Container Closure Integrity Testing for the Pharmaceutical Industry

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Managing Director

About us

- Established in 1989, family owned
- Sound experience in chemistry & pharma
- 21 Team Members, growing quickly
  - Pharmaceutical Chemists (some with validation experience)
  - Analytical Chemists
  - Engineers
  - Equipment Specialists
- Covering Australia and New Zealand with offices in Sydney, Brisbane, Melbourne, Perth, NZ with Partner
- Services include equipment consulting, application and technology support, equipment sales, installation, training and after sales service including recalibration services

What is it?

Container Closure Integrity Testing

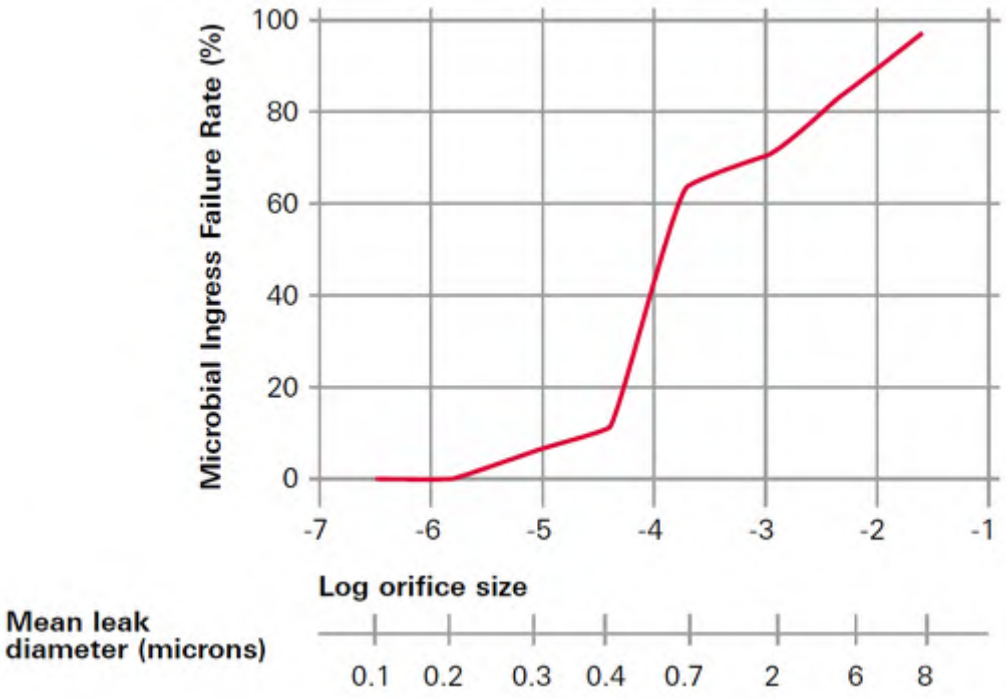
- (US FDA) obligation for “pharma” is that they must ensure “***the container-closure system to maintain the integrity of its microbial barrier, and hence the sterility of a drug product throughout its shelf life***”

- The key **sources** for ingress contamination are
  - **humidity (H2O)**
  - **oxygen and**
  - **Microbiological**

- Container integrity is also important to retain volatiles in your product

- Key guideline describing different test methods and selection process for sterile products is **<USP 1207>** published by the PDA

Microbial Ingress?



- Based on Lee Kirsch studies (presented in PDA J 51.5, 1997 p 195-202) the critical leak size for microbiological ingress is 0.2 µm
- The risk of contamination increases with defect size
- With a defect of 0.7µm the risk of contamination is already >60%
- Above 5µm the risk of contamination is >80%
- Only 2 test current methods available can detect <0.2 µm

Probabilistic Testing

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Blue Dye Ingress Testing

- the chance to detect a 10µm leak is only about 70%
- defects below 5µm are most likely not detected
- At 5µm our risk of contamination is >80%
- 0.2 µm is the ultimate target we aim for

