Optical Emission Spectroscopy, an innovative technology for CCIT

Instructor:

- ***Philippe BUNOD**, PhD. ; Pfeiffer Vacuum; philippe.bunod@pfeiffer-vacuum.fr*
  Business Development Pharma Europe – Integrity Test Solutions

PDA Parenteral Drug Association

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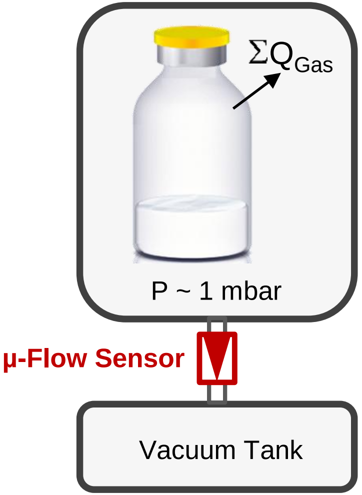
Structure

1. Pfeiffer Vacuum at a glance
2. The 3 CCIT technologies/equipments proposed by Pfeiffer Vacuum
3. Optical Emission Spectroscopy :
   – How does it work ?
   – Influence and limiting factors
   – Advantages
   – Detection of gross leaks
4. Comparative study He/O.E.S/Mass Extraction & Blue dye
5. Conclusions

Global leak test under vacuum

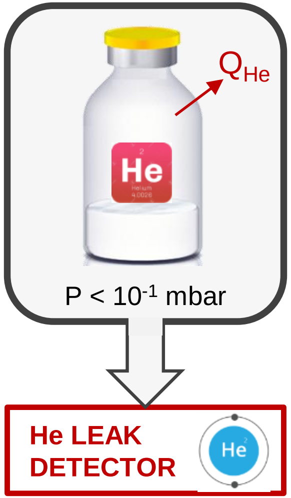
MICRO-FLOW AND MASS EXTRACTION

Micro-flow sensor



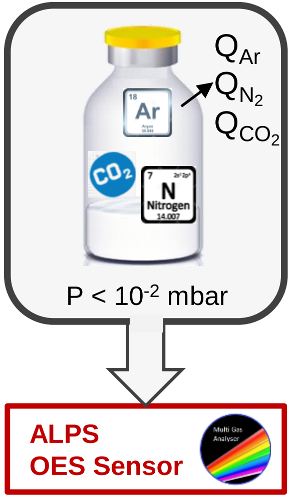
HELIUM MASS SPECTROMETRY

Magnetic deflection spectrometer



OPTICAL EMISSION SPECTROMETRY

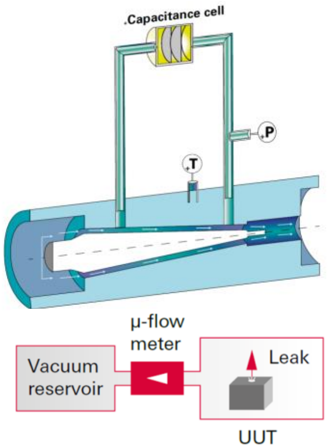
Multi-gas analyser (N_2, CO_2, Ar, H_20,..)



3 technologies for CCIT Solutions

MICRO-FLOW AND MASS EXTRACTION

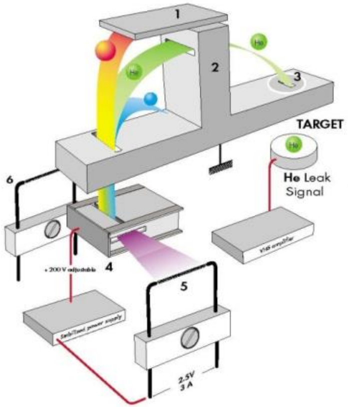
Micro-flow sensor



ASTM F3287-17

HELIUM MASS SPECTROMETRY

Magnetic deflection spectrometer



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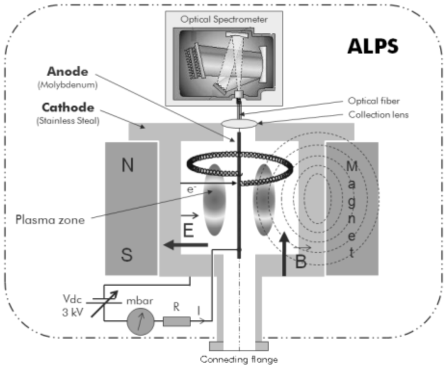
OPTICAL EMISSION SPECTROMETRY

Multi-gas analyser (N_2, CO_2, Ar, H_20,..)



Emerging Technology

3 technologies/equipments in our CCIT portfolio

MICRO-FLOW AND MASS EXTRACTION

Micro-flow sensor

USP ASTM **ASTM F3287-17**

HELIUM MASS SPECTROMETRY

Magnetic deflection spectrometer

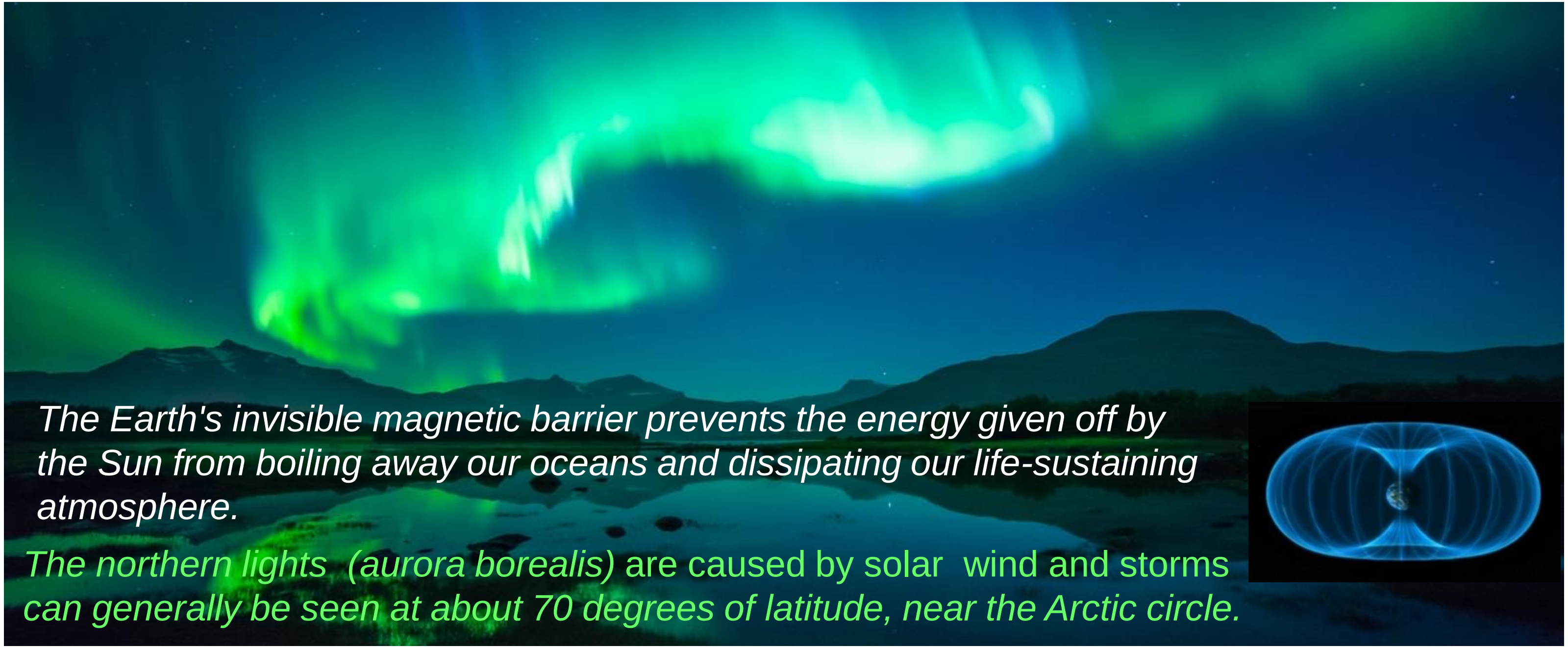
USP ASTM **ASTM F2391-05**

OPTICAL EMISSION SPECTROMETRY

Multi-gas analyser (N_2, CO_2, Ar, H_20,..)

