Optical Emission Spectroscopy, an emerging technology for CCIT

Instructor:

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

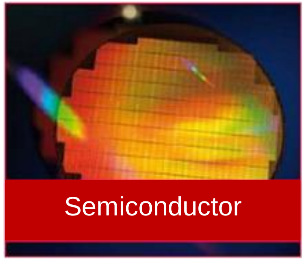
PDA
Parenteral Drug Association

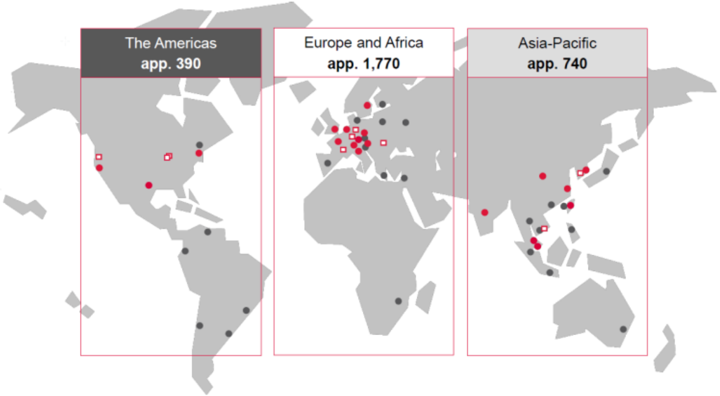
CONNECTING PEOPLE SCIENCE AND REGULATION®

Structure

1. Pfeiffer Vacuum at a glance
2. The 3 CCIT technologies proposed by Pfeiffer Vacuum
3. Optical Emission Spectroscopy :
   - How does it work ?
   - Influence and limiting factors
   - Advantages
   - Detection of gross leaks
4. Vacuum test methods / Microbial ingress risk
5. Conclusions

Pfeiffer Vacuum, leader in vacuum technology





Production
- Germany: Asslar & Göttingen
- France: Annecy
- South Korea: Asan
- Rumania : Cluj
- USA : Indianapolis & Yreka,
- Vietnam : Ho-Chi-Minh-City