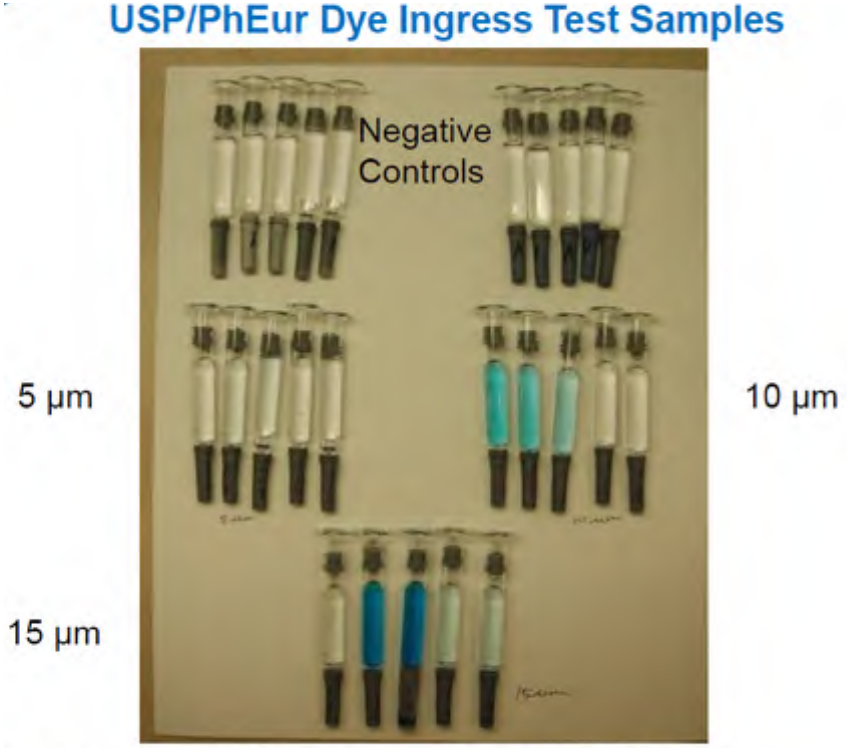
The detection limit of Blue Dye Tests varies with:

Technical:

Leak size, type, length, material of construction, type of blockage, tracer concentration, surface tension, cleanliness, tracer compatibility with product or immersion fluid

Operational:

Ambient temperature, ambient pressure, sample positioning, inspection conditions, operator training/skill, sample preparation



H. Wolf, T. Stauffer, S-Chen Chen, et al, PDA J Pharm Sci & Technol., 63, 2009, p. 489 - 498

USP 1207.2 (sterile products)

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Common "Technology Based" Test Methods

Leak Test Method	Measurement Outcome	Detection range
Tracer-gas (Helium Mass Spectrometry)	Helium flow (mbar.l/s)	<0.1µm to 10µm
Laser-Headspace (Frequency modulated spectroscopy)	[O_2] and/or [CO_2] (%) Gas pressure	<0.1µm to >50µm
AMI* (Optical Emission Spectroscopy)	Leakage (N_2, Ar, CO_2, H_20..) (mbar.l/s)	<0.5µm to >50µm
Mass Extraction (Micro/Mass flow sensors)	Mass Flow (µg/min)	>1.0µm to >50µm
HVLD (Leakage current)	Electrical current (µA)	>1.0µm to >50µm
Pressure Decay	Pressure drop (mbar/s)	>1.0µm to >50µm
Vacuum Decay	Pressure rise (mbar/s)	>1.0µm to >50µm

*not yet recognized in USP 1207, but has been presented on PDA conferences – emerging technology

3 Leak Detection Solutions

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MICRO-FLOW AND MASS EXTRACTION

Air micro-flow sensor

ASTM F3287-17

HELIUM MASS SPECTROMETRY

Magnetic deflection spectrometer

ASTM F2391-05

OPTICAL EMISSION SPECTROMETRY

Multi-gas analyser (N_2, CO_2, Ar, H_2O)