USP *Emerging Technology*

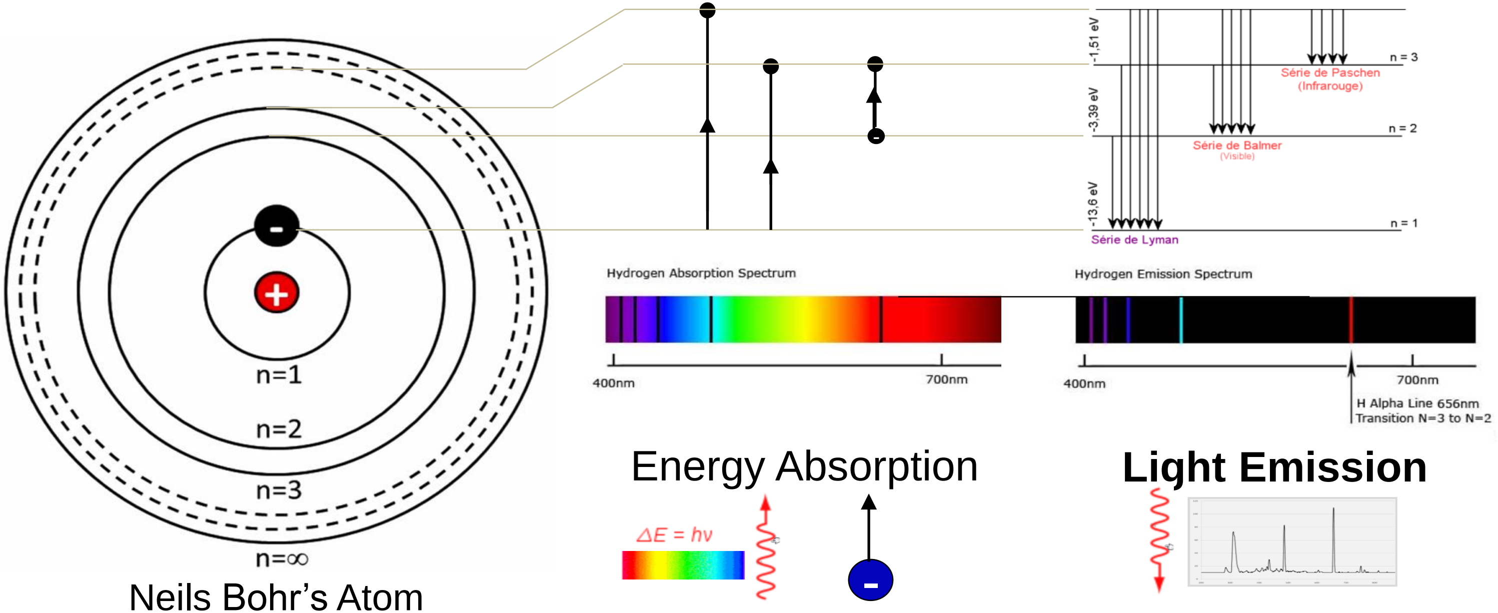
O.E.S. – Operating principle



The Earth's invisible magnetic barrier prevents the energy given off by the Sun from boiling away our oceans and dissipating our life-sustaining atmosphere.

The northern lights (aurora borealis) are caused by solar wind and storms *can generally be seen at about 70 degrees of latitude, near the Arctic circle.*

O.E.S. – Operating principle

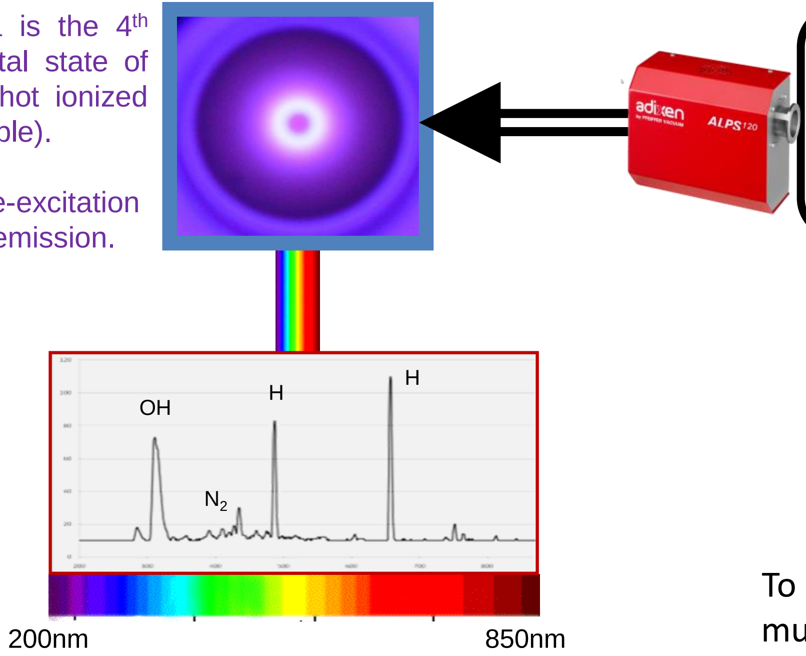


Neils Bohr's Atom

O.E.S. – Operating principle

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

Plasma de-excitation give light emission.



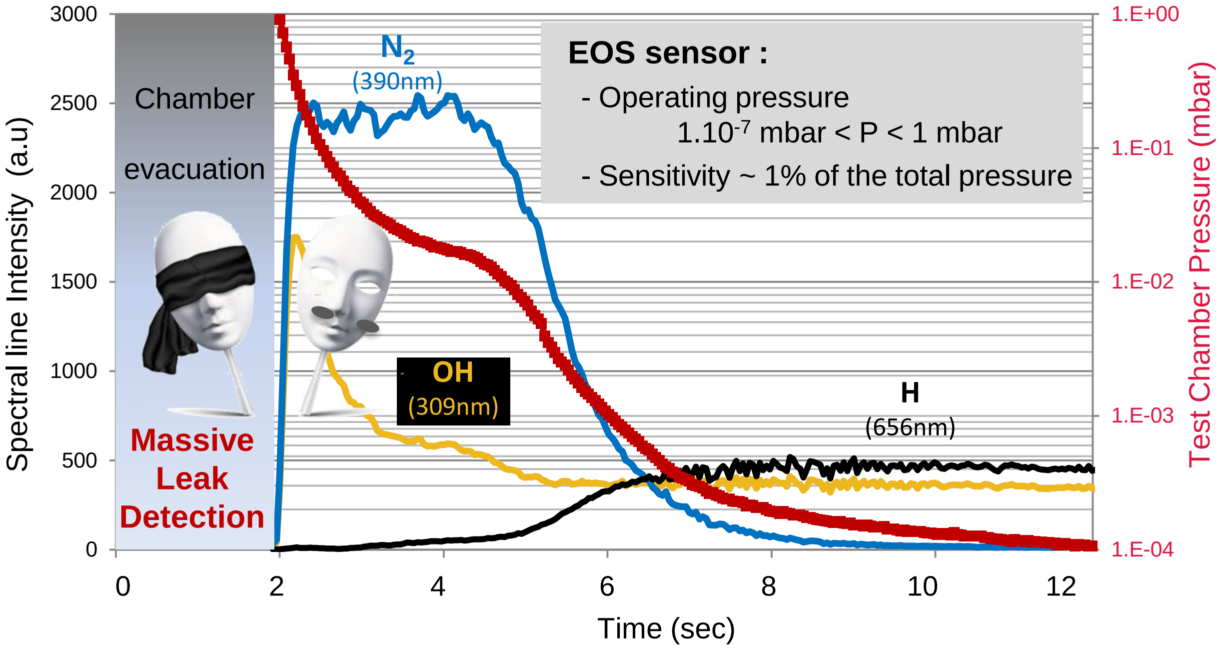
Test chamber (P<5.10^{-2} mbar)

