Technology Overview

2020 PDA European Two-Day Training:
Container Closure Integrity Testing
for the Advanced Users

Wohlen, Switzerland
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Instructors:
Dr. David Riesop; AbbVie; david.riesop@abbvie.com
Horst Koller; HR Packaging Consulting GmbH; hk@hkpackaging.com
Dr. Matthias Kahl; Wilco AG; matthias.kahl@wilco.com

PDA Parenteral Drug Association

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Agenda

- Introduction
- Leak test method overview
  - Pressure and vacuum decay
  - Head Space Analysis
  - Mass spectroscopy (HE and other gases)
  - High Voltage Leak dDtection
  - Force Sensor
- Method selection and development
- Comparison of the methods
- Comparison of positive controls
- Practical examples

Abbreviations

CCI	Container Closure Integrity
CCIT	Container Closure Integrity Testing
CCS	Container Closure System
CLD	Cross Leak Detection
DP	Differential Pressure
FS	Force Sensor
HSA	Head Space Analysis
HVLD	High Voltage Leak Detection
IPC	In-Process Control
LFC Method®	Liquid Filled Container Method (vacuum decay)
MS	Mass Spectroscopy
RSF	Residual Seal Force
TM	Test Methods

The role of the CCS

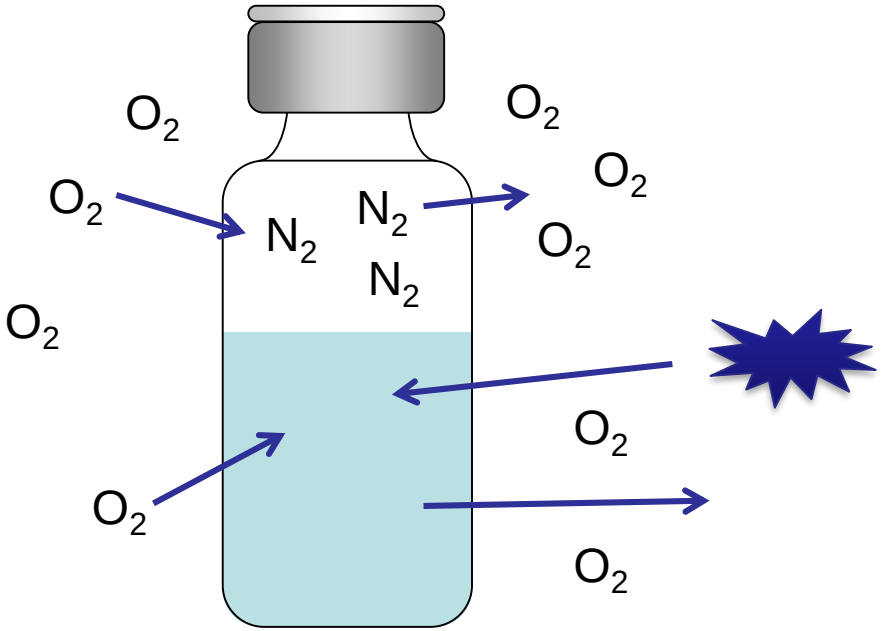
The ability of the container-closure-system to maintain the integrity of its microbial barrier, and, hence, the sterility of a drug product throughout its shelf life, should be demonstrated.

Source:
Guidance for Industry - Sterile drug products produced by aseptic processing - Current Good Manufacturing Practice

Definition: Sterile Product Package Integrity

"Sterile product–package integrity" is the ability of a sterile product container–closure system to **keep product contents in, while keeping detrimental environmental contaminants out**.

These contaminants may include **microorgansims, reactive gases, and other substances.**



- **Oxygen Ingress**
- **N_2 Loss**
- **Product Loss**
- **Microbial Ingress**

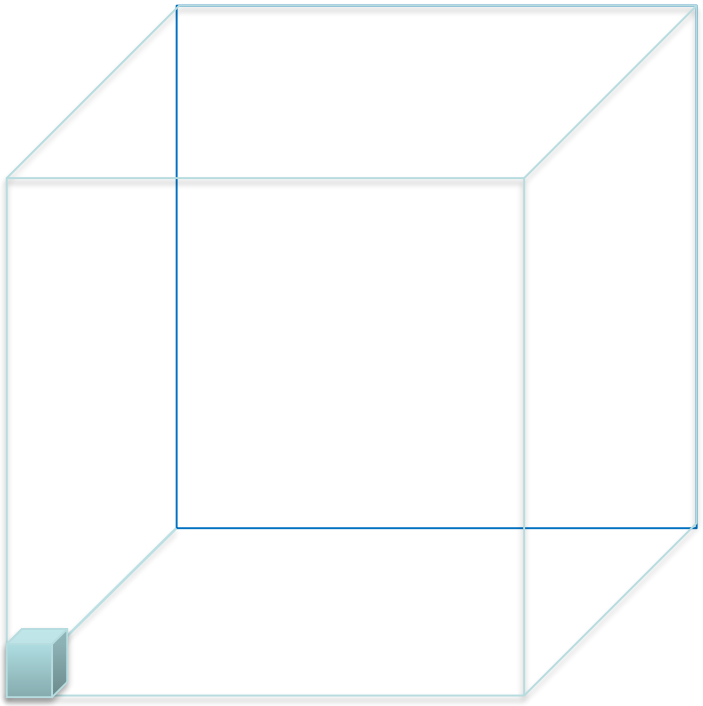
Source: USP<1207>

Definition: Leak and Leakage

- **“Leaks” are commonly perceived as holes of a certain diameter**, or channels of a certain diameter and length.

- **“Leakage” is a measure of the rate of gas flow** (in mass or volume units) that passes through a leak path under specific conditions.

Unit for Leakages



The leakage of **1 [mbar x l) / sec]** is given when the pressure in a closed container of **1 liter** rises or falls within **1 sec by 1 mbar**.

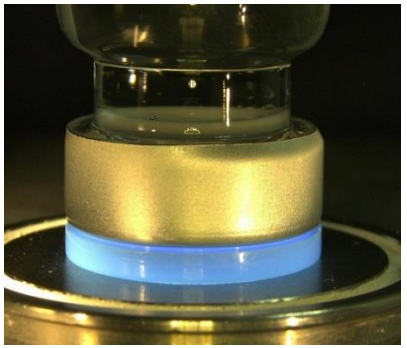
Making leakage “visible” – bubble test

Positive control sample pressurized with 1000mbar
Leakage measured in cc/min => mbar*l/sec => diameter of orifice in microns

Capping Associated Issues

Examples of defects
Scratches on vial neck, crimp cap wrinkles, scratches on the crimp cap
Partially crimped vials
Dimpling rubber stoppers
Removal of the crimp cap upon flip-off button removal
CCI failure because of low stopper compression

Partially crimped vials:

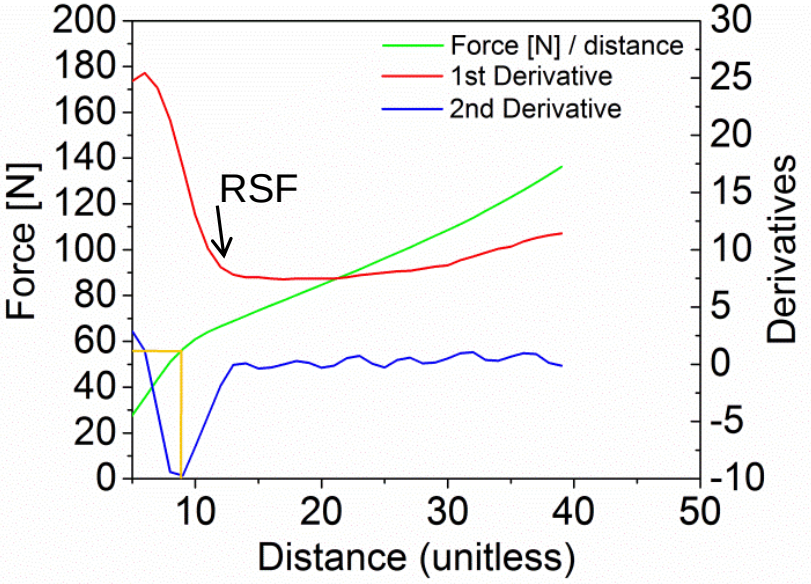


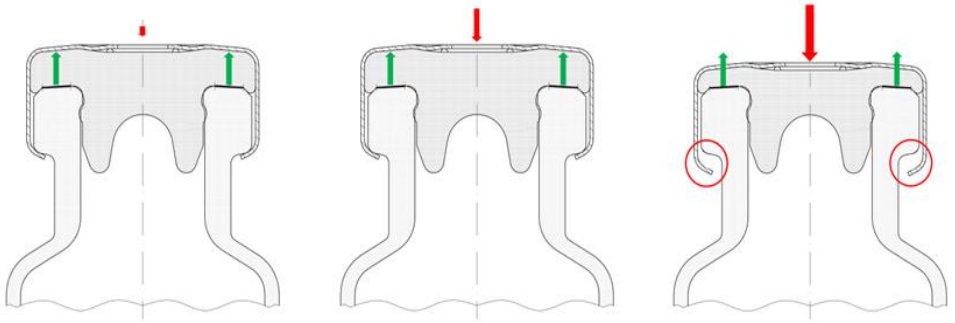
Dimpling:

Source: Lonza, Basel

Residual Seal Force

- The RSF tester measures the force / distance curve (green line).
- The RSF (56 N, yellow line) is derived from the minimum of the 2nd derivative of the force / distance curve.





Source: Lonza, Basel

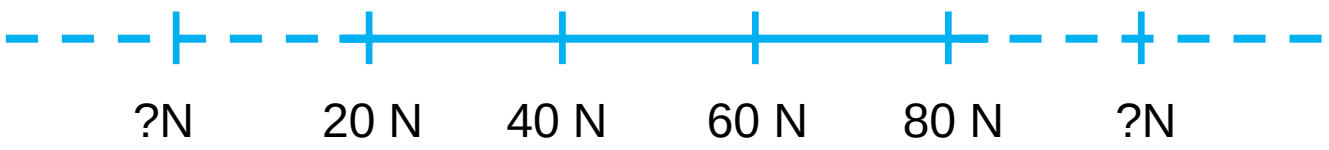
Defining an adequated RSF range for a CCS

- Vials capped with different capping equipment settings
- Measure RSF and use extended characterization methods
- Define a safety margin
- Define a secure RSF range for each CSS configuration
- Run commercial capping equipment in the secure RSF range

CCI or microorganism tightness not assured
Partially folded crimp cap

Secure RSF range

Stopper dimpling / rupture
Wrinkled crimp cap



Source: Lonza, Basel

Probabilistic vs. Deterministic CCIT USP acc. to USP<1207>

Probabilistic method	Deterministic method
Leakage is based on unpredictable, random events	Leakage is based on predictable fluid flow mechanics (gas/liquids)
Leak detection often relies on human interpretation	Leak detection relies on PC technologies
Mostly destructive	Non- destructive
Difficult to validate	Validatable, objective quantitative data
Not reproducable, random outcomes	Reproducable, monitored, controlled
Examples: Blue-dye test Bubble test Microbial ingress	**Examples:** Vacuum/pressure decay Head Space Analysis High Voltage Tracer Gas (e.g. Helium)

CCIT Technology Overview

Differential pressure (DP)

Pneumatic method

Permanent leaks

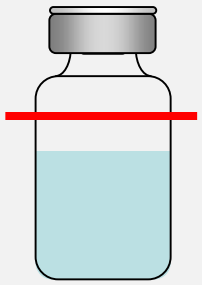
Instant testing possible

Head Space Analysis (HSA)

Laser absorbtion spectroscopy

Permanent & temporary leaks

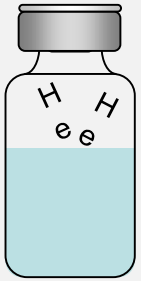
Requires a modified headspace



Mass spectrometry (MS)

Requires tracer Gas

Permanent leaks
Instant testing possible

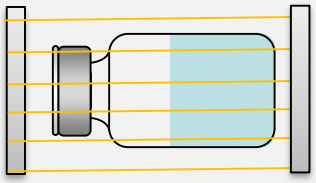


High Voltage (HVLD)

