CONTAINER CLOSURE INTEGRITY TESTING: ENSURING PURITY IN PARENTERALS

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Seidenader Maschinenbau GmbH

CONTAINER CLOSURE INTEGRITY

HIGH VOLTAGE LEAK DETECTION

LASER BASED HEAD SPACE ANALYSIS

Why Container Closure Integrity Testing (CCIT)

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What is Container Closure Integrity?

Sterile product–package integrity (or container closure integrity) is the ability of a sterile product container–closure system to keep product contents in, while keeping detrimental environmental contaminants out. (USP 1207)

Why Container Closure Integrity Testing (CCIT)

What are possible problems if CCI is not given?

Leaks of Concern	Product Quality Risks Posed by Leaks
Entry of microorganisms	**Failure** of product sterility quality attribute
Escape of the product dosage form or **entry of external liquid or solid matter**	**Failure** of relevant product physicochemical quality attributes
Change in gas headspace content. For example, loss of headspace inert gases (e.g., nitrogen), loss of headspace vacuum, and/or entry of gases (e.g., oxygen, water vapor, air).	**Failure** of relevant product physicochemical quality attributes and/or hindrance of product access by the end-user

(USP 1207)

Why Container Closure Integrity Testing (CCIT)

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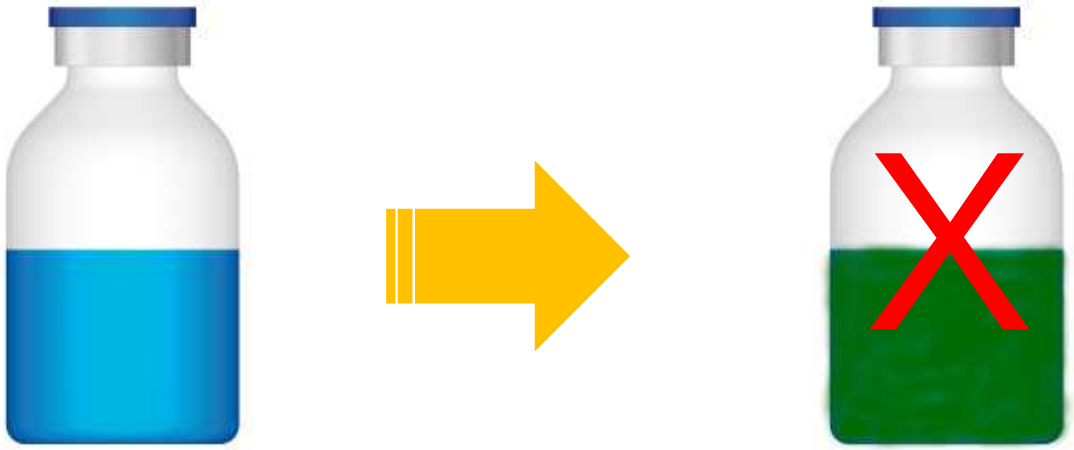
In other words:

If CCI is not given the product might become ineffective or even corrupted when it gets to the patient.



Why Container Closure Integrity Testing (CCIT)

But there are regulations too:

Code of Federal Regulations (CFR):

21CFR211.94 Drug Product Containers and Closures- (a) Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.

21CFR211.94 Drug Product Containers and Closures- (b) Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.

21CFR211.94 Drug Product Containers and Closures- (c) Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use. Such depyrogenation processes shall be validated.

www.americanpharmaceuticalreview.com

Why Container Closure Integrity Testing (CCIT)

and regulations …

21CFR211.94 Drug Product Containers and Closures- (d) Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures.

European Commission EudraLex- The Rules Governing Medicinal Products in the European Union **Annex 1-** Manufacture of Sterile Medicinal Products (Annex 1)- 117. “Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.”

Why Container Closure Integrity Testing (CCIT)

and regulations …

European Commission EudraLex- The Rules Governing Medicinal Products in the European Union **Annex 1**- Manufacture of Sterile Medicinal Products Volume 4- Part II Basic Requirements for Active Substances used as Starting Materials- 9.20. “Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.”

International Conference on Harmonisation (ICH) Harmonized Triplicated Guideline, Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products Q5C- Sterility testing or alternatives (e.g. container/closure integrity testing) should be performed at a minimum initially and at the end of the proposed shelf-life.

Why Container Closure Integrity Testing (CCIT)

and regulations …

Guidance for the Industry “Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products (Guidance for Industry, 2008).