Sealed component (N_2, Ar, CO_2…)

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

To detect leaks we are using our patented multi-gas "ALPS" sensor which is based on O.E.S.

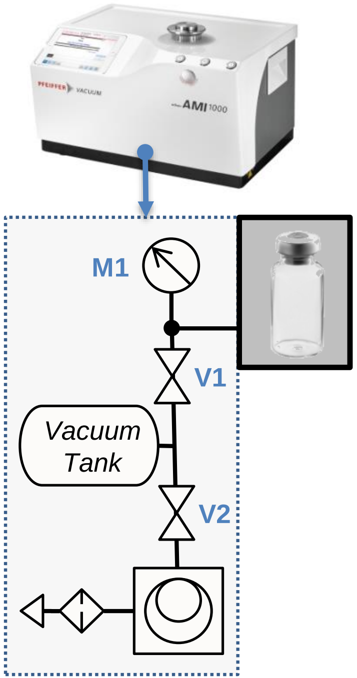
O.E.S. – Real time measurement



The air (N_2) inside the test chamber can be easily evacuated using vacuum pumps.

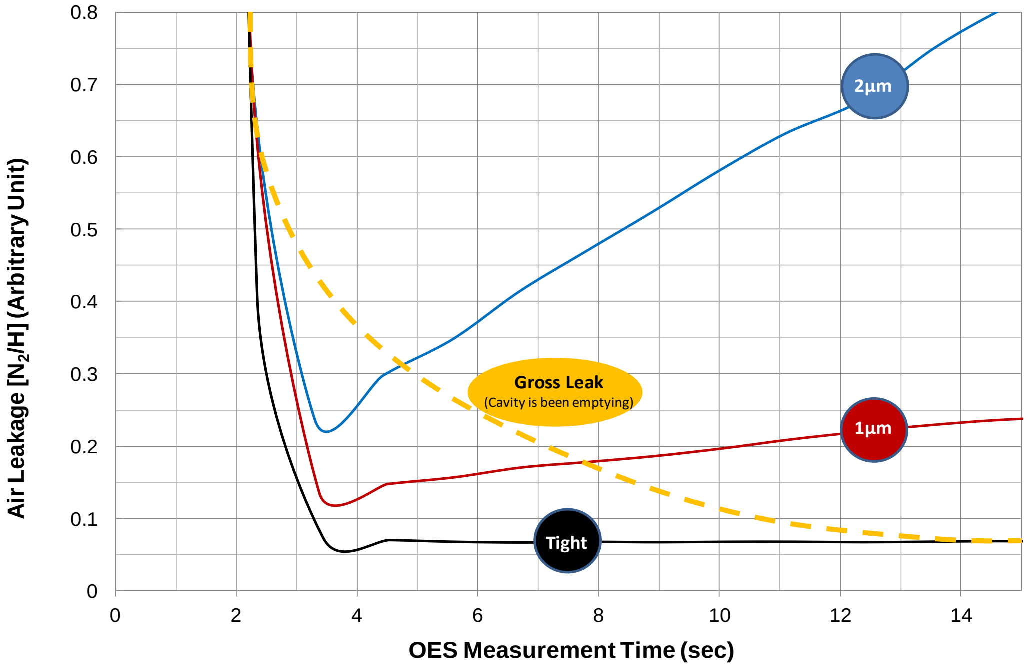
Moisture (H_20 → H & OH) is much more difficult to evacuate because it is coming from out-gassing of materials in contact with vacuum.

Massive leak detection prior to OES



- **AMI includes a Massive Leak Detection module (>100µm)**
  - *- GO/NOGO test = qualitative measurement.*
- **For Dry Filled Products, based on a volumetric method:**
  - *- Pressure equilibrium between a vacuum tank and the test chamber.*
  - *- The test chamber is designed in order to minimize the free volume around the sample and the vacuum tank is sized accordingly.*
- **For Liquid Filled Products, based on deep vacuum decay:**
  - *- Pressure must be below the vapor pressure of liquid.*
  - *- Free volume around the sample is not anymore an issue.*
- **Massive Leak Detection prevents equipment contamination**
  - *- In case of Gross Leak (air/liquid), the high vacuum circuit and OES sensor are not contaminated. Only few components can be easily cleaned and dry.*

OES – Typical air leakage signal (raw data)

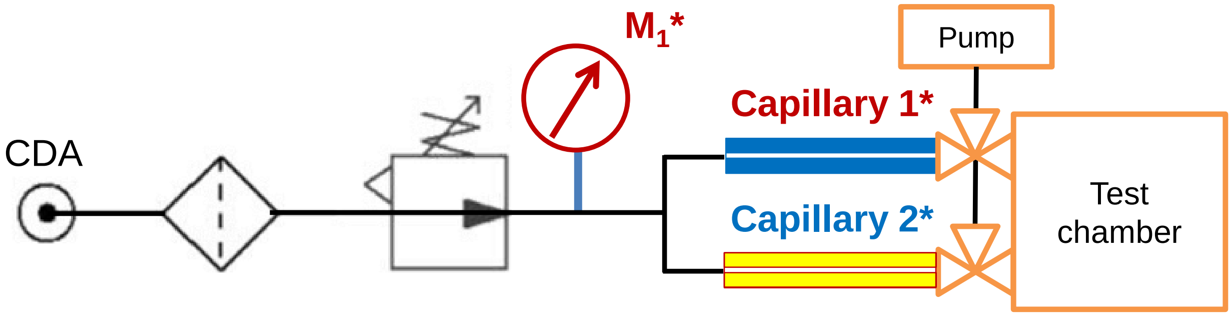


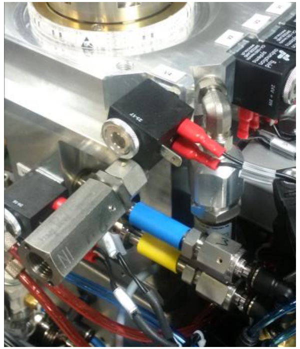
The air leakage corresponds to the intensity ratio [N_2/H]

In case of fine leak, the air leakage signal (N_2/H) increases as out-gassing (OH & H) is decreasing with time.