Differential current

Permanent leaks

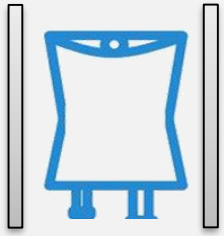
Instant testing possible



Force Sensor (FS)

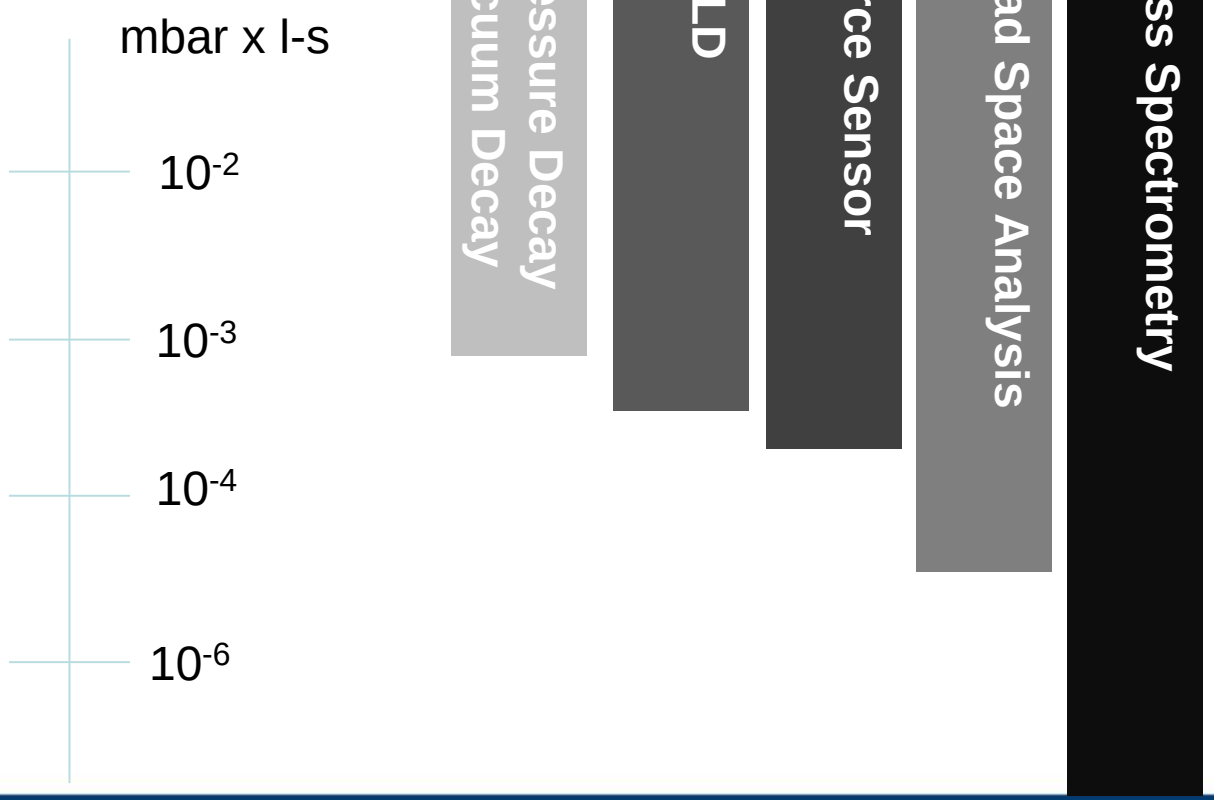
For flexible packaging
Regular vs. Vaccum mode

Permanent leaks
Instant testing possible



Sensitivity of the Test Methods

General definition
Water tightness
Vapor tight
Bacterial tight
Virus tight



CCIT Technology Overview

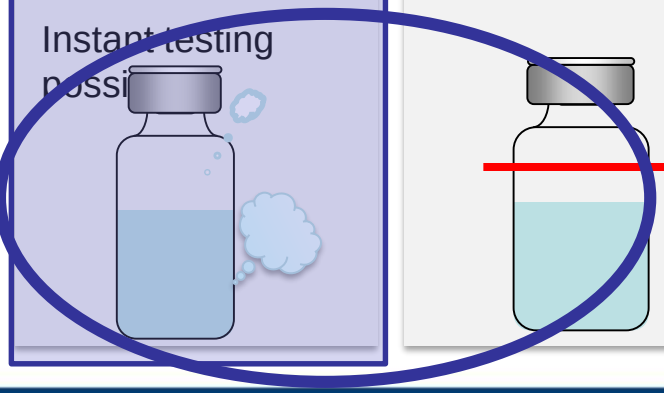
Differential pressure (DP)

Pneumatic method

Permanent leaks

Requires a headspace or liquid that vaporizes

Instant testing possi



Head Space Analysis (HSA)

Laser absorbtion spectroscopy

Permanent & temporary leaks

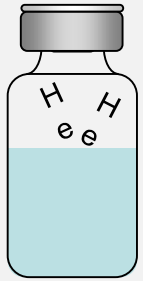
Requires a modified headspace

Mass spectrometry (MS)

Requires tracer Gas

Permanent leaks

Instant testing possible



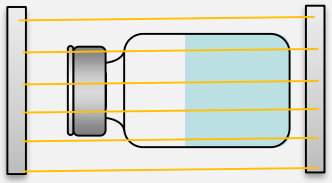
High Voltage (HVLD)

Differential current

Permanent leaks

Conductivity of liquid required

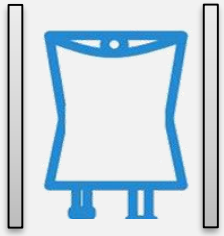
Instant testing possible



Force Sensor (FS)

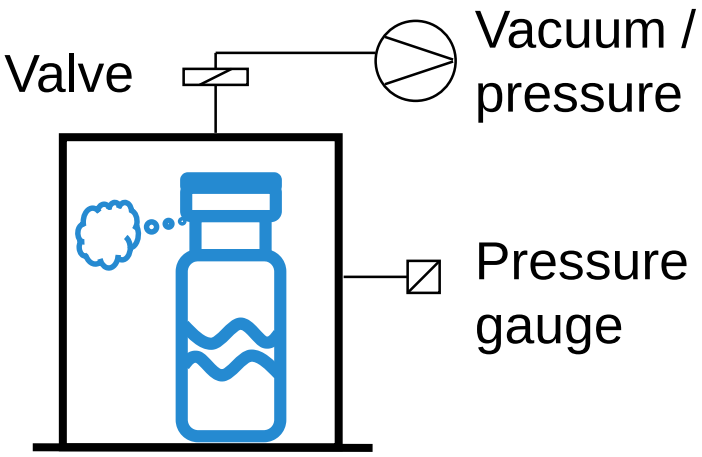
For flexible packaging Regular vs. Vaccum mode

Permanent leaks Instant testing possible



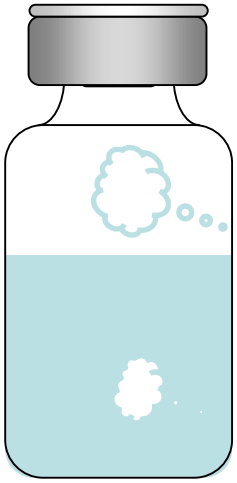
Pneumatic TM: Working Principle

- Samples is in a sealed chamber
- Either vacuum or pressure is applied to the chamber
- Sensitive sensors monitor the pressure conditions in the chamber
- If any gas exchange takes place with the sample pressure conditions will change and thus indicate a leak.



Pneumatic TM: Working Principle

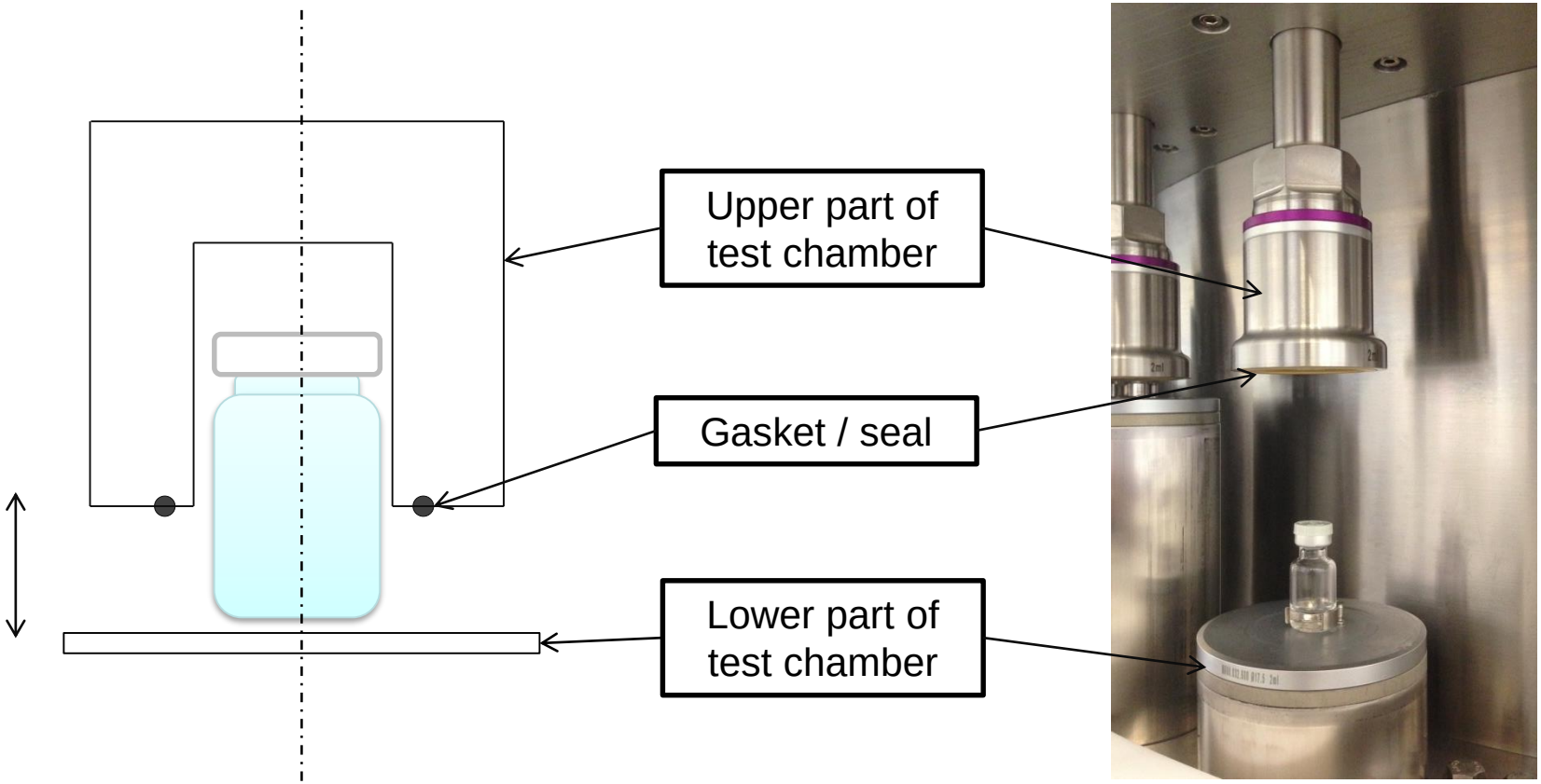
Pressure decay (P)