USP <1207> Sterile Product Packaging-Integrity Evaluation,<1207.1>Package Integrity and Test Method Selection,<1207.2>Package Integrity Leak Test Technologies and<1207.3>Package Seal Quality Test Methods

Parenteral Drug Association (PDA) Technical Report 27

PDA White Paper: Container Closure Integrity Control versus Integrity Testing during Routine Manufacturing (Ewan, S. et al., 2015)

Why Container Closure Integrity Testing (CCIT)

and regulations …

US Food and Drug Administration (FDA)

Compliance Program Guidance Manual, Chapter 56-Drug Quality Assurance Program 7356. 002A- 09/11/15- (5) Verification of Container and Closures. The physical and chemical characteristics of containers and closures can be critical to the sterility and stability of the finished product. Many containers and closures look alike (color and dimensions), but are made of different materials or have a different surface treatment such as silicone on stoppers and ammonium sulfate on Type I glass.

Why Container Closure Integrity Testing (CCIT)

and regulations …

FDA Compliance Program Guidance Manual, Chapter 56-Drug Quality Assurance Program 7356.002A- 09/11/15- Evaluate the firm's procedures for assuring containers and closure consistently meet appropriate specifications. FDA Compliance Program Guidance Manual, Chapter 56-Drug Quality Assurance Program 7356. 002A- 09/11/15- Determine what tests and examinations are done to verify the containers and closures are made of the correct materials with the correct dimensions (critical to ensuring continuing container-closure integrity) and are free of critical defects.

FDA Compliance Program Guidance Manual, Chapter 56- Drug Quality Assurance Program 7356. 002A- 09/11/15- (6) Container / Closure Integrity. The integrity of the container / closure system is critical to assuring that all units of drug products remain sterile through shipment, storage and use. Leaking containers or closures lead to product contamination.

Why Container Closure Integrity Testing (CCIT)

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and regulations …

FDA's 1994 Guidance for Industry for the Submission of Sterilization Process Validation in Applications for Human and Veterinary Drug Products- Evaluate the tests and studies performed to demonstrate the integrity of container / closure systems for all sterile drugs, including:
Verify that all incoming container-closure components meet specifications, including all appropriate dimensions.
Determine studies adequately simulate the stress conditions of the sterilization process, handling and storage.
Verify that the units tested in validation are appropriate (e.g., for terminally sterilized drug product, the units selected should be exposed to the maximum sterilization cycles using the production process).
Sensitivity of the test is specified.
Container-closure integrity is demonstrated during validation and as part of the stability program (in lieu of sterility testing), over the shelf life of the product.

Why Container Closure Integrity Testing (CCIT)

Neglecting these regulations regularly lead to warning letters:

This is a repeat violation … your … (QCU) failed to establish an adequate stability testing program designed to evaluate the integrity of the container-closure system

Puncturing a container compromises the integrity of the container closure system, and each puncture increases the chances of contamination…..

Your firm failed to ensure your container closure system

….

Different methods for CCIT

Probabilistic methods

A “probabilistic leak test method” is stochastic in nature in that it relies on a series of sequential and/or simultaneous events each associated with uncertainties, yielding random outcomes described by probability distributions. <USP1207.1>

Relying on stochastics

Deterministic methods

A “deterministic leak test method” is one in which the leakage event is based on phenomena that follow a predictable chain of events, and leakage is measured using physicochemical technologies that are readily controlled and monitored, yielding objective quantitative data. <USP1207.1>

100% testing

Different methods for CCIT

Probabilistic methods are e.g.

- Bubble Emission
- Microbial Challenge, Immersion Exposure
- Tracer Gas Detection, Sniffer Mode
- Tracer Liquid (e.g. Blue dye test)

Deterministic methods

- **Electrical Conductivity and Capacitance (High-Voltage Leak Detection)**
- Mass Extraction
- Pressure Decay
- Vacuum Decay
- Tracer Gas Detection, Vacuum Mode
- **Laser-Based Gas Headspace Analysis**

