Container Closure Integrity Testing (CCIT)

Solutions for the pharmaceutical industry

PFEIFFER VACUUM

The quality and effectiveness of drugs significantly depends on their proper packaging: Sterile products and moisture/oxygen sensitive drugs require excellent barrier during the shelf life of the product (up to a couple of years) to protect them from biological contamination, water and oxygen ingress. Otherwise, serious consequences might occur. This was proven by a grave incident in the 1970's: During this period, contaminated intravenous fluids packaged in glass bottles – which were typical at the time for packaging such dosage forms – caused an estimated 2,000 to 8,000 episodes of bloodstream infection, resulting in the deaths of about 10% of the patients. This severe package-integrity failure incident has triggered a heightened awareness of package integrity in the life science industry.

The key risks for contamination are by humidity, oxygen or microbiological ingress, which can impact the drug stability throughout the product life cycle. To prevent the risks of stability failure of highly moisture sensitive drugs (e.g. dry powder for inhalation) or the risk of biological ingress of sterile parenteral drugs, integrity tests with a high sensitivity are required.

Regulated market

The high risk in regards to pharmaceutical Container Closure Integrity Testing leads to a strictly regulated environment. Key authorities are the FDA (United States) and the EMA (Europe).

In 2008 the US FDA published a new guideline for the whole life science industry (pharmaceutical companies, veterinarian drugs and companies that manufacture sterile medical products) that obliges the sector to perform reliable physical measurement to ensure proper CCI.

In practice, the regulations of the FDA as well as the European Guideline for Good Manufacturing Practice with Annex 1 for the Manufacture of Sterile Medicinal Products are often interpreted quite broadly and without specific recommendations. The main obligation given to the manufacturers is that they must ensure "the container-closure system to maintain the integrity of its microbial barrier, and, hence, the sterility of a drug product throughout its shelf life" (US FDA).

What the official regulations often do not describe in detail is how the CCI testing should be performed. They usually only stipulate to use appropriate methods and procedures. The United State Pharmaceopia, the government body in-charge of standards and guidelines for the pharmaceutical industry – which typically are internationaly accepted – dealt with this issue and in 2016 presented a new guideline: the USP <1207>. This guideline focuses on sterile and critical pharmaceutical products (e.g. vials and syringes) and is divided into 3 chapters:

- 1207.1: Package Integrity and Test Method Selection
- 1207.2: Package Integrity Leak Test Methods
- 1207.3: Package Seal Quality Test Methods

The USP <1207> thereby does not claim to describe all possible methods, but gives a good overview and general guideline for the evaluation of various popular potential methods.

Test methods and detection limits

An initial list of the various test methods used for package integrity testing was already published in the late 90s. The report back then was very narrow in scope and recommended to validate chemico-physical leak test methods by comparing them directly to a microbiological ingress test. This probabilistic test method relies on a series of sequential and/or simultaneous events with random results. The findings are associated with uncertainties that demand large sample sizes and precise test condition controls. Some publications on microbiological ingress tests show that the method detects leakage pathways the size of a single microorganism. The

Sensitive drugs require packaging for prevention of moisture or oxygen or microbial contamination

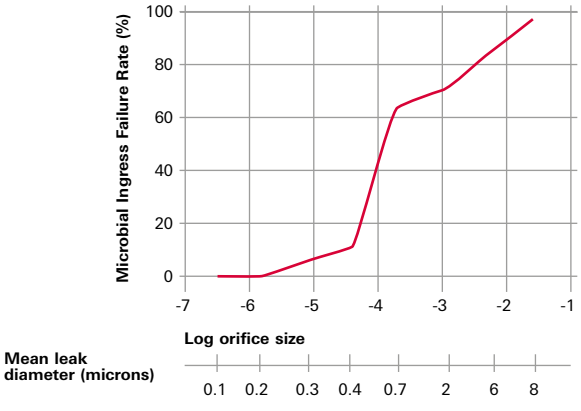

Figure 1: Microbial ingress failure rate in relation to leak size (source: Kirsh, PDA J Pharm Sci & Technol, 54,4, 2000 p. 305-314)

below chart describes the risk related to different orifice sizes: As shown in figure 1, the critical leak size is at 0.2 µm, respectively $6 \cdot 10^{-6}$ mbar l/s. This value is widely used as the so-called MALL (maximum allowable leak level). Furthermore, the chart says that a leak of 2 µm already poses a risk of close to 70 % for the contamination of the drug.

This must be kept in mind when looking at other studies, which have proven that classical probabilistic test methods could miss leaks, resulting in an impairment of product sterility. Specific examples are Microbiological Ingress Testing as well as Blue Dye Test Methods.

