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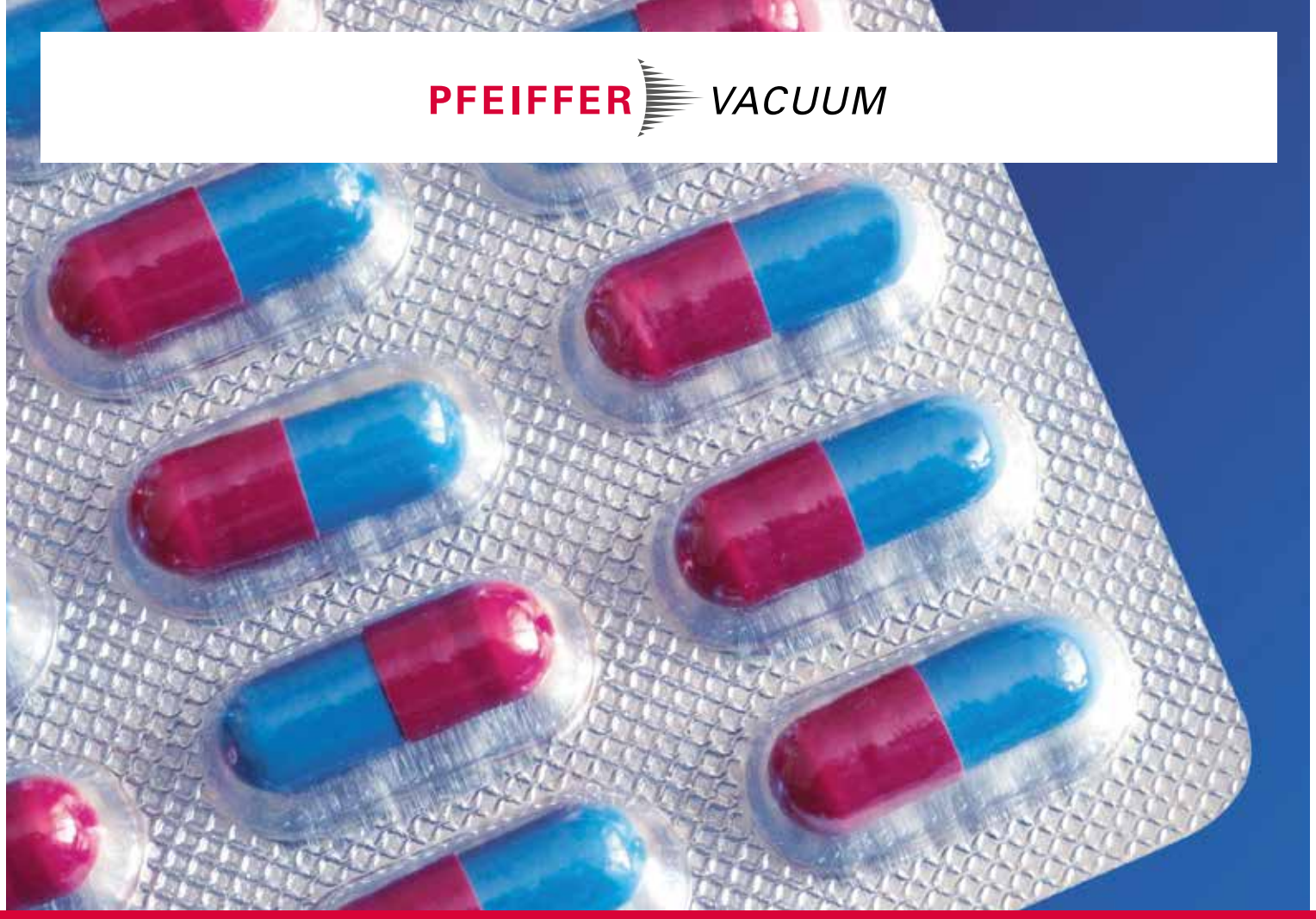

INNOVATIVE LEAK TESTING OF PHARMACEUTICAL BLISTER PACKAGES

AMI by Pfeiffer Vacuum

The quality and effectiveness of drugs significantly depends on their proper packaging: It needs to be unscathed and of the highest quality. Otherwise, serious consequences might occur. This was proven by a serious 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 early 1980´s, aspects of container closure Integrity (CCI) were described. The physical and mechanical properties of a vial container/closure system, which affect seal integrity, were described and methods for testing the seal integrity proposed. These microbiological testing methods were adopted by many in the pharmaceutical industry and accepted by pharmaceutical regulatory agencies as an unofficial standard for verifying the integrity of sterile product-package systems.

In the 1990´s, an exhaustive listing of various physicochemical and microbiological challenge test methods useful for package-integrity testing was provided. The report also recommended validation of physico-chemical leak test methods by a direct comparison to a microbial ingress test.

