# Mass Extraction Technology for Pharmaceutical Packaging CCIT

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# Pfeiffer Vacuum – Global Leader in Vacuum Technology & Leak Detection

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&

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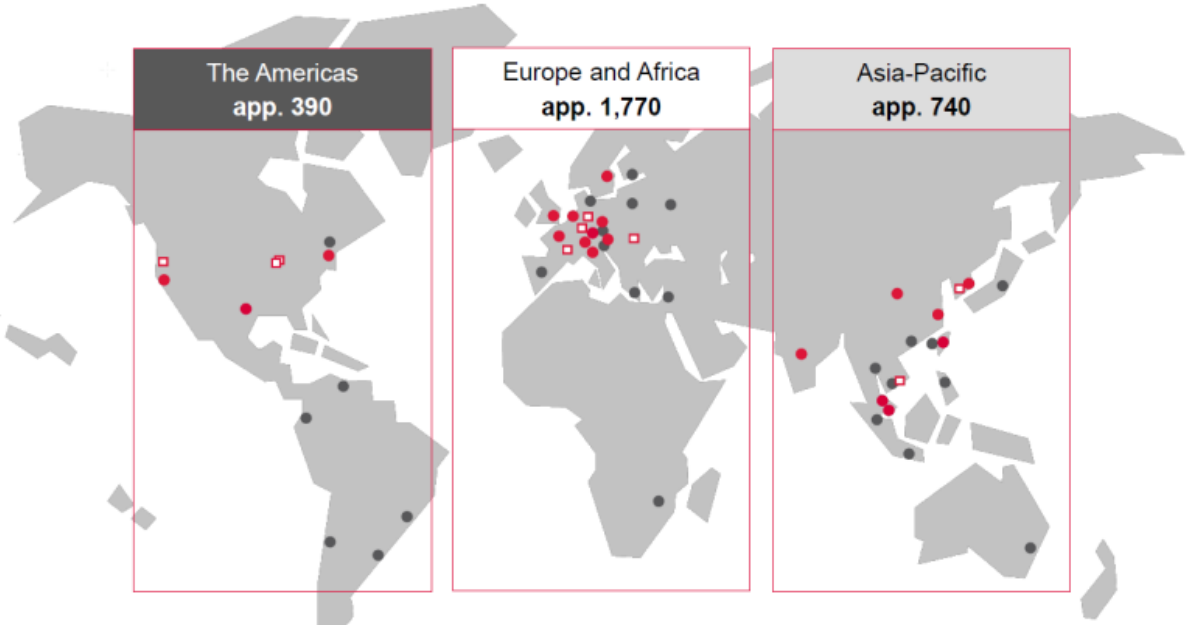
  - France: Annecy
  - South Korea: Asan
  - Rumania : Cluj
  - USA : Indianapolis & Yreka,
  - Vietnam : Ho-Chi-Minh-City
- **Sales and Service**
- **Distributors**




## CCIT Equipments

Helium Mass Spectrometry

Mass Extraction


Optical Emission Spectroscopy

# Pfeiffer Vacuum – Global Leader in Vacuum Technology & Leak Detection
# → Technologies for CCIT Solutions

## MICRO-FLOW AND MASS EXTRACTION

Air micro-flow sensor

ASTM F3287-17

## HELIUM MASS SPECTROMETRY

Magnetic deflection spectrometer


ASTM F2391-05

## OPTICAL EMISSION SPECTROMETRY

Multi-gas analyser ($N_2$, $CO_2$, Ar, $H_2O$)

# Structure

- Introduction of Mass Extraction & how does it work?
  - Method definition & System Overview
  - Test Signature & Equipment example
  - Sensor Types & Calibration
  - Design Configuration and Challenges
  - Differences to other Technologies
- ASTM Definition and Application Study
  - Description of Application Study
  - Measurement Results & Conclusion
- Application Example
  - Vial Testing for Lyophilized Products
  - IV Bags (100% Testing)
- Summary

# Introduction of Mass Extraction
# How does it work?

Mass Extraction: Use of Micro-Flow sensor measurement of the mass flow rate (µgram/min or scc/sec) from a Closed Container in a vacuum chamber to quantify and detect the presence of leaks equal to or larger than maximum allowed value/defect.

- The measured fluid is gaseous:
  - Air/Nitrogen.
  - At vacuum (for liquid filled containers: under the boiling point of water at room temperature ~ 18 torr) → water vapor.

