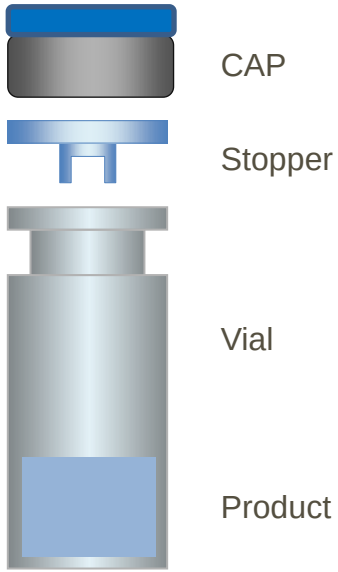
- Leak Detection

Session3

CCS Container Closure System

- In GSK Vaccines for Lyo Vials
- Lyo 3ml vials

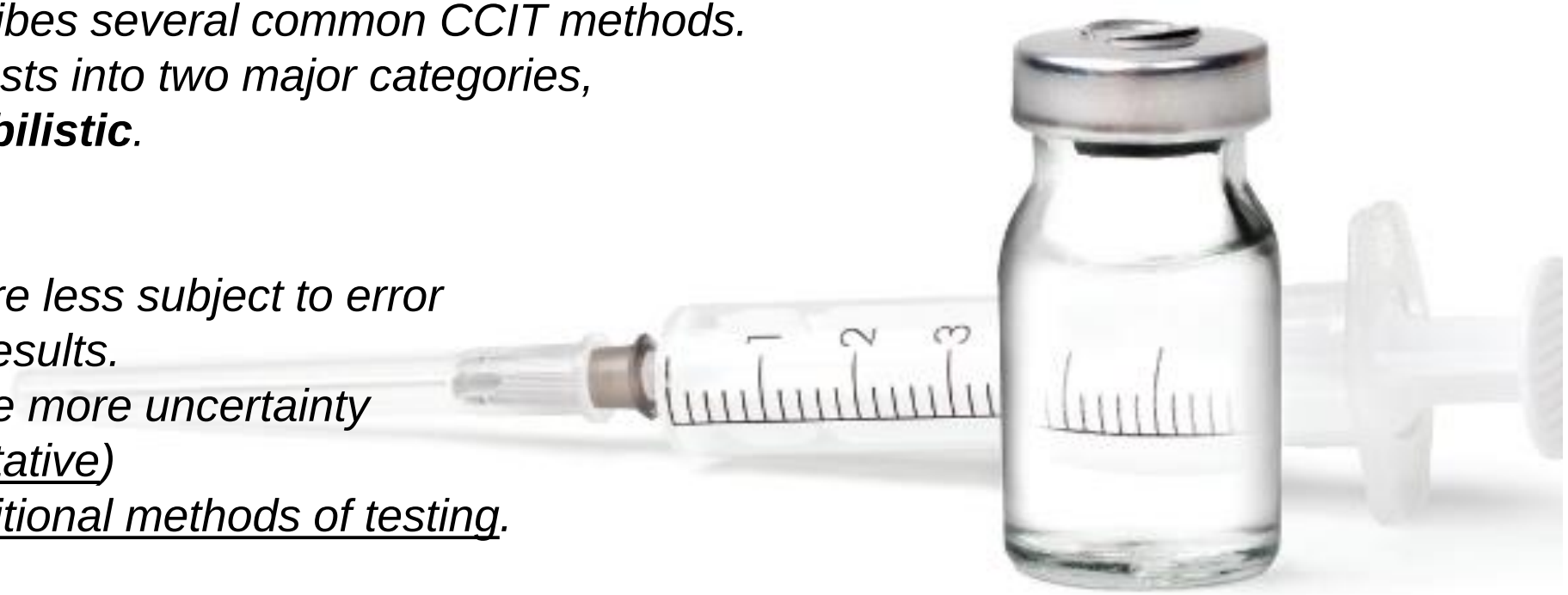


Lyo vial
CCS

Regulatory Landscape

Container Closure Integrity Testing (CCIT) evaluates the adequacy of container closure systems to maintain a sterile barrier against potential contaminants (USP <1207>).