Sales and Service

Distributors

Total employees
2,945

3 equipments in our CCIT portfolio

MICRO-FLOW AND MASS EXTRACTION

Micro-flow sensor

USP ASTM ASTM F3287-17

HELIUM MASS SPECTROMETRY

Magnetic deflection spectrometer

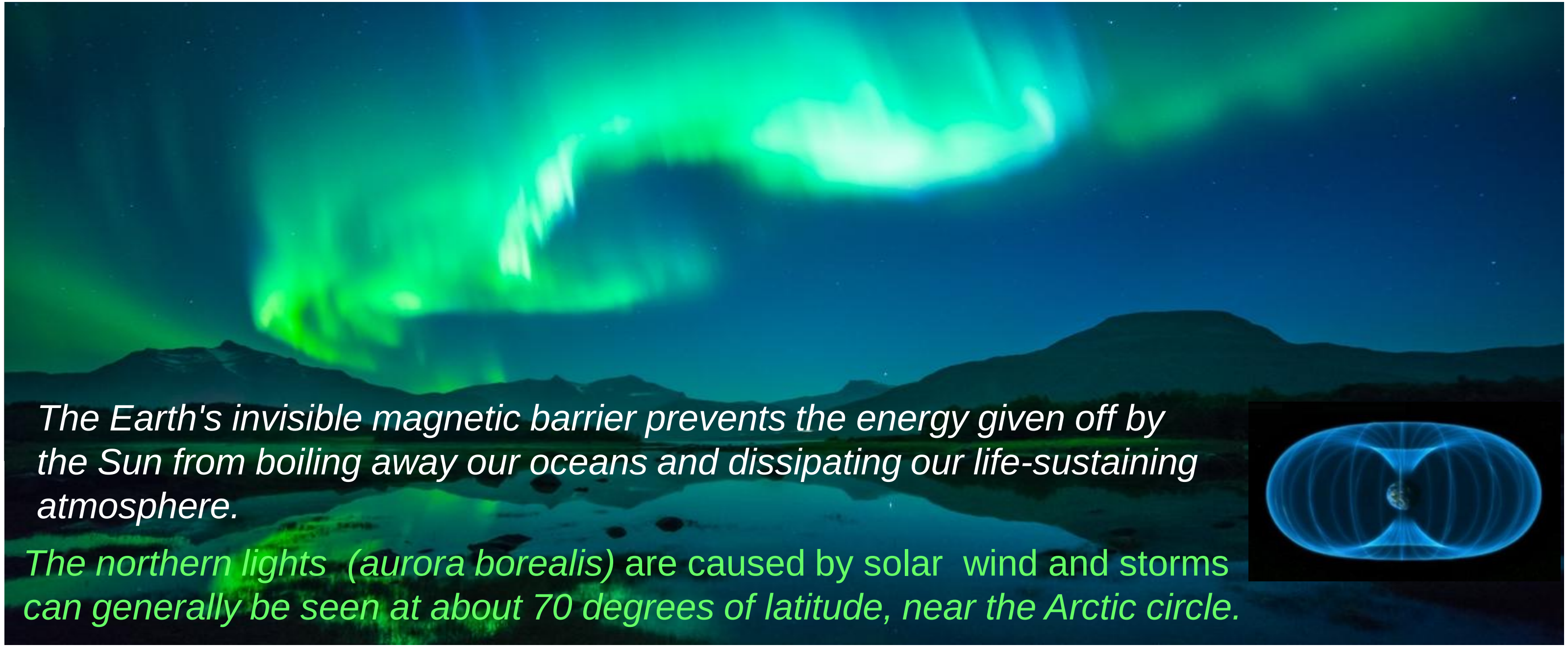
USP ASTM ASTM F2391-05

OPTICAL EMISSION SPECTROMETRY

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