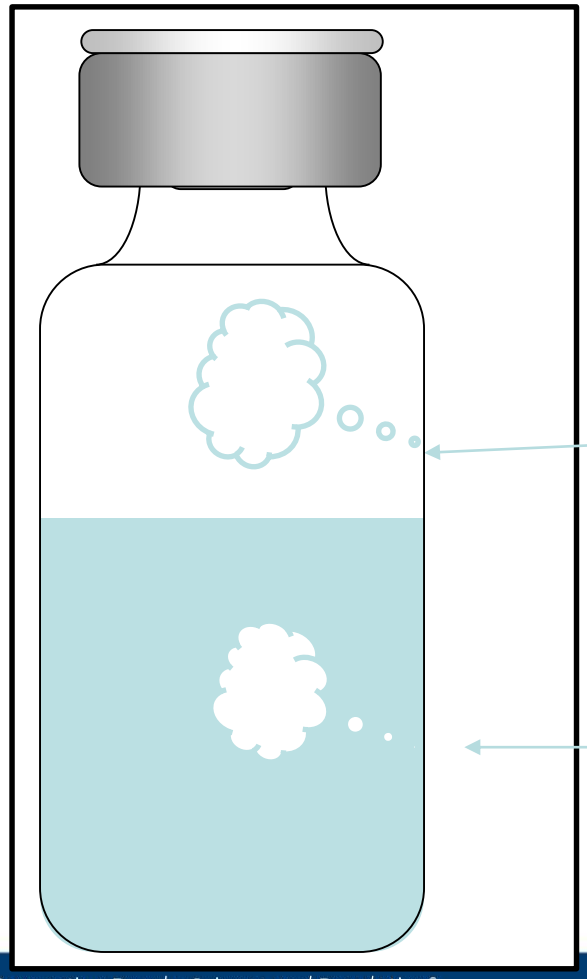
Vacuum decay (V)

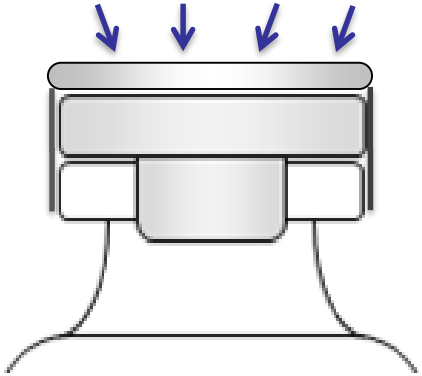
Deep vacuum with vaporization (LFC method®)

Pneumatic TM: Working Principle



Vacuum Decay TM: Working Principle

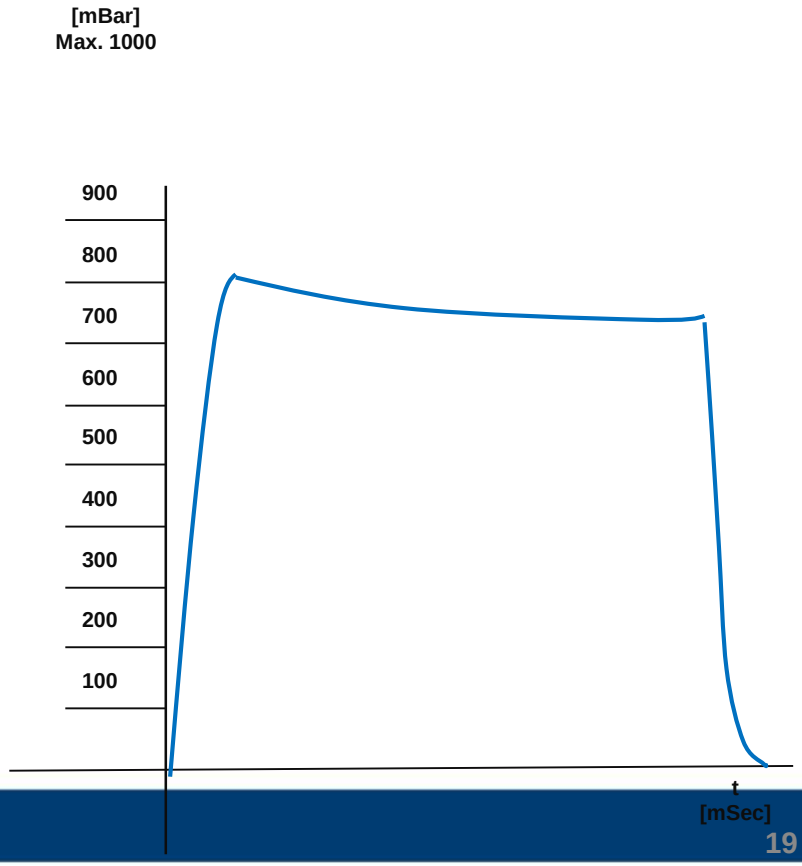




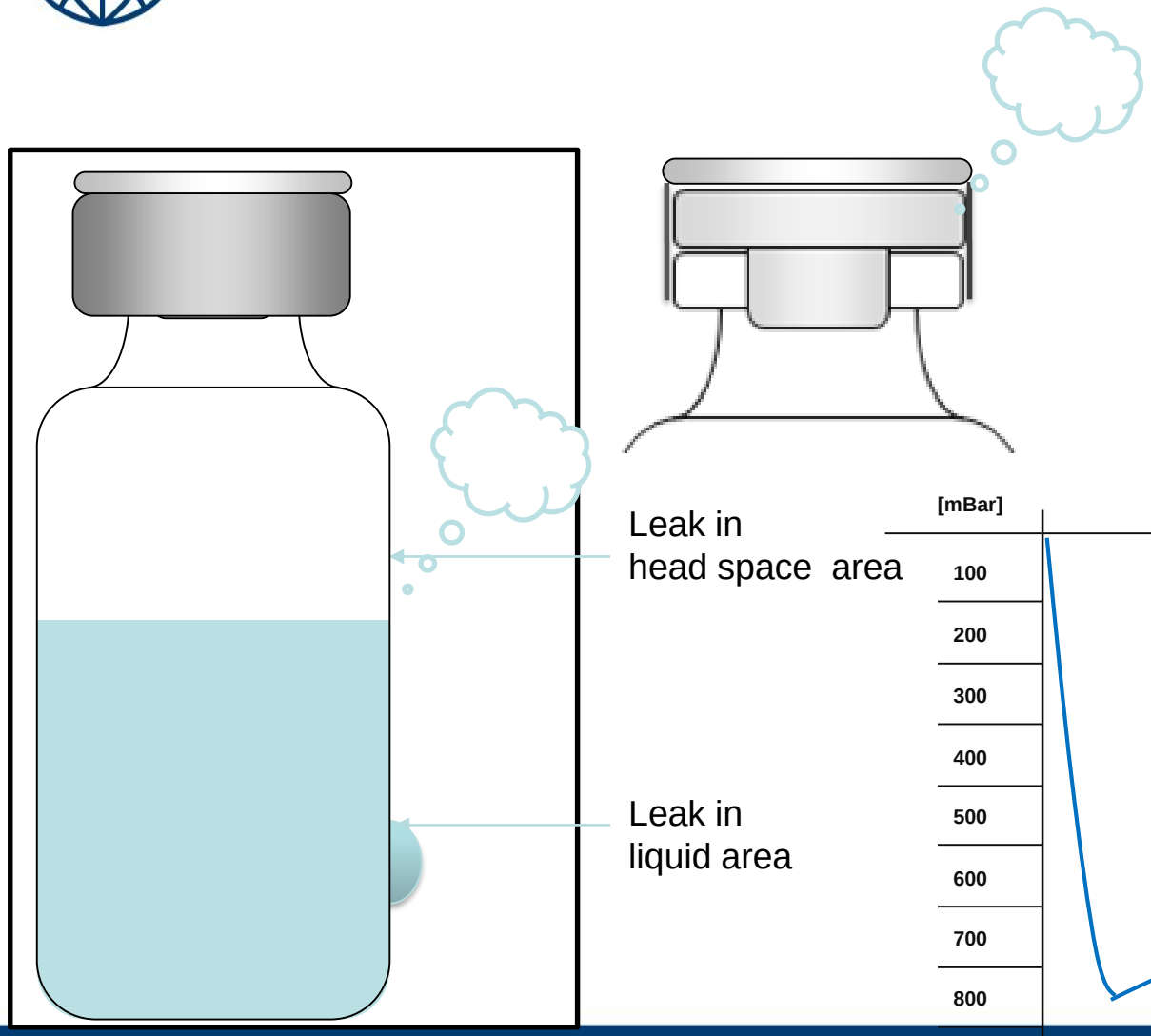
Pressure on crimp and stopper
=> Impact on primary sealing