# *Flow measurement is function of defect geometry*

*EXAMPLES:*

Hagen-Poiseuille for viscous flow (barometric, shallow vacuum)

$$Q = \frac{128}{\pi}\frac{d^4}{L} \times \frac{P_{IN} - P_{OUT}}{\mu}$$

Knudsen model for molecular flow (small defects, hard vacuum)

$$\dot{m} = \frac{\pi d^3}{\sqrt{2RT}} * \frac{P_{IN} - P_{OUT}}{L}$$

$P_{IN}$ - *pressure inside package*
$P_{OUT}$ - *pressure inside chamber*
*μ -Viscosity*
*T-temperature;*
*R-Specific gas constant*

Defect Size (EMG) diameter, Length

↑

Flow

Flow is **direct measurement** by mass extraction

↑

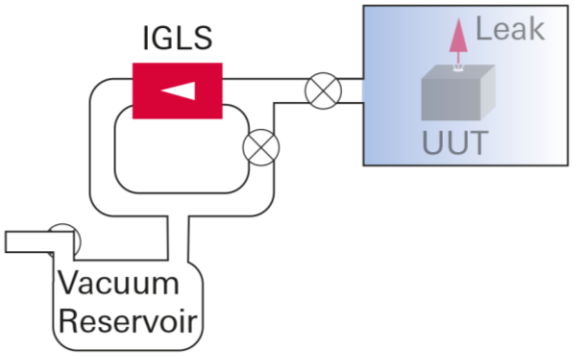
Q - volumetric flow *or*
*m* - mass flow

↑

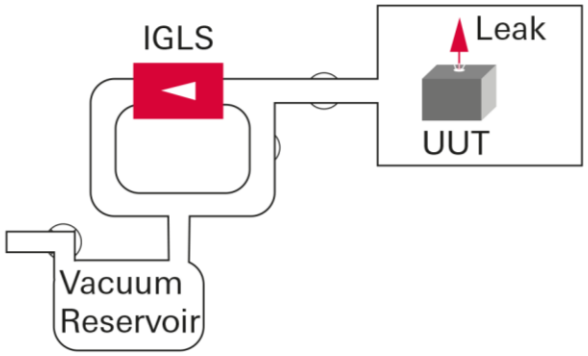
$\frac{\Delta P}{\Delta T}$

Flow is ***derived*** from Pressure increase rate (vacuum decay) **AND SPECIFIC KNOWN TEST VOLUME**

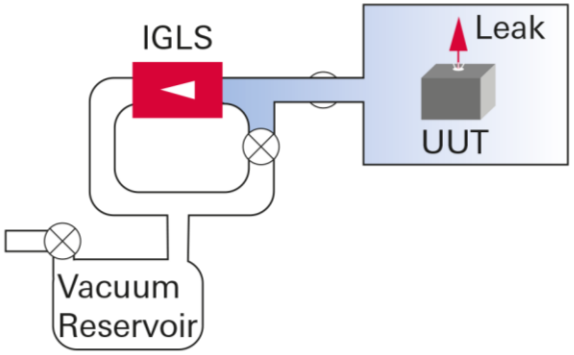
# Introduction of Mass Extraction - How does it work?
## → System Overview