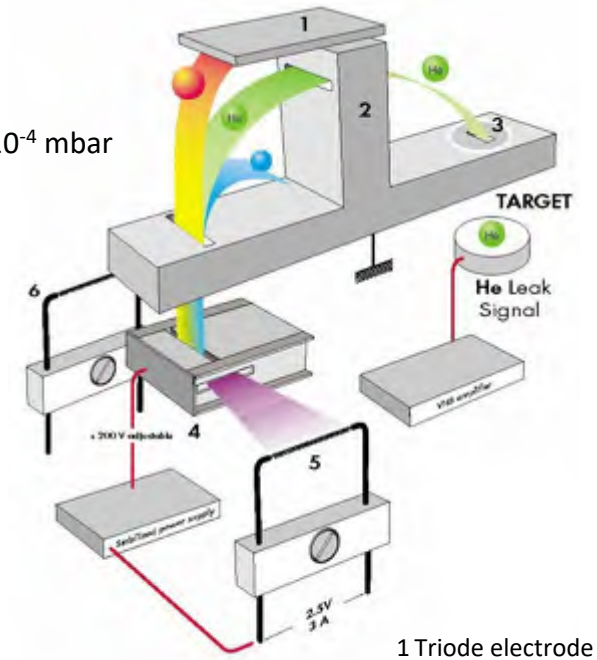
3 different technologies for CCIT solutions
→ because there is no one size fits all solution

- Non destructive test options
- Applicable for non-porous containers
- Global pass / fail test

Helium Leak Detection

- High Sensitivity and Quantitative
  - Mass Spectrometer (magnetic deflection)
  - Down to 10^{-10} mbar.l/s (sub-micron orifice)
- High Selectivity
  - Low natural background of 5 ppm (in air)
    - Sensitivity can be affected by background accumulation
  - High permeability, diffusivity & solubility
- Helium flows through cracks
  - Much smaller and faster than air

$P < 10^{-4}$ mbar



1 Triode electrode
2 Diaphragm
3 Braking electrode
4 Electron collector
5 Filament #1
6 Filament #2

ASM 2000

- Turn-key equipment dedicated for pharma
- Based on high performance helium leak detector
- All in one, including helium charging module
- PLC and HMI (3’’,5 touch screen)
- Customized test tooling according to the part to test
- Trolley includes all vacuum pumps
- Data storage / 3 access level / PDF test reports
- CFR 21 P 11 soon to be released

- *MALL TEST = Maximum allowable Leak Limit*
- *Global Pass & Fail*

R&D Testing with ASM 2000

Experimental Glass Bottle Cap Test - how to proceed ?

→ Helium injection inside the bottle must be controlled & performed during the test sequence

→ Leak testing must be performed before helium permeation appears (plastic)

ASM 2000 Test sequence:

1/. Start test on ASM 2000
2/. Bottle evacuation (remove air)
3/. Helium Charging (Patm)
4/. Helium test
5/. Helium evacuation
6/. N_2 venting/purge
7/. Stop test on HLD / Venting

Fully automated process, started with one button, settings can be customized

In production = non destructive test approaches

- Injection of He tracer gas prior to container closure
- "Bombing" Test – apply pressurized He