Leak in
head space area

Leak in
liquid area

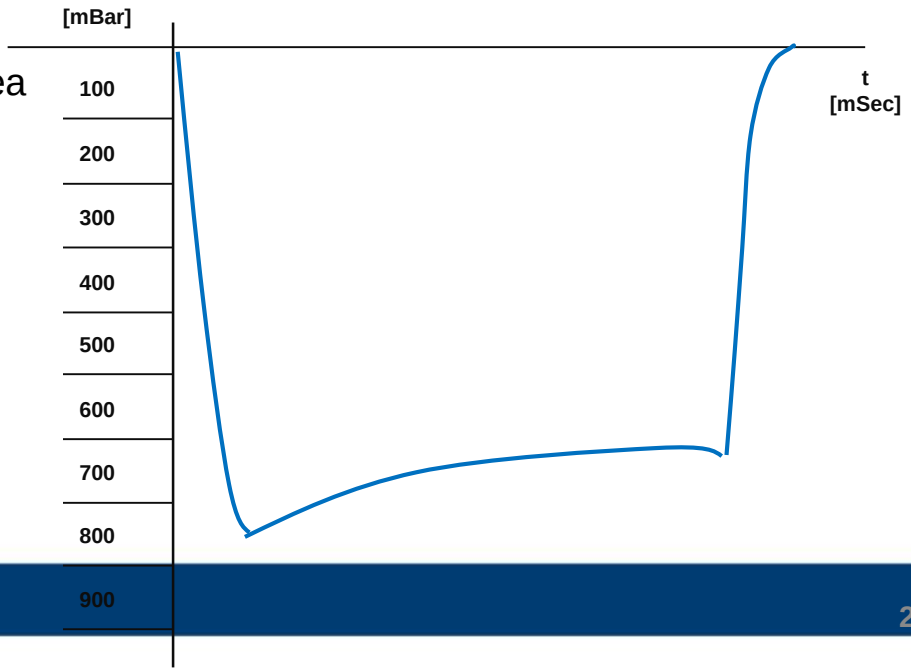


Vacuum Decay TM: Working Principle

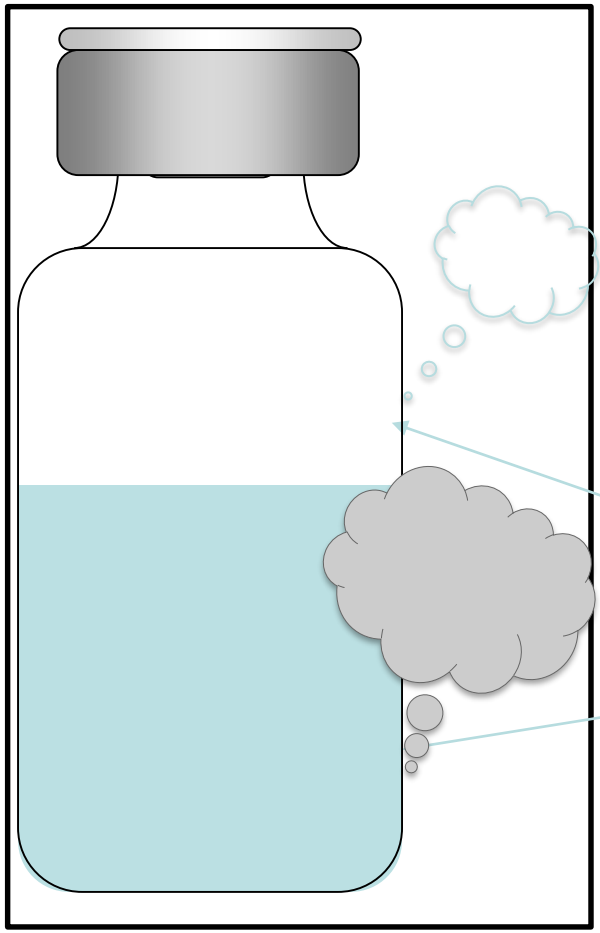


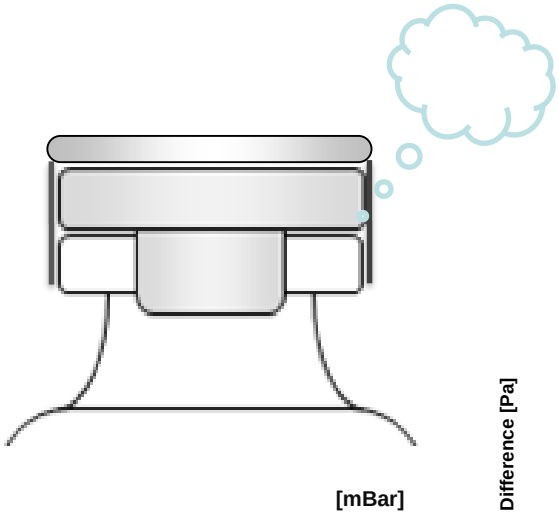
Leak in
head space area

Leak in
liquid area



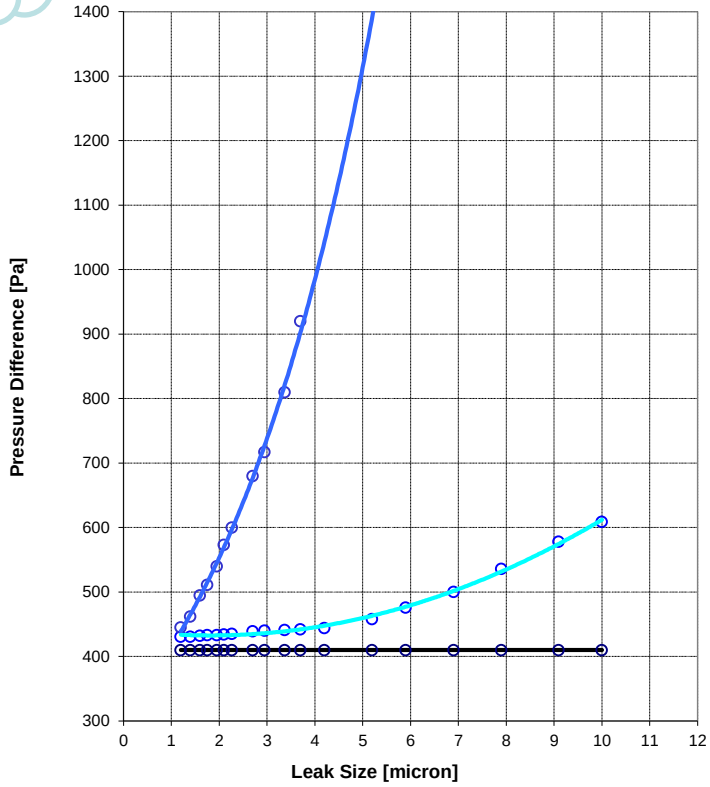
LFC Method®: Working Principle





Leak in head space area

Leak in liquid area

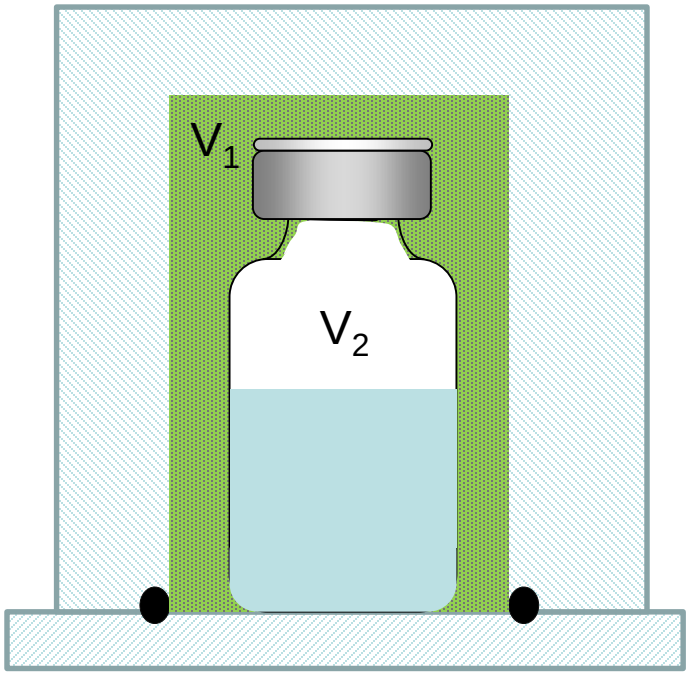


Test chamber evaporated below maximal water vapor pressure (20°C at 23.4 mbar absolute)

CLD of Vials: Working Principle

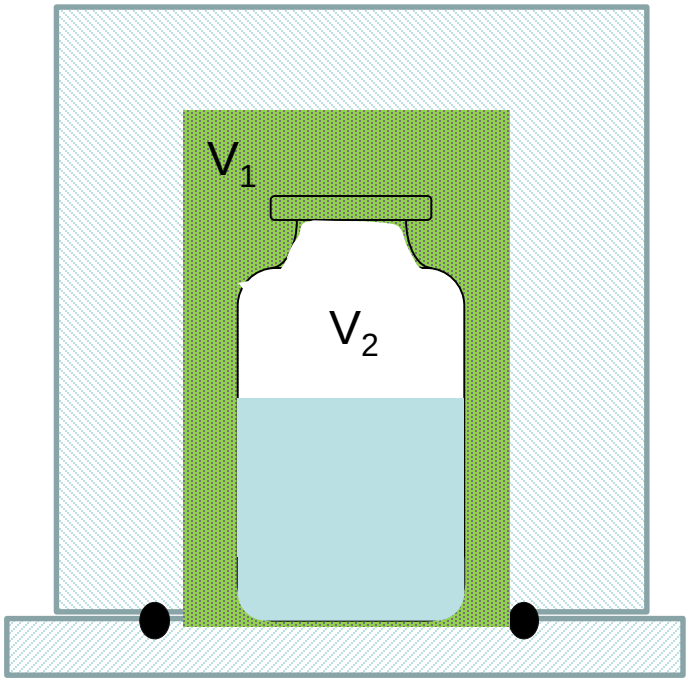
Vial without gross leak

$V_{test} = V_1$



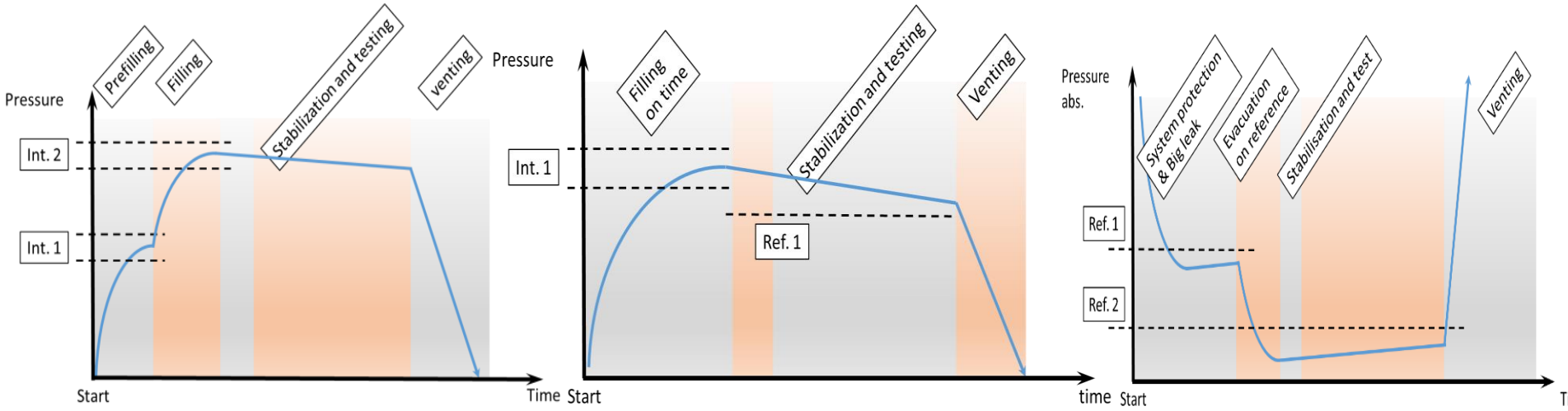
Vial with gross leak

$V_{test} = V_1 + V_2$



Pneumatic TM: Testing Cycles

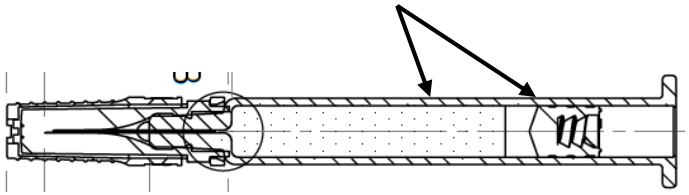
- Test cycle is adjusted to indivual package and product
- Testing time may vary from 2 to 15 seconds
- Depending on leak sensitivity and container size
- Machine size varies depending on testing time
- Output of up to 600/min

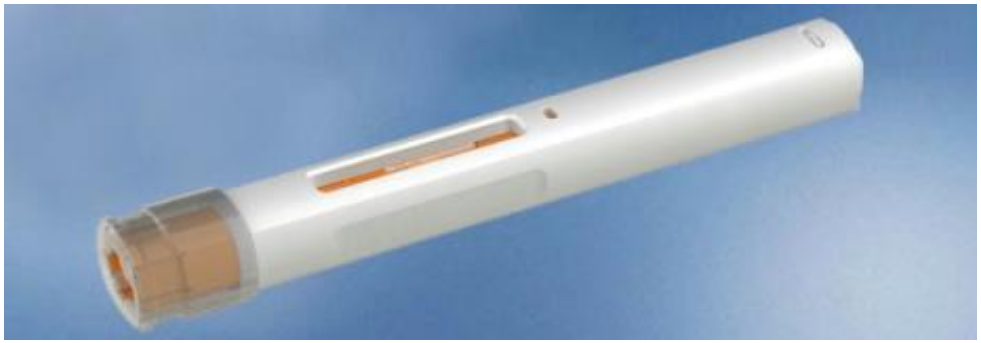


DP Measurements on Autoinjectors

- LFC method® for testing the mounted syringes
- Different head space / fill volume ratios
- Different initial positions of stoppers
- Artificial leaks in headspace and filled part with 10, 20, 30 micron leaks
- Verification of leaks using Helium leak testing

Syringes with laser drilled holes





Results:

- LFC method® is suitable for testing syringes assembled in auto-injectors
- Auto-injector design plays an important role
- Filling height, head space and stopper position impact feasability
- In the head space are 20 micron leaks could be detected
- In the liquid part 10 micron leaks could be detected

Laboratory Testing Equipment

Key Benefits

- Versatile use in terms of packaging and product types and sizes
- Three DP measuring technologies in one system
- Improved sensitivity of the DP measurement technology
- User friendly design of sample handling and HMI
- Intuitive operator support by LED status bar
- Customizable interface by means of widgets
- Enhanced recipe management system
- Deterministic test method preferred acc. USP<1207>

Additional Features

- One-hand operation
- Operator guidance system
- Simplified connection to SCADA/MES systems
- Enhanced batch handling system
- Simple format changeover
- Integrated UPS for prevention of data loss

DP Inline System for Vials and Ampoules

Key Benefits

- Up to 600/min
- From 1ml up to 250ml container on same system
- Sensitivity of down to 5 microns
- Non-destructive test method
- Applicable for liquid, powder and lyo products
- Applicable for Vials and ampoules
- Deterministic test method preferred acc. USP<1207>

Additional Features

- Integration of additional technologies (NIR/HSA)
- Simple format changeover
- Integrated UPS for prevention of data loss

Pro's and Con's of Pneumatic CCIT Methods

- Quantitative determination of leakage
- No modified headspace required
- No conductivity of liquid required
- High sensitivity
- Entire product is tested
- Applicable for liquid and lyo products
- No impact on product
- Applicable for alcohols
- Wide range of applications and sizes
- Combination of technologies possible

- Gas flow required (permanent leaks)
- Clogging effect needs to be considered
- Changing pressure may impact the leak
- Not all products may be vaporized

CCIT Technology Overview

Differential pressure (DP)