USP *Emerging Technology*

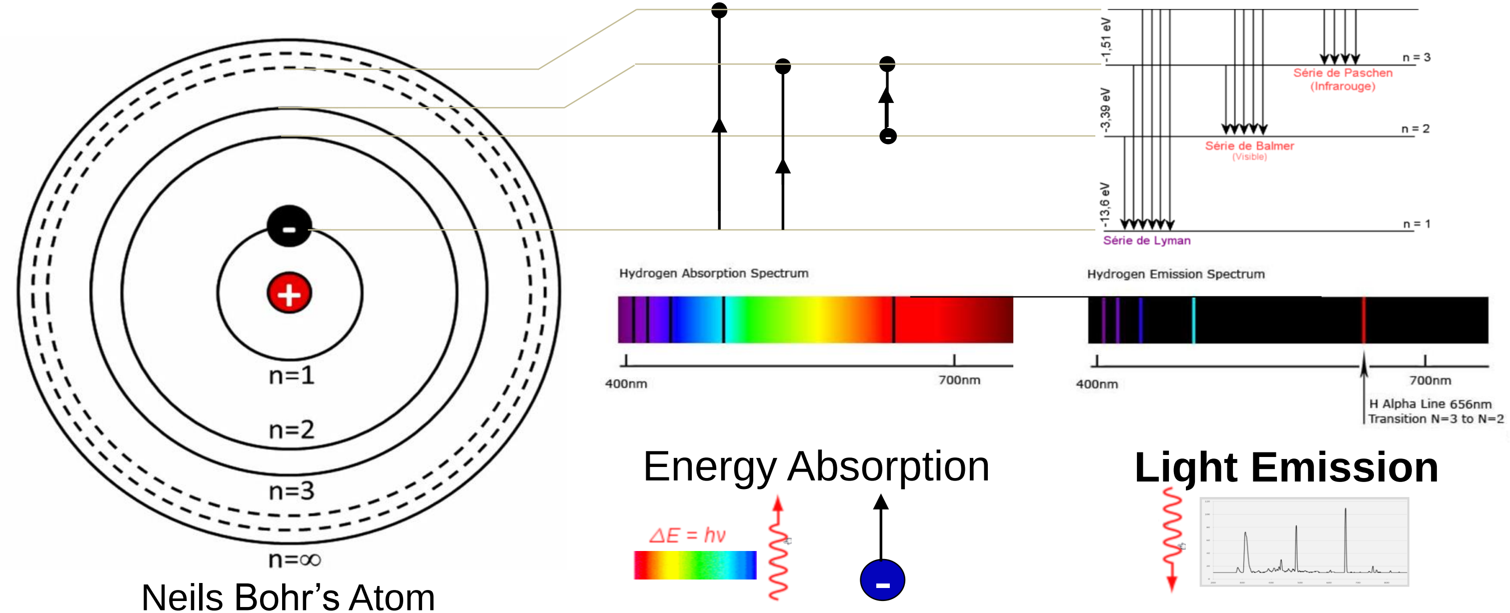
O.E.S. – Operating principle



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

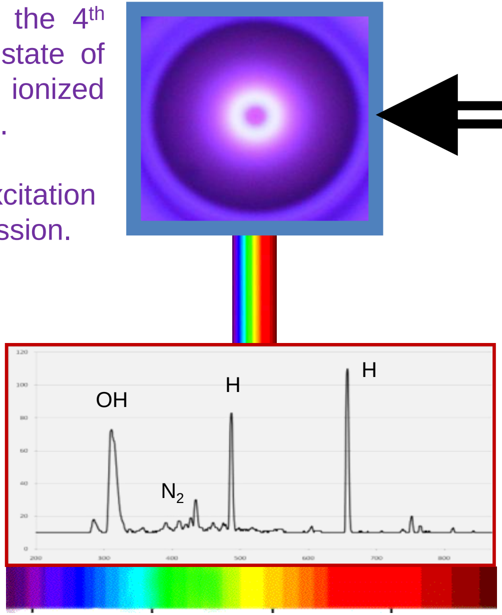


Neils Bohr’s Atom

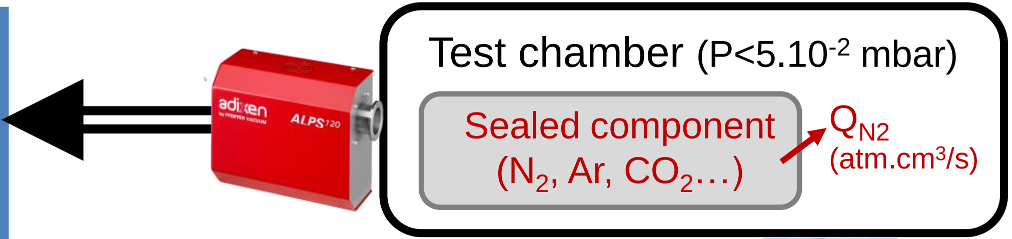
O.E.S. – Operating principle

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

Plasma de-excitation give light emission.