USP <1207> series describes several common CCIT methods.
The chapter divides the tests into two major categories,
***deterministic** and **probabilistic**.*



***Deterministic** methods are less subject to error and provide quantitative results.*
***Probabilistic** methods are more uncertainty in the assay results (qualitative) and include the more traditional methods of testing.*

Regulatory Landscape

- (New Annex1 – Effective in Aug 2023)

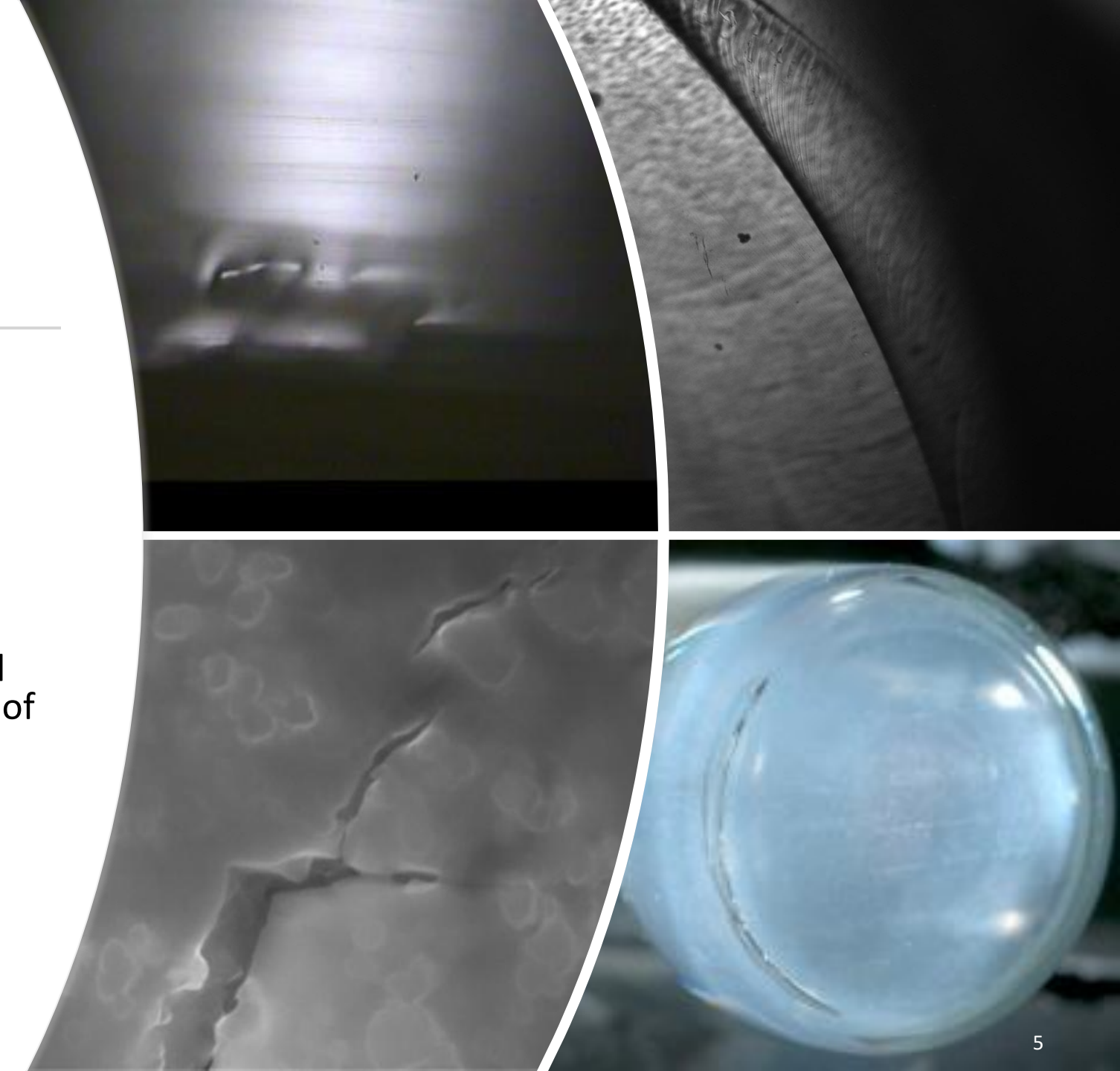
8.22 Where final containers are closed by fusion e.g. Blow-Fill-Seal (BFS), Form-Fill-Seal (FFS), Small and Large Volume Parenteral (SVP & LVP) bags, glass or plastic ampoules, the critical parameters and variables that affect seal integrity should be evaluated, determined, effectively controlled and monitored during operations. Glass ampoules, BFS units and small volume containers (≤100 ml) closed by fusion should be subject to 100% integrity testing using validated methods. For large volume containers (>100 ml) closed by fusion, reduced sampling may be acceptable where scientifically justified and based on data demonstrating the consistency of the existing process, and a high level of process control. It should be noted that visual inspection is not considered as an acceptable integrity test method.