Non Destructive Helium Testing

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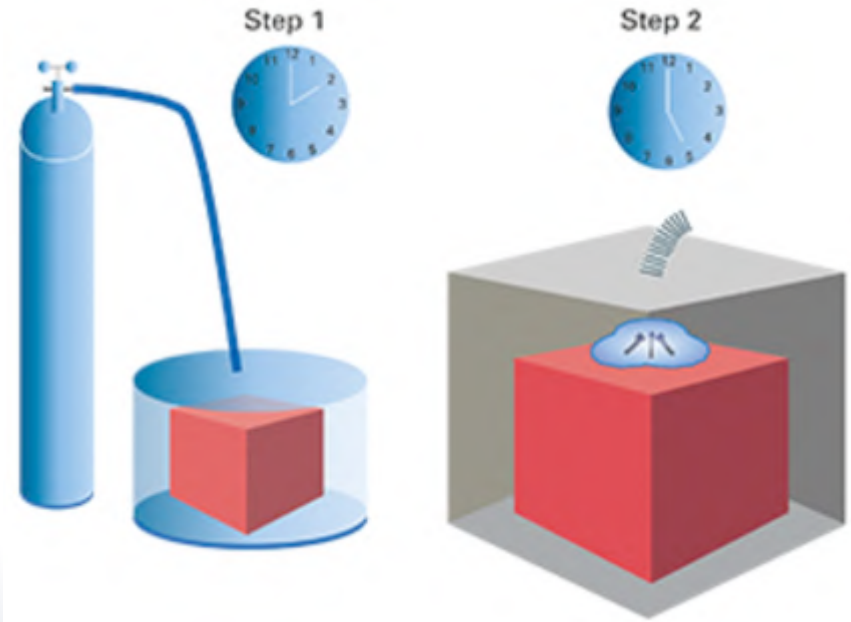
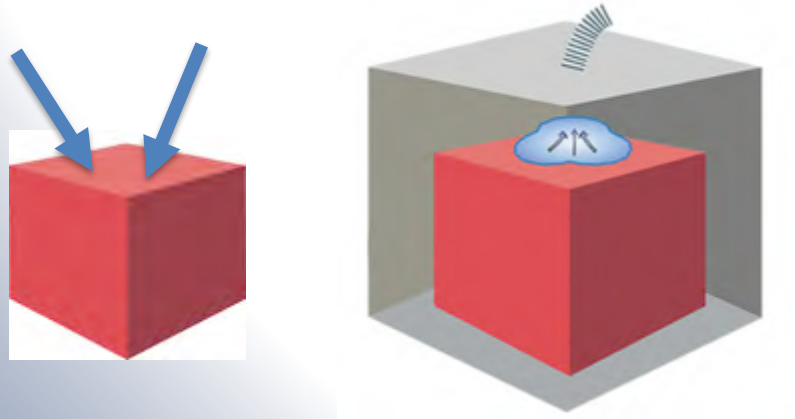
Container sealed



1) Bombard with helium tracer gas whilst sealed

2) Global vacuum pass & fail (MALL) test

Container open / unsealed for filling



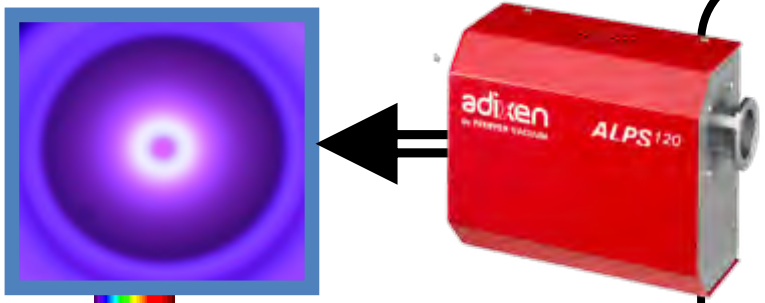
1) Inject helium tracer gas before sealing the package

2) Global vacuum pass & fail (MALL) test

Optical Emission Spectroscopy

A Plasma is the 4th fundamental state of matter = hot ionized gas (instable).

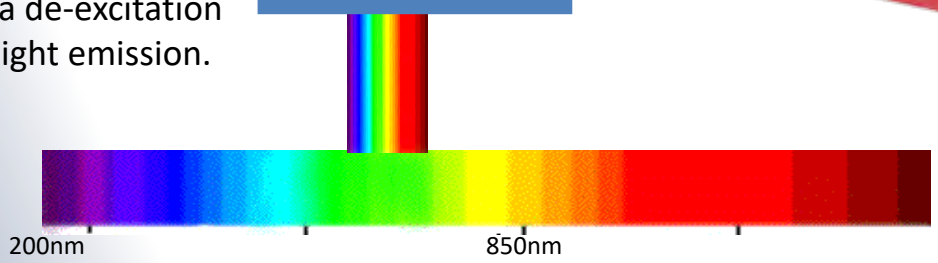
Plasma de-excitation gives light emission.