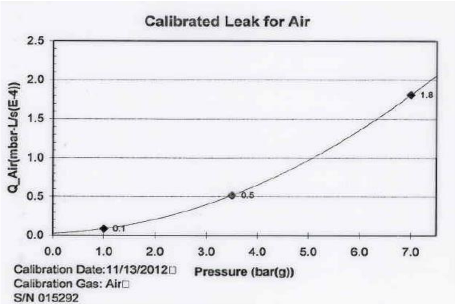
In case of gross leak (>100µm for 1cc headspace), depending on the headspace volume we can see the container being evacuated.

A set of 2 capillaries is used for calibration

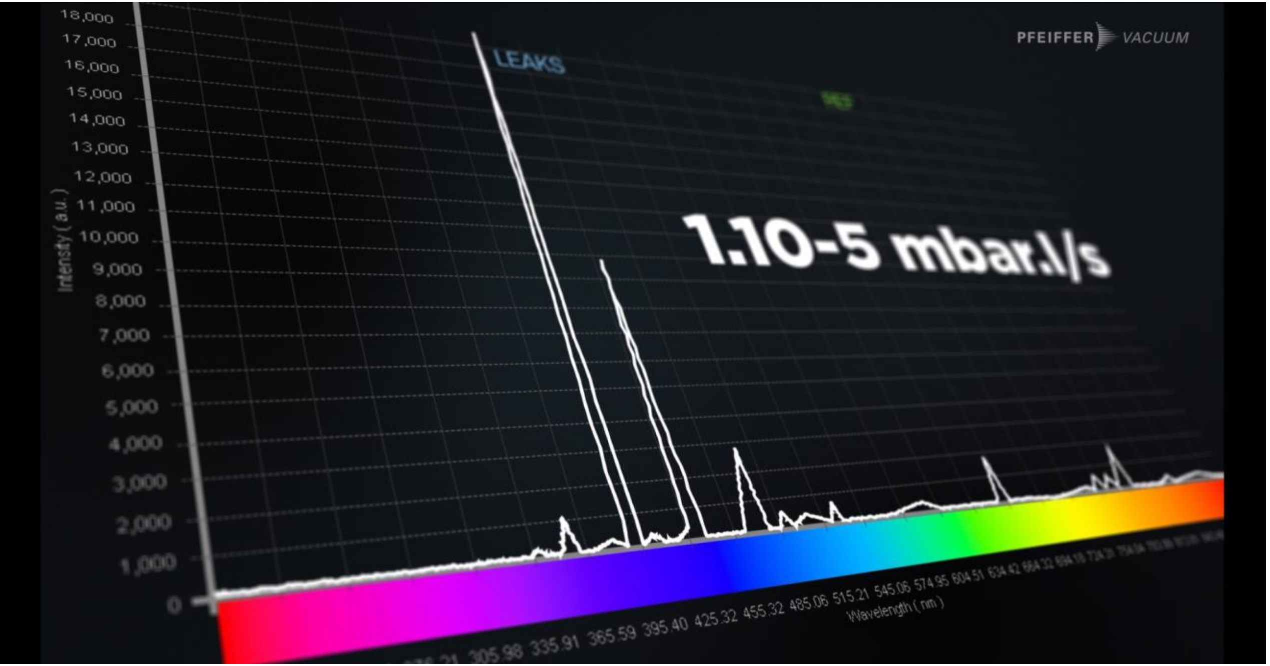




- A set of 2 capillaries allows to generate a calibrated air leak into the test chamber in the range: 2.10^{-5} – 1.10^{-3} mbar.l/s.
- The air leakage provided by the capillaries depending on the CDA inlet pressure set up by the automatic pressure reducer.
- The M1 gauge measures the exact pressure just among the capillaries
- Calibration certificates are delivered for capillaries & pressure gauge



A quantitative and **calibrated** leakage measurement !



OES – Influence & limiting factors

For all vacuum test solutions: **Detection limit ↘ when Test Duration ↗**

- Out-gassing limit the sensitivity of the test, it can be minimized by:
  - Design of Container and test chamber (material, surface, roughness)
  - Controlling operating conditions: temperature (°C) and humidity (<30%RH)
  - Increasing the test duration…
- Gross leak detection can be challenging in case of small gas headspace volume combined with a low out-gassing solid drug.
  - Specific Massive Leak test can be performed prior to O.E.S measurements

No sample preparation – Automatic test sequence

1/. Part loading (manually or automatically)

2/. Chamber evacuation (1000 → few mbar)
(Massive Leak detection)

3/. Chamber pumping (few mbar → <10^{-4} mbar)

4/. O.E.S. measurement start when pressure is < 10^{-2} mba

5/. Chamber venting (with Ambient air, dry N_2 or Argon)

6/. Part unloading

O.E.S. – Measurements are volume independent

Sensitivity are is not impacted by:

- container expansion during the test

→ Tests can be performed on semi-rigid containers

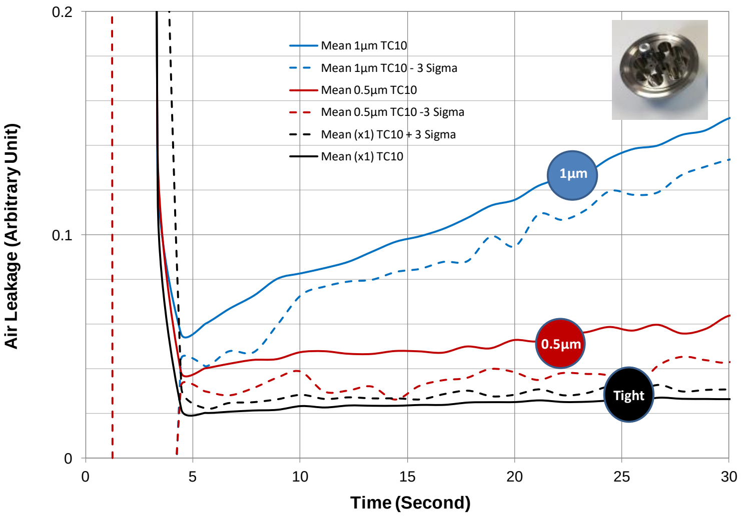
- the free space in the chamber around the container

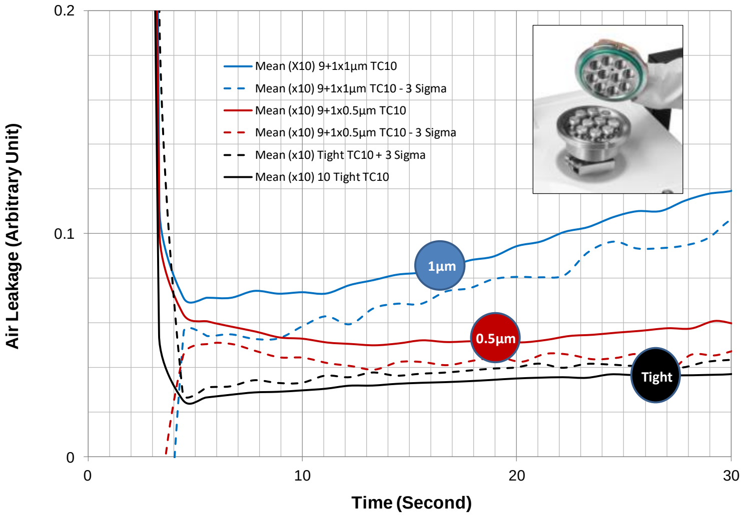
→ Test of complex design devices (i.e. auto-injectors)