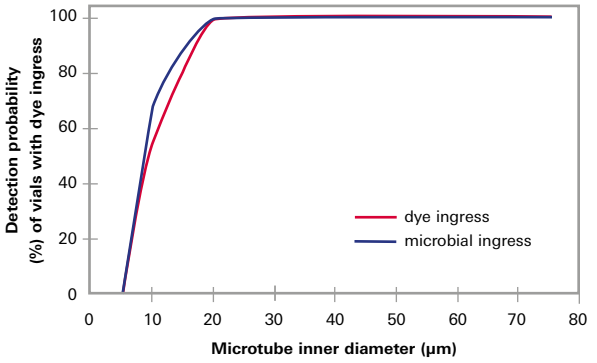

Figure 2: Detection probability in relation to microtube inner diameter (source: Burrell L.S. (et. al PDA J Pharm Sci Tech 54, p. 449-455), Figure 3)

As shown in figure 2, a dye ingress test has only an about 70 % chance to detect a 10 µm leak. Any leaks below 5 µm are more or less non-detectable.

It is therefore recommended to apply a deterministic integrity test method whenever leakage measurements are based on phenomena that follow a predictable chain of events. The chart below gives an overview of corresponding deterministic test methods, mainly based on PDA USP <1207>:

Leak test method	Measurement outcome	Row	Detection range
Tracer gas (Helium mass spectrometry)	Helium flow (mbar l/s)	1	< 0.1 to 10 µm
Laser-Headspace (Frequenzy modulated spectroscopy)	[O_2] and/or [CO_2] Gas pressure (%)	2	< 0.1 to > 50 µm
AMI[1] (Optical emission spectroscopy)	Leakage (N_2, Ar, CO_2, H_2O...) (mbar l/s)	2[1]	< 0.2 to > 50 µm
Mass Extraction (Micro/Mass flow sensors)	Mass flow (µg/min)	3[2]	< 1.0 to > 50 µm
HVLD (Leakage current)	Electrical current (µA)	3	< 1.0 to > 50 µm
Vacuum decay	Pressure rise (mbar/s)	3	< 1.0 to > 50 µm

[1] USP <1207> "Emerging Technology"
[2] ASTM Standard F-3287-17 proves capability to detect 1.0 µm defect, qualifies for USP <1207> row to rating

Figure 4: Overview of different leak test methods

The broad range of different methods can be traced back to the different challenges for CCIT within the pharma market. Those are related to the different process steps, the different packaging types and the different drug types.

Figure 5: Drug/container configuration matrix

While in the early development stage of a packaging ("packaging design phase"), the supplier is obliged to ensure that the packaging is by design capable to ensure the sterility. Therefore the packaging needs to be tested for defects in the range of 0.2 µm, respectively $6 \cdot 10^{-6}$ mbar l/s (MALL). These are the current requirements for stability and quality control of containers filled with drugs. Integrity tests are mainly performed in the range of 2 to 20 µm defect size. The main reason for this is the feasibility of the available methods to detect smaller defects in a reasonable test time. When dealing with a 100 % inspection of the production line that operates at speeds for 120 to 600 parts per minute, the allowed defect size is sometimes even increased to a significantly higher level. The Limit of Detection (LOD) for production units is defined as a risk-based decision between cost, technology and product. To compensate on this risk-based approach, additional off-line sample testing is performed to a tighter spec in the range of 1 to 10 µm. This also applies to stability testing which is performed in laboratory tests. Here again the sensitivity is more important than the test time.

Figure 5 gives a rough differentiation between the broad range of different packaging and drug types within the pharma industry. Not all test methods can be used for all kinds of packaging as well as all drug types.

Besides the below-mentioned characteristics of packaging types, also characteristics such as transparency of the packaging and its electrical conductivity play an important part in regards to the selection of the right integrity test method. Table 1 below gives a more detailed overview of available CCIT methods and also provides as a guideline for the selection by pointing out specific characteristics as well as limitations of the different test methods:

Pfeiffer Vacuum test methods

Pfeiffer Vacuum offers a wide range of different leak testing methods to adress the multitude of challenges within the pharmaceutical industry as there is no one solution that fits all different challenges connected to a specific product. Pfeiffer Vacuum can support you during the complete CCIT process definition and integration and also provide GMP support in regards to IQ/OQ (Installation Qualification/Operational Qualification) including the needed documentation for all our test methods. The following overview gives you an impression of Pfeiffer Vacuum´s portfolio of leak testing methods.

	Helium Mass Spectrometry	O.E.S (Optical Emission Spectroscopy)	Mass Extraction	Vacuum Decay
Deterministic	Yes	Yes	Yes	Yes
Non-Destructive	(Yes) only for open containers	Yes	Yes	Yes
Quantitative	Yes	Yes	Yes	Yes
Sample preparation	He charging Plausability test	No sample preparation		
Test pressure	Vacuum			
Detection range (Sharp edge orifice)	0.01< Q < 10 µm	> 0.2 µm	> 1 µm	> 5 µm
Drug Product Limitations	Lyophilized (dry) or liquid drugs			
	Plugging risk for small defects for protein based drugs			
Container Limitations	Container must handle 1 bar differential pressure			
	Non-porous material			
	He Permeation	High outgazing		
Method Limitations	Require gas headspace or liquid inside the container			
	Difficult to set-up ■ Requires proper He gas management ■ Requires plausability test to valid the test result. Not practical for mass production testing	Outgazing of the container and the drug type will impact the test duration and the detection limit		
		Detection limit is depending on packaging and drug type Detection limit depends on the gas used for the detection	Free volume inside the test chamber can limit sensitivity --> Test chamber must be optimized for each format parts. Sensitive to temperature and/or volume variations	
Method Advantages	High selectivity (He) High sensitivity test Possibility to localize the leak position with sniffing.	Selectivity: can detect simultaneously gas species (N_2, H_20, Ar, CO_2,…) Can test multiple containers with high sensitivity at the same time.	High sensitivity detection of water leakage Robust technology	Simple
Comments	Mainly used for the design and qualification phase of the packaging's, not practical for mass production testing.	Highly verstaile and sensitive test for different drug / packaging systems Can be used in laboratory or as IPC in production.	Highly verstaile and sensitive test for different drug / packaging systems In-line option available.	Older production test method. Reduced reliability for measurements at limit of detection.

