportional to the defect size. The Mass Extraction instruments have been qualified to test defects sized from 2 micron[3] directly proportional and more recently smaller defect sizes.

Figure 1: Mass Extraction for filled IV bags, aseptic room design

Section 2:
Filled IV bag test – Mass Extraction test

The IV bags are filled with fluid when tested for the integrity of the container. Leaky bags can pose a challenge if the product leaks into equipment and test chambers. IV bags come in a variety of sizes anywhere from 0.05 to 5 L, so ATC designs and produces 3 testing chambers (small, medium and large) to accommodate this variety for different size packages/bags. Each bag is constrained in an individual test chamber that is specially treated to prevent the sealing of possible leaks on surfaces that may come into contact with the test chamber walls. This special treatment helps to avoid a false reading.

Since the mass extracted from a bag is not sensitive to bag size, each chamber can test multiple bag sizes. ATC's equipment for large IV bags is set to detect a 5 micron defect size. But if there is water based solution behind the defect, smaller defects, as low as 2 micron, are detected. Defect sizes are glass micropipette type defects.

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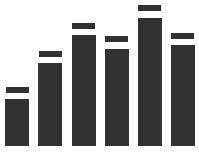
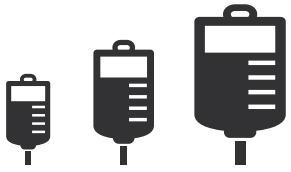
The Mass Extraction test for IV bags is performed while the chamber is at a vacuum level of less than 10 torrs (13,3 mbar). This ensures that leaks from defects with water behind them will be easily detected since water at room temperature (20 °C) boils at this pressure. The Mass Extraction sensor exhibits increased sensitivity to the presence of water vapor and can detect leaks from boiling liquid quite fast. This feature is important, enabling quick leak detection as drugs injected into these bags and other large molecules can eventually plug small defects once exposed to a longer vacuum time.

Higher Sensitivity and reliability



Can test multiple bag sizes with one setup



Long calibration cycles

Although the Mass Extraction and its IMFS are calibrated annually, there is a need to periodically verify the system for performance in order to qualify the test chamber seals from excessive wear and catch potential system failure (as concluded from a typical FMEA). In order to verify the test chambers, operators manually load a provided piece of aluminum into the chamber and run the equipment as though they were testing a filled IV bag. The aluminum piece is leak-proof and acts as a negative blank, thereby providing the machine a baseline reading for a bag without the smallest of leaks. Following is a test with a built-in 5 micron challenge orifice, which acts as a positive blank to ensure that this leak is detected. The challenge/verification method ensures the equipment runs correctly, and operators can reuse this method several times without concern of wearing out actual parts.

Once the equipment is verified, operators manually load filled IV bags in an appropriately sized chamber for testing and press the start button to begin the test. First, the instrument checks for gross leaks. Eliminating defective product early on in the test speeds efficiency and minimizes the possibility of leakage into the test chamber and the work to clean up the chamber. If a bag passes the gross leak portion of testing, it moves into the large leak test, testing for medium size defects (e.g.: 100 micron defect size) and then fine leak checks (e.g.: 5 micron defect size). Again, failed bags result in a clear red light with large leak flow values, and acceptable bags a green light. These tests are non-destructive and allow tested products to be shipped, providing a major cost savings in not having to throw out these products. Throughout the tests the instrument displays the bag's leak flow "signature" on its graphical screen as shown in Figure 2, and enables a remote computer to collect test results serially or over Ethernet. ATC's Leak Rx© software, which complies with the FDA 21 CFR Part 11 requirements, collects detailed test data and ensures traceability. Users can view test results and signatures to analyze the data, helping to improve the test process.

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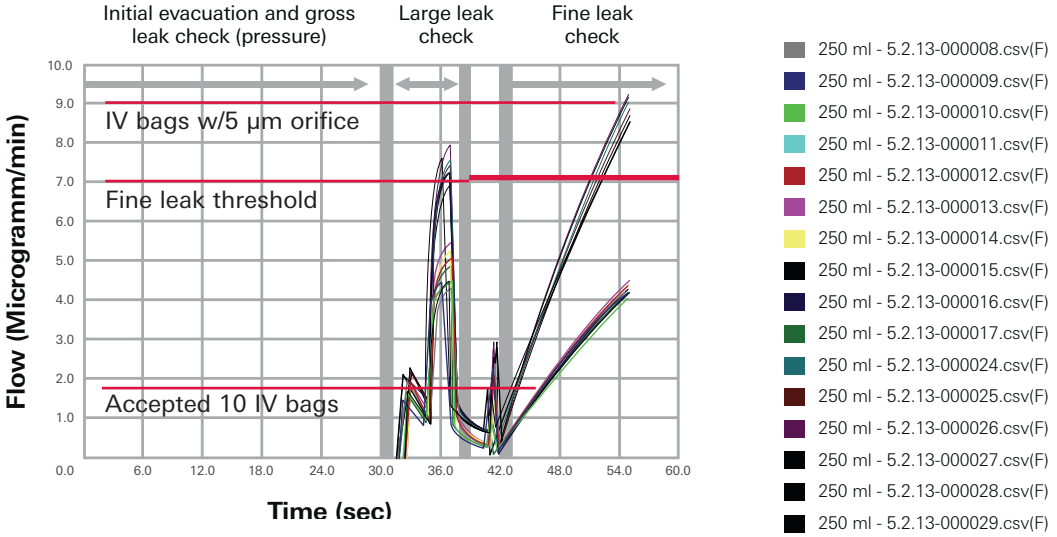