Different methods for CCIT

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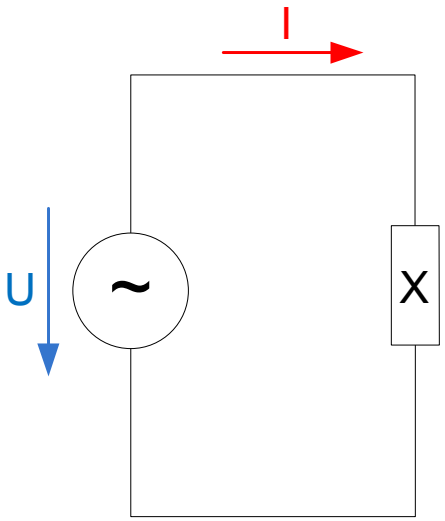
Electrical Conductivity and Capacitance (High-Voltage Leak Detection)

- For **liquid filled** containers
- Liquid has to have a **minimum conductivity**
- Apply **high frequency high voltage** to the container
- Electrical conductivity of the complete system is measured

=> In case of a leaking container, the electrical conductivity of the system will change and this can be measured

AC - circuit



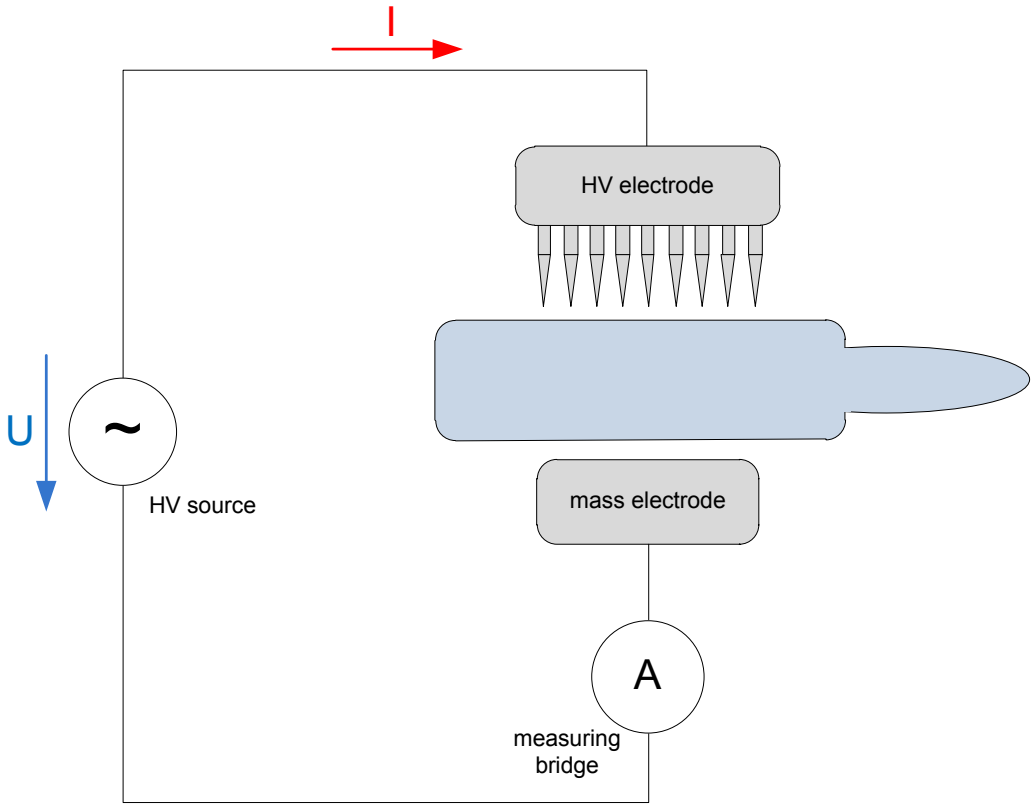
U: Voltage

I: Current

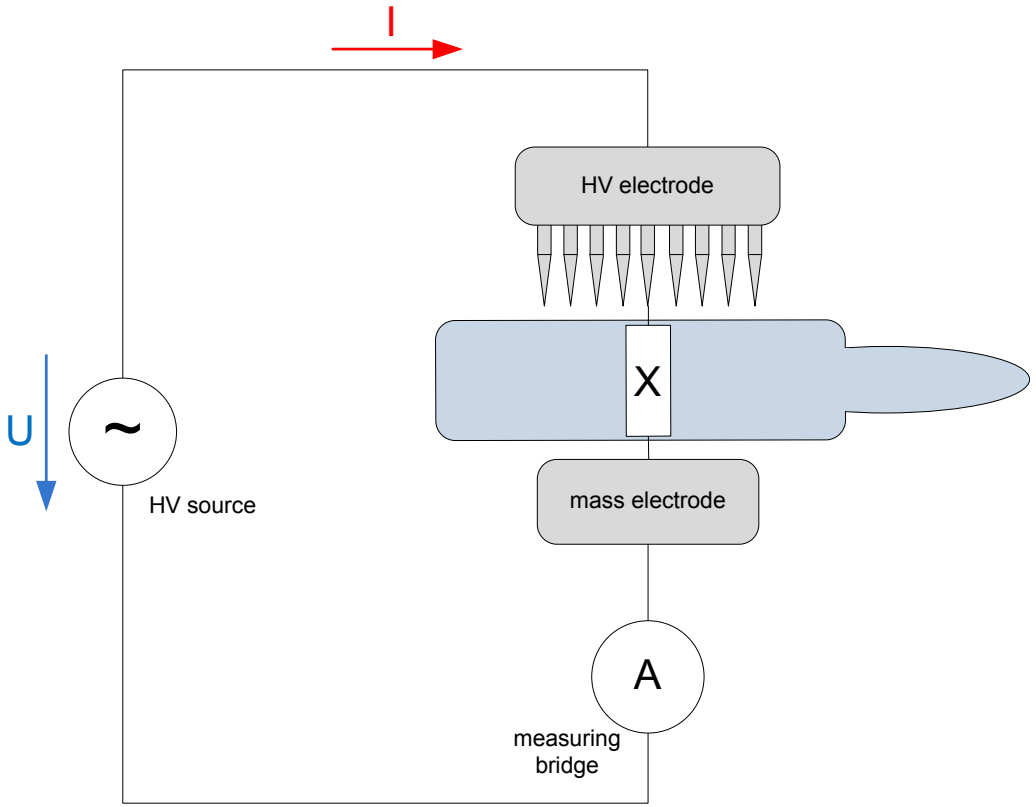
X: Impedance (AC-resistor)

$$I \propto \frac{U}{X} \qquad \overset{U=const.}{\Rightarrow} \qquad I \propto \frac{1}{X}$$