Table 1: Available CCIT methods and selection guideline

Helium Mass Spectrometry

Pfeiffer Vacuum helium leak detection solutions are perfect for MALL testing in the pharmaceutical industry. In order to ensure a correct measurement, it is very important to manage the tracer gas concentration during the measurement. This is especially tricky when handling vials or other sealed packages. Therefore, Pfeiffer Vacuum offers complete solutions including tracer gas handling and charging, as well as adaptations for your packaging and test chambers.

Figure 6: Leak detector for MALL testing from Pfeiffer Vacuum (conceptual design)

	Vision (Deflexion)	HSA (Head Space Analysis)	HVLD (High Voltage)	Dye Ingress	Microbial Challenge
	Yes	Yes	Yes		
	Yes	Yes	Yes		
		Yes			
		Storage time	No sample preparation	Immersion in dye or microbial media	
		Atmospheric Pressure		Shallow Vacuum	Atmospheric Pressure
	> 5 µm	> 0.01 µm	10-40 µm	> 20 µm	> 0.2 µm
		Lyophilized drugs	Conductive liquid drugs	Light colored drugs	–
		Rigid & Transparent	Non-conductive material	Non-porous material	
	Container Design (Semi-rigid or flexibe)				
		Require gas headspace	Test only at the point of electrode contact, with liquid behind. Limited usage for flexible packaging's. No real quantitative measurement Risk due Ozone generation	Destructive Probabilistic Poor sensitivity Operator & multi-parameters dependant	Long (few weeks) and Expensive
	Sensitivity depends on the product design: ■ Headpsace volume ■ Size of the cavity ■ Shape of the container	Requires waiting time before actual testing (hours up to weeks) Waiting time depends on the gas headspace and detection limit. Headspace needs to be either vacuum or 100% Nitrogen			
	Requires positive control to calibrate the equipment				
	Identification of the leaky cavity or container. Can test multiple containers with high sensitivity at the same time.	High selectivity (O_2) Very fast, high thorughput can be acheived	Very fast, high thorughput can be acheived	Low cost equipment Easy to understand	Direct measurement of the biological contamination
	Mainely used for blister packs.	Indirect leak test, we measure the consequence of oxygen ingress through defects.	Very fast method for production test, limited usage for flexible packaging's.	Widely-used for decades Industry & regulatory familiarity	

Mass Extraction

Our USP <1207> and ASTM (F-3287-17) recognized Mass Extraction Technology works on the principle of rarefied gas flow. Testing takes place in vacuum conditions to attain higher sensitivity. This patented technology type of testing is particularly suitable for pharmaceutical packaging such as IV-bags, pouches or glass vials. Larger defect and defects as small as 1 µm can be detected with this method. The technology is thereby suitable for laboratory applications as well as for the use in production environment allowing stability control as well as automated 100% testing (also in inline machines). FDA laboratories in the US and major pharmaceutical companies have been using the Mass Extraction instruments for over 10 years.

Figure 7: Mass Extraction system from Pfeiffer Vacuum

Optical Emission Spectroscopy
The Pfeiffer Vacuum Optical Emission Spectroscopy Instrument used in the AMI test systems measures leak tightness using a patented process that does not require a tracer gas. Instead, this method uses the existing gas mixture in the cavities inside the packaging to perform high-sensitivity testing over an extended measuring range. Thereby the AMI has the ability to differentiate gas species that are typical to pharmaceutical products. The procedure offers great flexibility and can test a variety of different packaging types such as blister packs, pouches, vials and plastic bottles and can also test multiple samples at the same time.
The wide measuring range of the AMI offers higher sensitivity than conventional tests, starting from 0.5 µm (and smaller) respectively leak rates of down to $1 \cdot 10^{-6}$ mbar l/s, but can also identify gross leaks as for example a completely open container. As a result, the AMI device can perform gross and fine leak testing in just one device. The procedure delivers deterministic test results with high repeatability, irrespective of the user, and with reliability and accuracy that within the range of

Figure 8: Compact leak test system AMI from Pfeiffer Vacuum

USP 1207.1. It can be used in laboratory testing as well as IPC (In Process Control) during production testing. Depending on the packaging, also the simultaneous testing of multiple parts at the same time is possible.

Are you looking for a perfect vacuum solution? Please contact us:

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