8.23 Samples of products using systems other than fusion should be taken and checked for integrity using validated methods. The frequency of testing should be based on the knowledge and experience of the container and closure systems being used. A scientifically justified sampling plan should be used. The sample size should be based on information such as supplier management, packaging component specifications and process knowledge.

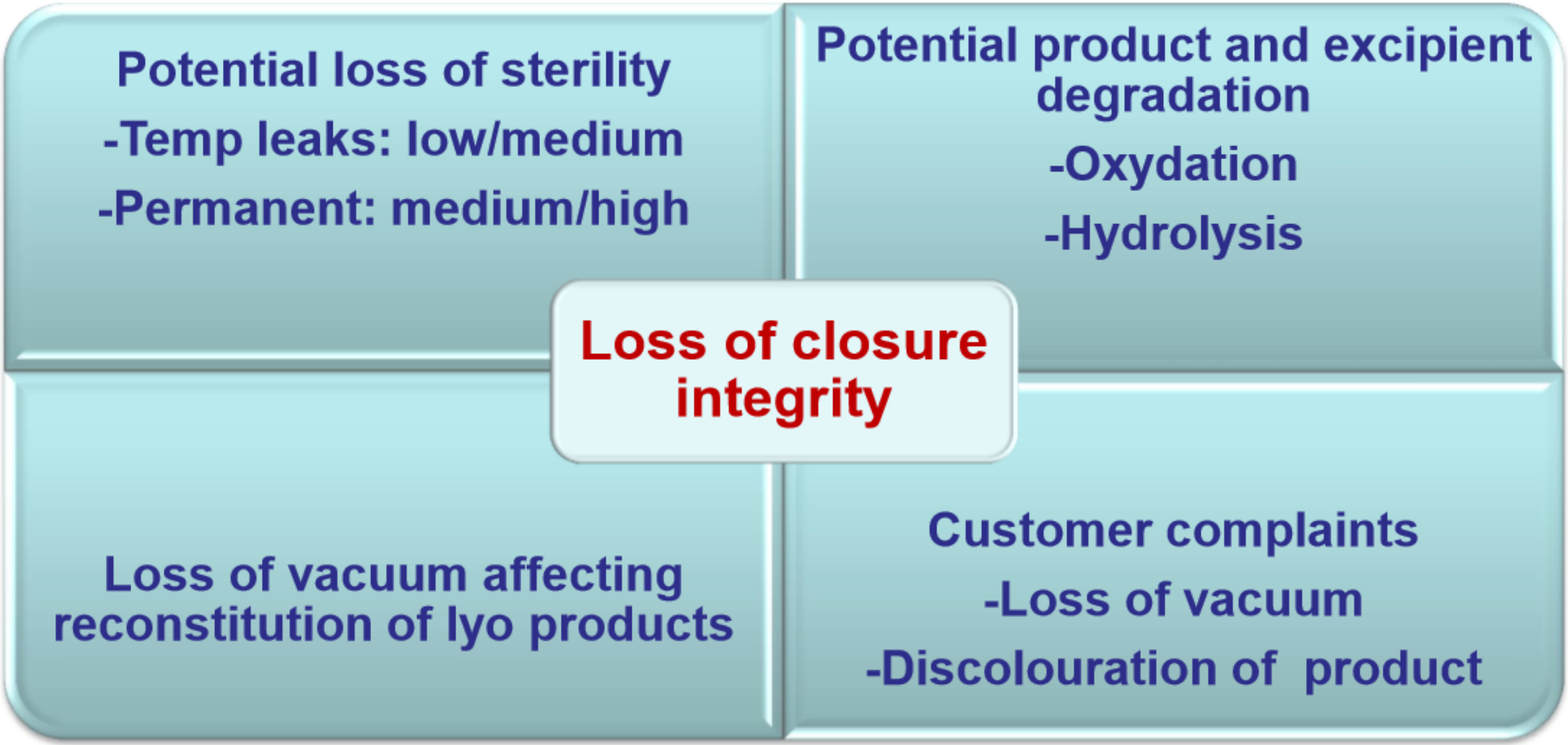
What is a Leak ?