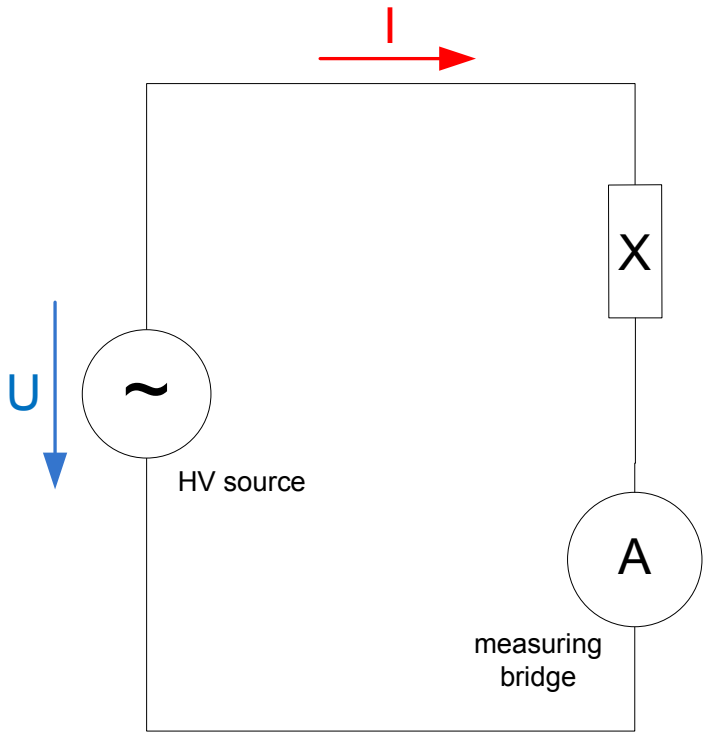
Simplified circuit diagram



Simplified and equivalent circuit diagram



Equivavlent circuit diagram



$$I \propto \frac{1}{X}$$

$$X_{ok} > X_{defect}$$

$$\Rightarrow I_{ok} < I_{defect}$$

Surrounding conditions for HVLD inspection

Electrical Conductivity and Capacitance (High-Voltage Leak Detection)

1. Liquid filled containers
2. Electrical conductivity of liquid (for Seidenader System: min 1µS/cm)
3. Leaks have to go through complete container enclosure
4. Complete wetting of inner surface of container
5. Very short distance between container surface and HV electrodes
6. Scanning of complete container surface by HV electrodes