Pneumatic method

Permanent leaks

Requires a headspace or liquid that vaporizes

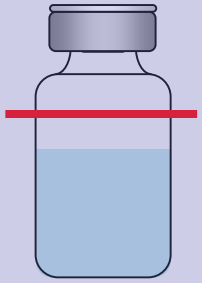
Instant testing possi

Head Space Analysis (HSA)

Laser absorbtion spectroscopy

Permanent & temporary leaks

Requires a modified headspace

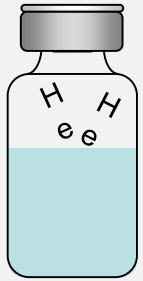


Mass spectrometry (MS)

Requires tracer Gas

Permanent leaks

Instant testing possible



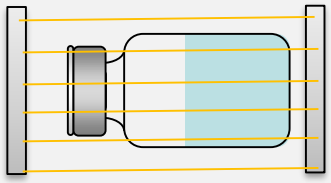
High Voltage (HVLD)

Differential current

Permanent leaks

Conductivity of liquid required

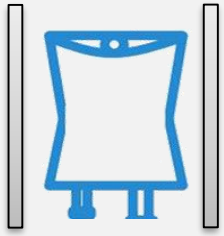
Instant testing possible



Force Sensor (FS)

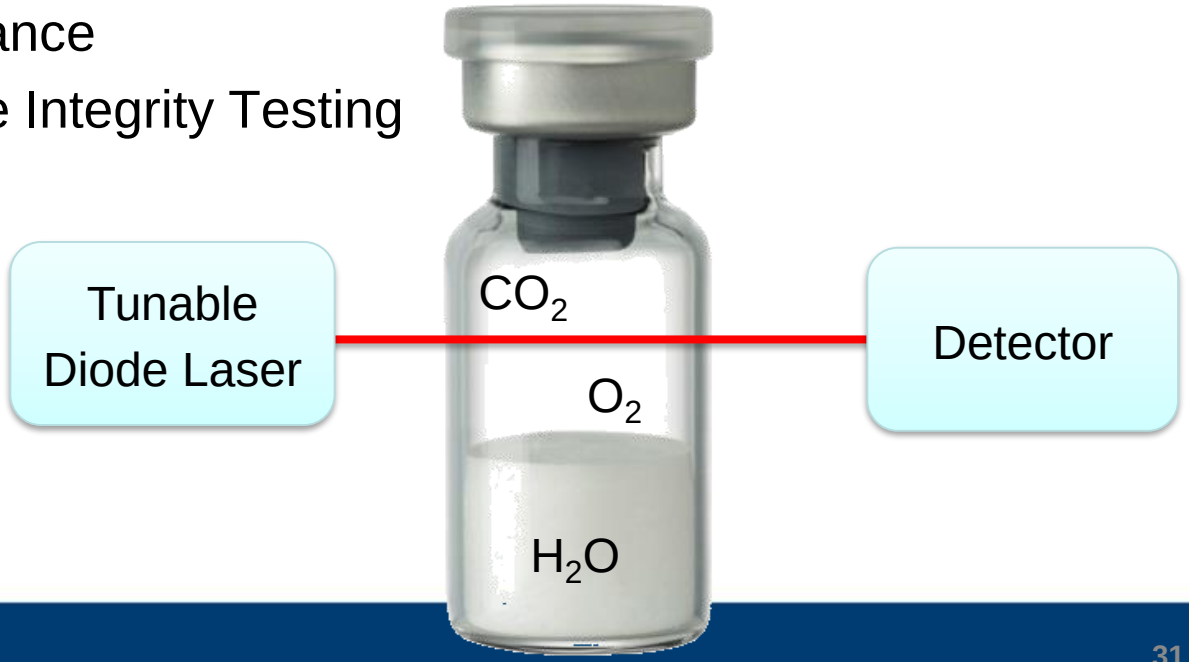
For flexible packaging Regular vs. Vaccum mode

Permanent leaks Instant testing possible



Head Space Analysis

- Measuring of O_2, CO_2 concentration or total pressure of in sealed containers.
- Laser absorption spectroscopy (TDLAS)
- Used for:
  - Verification of nitrogen gassing efficiency
  - Vacuum maintenance
  - Container Closure Integrity Testing



Head Space Analysis

O_2 Laser

Application:
- Residual O2 level in HS
- **CCI Testing**
- Process characterization
- Media Fill inspection

CO_2 Laser

Applications:
- **CCI Testing for Cold Stored CCS**
- Media Fill Inspection

H_2O Laser

Applications:
- Moisture in the Head Space
- Pressure measurement
- **CCI Testing**

Why implement Head Space Analysis?

- Leak testing
  - Identification of temporary leakers (e.g. raised stoppers)
  - Identification of permanent leakers

- Verification of vacuum in headspace
  - Current Annex 1:

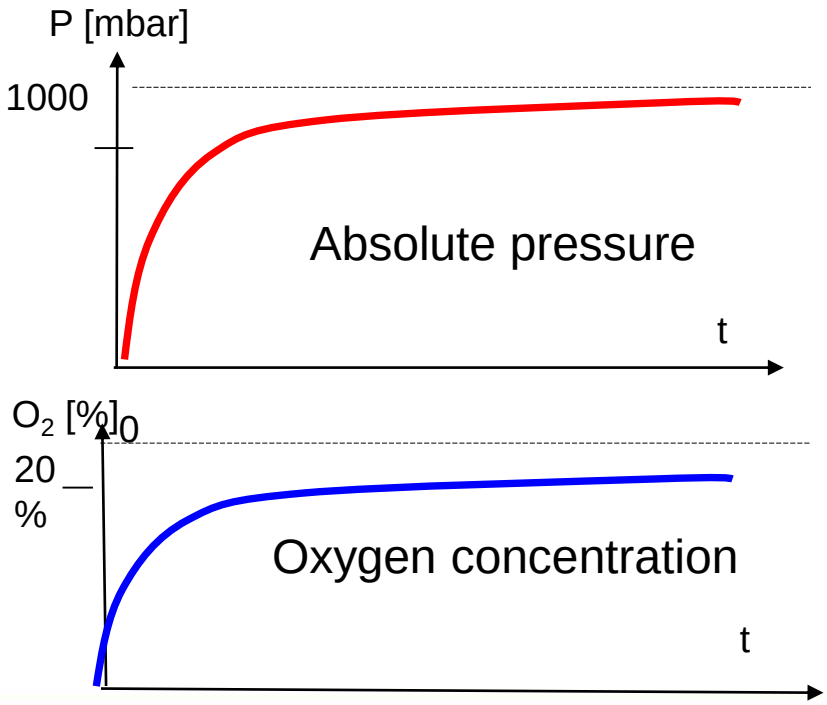
    123. Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.

  - Draft Annex 1 :

    8.19 Containers sealed under vacuum should be tested for maintenance of vacuum after an appropriate, pre-determined period and **during shelf life.**

Air Ingress for vials closed under vacuum

- Equilibration to atmospheric pressure by air ingress
  - Pressure and oxygen concentration will increase
- Equilibration vs. diffusion



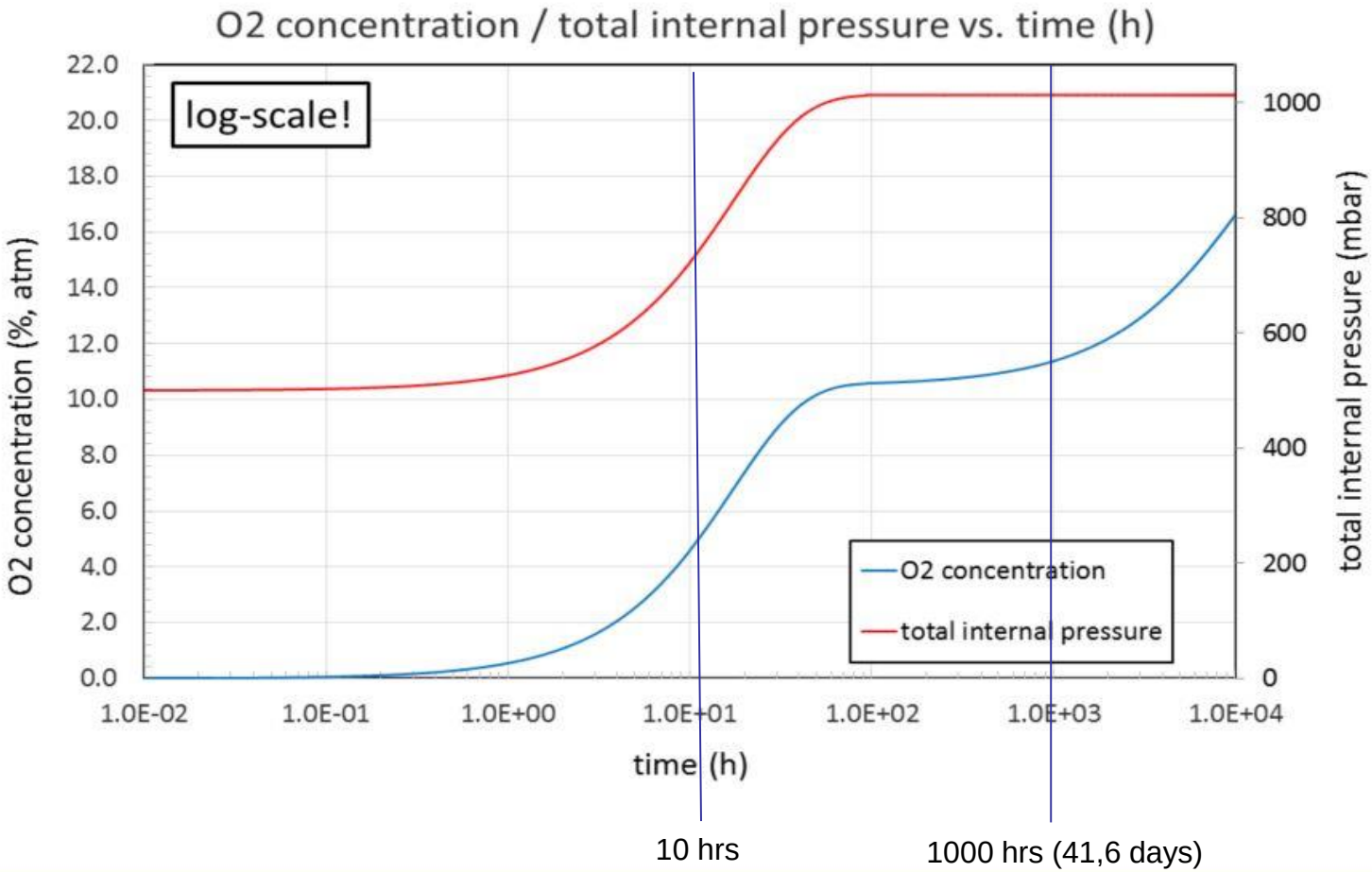
Waiting Time as a crucial parameter

- The time between closing and testing is a crucial parameter as part of the test method and depends on:
  - Air/oxygen ingress
  - Required test sensitivity
  - Sensitivity of test equipment

- Air/oxygen Ingress is depending on:
  - Initial Vial internal pressure
  - Initial gas concentration
  - Conditioning / process