- A leak can be described as a breach in a package wall, or a gap between package components capable of permitting the passage of gas or liquid.
- Leaks in glass are complex, multi-cavity tortuous paths.
- Associated risks to a leak can be potential loss of sterility, oxidation, hydrolysis, loss of vacuum affecting reconstitution of lyos, discoloration.

- A leak is measure in Mbar.L.s-1 or in STP conditions in CC/min



Risks associated with CCI failure



Leak detection - LoD

Be careful: a crack very visible may be a little leaking VS a crack less visible but very leaking.

VI

VI / dye test = probabilistic but dye test deterministic at 100% for 10µm.

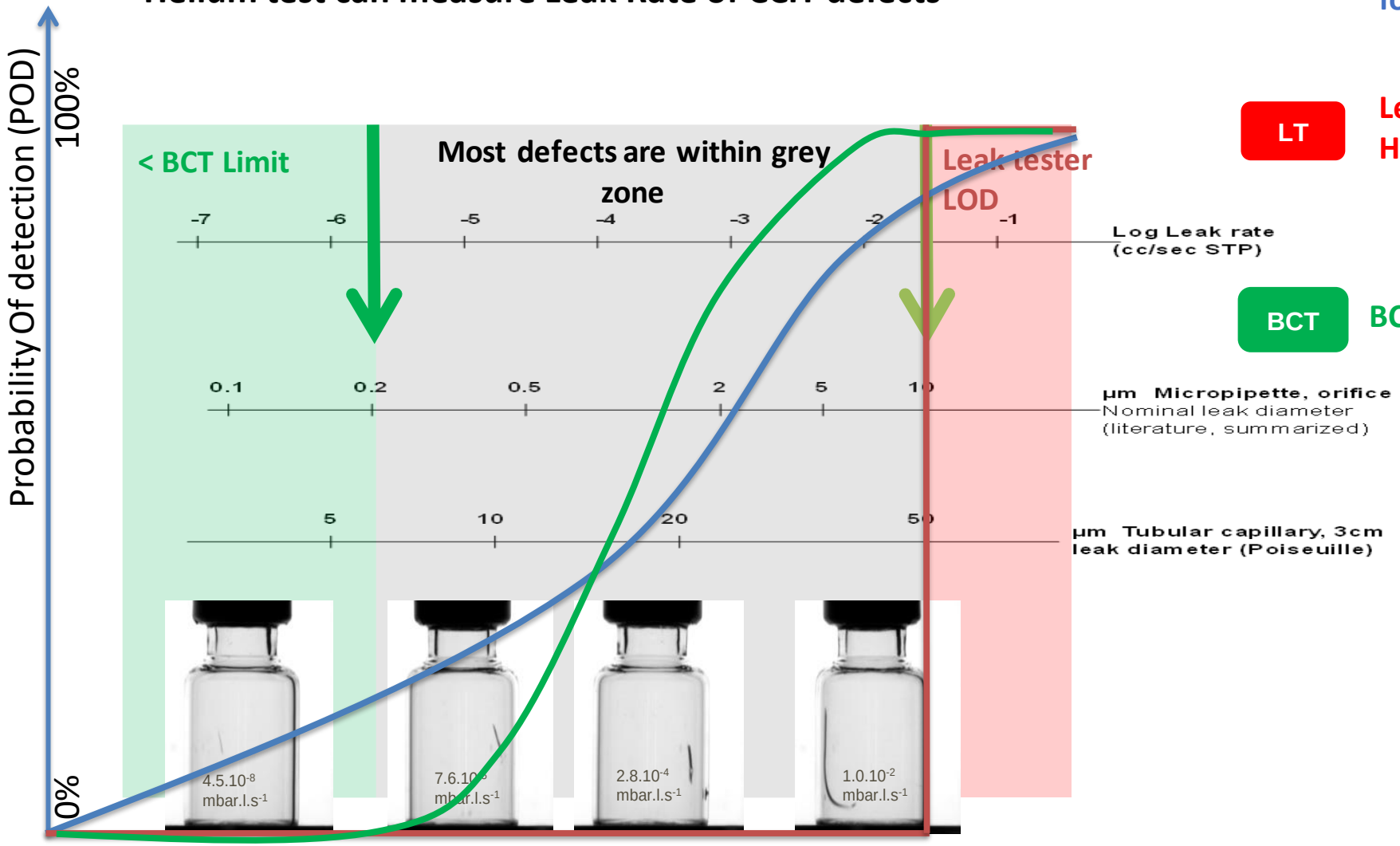
LT

Leak Tester Wilco or HSA = Deterministic

BCT

BCT = Deterministic

Helium test can measure Leak Rate of CCIT defects

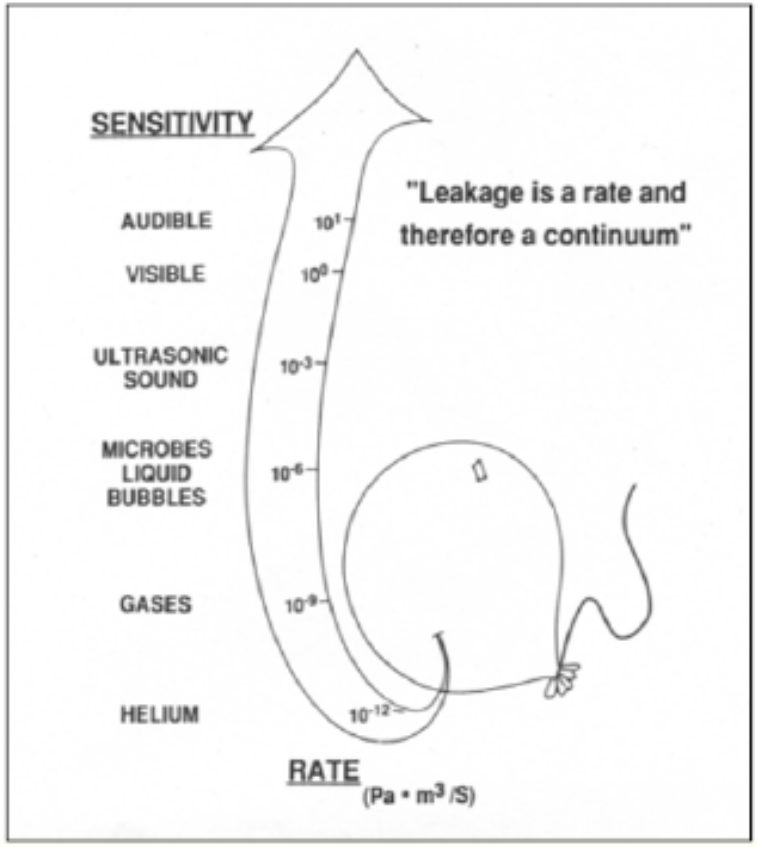


CCI Testing Technology Overview

Most advanced CCIT technologies rely on gas flow

– more reliable (for micron-size leaks)