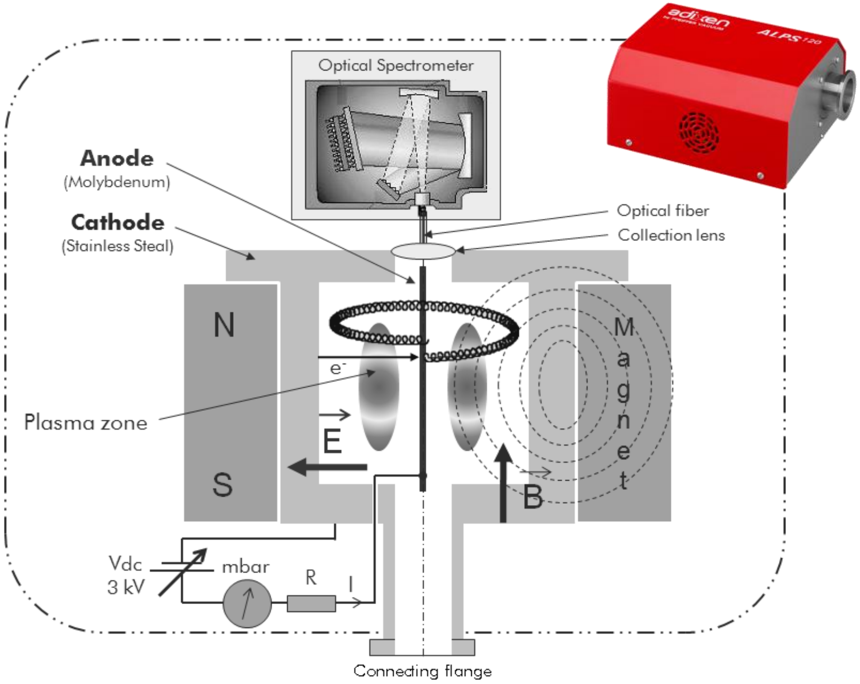


200nm 850nm



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

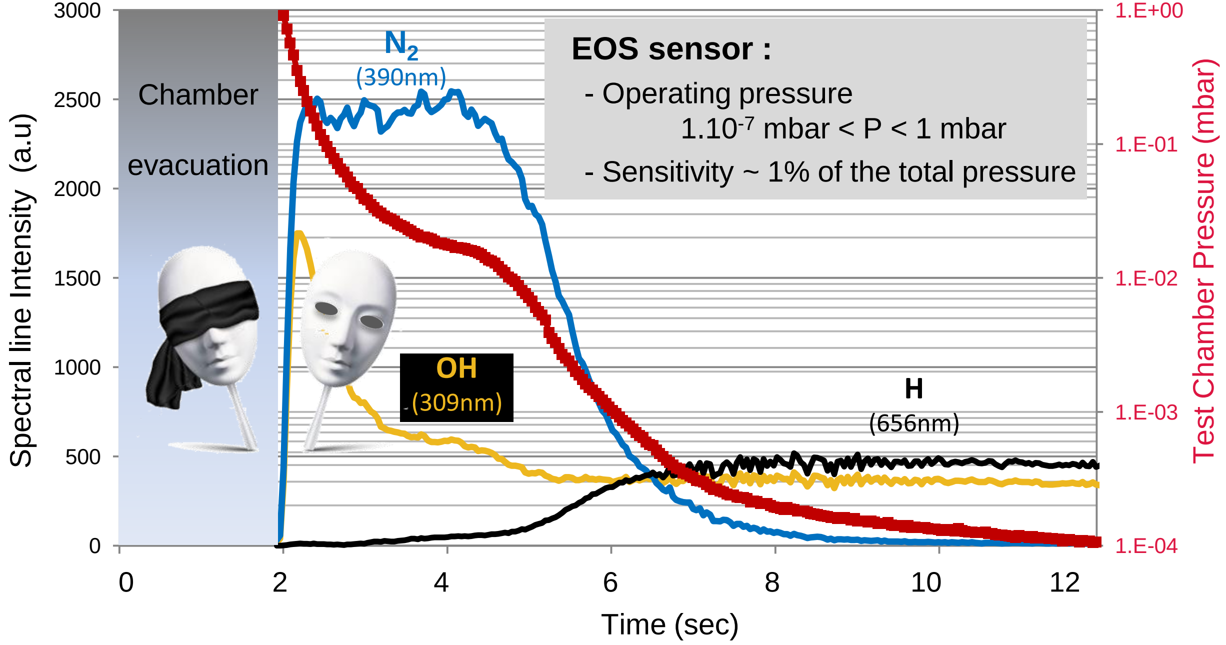
O.E.S. Sensor Design (Pfeiffer Vacuum patented technology)



Cold Cathode Inverted Magnetron design:

- Current (I) is fixed (few µA)
- High Voltage (Vdc) is adjusted to keep the intensity constant
- The plasma (ionized gas) is generated by electron collisions
- The light is collected by an optical lens and analyzed by an optical spectrometer