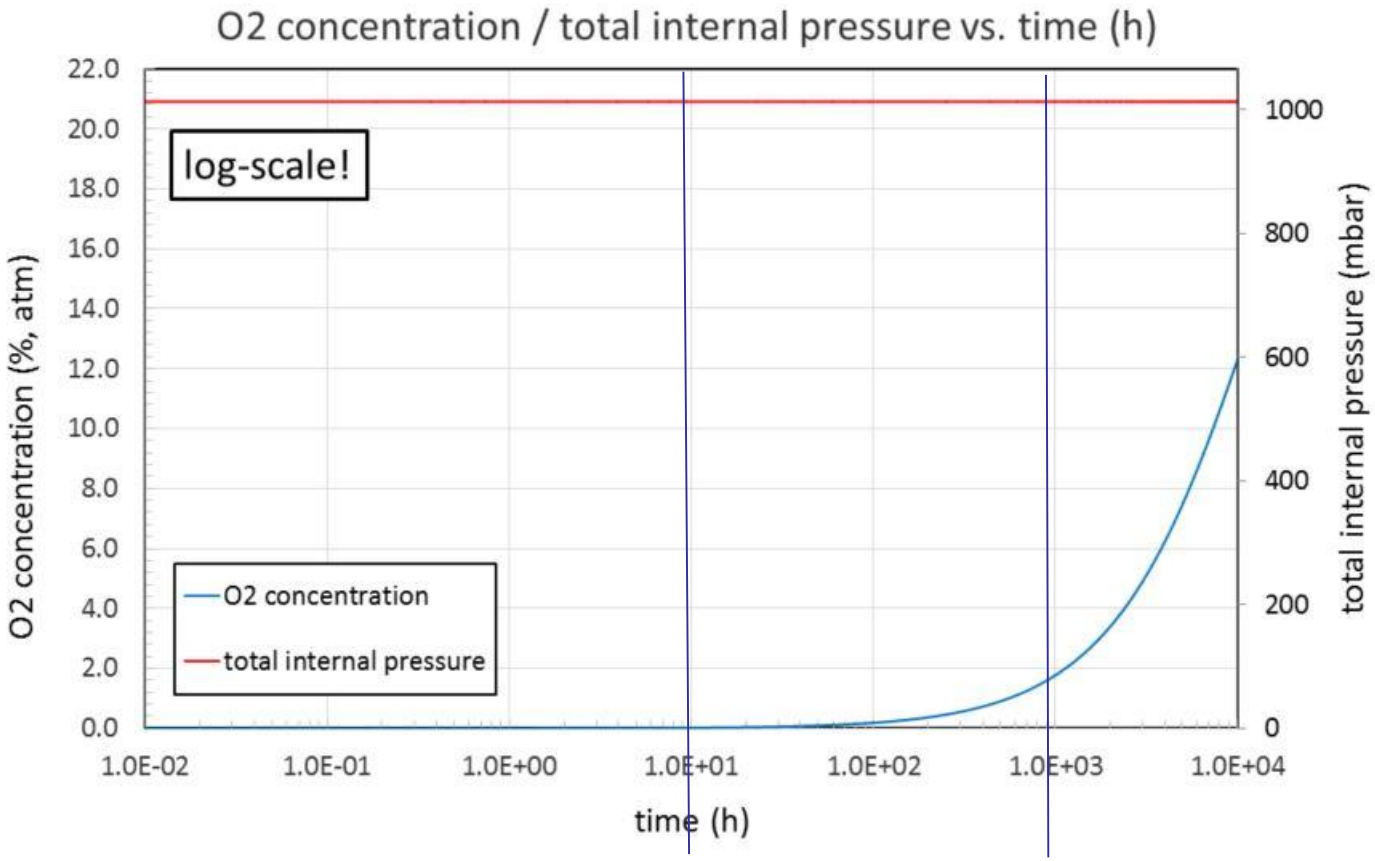
Example: Vial closed under vacuum

10 ml Vial
10 micron leak
500 mbar N2



Example: Vial closed under atmospheric pressure

10 ml Vial
10 micron leak
1013 mbar N2



10 hrs

1000 hrs (41,6 days)

Conditioning of samples by “Bombing”

- Apply higher pressures than ambient to a container
- If a leak is present a portion of the gas will enter

  → if gas is detected inside the container,

  a leak exists

Bombing chamber (source: Wilco)

☺ Gas can be chosen for it’s properties (CO_2, Air, calibration gases, …).

☺ The detection limit for CO_2 as a trace gas is approx. a factor of 100 lower than for O_2

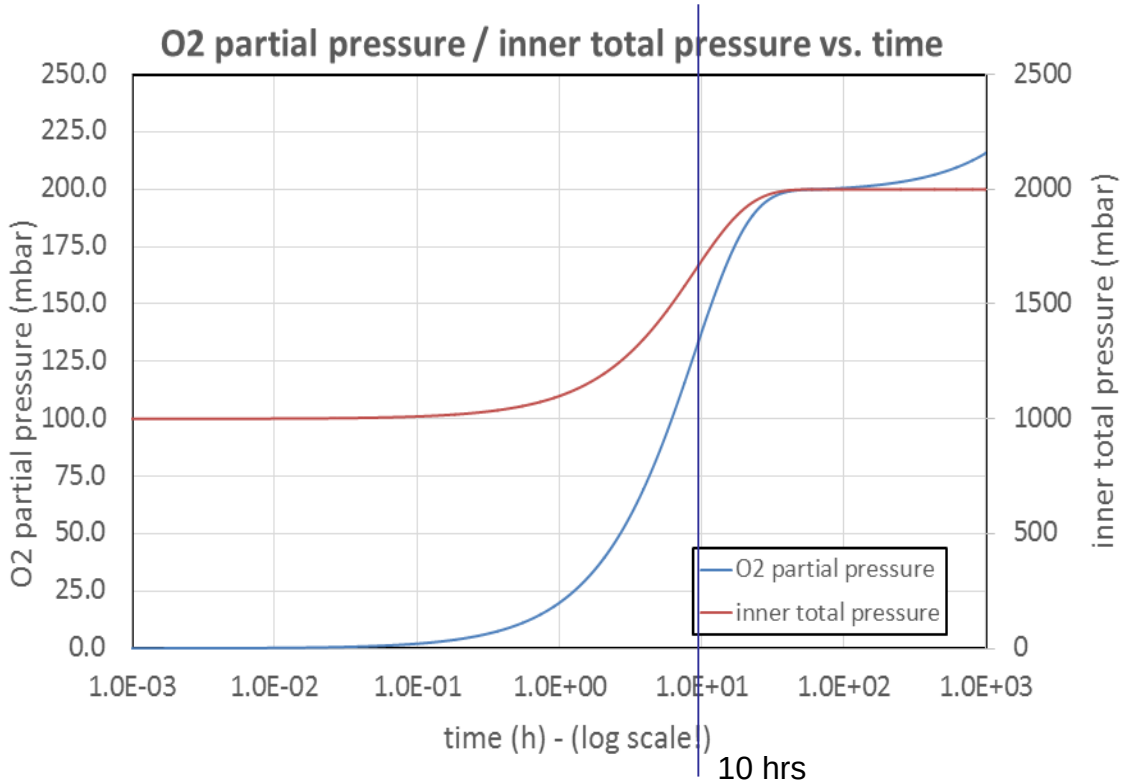
Bombing process patented by Wilco AG

Conditioning of samples “Bombing”

Bombing - Example:

Filling conditions: pure N_2 @ 1000 mbar
Bombing parameters: calibration gas 20% O_2 / 80% N_2 @ 2000 mbar (abs.)

10ml Vial
10 micron leak
1013 mbar N2



Conditioning of samples by Cold Storage

- Cold storage of container after filling and closing
- Gas of headspace will cool → internal total pressure will drop
- If leak is present, air and oxygen will enter the container
- Driving force is pressure difference → fast, typical timescale hours / days
- Equation for ideal gas yields: $p_{fill} / T_{fill} = p_{int} / T_{int}$

Example:

Filling temp. 25°C (T_{fill} = 298,15 K)

Cold storage 5°C (T_{int} = 278,15 K) → $T_{int} / T_{fill} = 0.933$

→ Internal pressure will drop to 93.3 % of filling pressure, e.g. from 1000 to 933 mbar

→ 67 mbar of air will enter if leak is present (timescale hours / days)

→ 20.9 % * 67 mbar = 14 mbar of oxygen will enter with it

Qualification / Validation

- System qualification
  - Use calibration standards
  - Evaluate precision and accuracy

- Method validation
  - Calculate critical leak rate
  - Prepare positive controls with critical leak size
  - Verify leak size using helium leak test
  - Stopper vials under process conditions
  - Monitor air ingress over time (e.g. using a lab instrument)
  - Compare with predicted air ingress model
  - Verification of inline system with positive controls

Pro's and Con's of Head Space Analysis as CIT

- Permanent and temporary leaks may be detected
- Non-destructive testing
- Integration in other machines possible
- Established technology since 2003

- Modified headspace or preconditioning of samples is required
- Waiting time is required to allow oxygen ingress
- Clogging may stop oxygen ingress

CCIT Technology Overview

Differential pressure (DP)

Pneumatic method

Permanent leaks

Requires a headspace or liquid that vaporizes

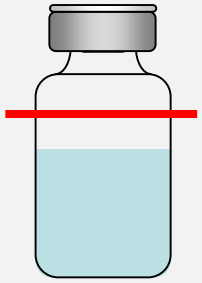
Instant testing possi

Head Space Analysis (HSA)

Laser absorbtion spectroscopy

Permanent & temporary leaks

Requires a modified headspace

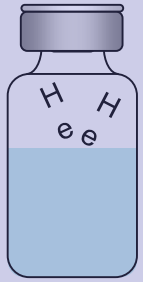


Mass spectrometry (MS)

Requires tracer Gas

Permanent leaks

Instant testing possible



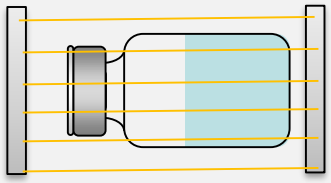
High Voltage (HVLD)

Differential current

Permanent leaks

Conductivity of liquid required

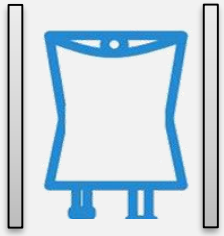
Instant testing possible



Force Sensor (FS)

For flexible packaging Regular vs. Vaccum mode

Permanent leaks Instant testing possible

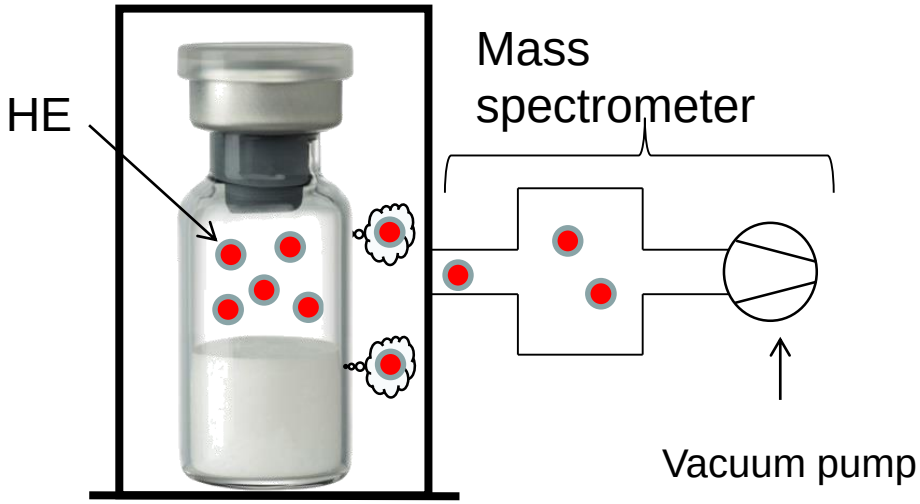


Helium Leak TM: Working Principle

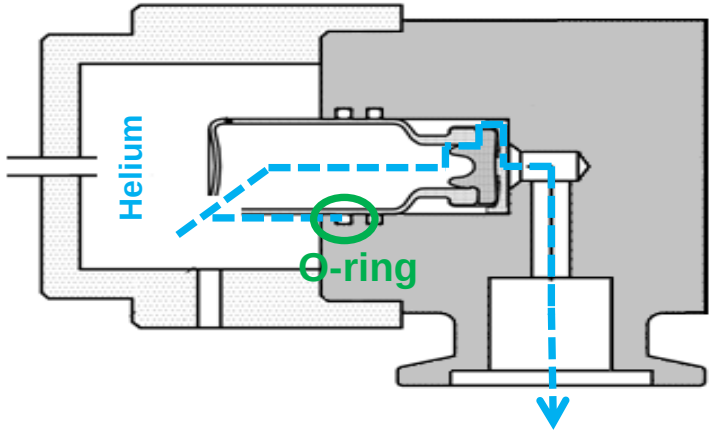
- Measuring of tracer gas (such as Helium)
- Applicable for rigid and flexible packaging
- Most sensitive leak test method
- «Standard» method for verification of leak rates
- Detection limit at 10^{-9} mbar*l/s
- ASTM F 2391 – 05 describes:
  - Pre-filling of Packages vs. Post-filling of Packages
  - Sniffer mode vs. vaccum mode