Probabilistic versus deterministic test methods
Microbiological immersion challenge tests are probabilistic test methods. Such tests rely on a series of sequential and/or simultaneous events, each associated with random outcomes described by probability distributions. The findings are associated with uncertainties that necessitate large sample sizes and rigorous test condition controls in order to obtain meaningful results. Microbiological immersion challenge tests can be quite sensitive and are able to detect leakage pathways the size of a single microorganism. However, studies have also shown that such tests lack reliability, often missing leaks that could compromise product sterility.

It is thus desirable that the integrity test method is deterministic. In this kind of test method, the leakage event being detected or measured is based on phenomena that follow a predictable chain of events. An example for a deterministic, well-established, highly sensitive method is helium leak detection.

Helium leak detection of hermetically sealed objects
Helium leak detection of hermetically sealed parts like closed pharmaceutical packages requires special actions for sample preparation and tracer gas admittance. Helium tracer gases can be applied in various ways:

- Sealing of the object in a tracer gas containing atmosphere

This method requires a special helium containing atmosphere during the sealing process of the packaging. It can be achieved either in a sealed station of a production line as in the case of gas generator production for airbag applications or in a glove box for batch type production. During the sealing process, the tracer gas concentration must be monitored precisely in order to provide quantitative information regarding tracer gas concentration inside the free volume of the part to be tested and at the entrance of the leak channel.

- Bombing test

In a first step, the part to be tested is exposed to the tracer gas helium at high pressure in a so-called bombing chamber. Tracer gas is backfilled to interior volumes of the sample through the leak channels. In a second step, the part is tested in a vacuum chamber connected to a Helium leak detector. The theory of this method is well-established and classified as a quantitative test method

Limitations of helium leak testing of hermetically sealed objects
Helium leak detection of hermetically sealed objects is subject to several drawbacks. During backfilling of the parts in the pressurized chamber, the tracer gas must diffuse through small leak orifices or capillaries. This means that the build-up of tracer gas concentration follows an exponential rise curve. The process is the slower the smaller the leak is. Back-pressurization is often too slow to allow for a 100% leak testing during production. Helium concentration in the free volume of the part to be tested depends on bombing pressure, bombing time, and internal volume of the part. It also depends on the leak rate, which is unknown prior to performing the test. After back-pressurization, the concentration of tracer gas in the internal volume of the sample can only be calculated, but not measured.

After both back-pressurization and sealing under tracer gas atmosphere, the part to be tested resides at atmospheric conditions for some time. This is necessary to allow for the desorption of tracer gas which is condensed to the surface or trapped or dissolved in a condensate film (mainly water vapor) on the outer surface of the tested part. If a component of the housing acts as a "Helium sponge", the low detection limit will be impacted and the theoretical models to describe quantification will fail.

During the waiting period between tracer gas admittance and leak test, a loss of tracer gas will occur because of the diffusion through the leak. This means that parts once filled cannot be stored infinitely. So a strictly timed recipe must be developed for any Helium test of a sealed object. In practice, some regulations are defining test procedures for classes of parts (see table 1). Bombing pressures and exposure times are recommended depending on the internal free volume of the part. The maximum waiting time (dwell time) for all types of products must not exceed one hour.

To summarize, the low detection limit is improved when the dwell time is increasing due to decreasing background signal. But the upper detection limit (capability to detect coarse leaks) decreases as well due to tracer gas loss from the internal volume of the part.

Volume of package [cm^3]	Bomb condition			Reject limit [atm cc/s] for tracer gas Helium
	Pressure [Psia]	Minimum exposure time [h]	Maximum dwell time [h]	
< 0.05	75 +/- 2	2	1	$5 \cdot 10^{-8}$
>= 0.05 ... < 0.5	75 +/- 2	4	1	$5 \cdot 10^{-8}$
>= 0.5 ... < 1.0	45 +/- 2	2	1	$5 \cdot 10^{-8}$
>= 1.0 ... < 10.0	45 +/- 2	5	1	$5 \cdot 10^{-8}$
>= 10.0 ... <= 20.0	45 +/- 2	10	1	$5 \cdot 10^{-8}$

Table 1: Parameters for bombing type leak tests according to Mil-883E

When testing blister packages, tracer gas can be applied by piercing the aluminum foil of the blister and inserting Helium with a syringe. The blister cavity is purged and the gas exchange from ambient air trapped in the blister cavity against Helium can occur via a second hole in the blister foil. During the following test, the two holes are taped. This method is used in pinpointing type leak tests which are targeted to identify failures of packaging machines. The method is destructive and does not allow for testing during production.