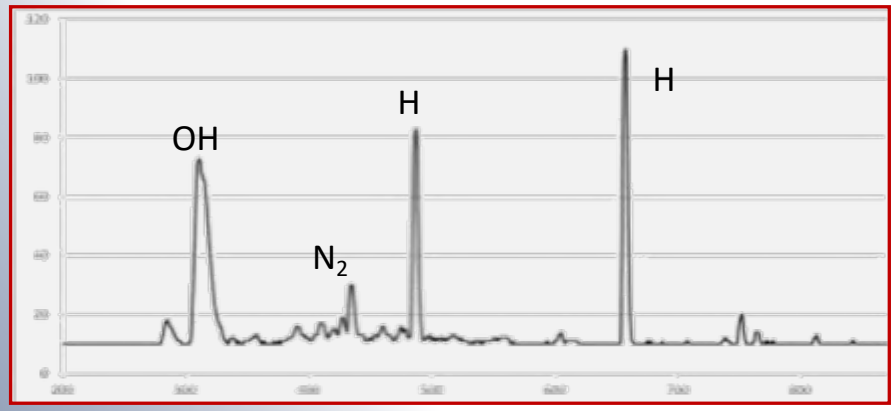


Test chamber (P<5.10^{-2} mbar)

Sealed component (N_2, Ar, CO_2…)

Q_{N2} (atm.cm^3/s)





patented OES multi-gas “ALPS” sensor

AMI 1000

- Detection limits / cycle times for different package types

Samples	Sensitivity Orifice diameter[3] Air/N_2 Leakage		Test duration	Advantages
	Air/N_2 leak	Water leak		
Blisters	0.4 µm $2 \cdot 10^{-5}$ mbar l/s	n.a.	> 20-30 sec	Highest sensitivity test method available on the market Outgazing of the drug itself can be used for gross leak detection Applicable to peeling blisters
Syringes & Vials	0.4 µm $2 \cdot 10^{-5}$ mbar l/s	2 µm	> 15 sec	Air and water detected simultaneously Test per batch to increase the troughput
	0.2 µm $6 \cdot 10^{-6}$ mbar l/s		~45 sec. (high sensitivity mode)	MALL level can be achieved in high sensitivity mode
IV bags	0.4 µm $2 \cdot 10^{-5}$ mbar l/s	3 µm	> 20 sec	Air and water detected simultaneously
Plastic bottles	0.5 µm $4 \cdot 10^{-5}$ mbar l/s	n.a.	> 20 sec	Test per batch (up to 50 or 100) to increase the troughput

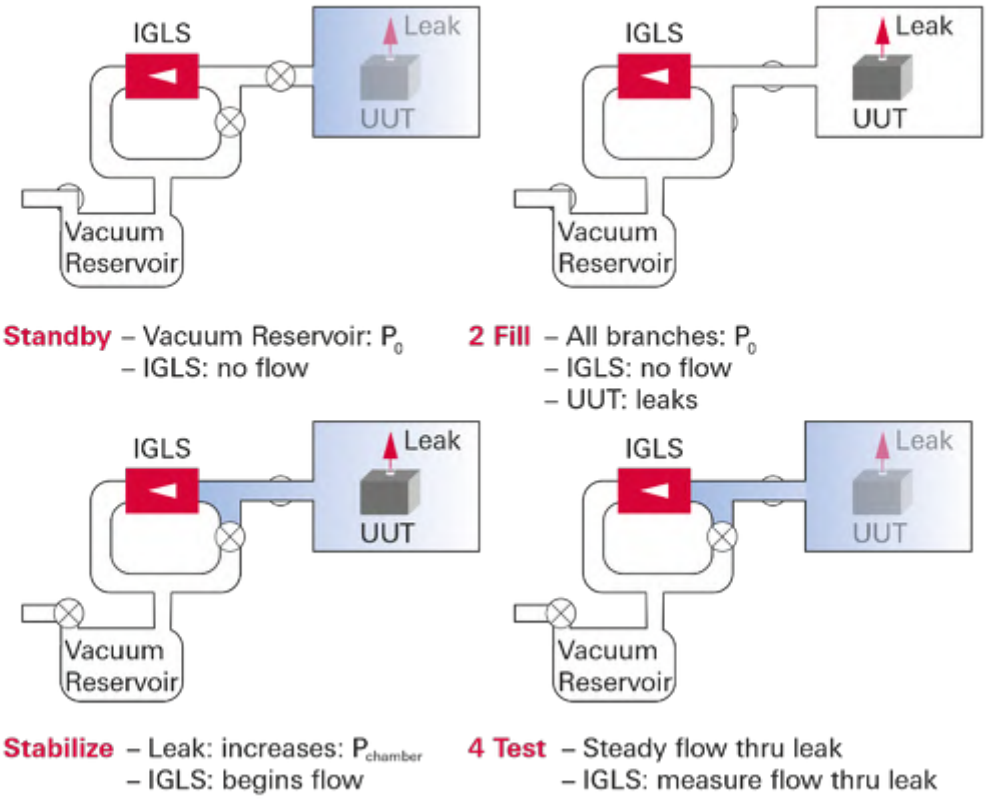
[3]Sharp edge orifice as defined in USP <1207> guidelines