Helium Leak TM: Working Principle Inside - Out

Helium in Head Space

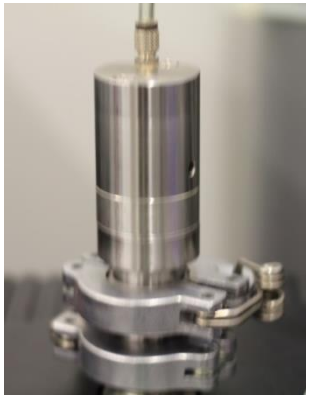


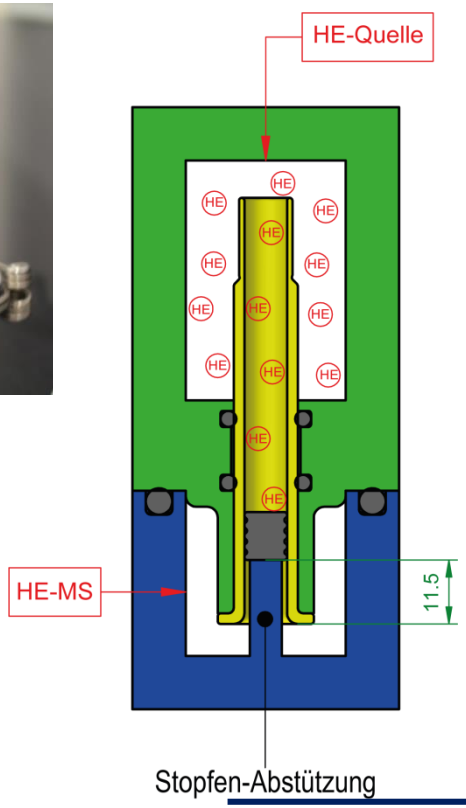
Helium flush through hole

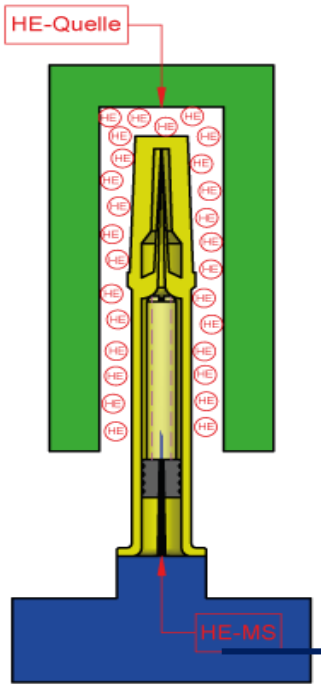


Morrical BD et al. Leak Testing in Parenteral Packaging:,Types. PDA J Pharm, Sci Technol. 2009

Helium Leak TM: Working Principle Outside - In







Pro's and Con's of Helium Leak as CCIT

- Very sensitive method
- 100% testing possible when tracer gas is in headspace
- Established technology for leak testing

- Tracer gas required
- May be destructive
- Contamination with tracer gas increases risk of false rejects
- No standard test setups for parenteral packaging available (gaskets, valves, etc.)

CCIT Technology Overview

Differential pressure (DP)

Pneumatic method

Permanent leaks

Requires a headspace or liquid that vaporizes

Instant testing possi

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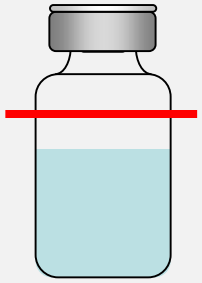
Laser absorbtion spectroscopy

Permanent & temporary leaks

Requires a modified headspace

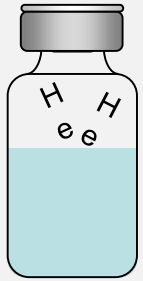


Mass spectrometry (MS)

Requires tracer Gas

Permanent leaks

Instant testing possible



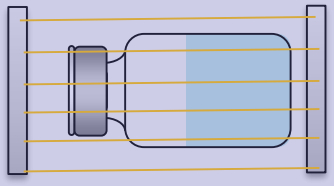
High Voltage (HVLD)

Differential current

Permanent leaks

Conductivity of liquid required

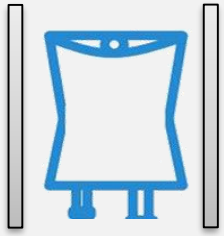
Instant testing possible



Force Sensor (FS)

For flexible packaging Regular vs. Vaccum mode

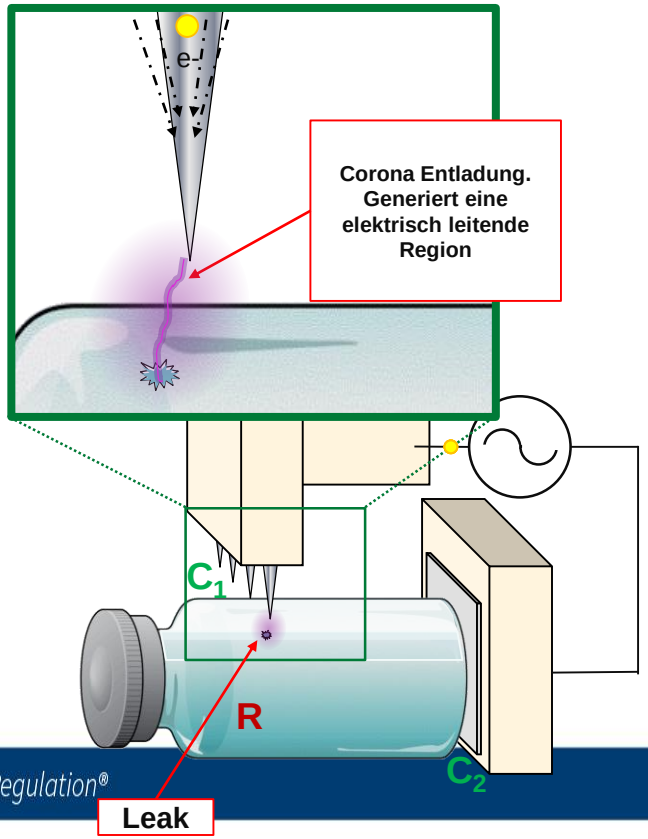
Permanent leaks Instant testing possible



HVLD TM: Working Principle

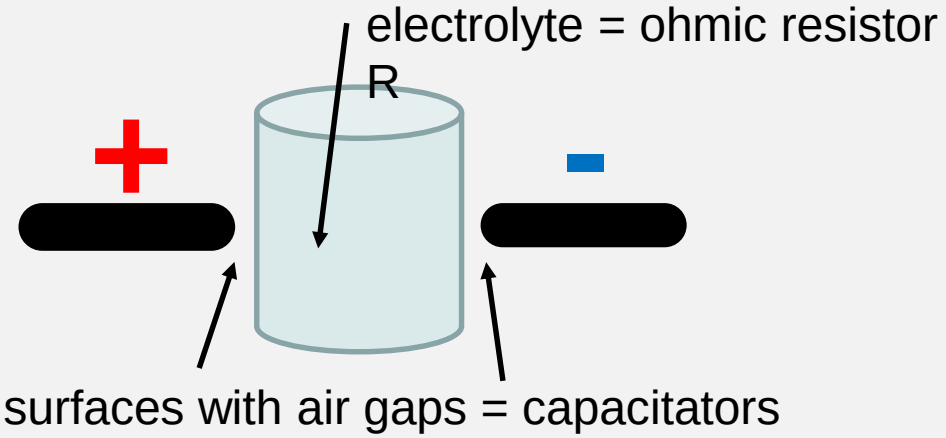
Working principle:

- Based on Law of Ohm
- High Voltage is applied
- When a leak is present there is a short circuit
- Electric current changes and indicates the leak