Once the part is tested, the tracer gas loss may be very fast for large leaks. During pump down of the vacuum chamber, the complete internal volume of the part may be evacuated and the highly sensitive helium leak detection method gets blind against large leaks. For this reason, a bombing test is used as fine leak test mainly, which is complemented by a gross leak test. The second method can be water bath test, optical inspection, or any other test method which overlaps with the sensitivity range of the helium fine leak test.

A Helium vacuum test cannot be applied if the mechanical stability of the tested part does not tolerate a differential pressure of 1 bar between internal gas-filled cavities and the evacuated test chamber. In this case, special action needs to be taken to support the part in the test chamber. Typical samples are food packages or pharmaceutical packages.

The way to a new sensor technology

Helium leak detection is still the most sensitive method for container closure integrity testing. However, some limitations are related to the admittance of the tracer gas. So it would be desirable to utilize a method which offers a low detection limit and does not require a specific tracer gas.

Consequently, attempts have been made to quantitatively measure leakage rates with the gas trapped in a blister cavity. These methods are e. g. pressure decay or laser-based gas headspace analytics. An overview of leak testing methods used in container closure integrity testing is shown in table 2:

Test method		Microbi-ological	Helium				
	Blue Dye ingress	ingress	Sniffing	Vacuum	Vacuum decay	Force decay	Laser / Camera	AMI
Deterministic (objective)	No	No	No	+	+	+	+	+
Non destructive	No	No	+	+	+	+	+	+
Quantitative measurements	No	No	No	+	+	+	+	+
Leak location	+	+	+	No	No	No	No	No
Sensitivity (lowest detectable limit)	++	++	++	+++	++	++	++	+++
Repeatability	+	+	+	+++	+++	+++	+++	+++
Accuracy	+	+	+	+++	++	++	++	+++
Testing speed / handling	+++	+	+	+	++	++	++	+++
Ease of use	+	+	+	+++	+++	+++	+++	+++
Ease of implementation	+++	+	+	++	+++	+++	+++	+++
Flexibility	+++	+	+++	+++	+	+	++	+++
PDA and SCADA compatible[1)]								+++*
Cost effectiveness	+	+	+	+	++	++	+++	+++
Comments	Test results and data traceability are operator dependant	depending on bacteria selected	Requires Helium in headspace	No detection of largest leaks	Requires specific tooling for each blister Limited flexibility		Limited sensitivity for peel blisters	Applicable to other types of packaging (vial, syringe, pouches)

[1)] PDA (product data acquisition) /SCACA (supervisory control and data acquisition) - advertising

Table 2: Leak detection methods for container closure integrity testing

Highly sensitive, quantitative measurements in real-time without specific tracer gases

In a new approach, Pfeiffer Vacuum has introduced optical emission spectroscopy as a method with lower detection limits compared to any other method that uses gas trapped in the cavity. The blister package to be tested is put into a test chamber which also provides a viewport and mechanical support for the package. With dimensions of 150 mm x 100 mm x 10 mm, the test chamber is large enough for the biggest blister package available. However, customizations can be made to tailor the chamber to larger samples as well.

After loading the sample, the chamber is evacuated. At pressures lower than 10^{-2} mbar, a plasma is ignited and its optical emission analyzed with an optical emission spectrometer. The lowest detectable signal corresponds to an orifice diameter of roughly 0.1 µm. Since the gas amount is restricted by the free volume of the blister package, the maximum pore size is limited to roughly 200 µm for 1 cm^3 cavity volume. The AMI sensor technology can be complemented with an oxygen sensing method integrated into the same test equipment. It can detect pore sizes up to 2 mm.

The software solutions used in the AMI are compliant with 21 CFR part 11. Optional software solutions are available for a manufacturing execution system. Trend analysis can be implemented in the software for early indication of drift production and packaging equipment.

This method is easy to set up and use and yields quantitative and highly repeatable results. In addition to the information achieved by a simple GO/NOGO test method, the new method of the AMI allows the detection of drifts in sealing parameters in real time. The loss of valuable pharmaceuticals is prevented and production stops for corrective measures are minimized.

The cycle time depends on the desired detection limit. For a leakage rate of $1.0 \cdot 10^{-4}$ mbar·l/s, a cycle time of 30 seconds can be expected.

Automatic calibration is implemented into the test equipment using certified calibrated leaks. Thereby, operator-independent calibration and test results are provided.

Future developments of AMI sensor technology

The AMI sensor technology and test equipment is consistently refined. The implementation of the sensor technology as a tracer gas specific sensor technology can be expected in the near future. It will be an alternative to mass spectrometry with the potential for alternative selectivity regarding mass range or optical emission signals. This also includes test stations with specific tracer gases other than helium or forming gas offering leak testing and permeation measurements with operational fluids.

Figure 1: Testing chamber and user interface of the AMI leak detection system

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Figure 2: The AMI leak detection system for pharmaceutical blister packages

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