The special **Seidenader HVLD modules** (pro and slim) address especially points 4 to 6

The Seidenader Solution

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Infeed Visual Inspection HVLD Sorting

The Seidenader Solution

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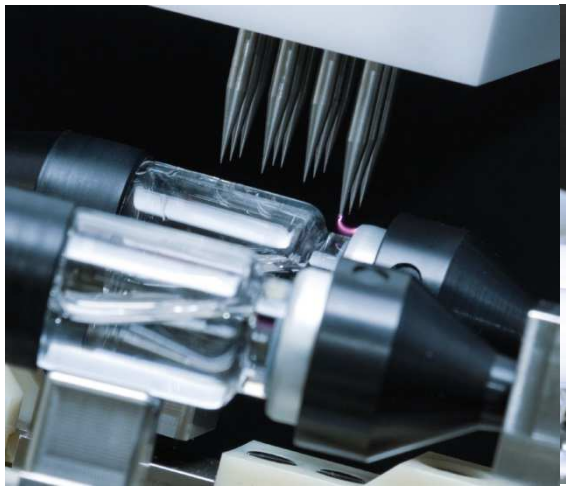
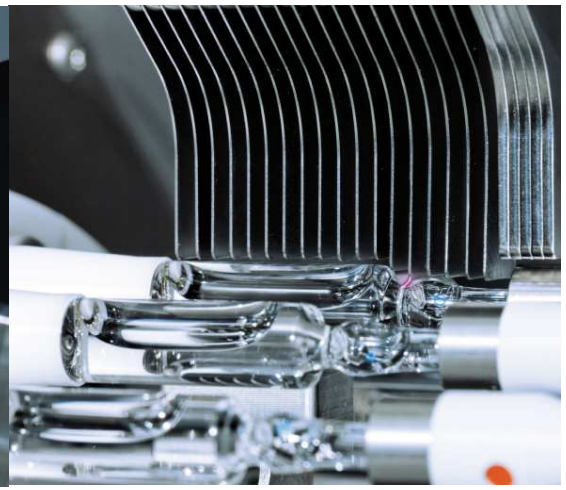




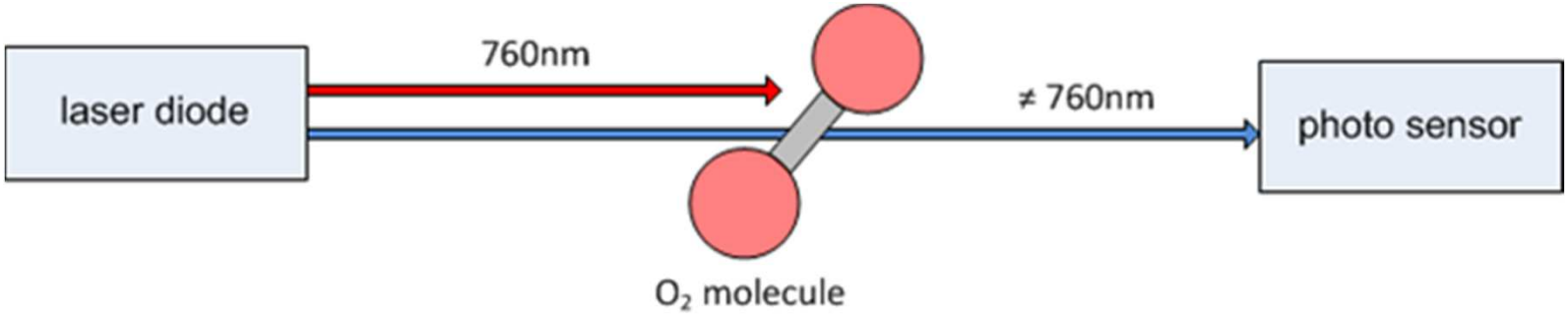
Different methods for CCIT

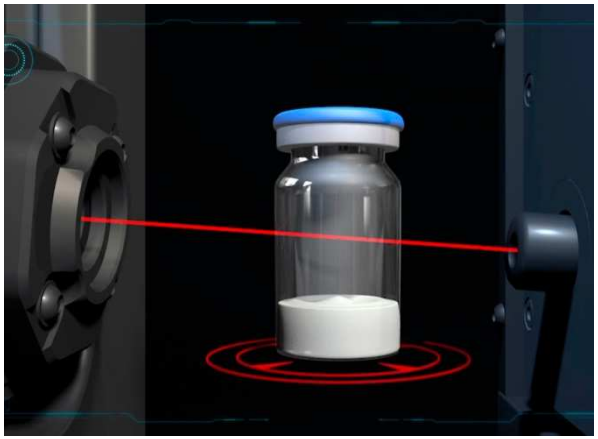
Laser-Based Gas Headspace Analysis (short: Headspace Analysis HSA)