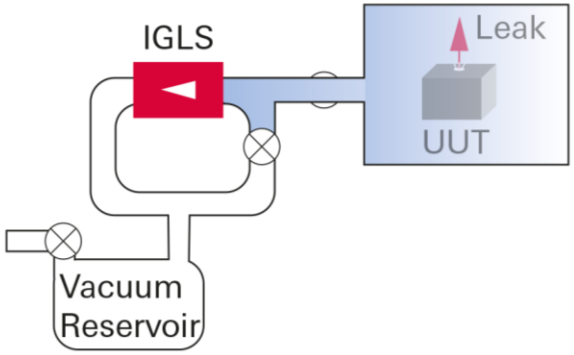

**1 Standby** – Vacuum Reservoir: $P_0$
– IGLS: no flow




**2 Evac** – All branches: $P_0$
– IGLS: no flow
– UUT: leaks



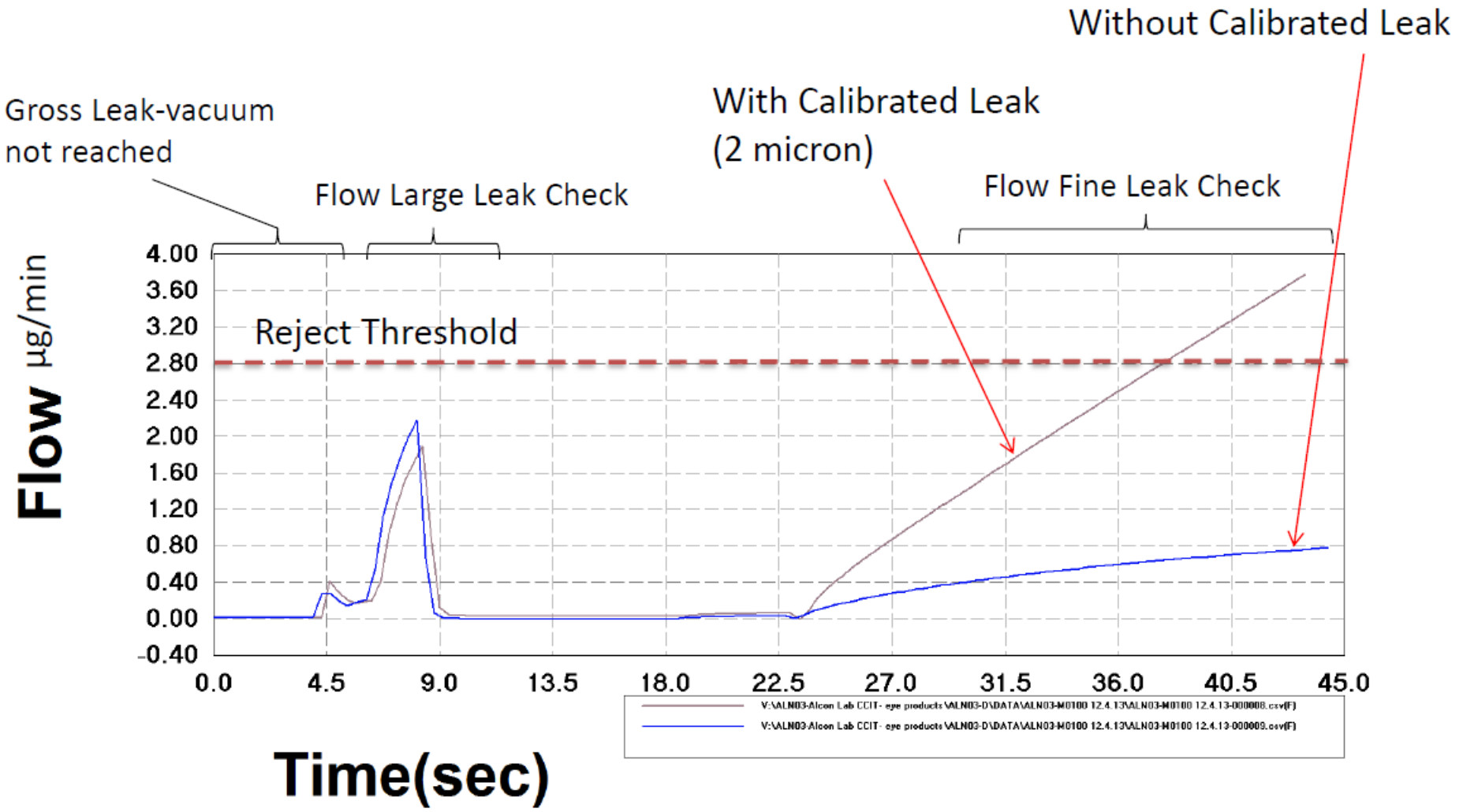

**3 Stabilize** – Leak: increases: $P_{chamber}$
– IGLS: begins flow




**4 Test** – Steady flow thru leak
– IGLS: measure flow thru leak

**Mass Conservation law: Mass extracted = mass leaked at steady state**

# Introduction of Mass Extraction - How does it work?
## → Test Signature



# Introduction of Mass Extraction - How does it work?
## → Equipment example: ME2 – Mass Extraction Cart

Test chambers for different vials

Storage area for laptop, packaging


additional chambers for other packaging

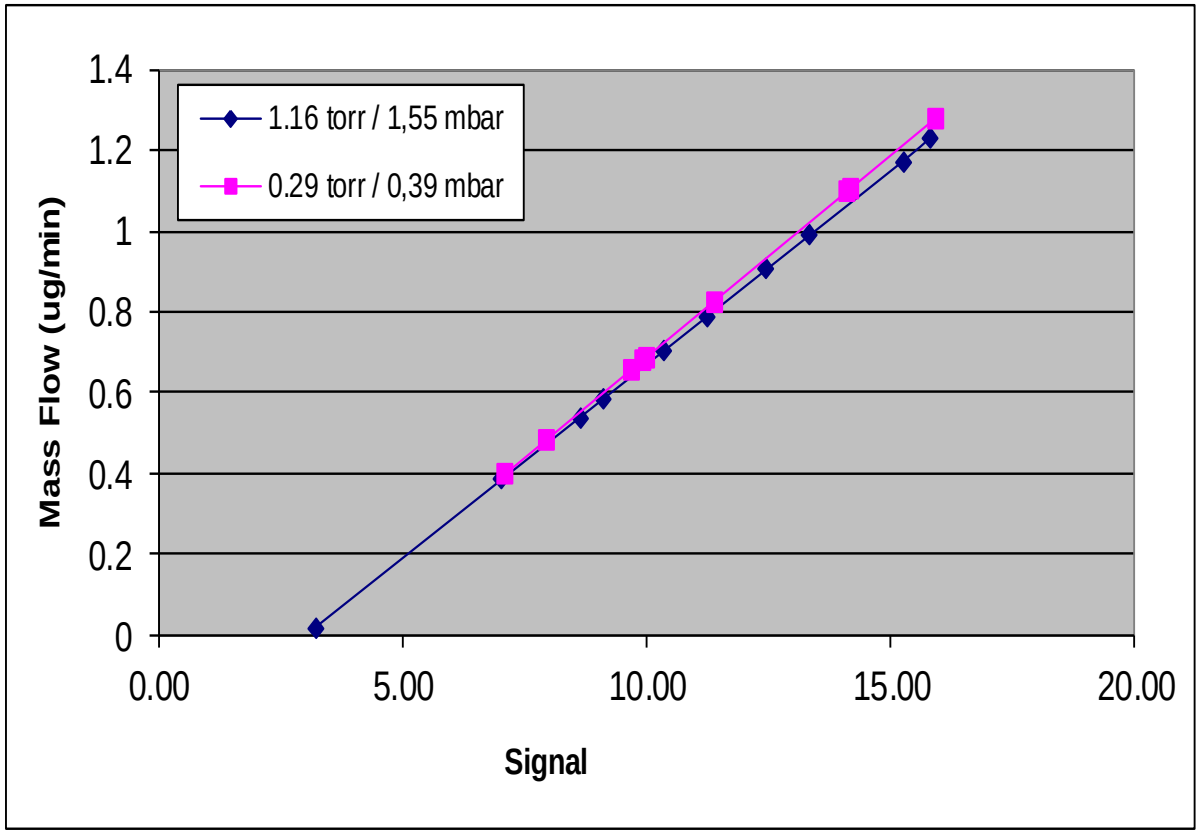
Vacuum System

ME2 Integrity Test Unit

Check also (video for vial testing):
https://youtu.be/q9EAsC1Btj0

**ME3**
**For in-line testing**

# IMFS* – Sensor Calibration (for operation in molecular flow regime)




MEASURES MASS FLOW
at Transitional /
Molecular Flow

Note:

0.05 micro-gram/min N2 =
$6.9*10^{-7}$ atm-cc/sec @20 ºC

1µg/min=$1.3*10^{-5}$ mbar*l/s at STP

*Intelligent Molecular Flow Sensor

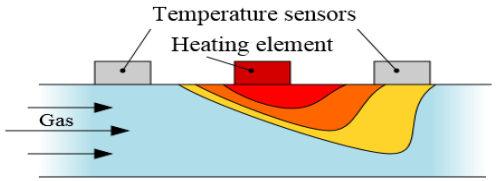
# Introduction of Mass Extraction - How does it work? → Design Consideration and Challenges

- Chamber design is critical for consistency and repeatable results.
  - New design allows to catch portentous drug leakage after filling for defects from 5-10 micron during FAST large leak check using water evaporation (drug dependent).
- Built in verification tools are important to identify reject vs. system issues (false reject):
  - Blanks (also used after massive leaks for system self cleaning).
  - Built in calibration leaks.
- Out-gassing (water desorption, part virtual leaks) should be considered when setting up vacuum level and test parameters.
- One Setup can work for multiple products:
  - Capable Large Leak Check is important for products with very small headspace.
  - Finding fine leaks is quite straight forward.