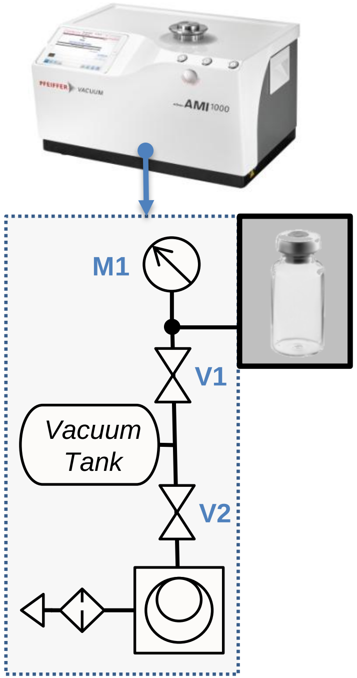
O.E.S. – Real time measurement



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:**

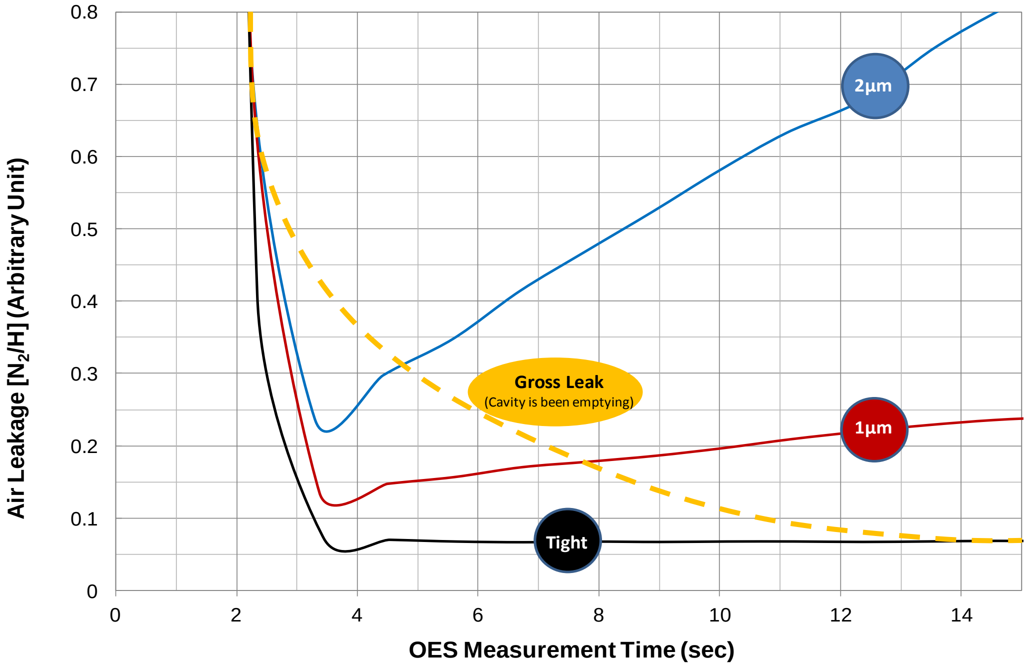
  - Pressure must be below the vapor pressure of water.

  - 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)

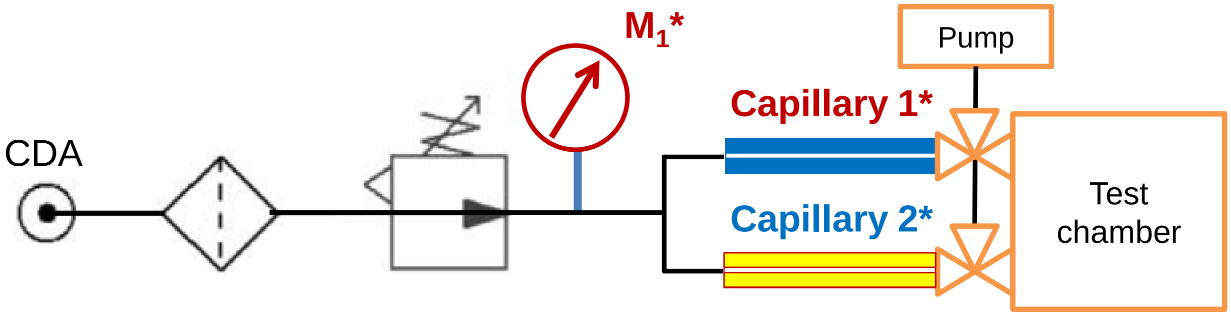


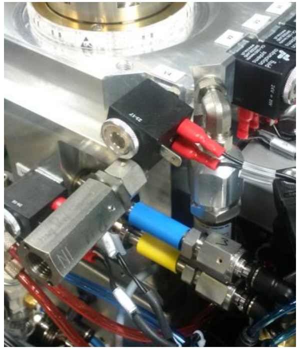
The air leakage corresponds to the intensity ratio [N_2/H]

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

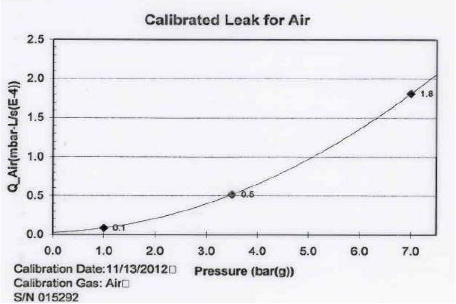
In case of gross leak (>100µm for 1cc headspace), depending on the headspace volume we can see the container being evacuated.