Gas headspace analysis via laser-based techniques provides a quantitative, nondestructive measure of **oxygen content**, **water vapor content**, and low internal pressure in the headspace of a nonporous, rigid or nonrigid package (6–8). Some instruments are capable of measuring headspace carbon dioxide concentration as well. *<USP 1207.2>*

Laser-Based Gas Headspace Analysis (HSA)

Laser absorption spectroscopy

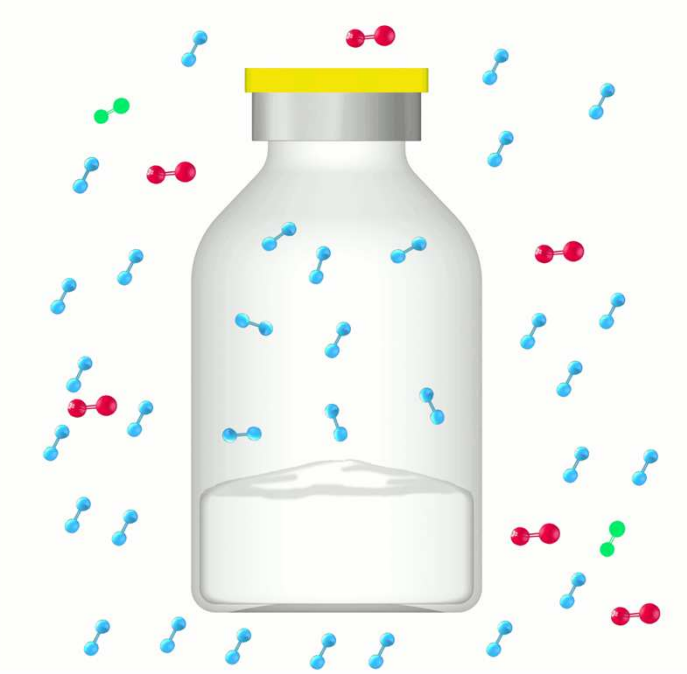




Laser-Based Gas Headspace Analysis (HSA)

Indirect detection of leakage

HSA does not detect the leak itself, but the change in the composition of the gas in the headspace of a container



Laser-Based Gas Headspace Analysis (HSA)

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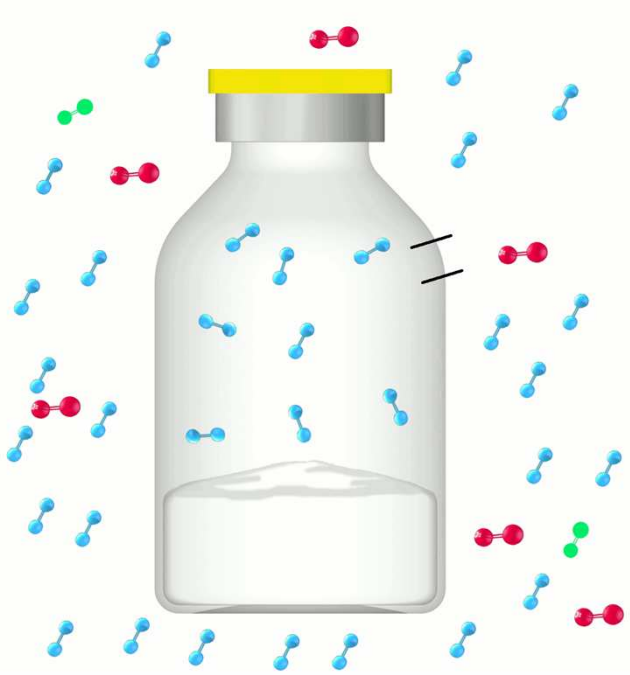
What happens if there is a leak?