– More predictable, some are quantitative

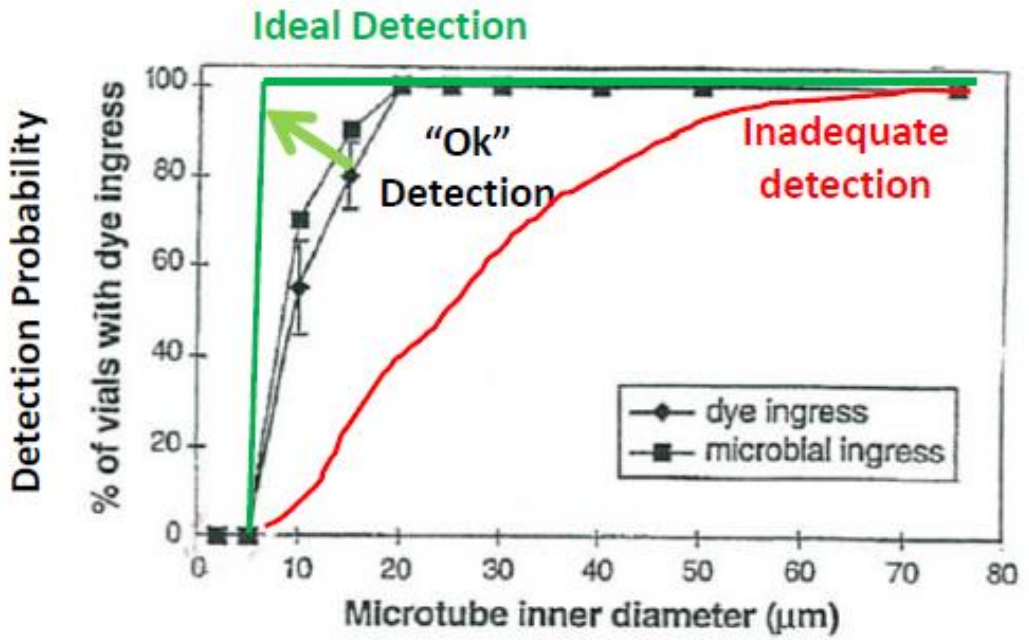


Smallest leaks **only** allow gas flow

Larger leaks **may also** allow liquid flow

Largest leaks **may also** allow microbial ingress

Detection of Leaks Critical to Microbial Ingress



Burrell L. S., et. al. PDA J Pharm Sci Tech 54, 449-455

Package Integrity and MALL

“A package with integrity”

Means that

*Gaps/breaches that **COULD** risk product quality are absent*

i.e., *The package meets the*

MAXIMUM ALLOWABLE LEAKAGE LIMIT (MALL)

****

What’s the difference?

Connecting People, Science and Regulation®

Maximum Allowable Leakage Limit (MALL)

is that smallest gap or leak rate that puts product quality at risk

(sometimes called the '***critical leak***')

Package Integrity and MALL

Sterile product package integrity (CCI)

Category	Leaks of concern	Product quality risks
1	Capable of allowing entry of microorganisms	Failure of product sterility
2	Capable of allowing escape of product dosage form, or entry of external of liquids/solids	Failure of relevant physicochemical quality attributes
3	Capable of allowing change in gas headspace content e.g., escape of nitrogen, loss of vacuum, entry of oxygen, water vapor, or air	Failure of relevant physicochemical quality attributes, And/or hindrance of product access by end-user.

Leak Detection Equipment

Current Technology Mapping available

as Leak Detection Equipment (YES = available / NO = not available)

Leak Detection Technology	AVI/MVI or SAVI	Pressure Decay	Vacuum Decay	High Voltage Leak Detection	HeadSpace Analyser
Liquid Syringe	Yes	No	No (Limited to bench)	Yes	No (Limited to inert gas)
Liquid Vial	Yes	Yes	Yes	Yes	No (Limited to inert gas)
Lyo Vial	Yes	Yes	Yes	No	Yes
Ampoule	Yes	No	No	Yes*	No
BFS / Tubes	No	No	Yes**	Yes*	No
Cartridge	Yes	No	No (Limited to bench)	Yes	No (Limited to inert gas)

** limited LOD with deformation/viscosity.
* limited LOD due to wettability conductivity.

Leak Detection Equipment

Pro & Cons for LD technologies

Leak Detection Technology	Principle	Advantage	Limitation
AVI / MVI (Seidenader, Brevetti, Bosch, Innoscan, …)		- Only technology to detect leaks in grey zone (>BCT but lower than 10µm). - Can detect liquid leaking cracks but also gas leaking cracks (very sensitive).	- Remains probabilistic (< 100% detection rate for small cracks). - Limited specificity (generates false rejects). - Low sensitivity for Lyo.
Pressure Decay (Wilco/Bonfig.)		- Deterministic method 100% Detection for leaks > 10µm. - Can only be used for Lyo and overfilled liquid vials.	- Can only detect leaks > 5-10µm
Vacuum Decay (Wilco/Bonfig.)		- Deterministic method 100% Detection for liquid & gas leaks > 10µm. - Can be used for Lyo and liquid vials (partial fill). - Can be used for tubes and BFS.	- Can only detect leak > 5-10µm - For Syringe, there is only offline benchtop not yet industrial machine. - Maintenance is complex