→ Possibility to test per batch to increase the throughput

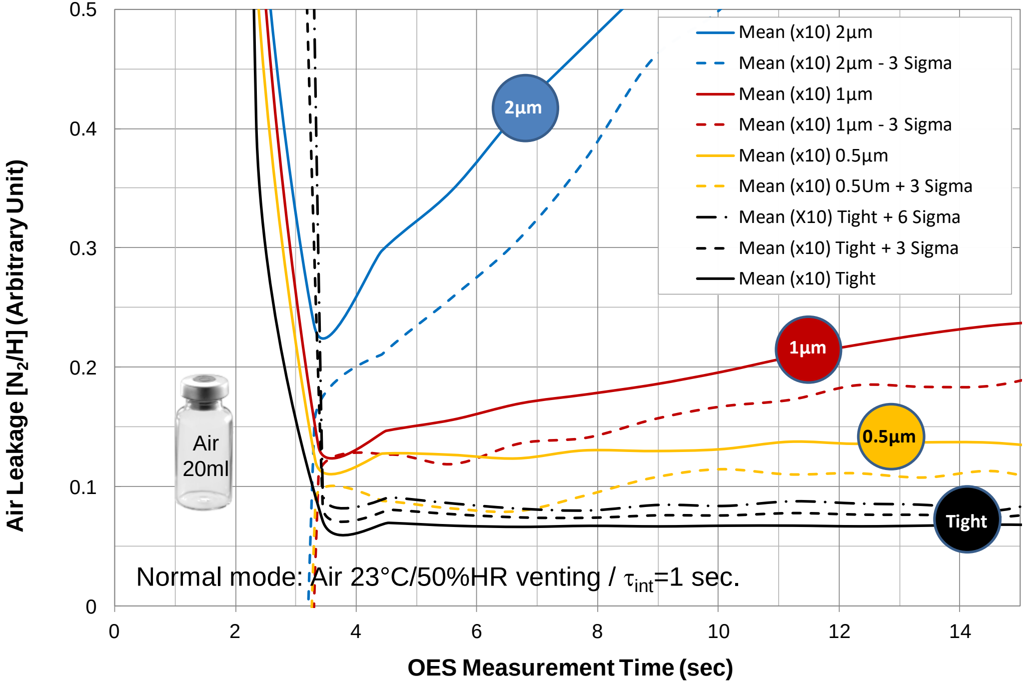
O.E.S. – Method is not volume dependant

→ 0.5µm defect (sharp edge orifice) can de detected in a batch of 10 vials and/or on 1 vial in the same test chamber.





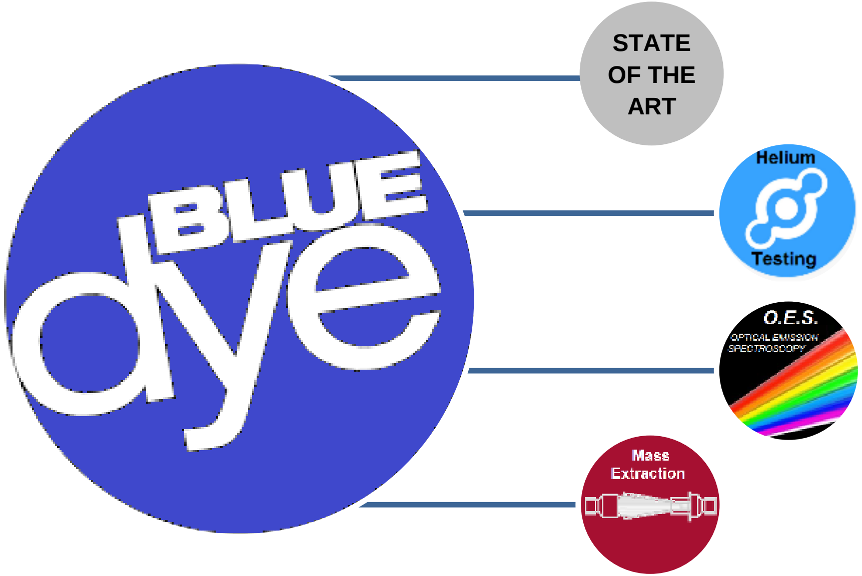
O.E.S. - Fast and sensitive



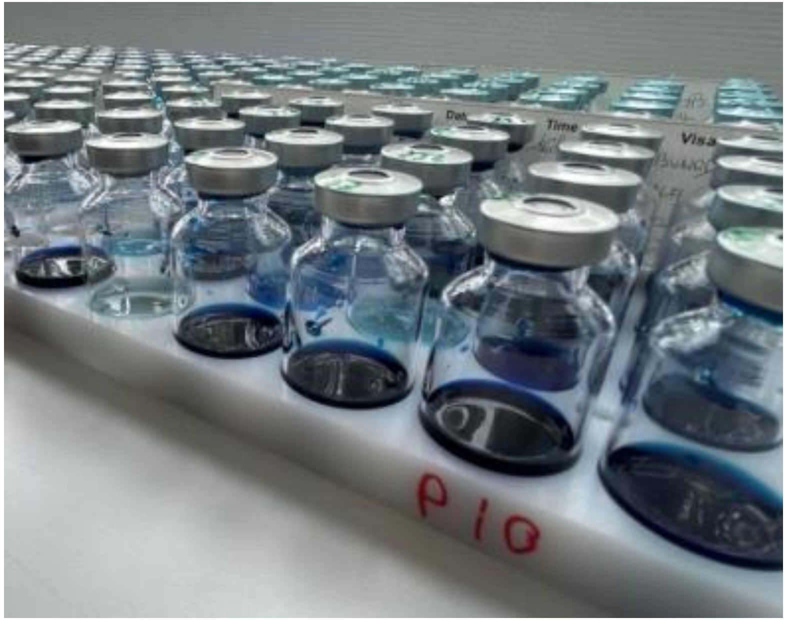
The Air Leakage raw signal corresponds to the intensity ratio $[N_2/H]$.

OES (Ambiant air venting) 23°C / 50% RH		
Detection Limit	Total Test Duration	
	Leak-3σ Blank+**3σ**	Leak-3σ Blank+**6σ**
2 µm	10 sec	10 sec
1 µm	10 sec	10 sec
0,5µm	10 sec	14 sec

Pfeiffer Vacuum Comparative Study



CCIT Comparative Study – Sample Preparation



Glass µ-pipettes

Φ: 0.1 / 0.2 / 0.4 / 1 / 2 / 5 / 10 µm

30 for each diameter

30 Negative controls (glue on the hole)

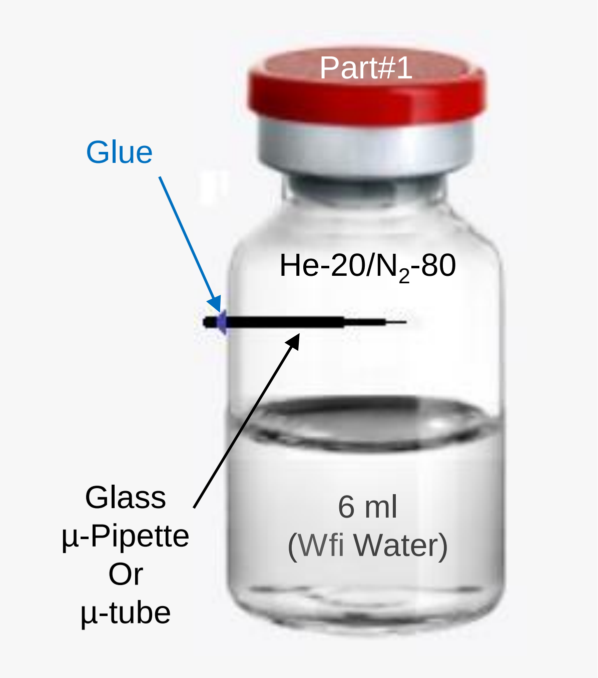
Capillaries (3 cm long)

