Optical Emission Spectroscopy, an emerging technology for CCIT

Instructor:

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Parenteral Drug Association

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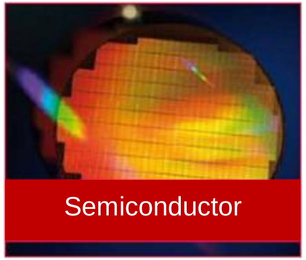
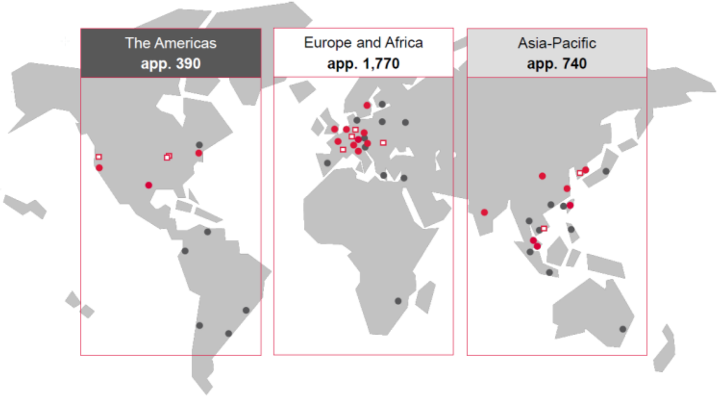
Structure

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

587 M€ in 2017

Total employees
2,945

3 technologies for CCIT solutions

ASTM F3287-17 **ASTM F2391-05**

Typical features of PV CCIT solutions

- Deterministic & non-destructive
- Applicable for non-porous containers
- Global test under vacuum (integral leak test)
- The test pressure depends on the technology:
  Helium < 10^{-1} mbar / Mass Extraction~1 mbar / OES < 5.10^{-2} mbar

HELIUM MASS SPECTROMETRY

OPTICAL EMISSION SPECTROSCOPY

MASS EXTRACTION

Typical features of PV CCIT solutions

- We are **detecting** gas flow escaping from a leaky container
  → *it is impossible to detect a defect when it is clogged !*

- We are **measuring** a gas leakage (atm.cc/s)
  → *leakage can be converted in an equivalent defect size, i.e: sharp edge orifice Φ (µm)*

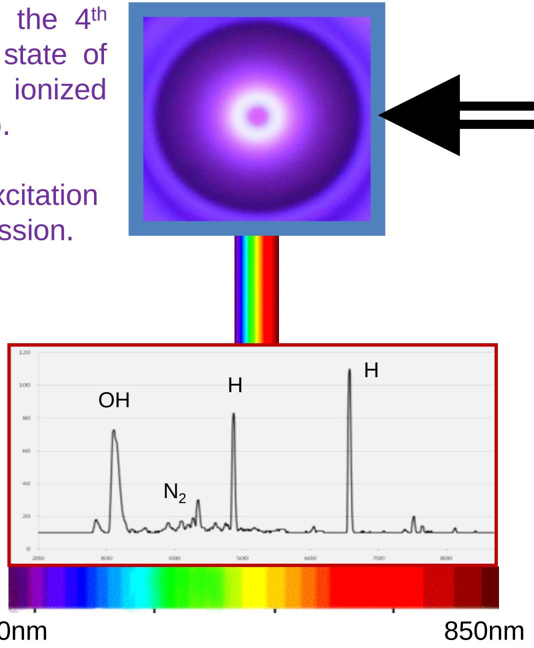
- The **calibrations** are performed using **certified leaks or orifices**
  → *no need to generate positives for calibration.*

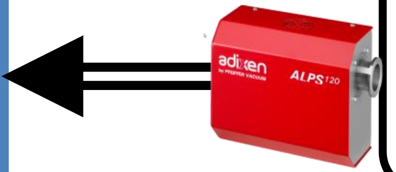
- The **detection of gross leaks** is challenging for low headspace dry filled containers due to the risk to empty the container before testing
  → *However, there are multiple countermeasures implemented to address this concern.*

O.E.S. – Operating principle

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

Plasma de-excitation give light emission.