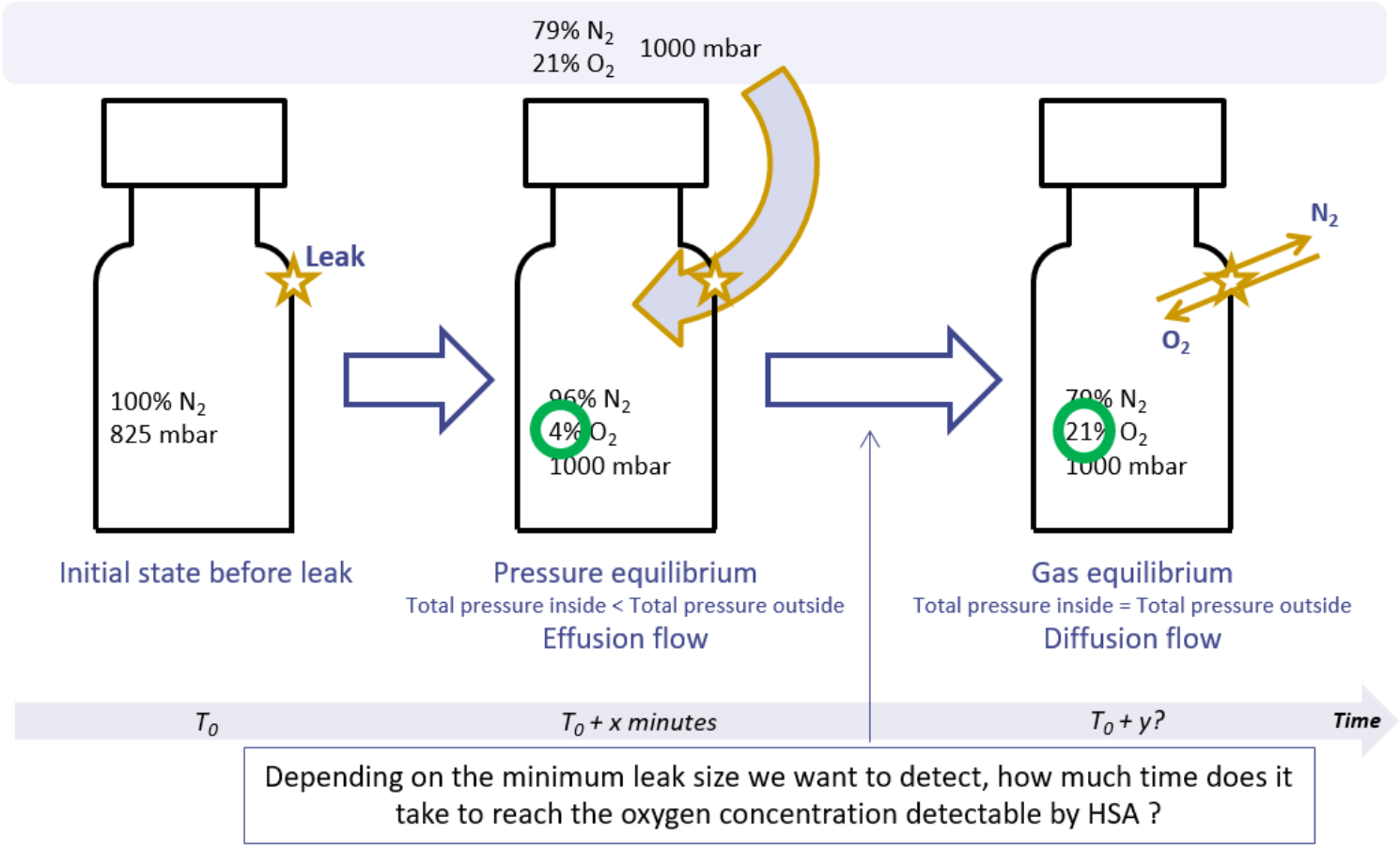
Leak Detection Equipment

Pro & Cons for LD technologies

Leak Detection Technology	Principle	Advantage	Limitation
High Voltage (Seidenader/ Brevetti / Bosch, …)	 High voltage detection of current shift with conductive liquid through leaking cracks.	- Deterministic method 100% Detection for liquid leaks. - Can be used for syringe and liquid vials. - correlated to leak size with calibrated laser holes	- Ozone generation that require product impact validation + non impact study per product. - Limited detection for small cracks - Wettability for long objects - Conductivity of product - Mechanical handling must be accurate in front of electrodes - Maintenance is complex
Head Space (Wilco / Bonfig. / Seidenader / Bosch Lighthouse/ Brevetti, Innoscan)	 Measure Oxygen ingress in leaking vials.	- Deterministic method 100% Detection for gas leaks. - Very sensitive method down to 1µm with holding time XX days product dependent. - As it test Oxygen ingress it is a good control for sensitive to oxidation products	- Limited to Lyo vials (or any inerted container). - Holding time minimum (can be few hours) before testing to allow ingress - Recalibration with reference O2 samples - Offsetting of measurement to avoid drifts