# Introduction of Mass Extraction - How does it work? → Differences to other Technologies

- This is **Vacuum Decay**? → NO it is not.
  - Both Methods work in vacuum conditions, but Vacuum Decay measures the Pressure Increase and is then calculating a flow depending on the operating conditions – pressure level, temperature and volume. Therefore the leak flow is an indirect result of this method.

- This is **Flow Measurement**! → Yes, BUT
  - Standard „Flow Measurement“ tools work on the principle of thermal mass flow measurement based on temperature differences due to gas transport and can not work in deep vacuum conditions




- **Mass Extraction** is directly measuring the mass flow through the molecular flow sensor and is calibrated to traceable standards. This gives Mass Extraction the increased capability in regards to sensitivity and ease of use.

# ASTM Definition and Application Study

# ASTM Definition and Application Study
## → Description of Application Study

- Correlation Study Testing:
  - Glass Vials, LDPE Bottles, Glass Syringes
- Four different labs, each labs operator tested over two days
- Four different Mass Extraction Instruments – some 2 to 6 years in usage
  - Calibration or calibration verification was completed prior to tests
- Same chambers were rotated between labs
- Over 42 samples of each products were tested. Each 3 times per lab
- Samples included Negative and Positive samples air of WFI water filled:
  - 10 samples intact with air only & 10 samples intact with WFI Water
  - Positive groups. Each group had 3 samples each with a micropipette inserted defect - Defect sizes were 1µm, 2µm, 5µm, 10µm
  - All Micropipette size were verified by ATC Flow Calibration Standards (ISO 17025)
- Total of 1069 tests
- Each Lab submitted its results to an independent body (ASTM)

F3287 – 17

**TABLE 2 Gas Leak Detection Results—LDPE Bottle 4mL**

NOTE 1—Liquid filled LDPE that included a 10µm micropipette were removed from the sample population due to liquid leakage into vacuum test chamber during CCIT.

| Package Description | Number of Samples | Number of Replicate Tests | Number of Failed Tests (Defects Detected) | Number of Passed Tests (No Defects Detected) | Success Rate (% Accurate) |
|---|---|---|---|---|---|
| No Defect – Liquid Filled – Negative Control | 10 | 120 | 0 | 120 | 100% |
| No Defect – Air Filled – Negative Control | 10 | 120 | 0 | 120 | 100% |
| 1 µm micropipette – Liquid Filled | 3 | 36 | 36 | 0 | 100% |
| 1 µm micropipette – Air Filled | 3 | 36 | 36 | 0 | 100% |
| 2 µm micropipette – Liquid Filled | 3 | 36 | 36 | 0 | 100% |
| 2 µm micropipette – Air Filled | 3 | 36 | 36 | 0 | 100% |
| 5 µm micropipette – Liquid Filled | 3 | 36 | 36 | 0 | 100% |
| 5 µm micropipette – Air Filled | 3 | 36 | 36 | 0 | 100% |
| 10 µm micropipette – Air Filled | 3 | 36 | 36 | 0 | 100% |

**TABLE 6 Gas Flow Results (µg/min)—LDPE Bottle 4mL**

| Package Description | Number of Samples | Average[A] $\bar{x}$ | Repeatability Standard Deviation $s_r$ | Reproducibility Standard Deviation $s_R$ | Repeatability Limit r | Reproducibility Limit R |
|---|---|---|---|---|---|---|
| No Defect – Air Filled – Negative Control | 10 | 1.138 | 0.122 | 0.137 | 0.342 | 0.385 |
| No Defect – Liquid Filled – Negative Control | 10 | 1.132 | 0.113 | 0.123 | 0.318 | 0.345 |
| 1 µm micropipette – Air Filled | 3 | 2.539 | 0.168 | 0.195 | 0.471 | 0.546 |
| 1 µm micropipette – Liquid Filled | 2 | 2.184 | 0.141 | 0.174 | 0.394 | 0.488 |
| 2 µm micropipette – Air Filled | 3 | 7.520 | 0.135 | 0.209 | 0.377 | 0.585 |
| 2 µm micropipette – Liquid Filled | 3 | 6.548 | 0.127 | 0.249 | 0.356 | 0.696 |