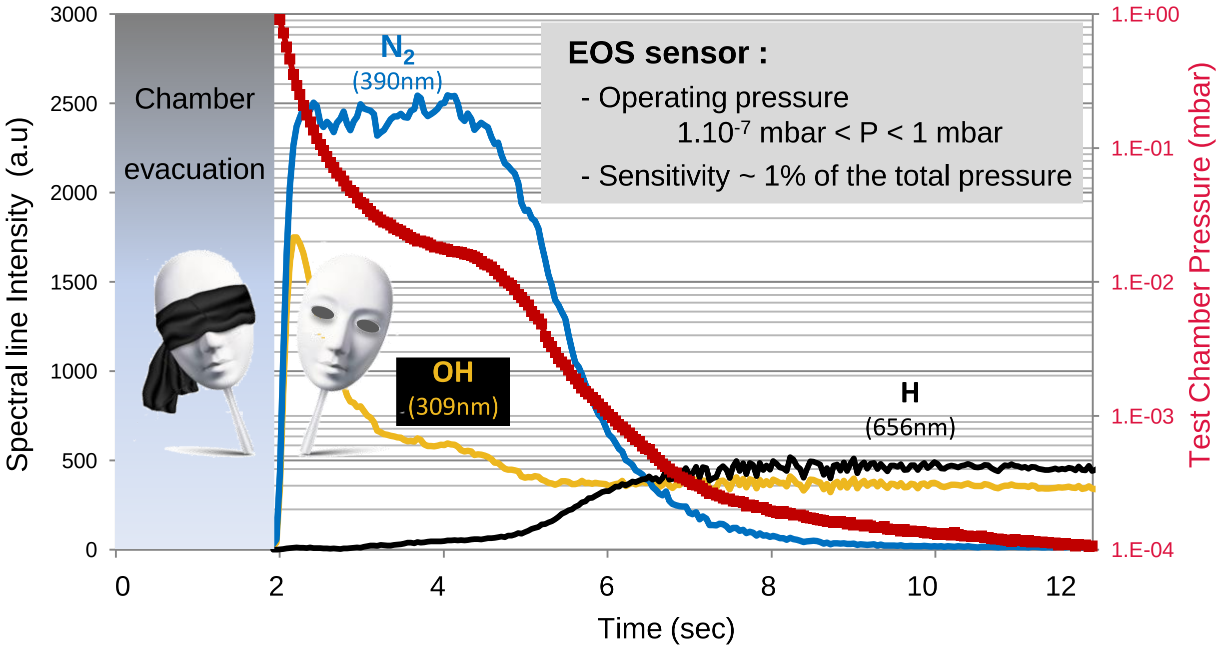
Test chamber (P<5.10^{-2} mbar)

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.

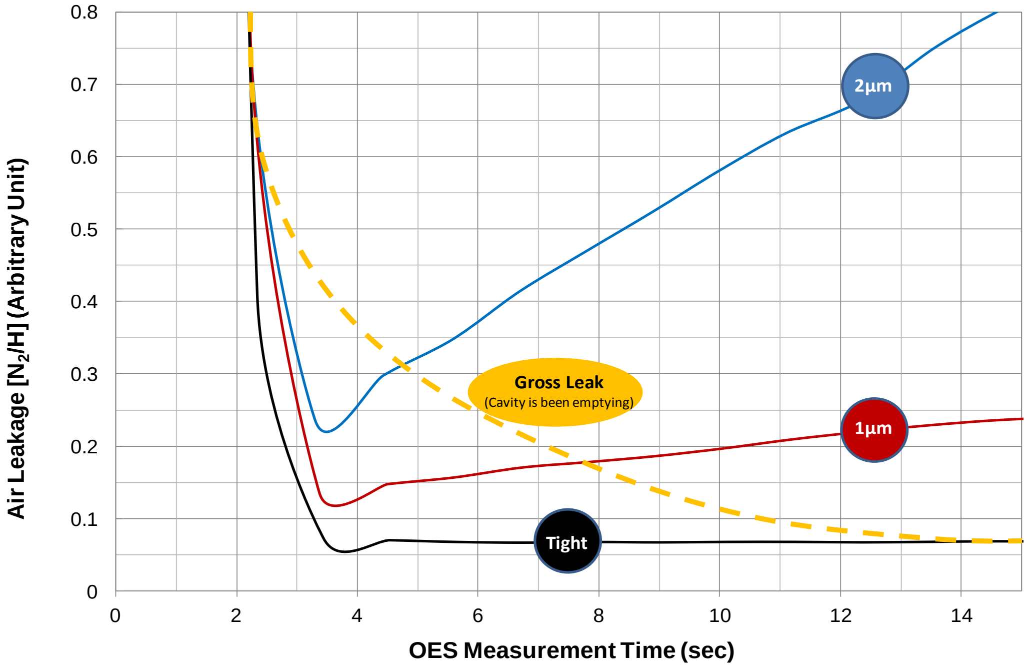
O.E.S. – Real time measurement



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

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

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), depending on the headspace volume we can see the container being evacuated.