Φ: 2 / 5 / 10 / 15 / 18 / 30 / 40 µm

30 for each diameter

30 Negative controls (glue on the hole)

CCIT Comparative Study – 20 mL Vial



→ **Gas Headspace: He 20% / N_2 80%**

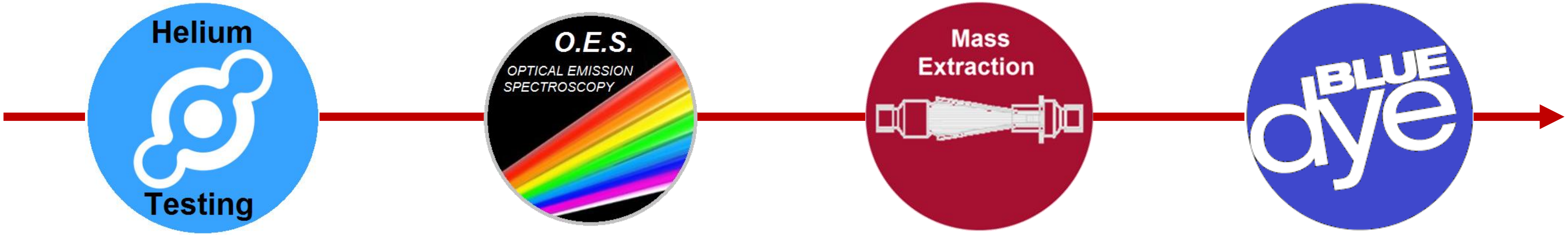
- 20% for He measurements.
- 80% N_2 for O.E.S measurements (~ [N_2] in air)
- Mass Extraction measures the global flow escaping from the sample.

→ **Leak artifacts are located in the gas headspace** no contact with the liquid.

CCIT Comparative Study

1/. HELIUM MASS SPECTROMETRY

3/. MASS EXTRACTION



2/. OPTICAL EMISSION. SPECTROSCOPY

4/. BLUE DYE INGRESS TEST

CCIT Comparative Study – 20 mL Vial

Photos Philippe Bunod – May 2021

1/. Drilling Holes
1,5 & 0,5 mm

2/. Fixing capillaries and glass µ-pipettes with UV-glue

3/. Filling with 6ml of Wfi Water

CCIT Comparative Study – 20 mL Vial

Photos Philippe Bunod – May 2021

4/. Air evacuation
He:20%/N_2:80% filling

5/. Installation of the rubber plug

6/. Crimping, removing flip cap
& Labeling

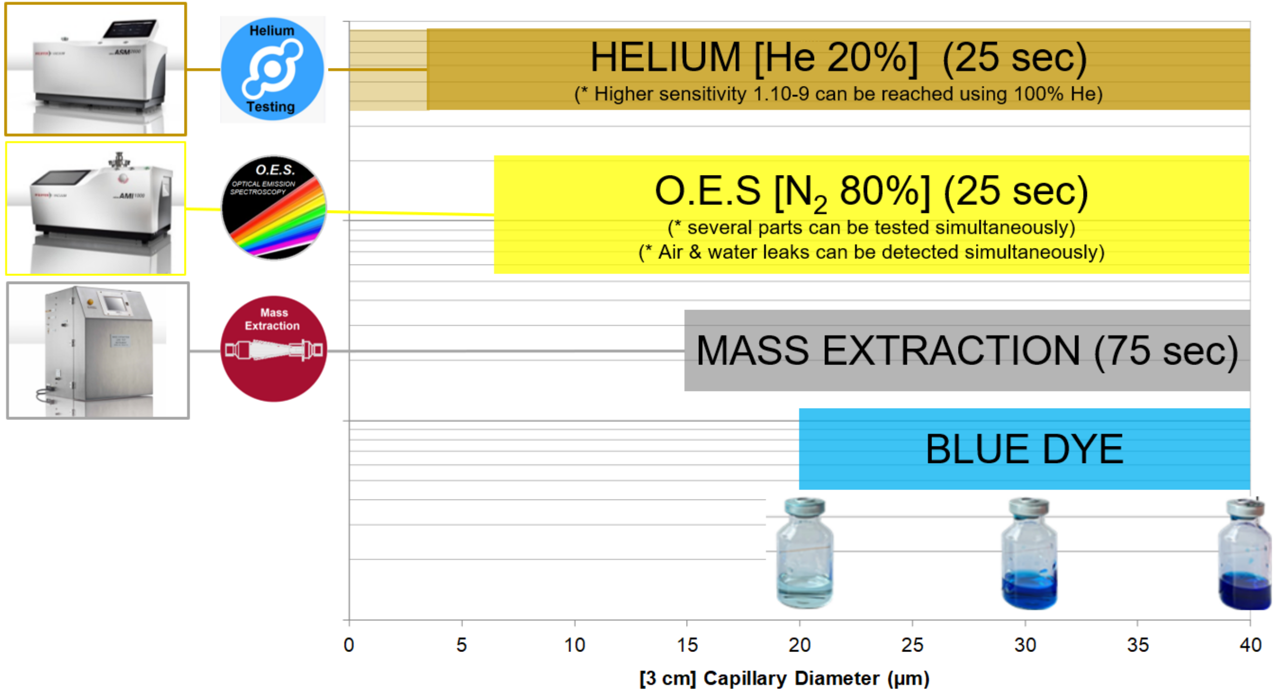
Blue Dye Ingress Standard Test Conditions

Method Parameters	USP 31<381> Ph.Eur. 3.2.9	ISO 8362-5 Annex C	Modified ISO	Pfeiffer Vacuum
Dye solution	1% aq. Methylene Blue			
Vacuum	-27 kPa	- 25 kPa	-37 kPa	-37 kPa
Immersion time at Vacuum	10 min	30 min	30 min	60 min
Time at P_{Atm}	30 min	30 min	30 min	30 min
Detection	Visual Inspection			

Dye solution: 1% FD&C Red No. 40 and 0.25% sodium dodecyl sulfate (SDS) in de-ionized water.

Dye recipe has been set-up to get detection limit measured by Burrel & all using 3ml water filled vials (Bigger headspace and dilution volume (6ml). → Immersion time at vacuum = 60 min

Summary – Capillaries (3 cm)