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



PDA Parenteral Drug Association

O.E.S. – Operating sequence

1/. Part loading (manually or automatically)

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

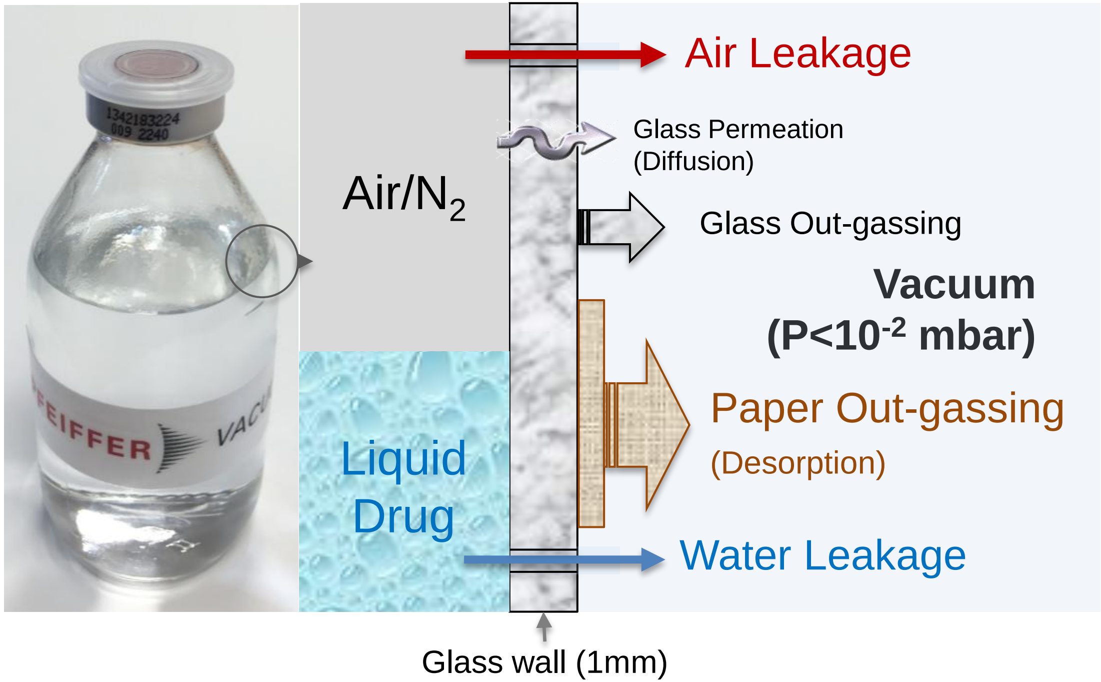
3/. Chamber pumping (few mbar → $<10^{-4}$ mbar)

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

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

6/. Part unloading

Permeation / Out-gassing / Leakage



For all global vacuum test methods, **Permeation** and **Out-gassing** flows correspond to virtual leaks and **limit the sensitivity.**

Permeation of air is generally slow and far below the MALL level. **It does not limit the sensitivity**.

Out-gassing flow is made of Water (80%) and others gas (20%).
It decreases slowly when the time under vacuum increase.
It **strongly impacts the sensitivity and/or cycle time.**

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… but that increase the risk to miss gross leaks!
- Gross leak detection can be challenging in case of small gas headspace volume combined with a low out-gassing drug.
  - Specific Massive Leak test can be performed prior to O.E.S measurements

O.E.S. – Measurements are volume independent

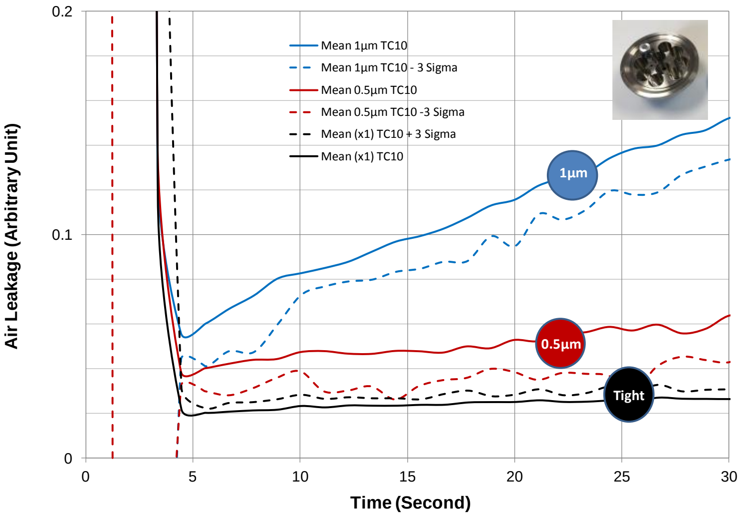
Measurement and sensitivity are not impacted by:

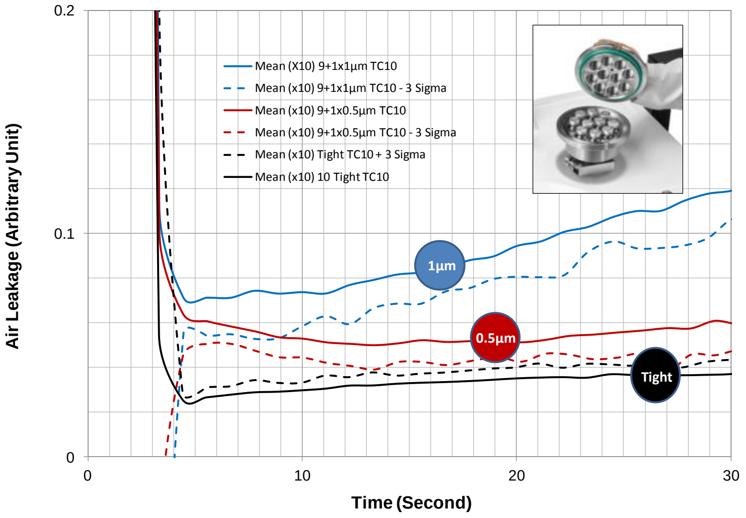
- container expansion during the test
  → Tests can be performed on semi-rigid containers

- 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. – Selectivity

OES multi-gas sensor:

- different gases (N_2, H_20, Ar, CO_2…) can be detected simultaneously
  → detection limit depends on the gas which is tracked for leak detection

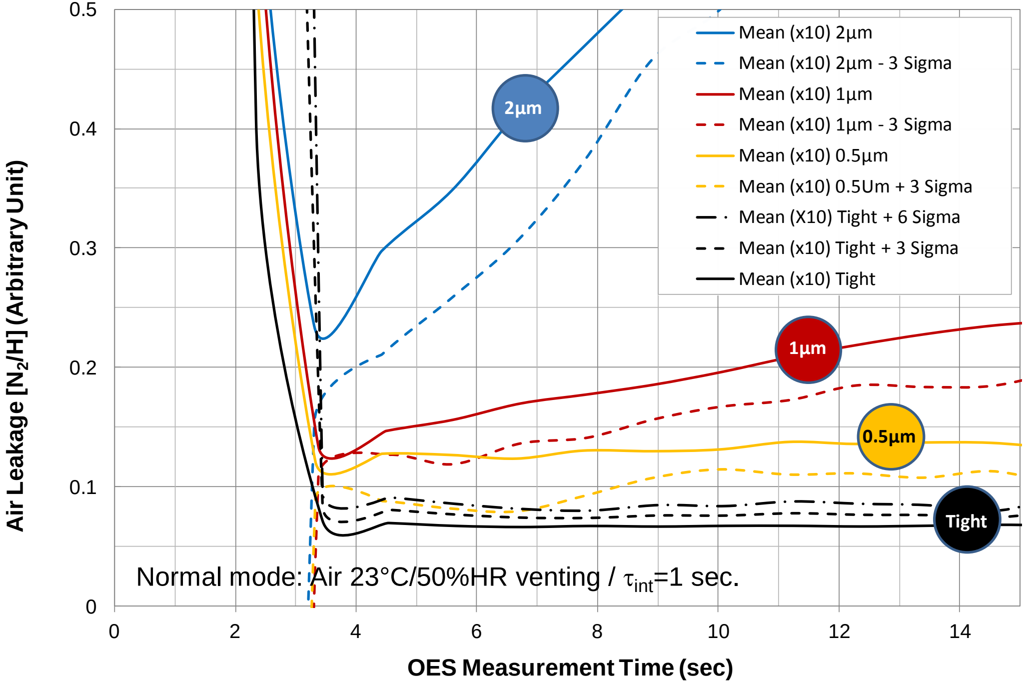
- no interference with out-gassing,
  → Air / N_2 is tracked independently of moisture (out-gassing)
  → Air / N_2 is tracked independently of Argon used for chamber venting