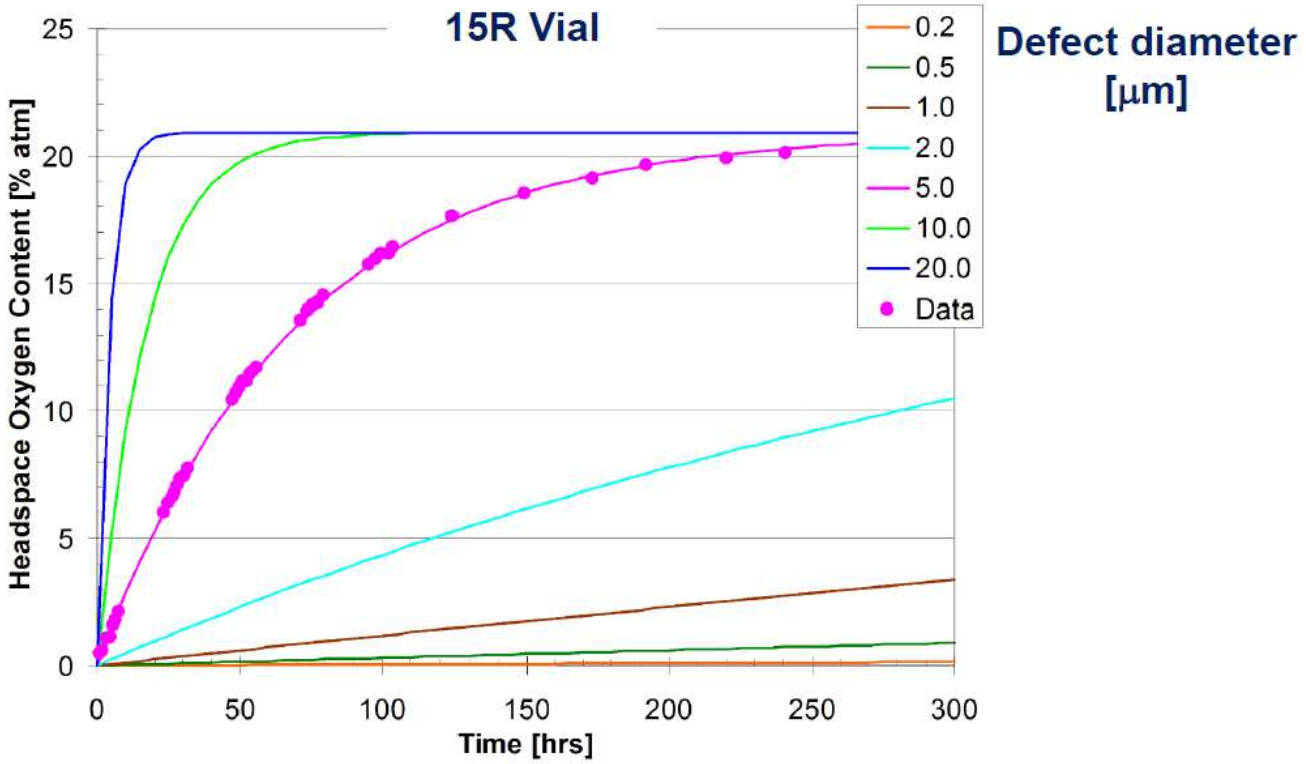
Laser-Based Gas Headspace Analysis (HSA)

As the HSA system does not detect the leak itself, but **Oxygen** that **diffused through the leak into the headspace**, certain conditions have to be fulfilled to reach the needed Oxygen concentration of about 20%

- Waiting time
- Maximum altitude
- Storage conditions

Laser-Based Gas Headspace Analysis (HSA)

Waiting time



Source: Lighthouseinstruments.com

Laser-Based Gas Headspace Analysis (HSA)

Influencing variables on measurement quality

- Nr. of O_2 molecules within the laser beam
  - The higher the O_2 partial pressure the more molecules
  - The larger the container diameter the more molecules
  - The higher the altitude the less partial pressure => the less molecules

- Quality of container material
  - The better the quality, the lower the distortions, the better the measurement quality

Laser-Based Gas Headspace Analysis (HSA)

Influencing variables on measurement quality

- Time available for measurements (more time => better measurement)
  - The slower the machine, the more time per container
  - The bigger the container diameter, the more time per container
- Space available for Laser beam to cross the container
  - If laser beam is blocked (splashes, bad cake, high cake etc.) no measurement is possible
- Composition of Headspace
  - If filled under normal air, no change in headspace would be recognized

Laser-Based Gas Headspace Analysis (HSA)