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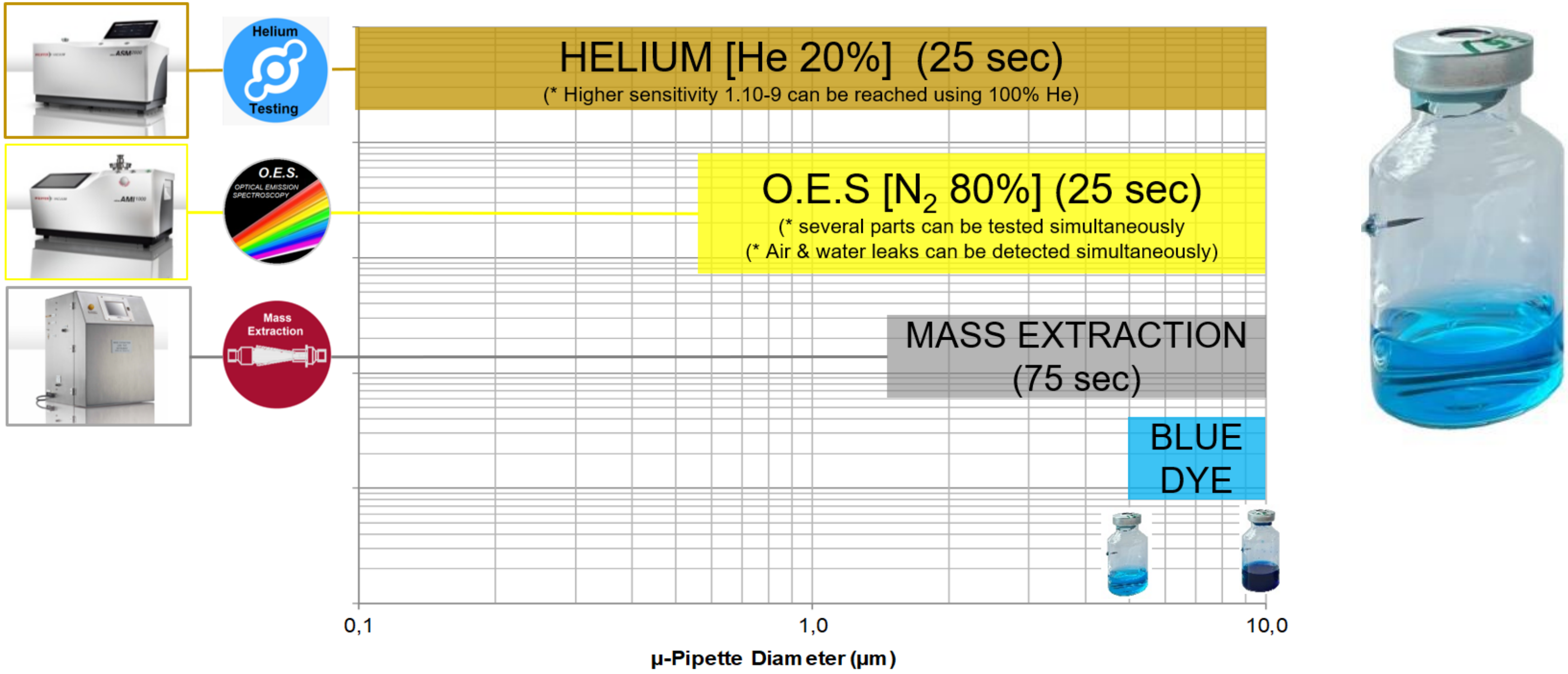
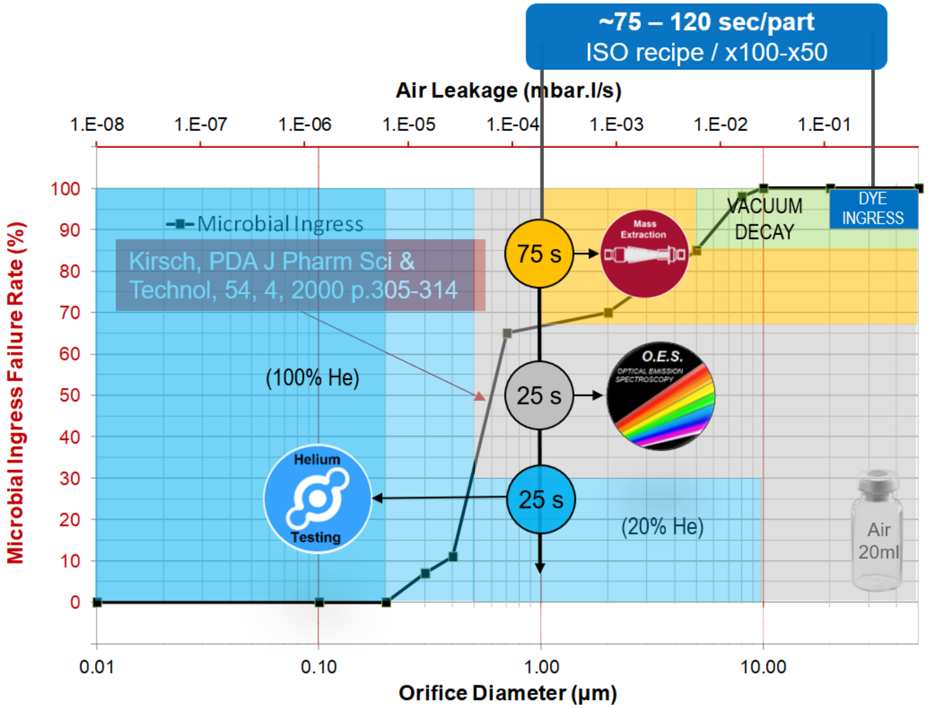
Summary – µ-pipettes (orifice)



Global Overview of vacuum CCIT Solutions



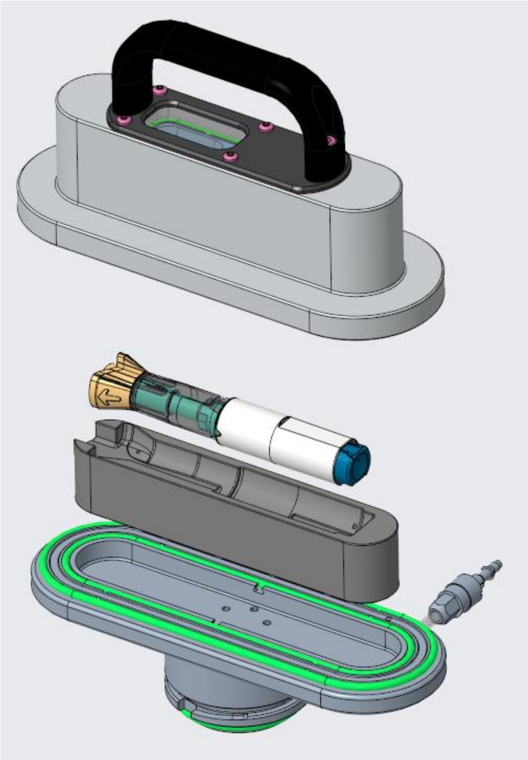
Correlation established by Kirsch & all, has been performed on glass vials using glass µ-pipettes artifacts.

The microbial ingress conditions used for this study corresponds to a **worst case:**

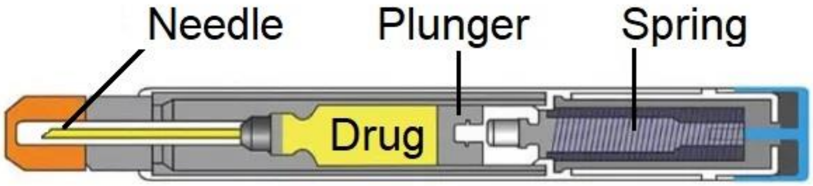
Figure 2 – The correlation of microbial failure rate (%) and the mean logarithm of the absolute leak rate and nominal leak diameter for modified SVPs. The absolute leak rate (standard cubic centimeter per second) was determined by mass-spectrometry based helium leak rate detection. Microbial failure was measured by microbial ingress after 24 hour immersion in a bath (37°C) containing 10^8 to 10^{10} *P. diminuta* and *E. coli* organisms/ml and a 13 day. 35°C incubation

Test of Auto-Injectors

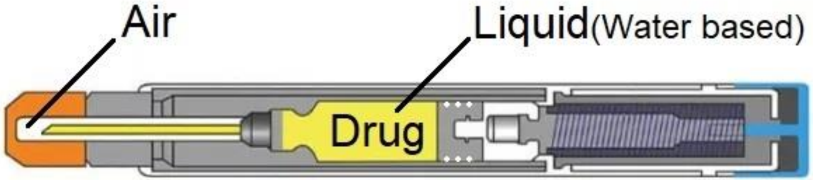
O.E.S. the perfect solution for the CCI test of auto-injectors ?