# ASTM Definition and Application Study F3287 – 17: Conclusion

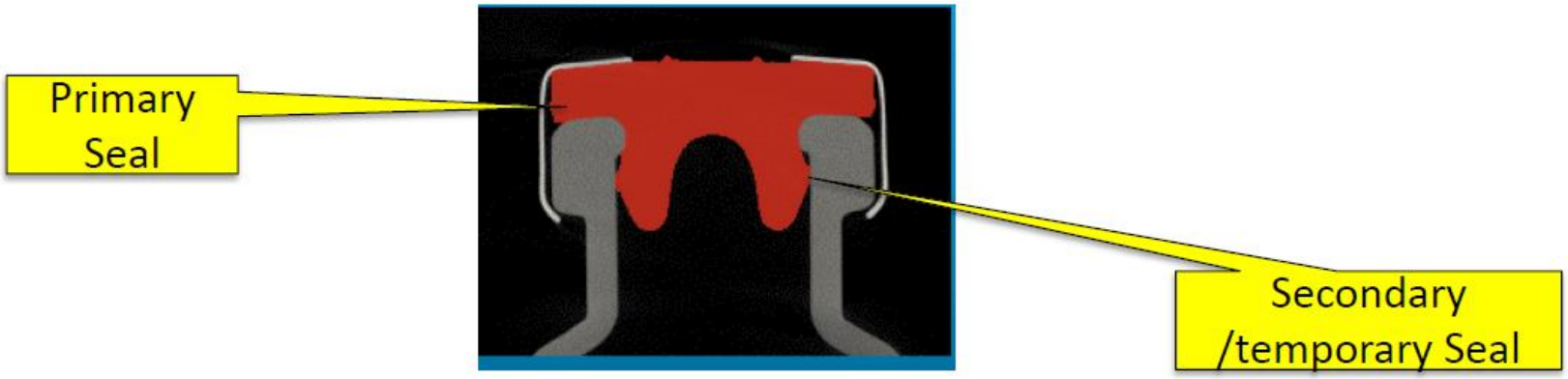
- Glass Vials and LDPE Bottles Mass Extraction tests detected 1 micron and 2 micron defects at all labs and samples at over 95% confidence level.
  - Therefore meets the requirements of USP1207.1 Table 1 Class (Row) 2 and 3 for these products.
- Glass Syringes Mass Extraction tests detected 1 micron air filled syringes and 2 micron air and water filled syringes at all labs and samples. 2 micron were detected at confidence level equal or greater then 95%.
  - 1 micron liquid filled Syringe plugged - suspected by silicon lubricant.
  - Samples with 1 micron with air under defect can be detected at 95% confidence level.
  - The requirements of USP1207.1 Table 1 Class (Row) 3 for glass Syringe are met.

NOTE: All Leak Artifacts/positives were micro-pipette type, same as used at earlier microbial ingress studies by Lee Kirsch et al.