O.E.S. – Operating sequence

1/. Part loading (manually or automatically)

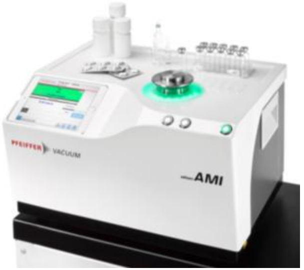
2/. Chamber evacuation (1000 → few mbar)
(Gross Leak detection)

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.**

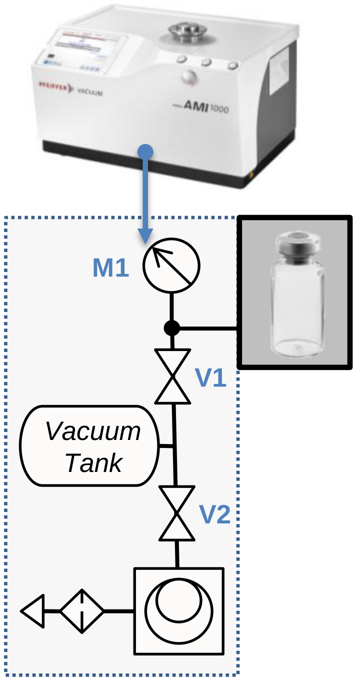
OES – Influence & limiting factors

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

Massive leak detection prior to OES



- **AMI includes a gross leak detection module**

  - GO/NOGO test = qualitative measurement.

- **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.

- **Fast detection preventing equipment contamination**

  - In case of Gross Leak (air and/or <u>liquid</u>), the high vacuum circuit and OES sensor are not contaminated.

  - Only few components need to be cleaned or replaced.

O.E.S. – Measurements are volume independent

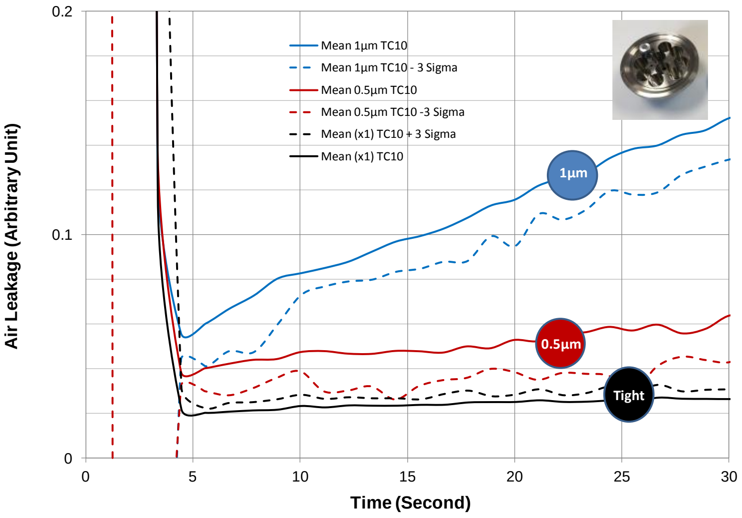
Measurement and sensitivity are not impacted by:

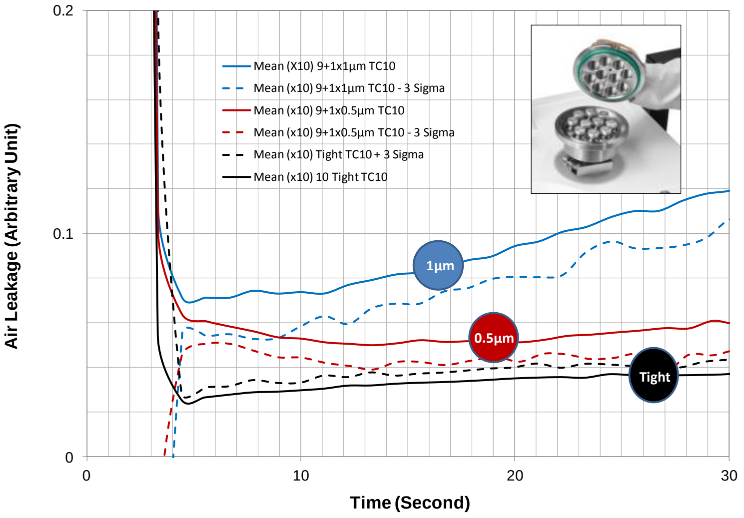
- container expansion during the test
  → Tests can be performed on semi-rigid containers