Leak Detection Technologies in detail

HSA challenge

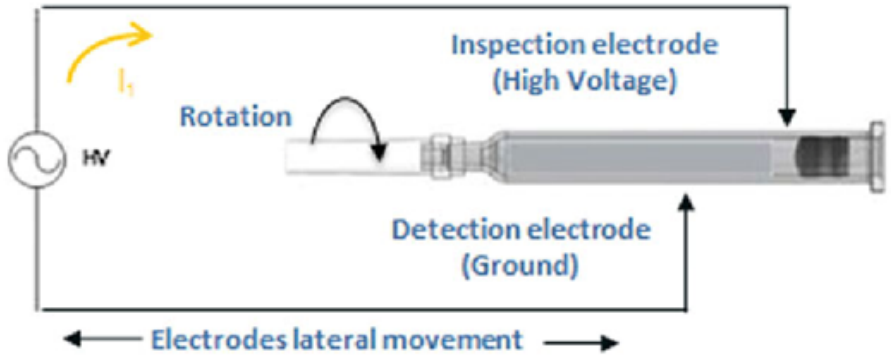


Leak Detection Technologies in detail

HVLD challenge

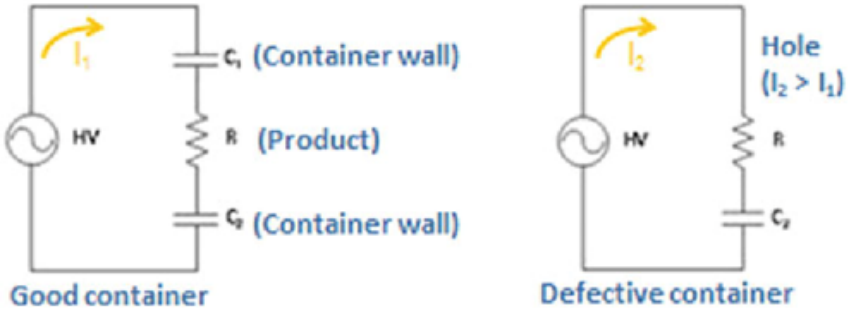
Principle: Based on **conducting electricity through materials** with different electrical conductivity.

- Requires that the container be made of electrical insulation materials such as **rubber, glass**, or plastic.
- Solution in the container should contain **conductive** substances.



A high voltage is applied on the container to pass through the inspection electrode.

Units are conveyed horizontally or vertically with rotation in front of multiple electrodes.



When a leak exists in a container, the flow (liquid) will move through the hole. The current that passes through the container and the **conductive** solution will then be collected at the detection electrode creating a peak ang higher value than a good container.

Leak Detection Equipment

RECAP

You have learnt

LT

- What is a leak
- How to measure a leak
- USP
- Annex1
- MALLS
- Vacuum decay
- Pressure Decay
- AVI
- HV
- HGA

LT

- Why do we still inspect sidewall cracks with AVI
- What does BCT mean
- What's the importance of MALL
- Can head space be integrated in AVI