- Air/N_2 leak and water leak can be detected simultaneously

AMI 1000, Unique Selling Proposition

- **High sensitivity & high throughput**
  - 10 sec to detect orifice < 0.4µm on glass vial
  - No impact of the test volume on the sensitivity (test per batch possible, up to 10, 50, 100)
- **Selectivity**
  - Air & water leaks can be measured/detected simultaneous
  - Possible selection of the tracer gas (N_2, CO_2, Ar, H_20,…)
- **Versatile and easy to use**
  - Applicable for various kind of non-porous packaging's
  - No sample preparation

O.E.S. - Fast and sensitive

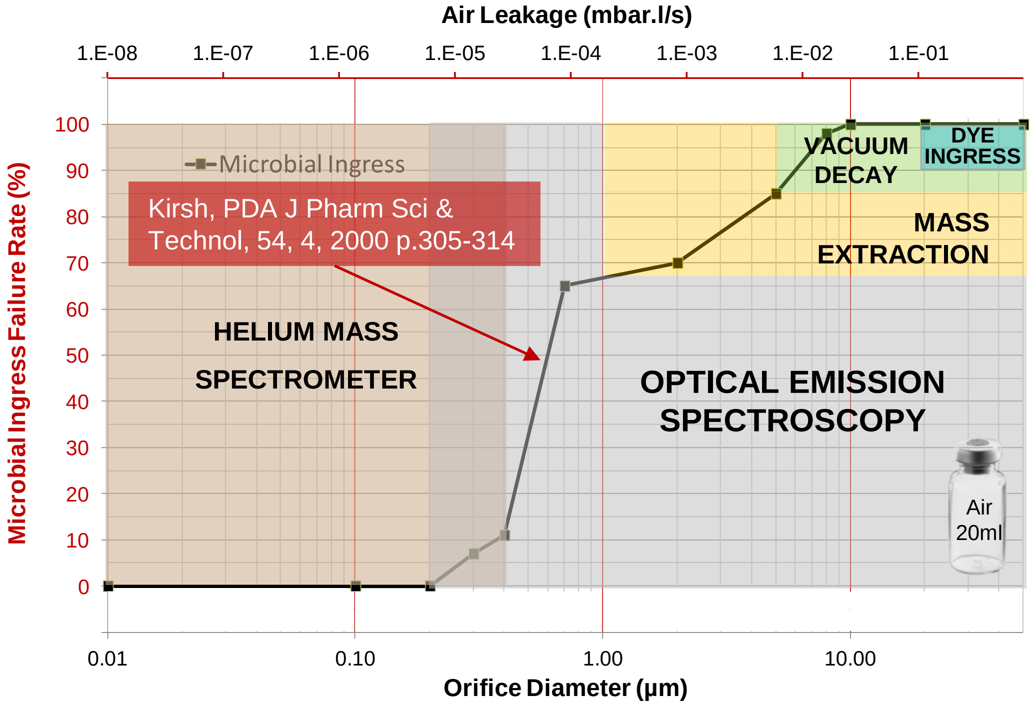


The Air Leakage raw signal corresponds to the intensity ratio [N_2/H].

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

CONNECTING PEOPLE SCIENCE AND REGULATION®

Vacuum Test Methods/Microbial Ingress Risk



Correlation established by Kirsh & 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

Conclusions

O.E.S. technology offers many advantages:

- **Non-destructive** and **deterministic**
- **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)
- In high sensitivity mode **0.2µm orifice can be detected**

Conclusions

- AMI equipments, using O.E.S. spectroscopy have been qualified as IPC test for the production of 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 10 sec on glass vial tested one by one or by batch of up to 10.

Thank you

for your attention !

Links http ://www.pfeiffer-vacuum.com
Email : philippe.bunod@pfeiffer-vacuum.fr