# Application Examples

# Application Example
## → Vial Testing for Lyophilized Products

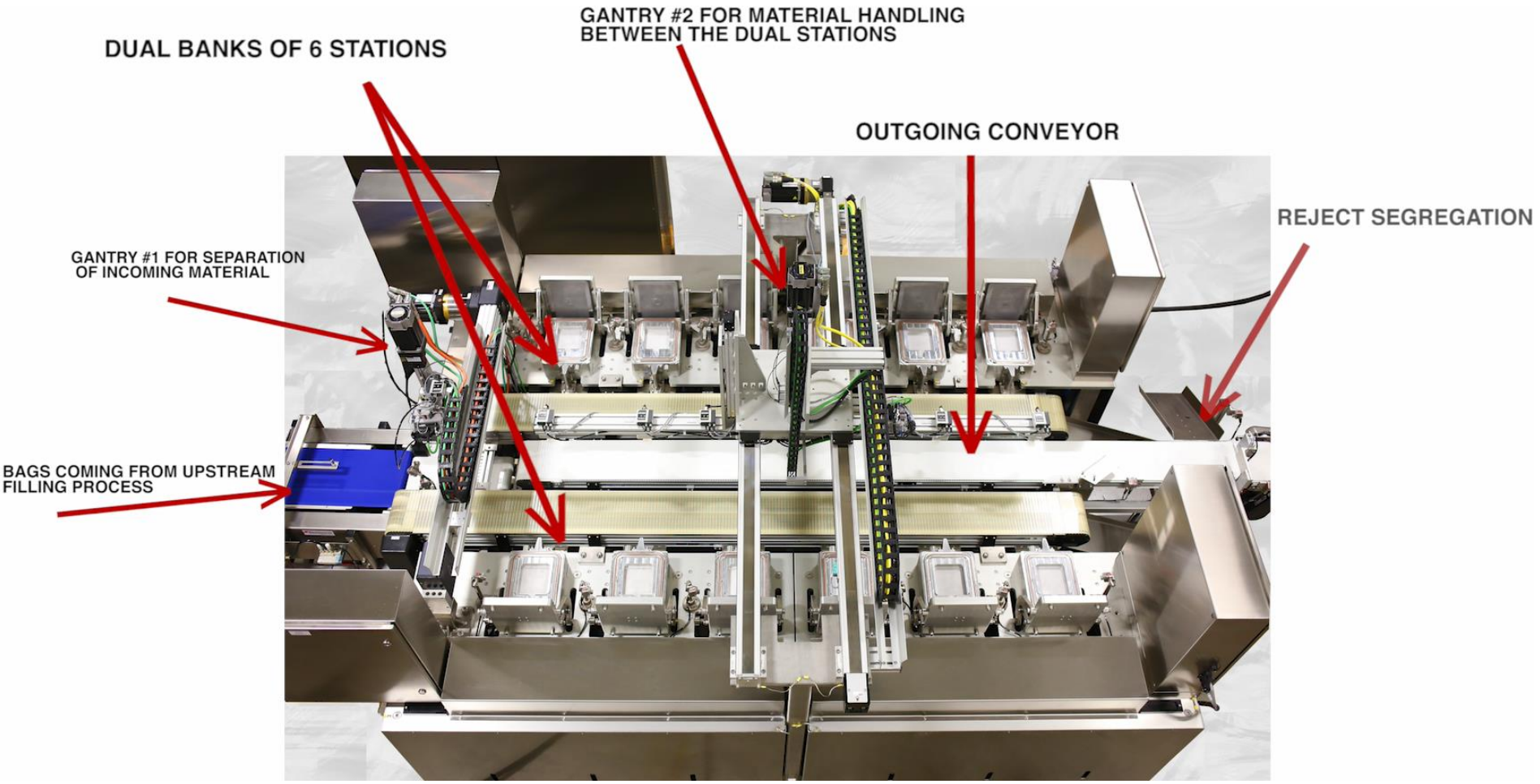
Can the secondary seal –seal while primary seal is defective? YES
Is vial sterility/integrity assured?
Per EMEA Annex 1: *Manufacture of Sterile Medicinal Products 118:* NOT ALLOWED




**Mass Extraction: Failed Large Leak Check, due to air trapped between primary and secondary seal.**

Reference: Genesis Roger's presentation Jan-26-2017

# Application Example
# → IV Bags (100% Testing) [VIDEO]



# Summary

# Mass Extraction Technology for Pharmaceutical Packaging CCIT → Summary

- Mass Extraction is a USP 1207 recognized DETERMINISTIC test method for different kinds of pharmaceutical packages
  - It is based on traceable calibrations in ISO 170265 certified Labs
- Compared to similar technologies it has significant benefits in regards to sensitivity and accuracy
  - One equipment can be used for multiple type of packages without recalibration and change of settings.
  - The systems can also perform fast Go/NoGo results for production processes and can be 100% automated
- FDA-CFR 21 part 11 compliant software for data collection is available

- The Limit of Detection
  - The smaller the defect size that Mass Extraction is set to detect, the lower the risk the user takes

# Mass Extraction Technology for Pharmaceutical Packaging CCIT
# → Customer Benefits

Enhanced **Sensitivity** combined with high **accuracy and repeatability** for quantitative measurement results


**Ease of use,** different packages can be tested with same set up for **operator independent and immediate results**


**Periodic (typically yearly) ISO calibration** of sensors with **traceable leaks** and simple **verification tools** on the equipment.

## → Increased Safety & Robustness for your Production / Quality Process

# Acknowledgements


- ATC Engineering Research Team
- Our pharmaceutical Customers collaborating and allowing the multiple lab. correlation study
- ASTM for the approval to use data out of official standard