- OES is unique amongst leak detection due to its ability to track various gases, moisture etc (N_2, H_20, Ar, $CO_{2...}$)
- Detection limits depends on tracked gas species
- All can be tracked simultaneously

Mass Extraction

- Measurement of mass flow rate from test chamber to a reference
- Flow equals defect (down to 1 um)
- Gas based – typically air or nitrogen
- For vacuum testing water vapour flow is used

Mass Conser-vation law: Mass extracted = mass leaked at steady state



Example IV Bag Testing

Storage area for laptop, packaging

ATC calibrated leak device (inside)

Vacuum System

Fillers for different bag sizes

Customized test chamber (IV-bag)

ME2 Integrity Test Unit

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Storage area for laptop, packaging

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ASTM F3287 − 17 (Mass Extraction) Result Extract

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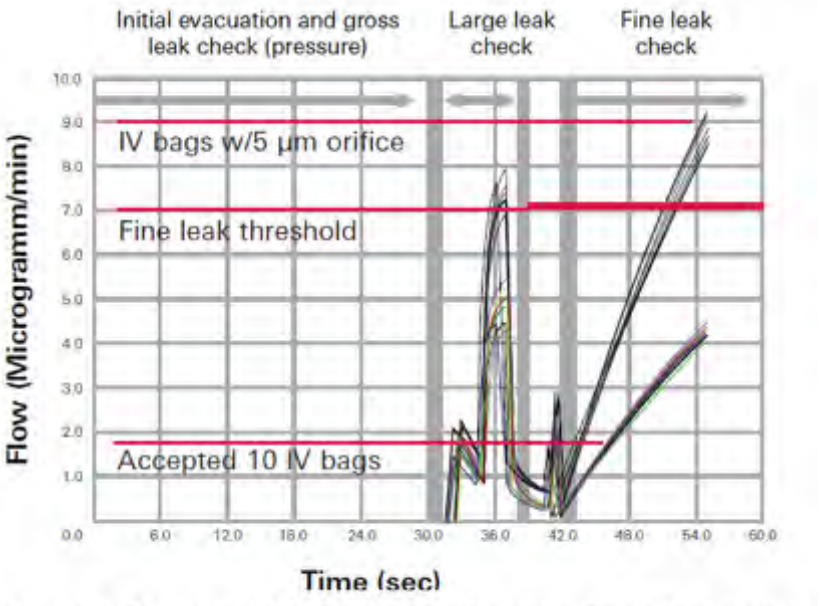
- Glass vials and LDPE Bottles Mass Extraction tests detected 1µm and 2µm defects at all labs and samples at over 95% confidence level
- Glass syringes Mass Extraction tests detected 1µm air filled syringes and 2µm air and water filled syringes at all labs and samples. 2µm were detected at a confidence level equal or greater that 95%