- 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

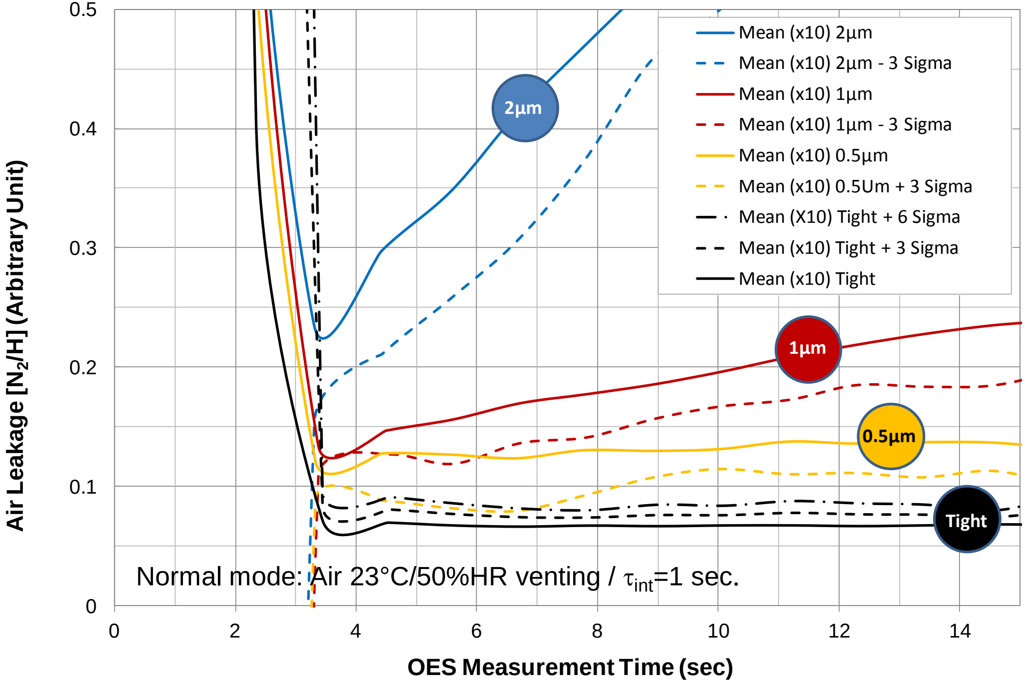
OES multi-gas sensor:

- 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

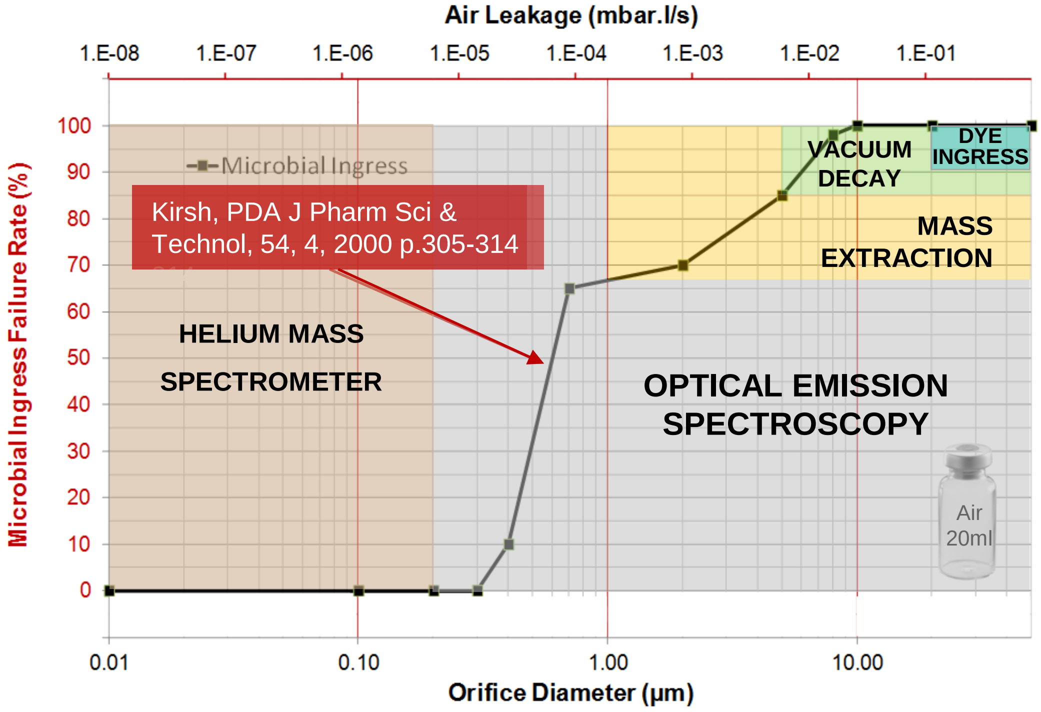
O.E.S. - Fast and sensitive



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

Vacuum Test Methods/Microbial Ingress Risk



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

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 and water leaks can be detected simultaneously)
- **Volume independent** (test of complex product or to 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 !

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