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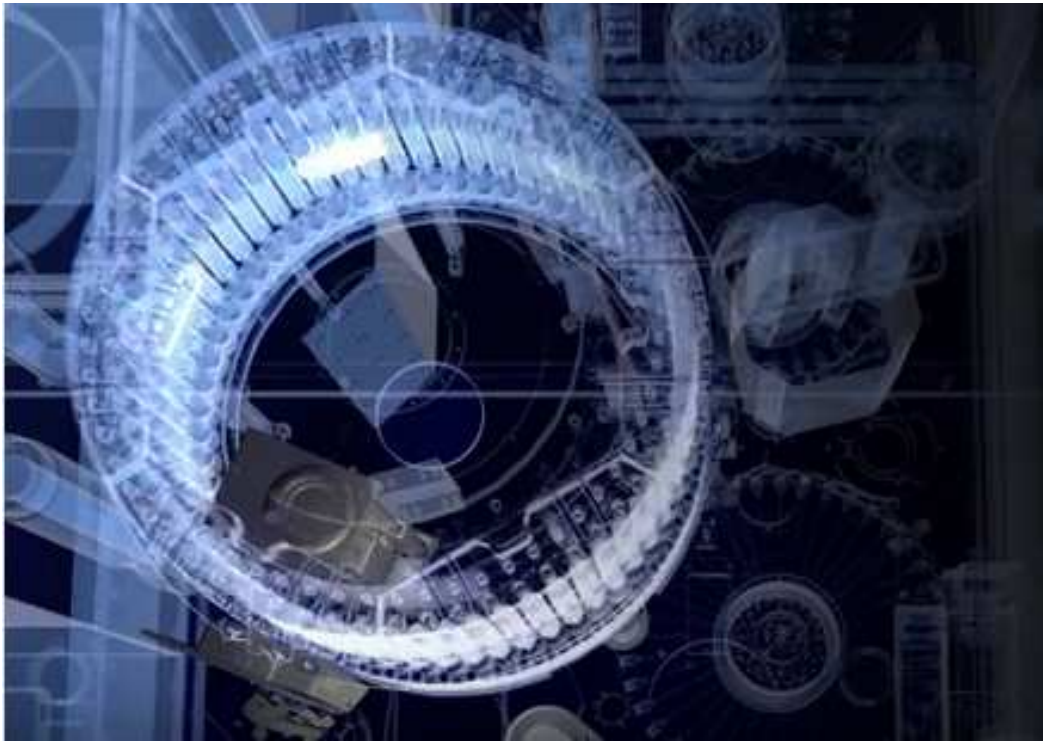
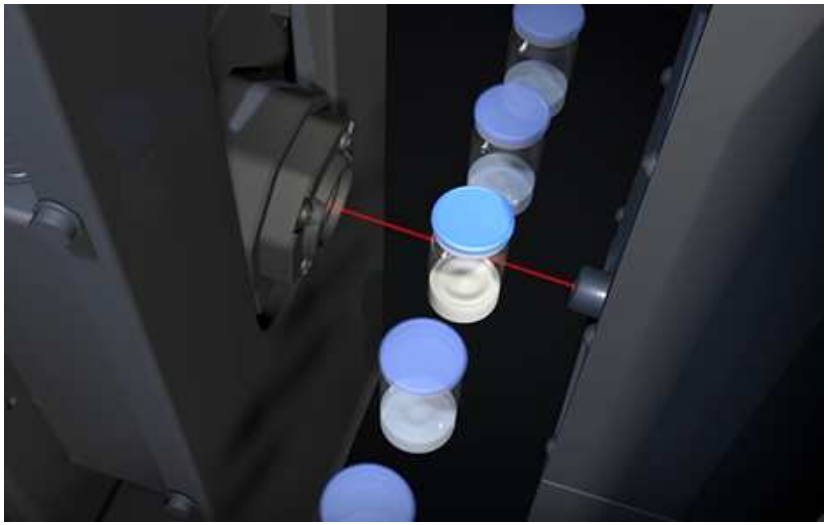
Advantages of the Seidenader HSA system

- **Integrated** HSA system into Seidenader fully automatic inspection machine
- No separate machine needed (saves floor space and investment costs)
- **Retrofitting** into existing inspection machines possible
- **Stand alone** HSA machine possible if needed

The Seidenader Solution





Full product videos are available on the Seidenader Youtube channel
https://www.youtube.com/channel/UCEI-yWrwbk1jwrHgFR_ffnQ