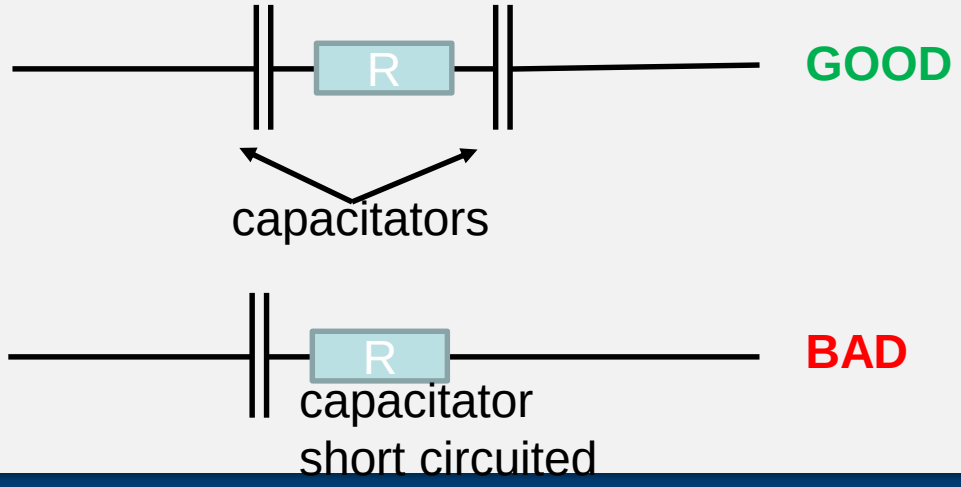


HVLD TM: Working Principle

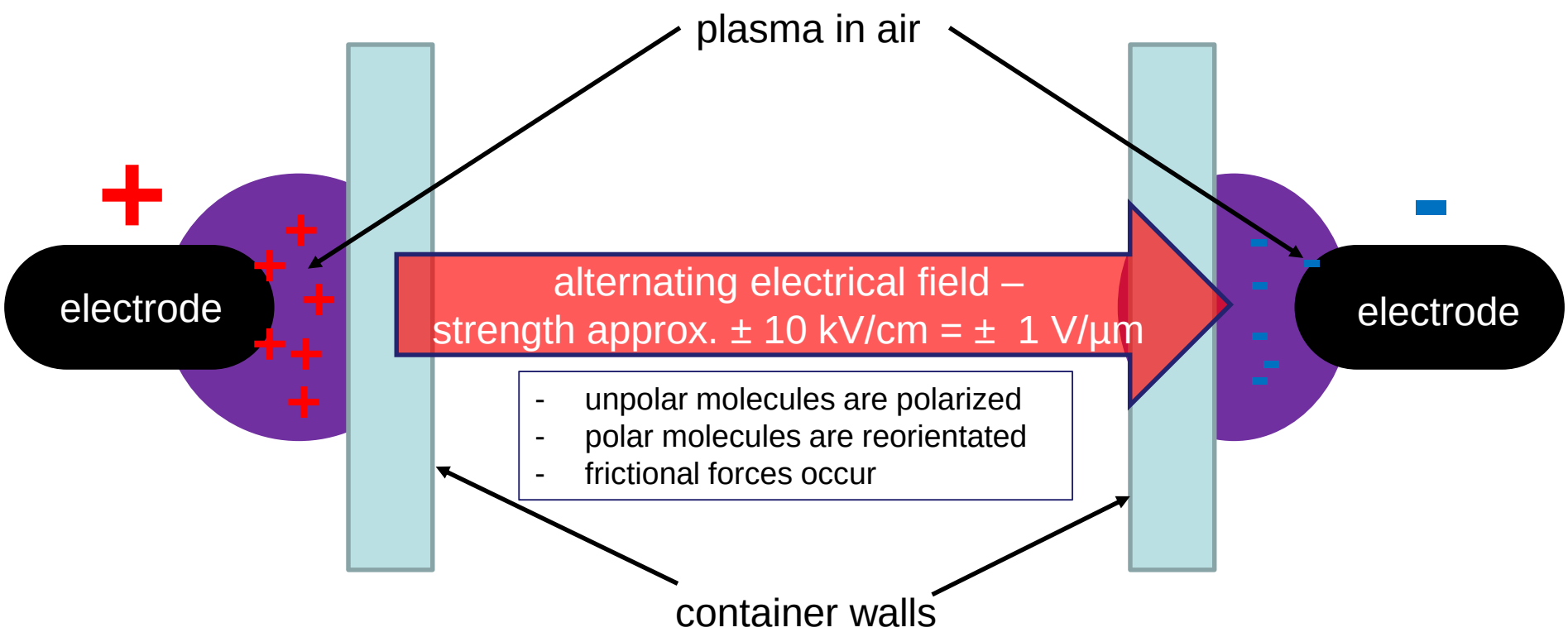
HVLD –
scheme of setup



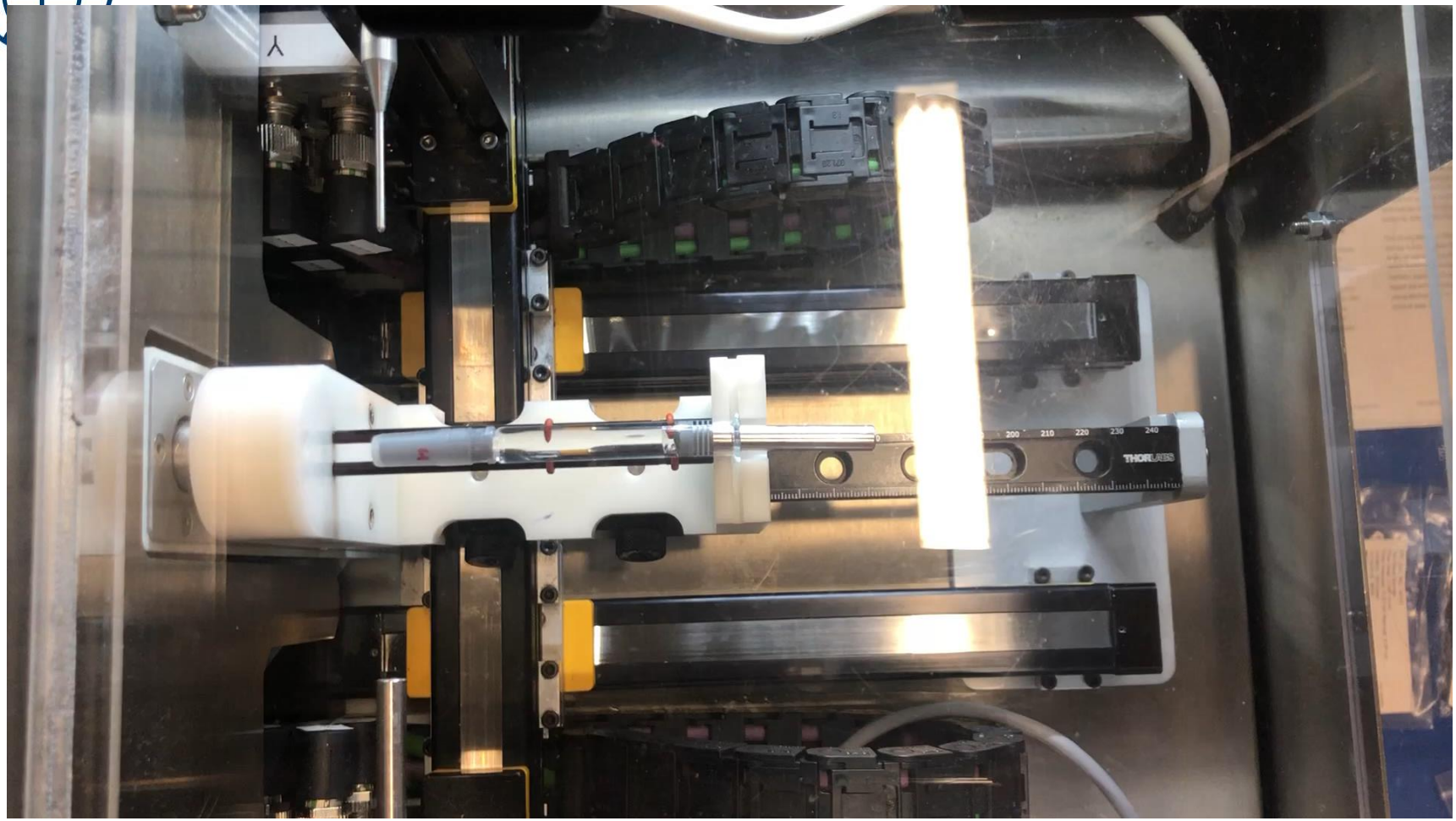
HVDL –
equivalent circuit diagram



HVLD: Snap Shot on Charge Distribution



Video of HVLD Set-up



Pro's and Con's of HVLD as CCIT

- Very sensitive
- Quick measurement allows high speed
- Well established method
- Applicable for different CCS and products
- No gas flow is required, thus also clogged leaks may be detected
- Applicable for different CCS and sizes

Not applicable for lyo products

- Requires conductivity
- Impact on drug product needs to be evaluated
- Signal does not give indicatation about the leak size
- Container walls need to be covered with electrolyte
- Containers need to be rotated

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Permanent leaks

Requires a headspace or liquid that vaporizes

Instant testing possi

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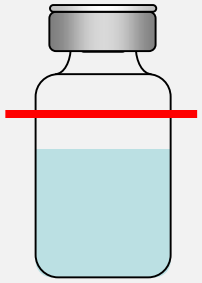

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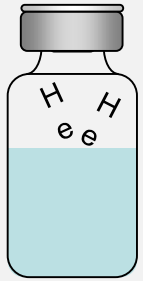
Requires tracer Gas

Permanent leaks

Instant testing possible



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Differential current

Permanent leaks

Conductivity of liquid required

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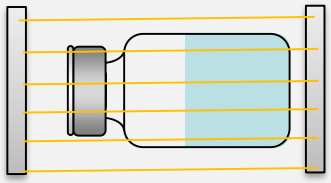
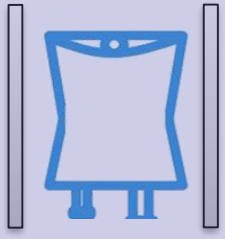


Force Sensor (FS)

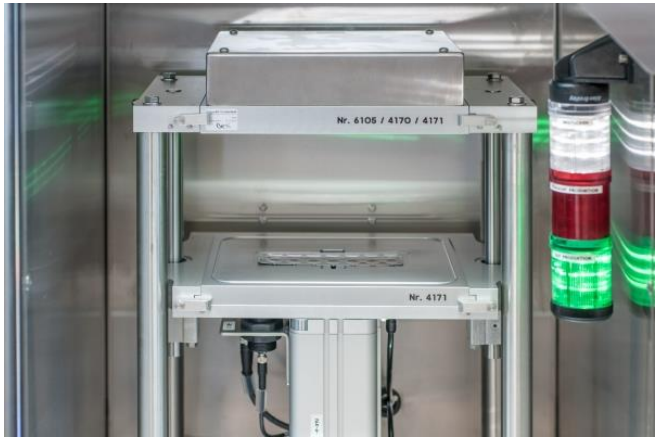
For flexible packaging Regular vs. Vaccum mode

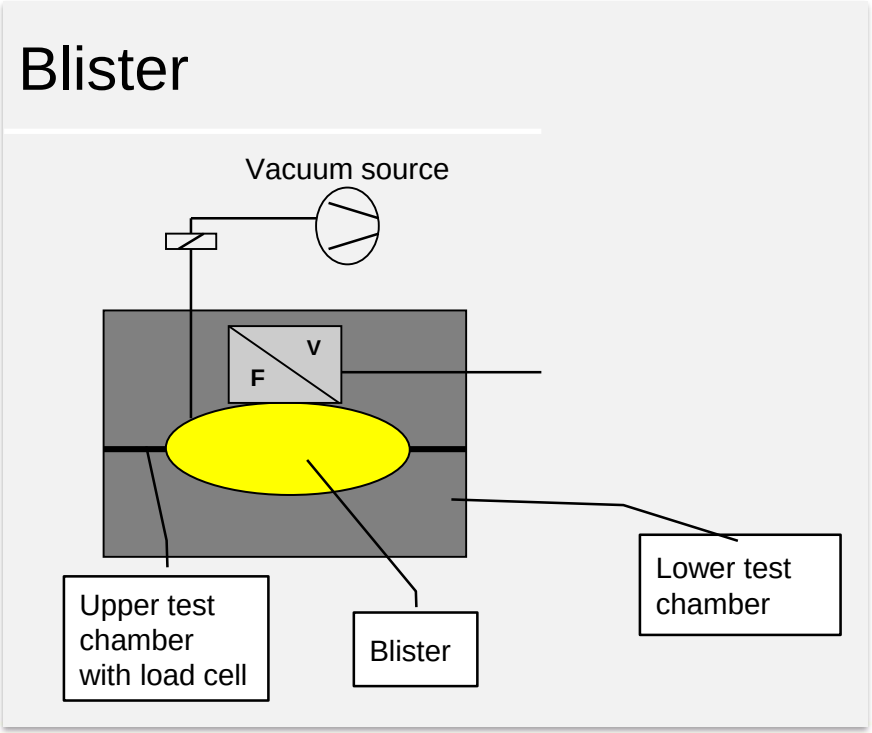
Permanent leaks Instant testing possible



Force Sensor (Vacuum Mode) : Working Principle

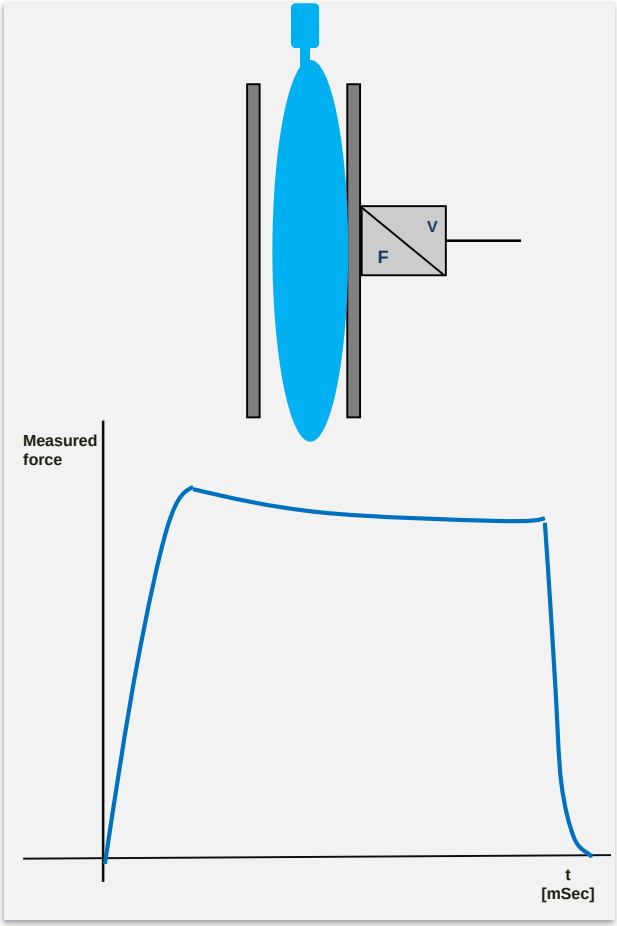
- Measuring of differential force
- Foil shall bent due to under pressure in surrounding area
- Detection limit of 10-5 mbar*l/sec (1 micron)





Force Sensor (Regular Mode) : Working Principle

- Measuring of differential force
- Moving plates
- Inspection of critical welding areas (port)
- Lab scale and 100% inline testing possible



Pro's and Con's of Force Sensors as CCIT

- Applicable for flexible containers
- Very sensitive in vacuum mode
- Applicable for small volumes as well as large volume parenterals
- Lab scale as wellas 100% inline inspection possible

- Requires rel. long testing times
- Requires a gas exchange at point of testing
- Only permanent leak can be detected

- Thank you for your attention!