Figure 2: Example: 250 ml IV bag with and without 5 µm orifice

Section 3:
Empty IV Bags Tests – Pressure Testing

Pressure leak testing evaluates the integrity of the seals around the perimeter of the IV bags and can be non-destructive, while burst testing evaluates the seal strength and is a destructive test. These types of tests are currently treated as destructive to the product since they are testing the physical characteristics of the container on a sampling base. ATC has developed equipment designed to test four empty IV bags at one time. These chambers are also treated so the chamber walls do not seal expanding bags and mask possible leaks. The test chamber constrains the bag to minimize the bag's expansion and creep under pressure. The ports on the bag are sealed with custom automatic seals, through which air test pressure is applied. Once the bag is pressurized, the leak rate is measured by ATC's patented micro-flow sensor. The test throughput is 48 seconds for each 1 liter bag.

Test limits are set according to a calibrated leak orifice, which has been verified to the leak specification or defect size. The empty IV bags are tested for defect sizes typically from 10 micron and higher. ATC's IV bag leak test systems provide variable leak flow rates and a pass/fail result. If the bag passes, the green light turns on. Bags that pass are automatically released from the clamps that held them in place. But failed bags remain clamped and must be manually removed by the operator, ensuring that failed bags don't make it through the process and get shipped to consumers.

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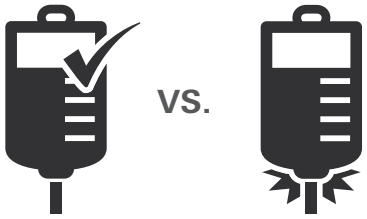

while burst testing evaluates the seal strength and is a destructive test.

Conclusion

ATC's container closure integrity test systems provide users with a robust system that will help them to meet the strict safety requirements established by the FDA and USP for sterile products. Designed to minimize false readings and dependence on operator set-up, ATC is unique in the leak testing industry for having proprietary micro-flow sensors with the Mass Extraction technology and software. Using ATC's technology and software saves you worry, time and effort. Add even more efficiency with one of the leak test systems with automated robotic sampling to test your product for high speed sampling. ATC support includes providing our users with IQ/OQ packages, leak artifacts for PQ, annual calibration and service contracts. The high level of quality and service stems from the reliability of our testing equipment and user confidence has been proven over numerous applications with clear advantages over other methods of leak testing for flexible packages.

Please visit our website **www.atcinc.net** for more information on our CCIT solutions and pressure leak testing systems or contact us directly at **+1 866.282.4621.**References

- "Guidance for Industry: Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products," U.S. Food and Drug Administration, February 2008, **http://www.fda.gov/RegulatoryInformation/Guidances/ucm146074.htm**
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- Yoon, S., Sagi, H., Goldhammer, G., & Li, L. (September/October 2012). Mass Extraction Container Closure Integrity Physical Testing Method Development for Parenteral Container Closure Systems. PDA Journal of Pharmaceutical Science and Technology, vol. 66 no. 5, 403-419 **http://atcinc.net/mass-extraction-container-closure-integrity-physical-testing-method-development-for-parenteral-container-closure-systems/**

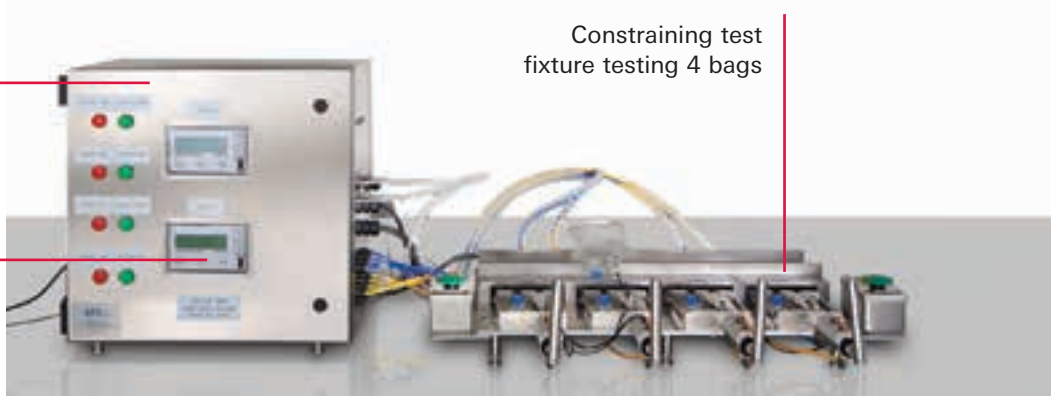

Figure 3: Example: 250 ml IV bag with and without 5 µm orifice