- 1µm liquid filled syringe plugged – suspected by silicon lubricant

	Package Description	Sample Qty.	Qty. of Tests	Qty. of Failed Tests	Qty. of Passed Tests	Success %
Glass Vial 2 ml	Liquid Filled – Negative Control	10	120	0	120	100 %
	Air Filled – Negative Control	10	120	0	120	100 %
	1 µm micropipette – Liquid Filled	3	36	36	0	100 %
	1 µm micropipette – Air Filled	3	36	36	0	100 %
	2 µm micropipette – Liquid Filled	3	36	36	0	100 %
	2 µm micropipette – Air Filled	3	36	36	0	100 %
	5 µm micropipette – Liquid Filled	3	36	36	0	100 %
	5 µm micropipette – Air Filled	3	36	36	0	100 %
	10 µm micropipette – Air Filled	3	36	36	0	100 %
LDPE Bottle 4 ml	Liquid Filled – Negative Control	10	120	0	120	100 %
	Air Filled – Negative Control	10	120	0	120	100 %
	1 µm micropipette – Liquid Filled	3	36	36	0	100 %
	1 µm micropipette – Air Filled	3	36	36	0	100 %
	2 µm micropipette – Liquid Filled	3	36	36	0	100 %
	2 µm micropipette – Air Filled	3	36	36	0	100 %
	5 µm micropipette – Liquid Filled	3	36	36	0	100 %
	5 µm micropipette – Air Filled	3	36	36	0	100 %
	10 µm micropipette – Air Filled	3	36	36	0	100 %
Glass Syringe 1 ml	Air Filled – Negative Control	10	120	0	120	100 %
	1 µm micropipette – Air Filled	3	36	36	0	100 %
	2 µm micropipette – Air Filled	3	36	36	0	100 %
	5 µm micropipette – Air Filled	3	36	36	0	100 %
	10 µm micropipette – Air Filled	3	36	36	0	100 %
	Liquid Filled – Negative Control	10	120	0	120	100 %
	1 µm micropipette – Liquid Filled	3	36	0	36	0 %
	2 µm micropipette – Liquid Filled	3	36	36	0	100 %
	5 µm micropipette – Liquid Filled	3	36	36	0	100 %

Example IV Bags- Inline Testing



Example Vial Batch

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Summary

- Scitek offers highly reliable DETERMINISTIC test methods for different kinds of pharmaceutical packages and drug types (liquid or solid) – applicable for…

and more…

- We offer project support including design of customized tooling, IQ/OQ support as well as FAT / SAT support
- All our tools are factory calibrated based on traceable leak standards
- CFR 21 part 11 compliant software is available for He and Mass Extraction testing

Whitepaper

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- Overview of existing CCIT Technologies (not all covered today)

	Helium Mass Spectrometry	O.E.S (Optical Emission Spectroscopy)	Mass Extraction	Vacuum Decay	Vision (Deflation)	HSA (Head Space Analysis)	HVLD (High Voltage)	Dye Ingress	Microbial Challenge
Deterministic	Yes	Yes	Yes	Yes	Yes	Yes	Yes		
Non-Destructive	(Yes) only for open containers	Yes	Yes	Yes	Yes	Yes	Yes		
Quantitative	Yes	Yes	Yes	Yes		Yes			
Sample preparation	He charging Plausability test	No sample prepiration				Storage time	No sample preparation	Immersion in dye or microbial media	
Test pressure	Vacuum					Atmospheric Pressure		Shallow Vacuum	Atmospheric Pressure
Detection range (Sharp edge orifice)	0.01< Q < 10 µm	> 0.2 µm	> 1 µm	> 5 µm	> 5 µm	> 0.01 µm	10-40 µm	> 20 µm	> 0.2 µm
Drug Product Limitations	Lyophilized (dry) or liquid drugs Plugging risk for small defects for protein based drugs					Lyophilized drugs	Conductive liquid drugs	Light colored drugs	–
Container Limitations	Container must handle 1 bar differential pressure Non-porous material He Permeation	High outgazing			Container Design (Semi-rigid or flexible)	Rigid & Transparent	Non-conductive material	Non-porous material	
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		Sensitivity depends on the product design: ▪ Headspace volume ▪ Size of the cavity ▪ Shape of the container Requires positive control to calibrate the equipment	Require gas headspace 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	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
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_2O, Ar, CO_2,...) Can test multiple containers with high sensitivity at the same time.	High sensitivity detection of water leakage Robust technology	Simple	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 thoroughput can be achelved	Very fast, high thoroughput can be achelved	Low cost equipment Easy to understand	Direct measurement of the biological contamination
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.	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	

Thank you

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