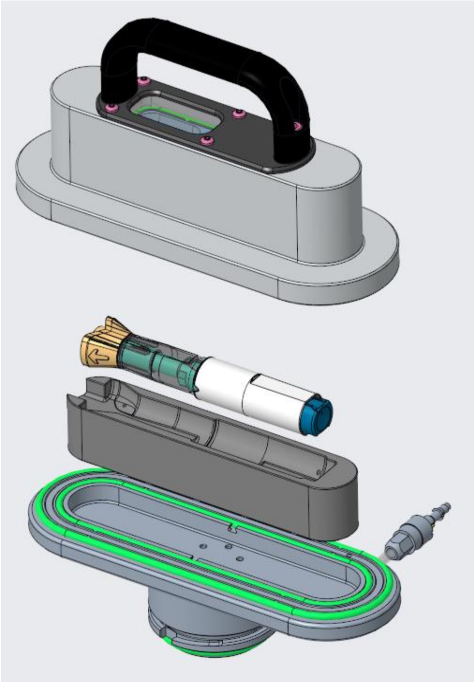


CCIT challenges on Auto-injectors

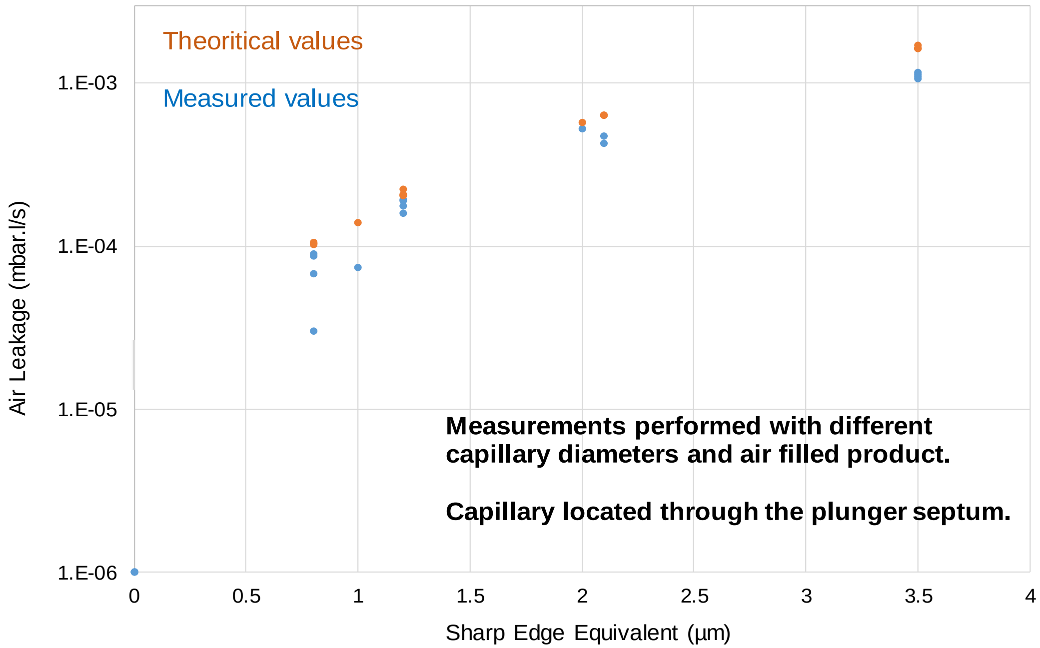


- **Detection of small Air leakage or Large Water leakage at the needle shield → bigger risk during the assembly process !**
- Water leaks at the plunger
  → Difficult to detect with the 3 sealing rings in serie





OES tests on Air filled AI equipped with capillaries



1 µm orifice (equivalent ~1,5.10^{-4} mbar.l/s Air Leakage) can be easily detected with O.E.S.

O.E.S. to test Auto-injectors

- In a single test sequence O.E.S. is able to:

  - measure air leakage > 1 µm orifice

  and/or

  - detect water leak > 5 µm (qualitative test)

  within about 45 seconds !

Conclusions

O.E.S. technology offers many advantages:

- **Non-destructive** and **deterministic** and **quantitative**
- **Easy to operate** and easy **to set-up** (non sample preparation)
- **Versatile** (no format parts required)
- **Selective** (Air/N_2, Ar, CO_2, and water leaks can be detected simultaneously)
- **Volume independent** (test of complex product or test per batch)
- **High sensitivity** combined with **high throughput** (i.e.: 0.4µm orifice detected within 7 seconds on 20ml glass vials)

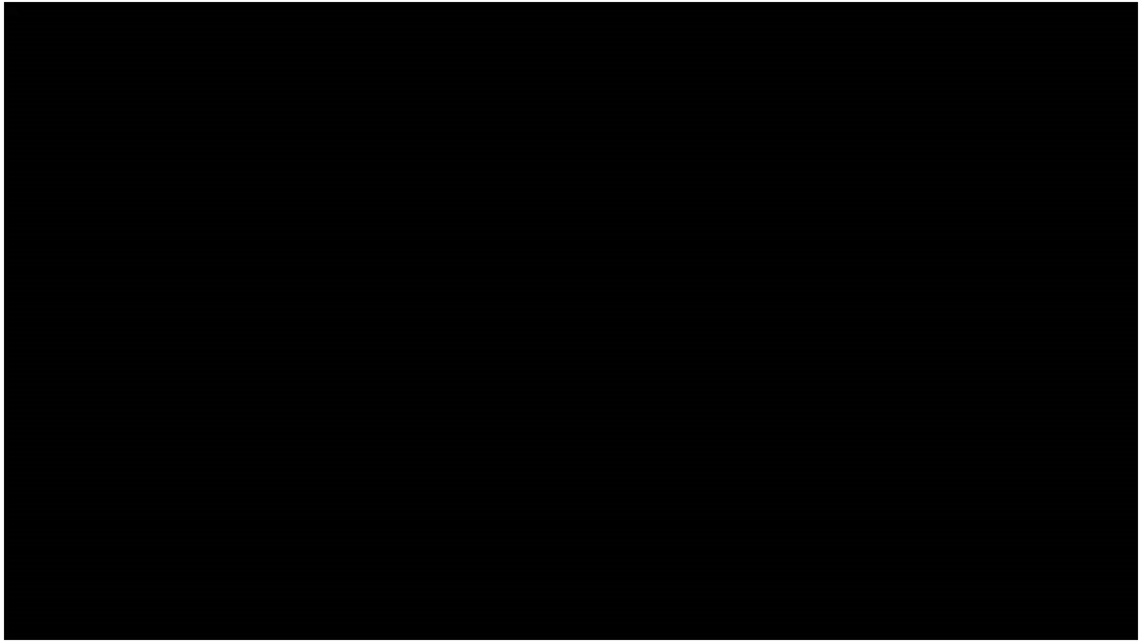
Conclusions

- AMI equipments, using O.E.S. spectroscopy have been qualified as IPC test for blister packs (high sensitive inhalation drugs).

- Promising technology to perform high sensitivity 100% in-line leak testing.

→ 0.4µm defect (sharp edge orifice) can be detected in 30 sec on glass vial tested one by one or by batch of up to 10, 50, 100.

Thank you for your attention !



Links http ://www.pfeiffer-vacuum.com
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