Mass Extraction Technology
for Pharmaceutical Packaging CCIT

By: Dennis Seibert, Pfeiffer Vacuum
prepared with: Hemi Sagi, Advanced Test Concepts (ATC), LLC.

PFEIFFER VACUUM & **ATC** by PFEIFFER VACUUM

Container closure integrity test

NEW

HLD
(MALL Test)

Mass Extraction
ME2/ATC

AMI Compact

The Americas
app. 390

Europe and Africa
app. 1,770

Asia-Pacific
app. 740

□ Production
● Sales and Service
● Distributors
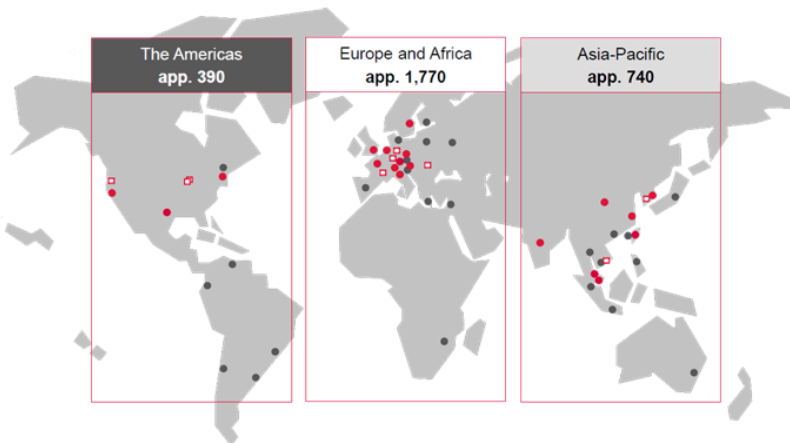
2017 Sales Total
587 Mio €

Total employees
2,900

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?
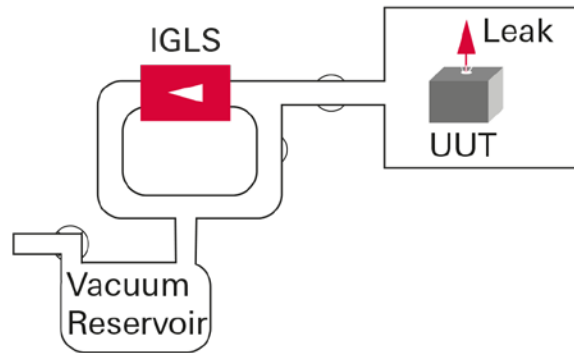
- ## Mass Extraction

  Package leaks are detected by **measuring the mass flow extracted from a package** while the package is enclosed **inside an evacuated test chamber**. The test system is a **closed system** during the leakage measurement portion of the test cycle. The closed system includes a **vacuum reservoir, Intelligent Molecular Flow Sensor (IMFS), and vacuum test chamber**. **Mass extracted from the test package** into the vacuum test chamber **flows to the vacuum reservoir through the IMFS to equalize the system**. This flow is measured by the IMFS. Based on the conservation of mass law, **mass flow within the closed system is equal to the mass loss from the test package**. The test system is capable of producing quantitative (variable data) or qualitative (pass/fail) results depending on the requirements.
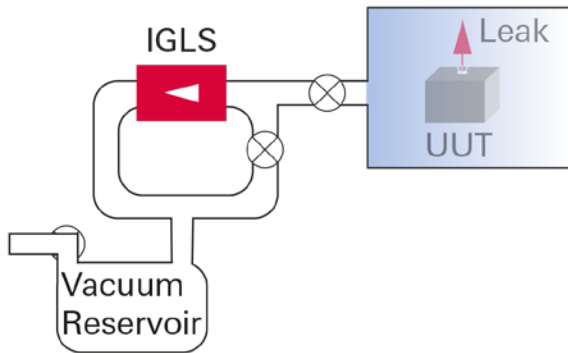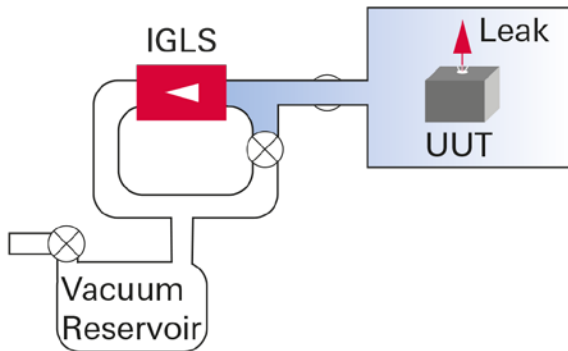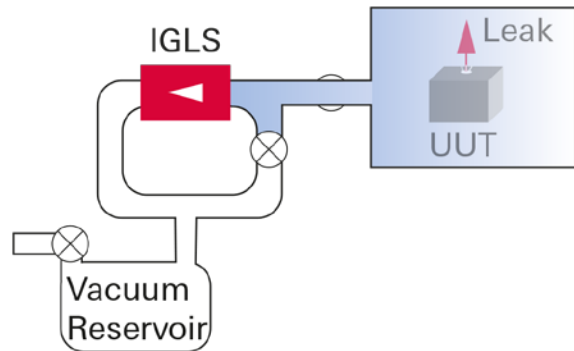
**Mass Conversation law:
Mass extracted = mass leaked at steady state**
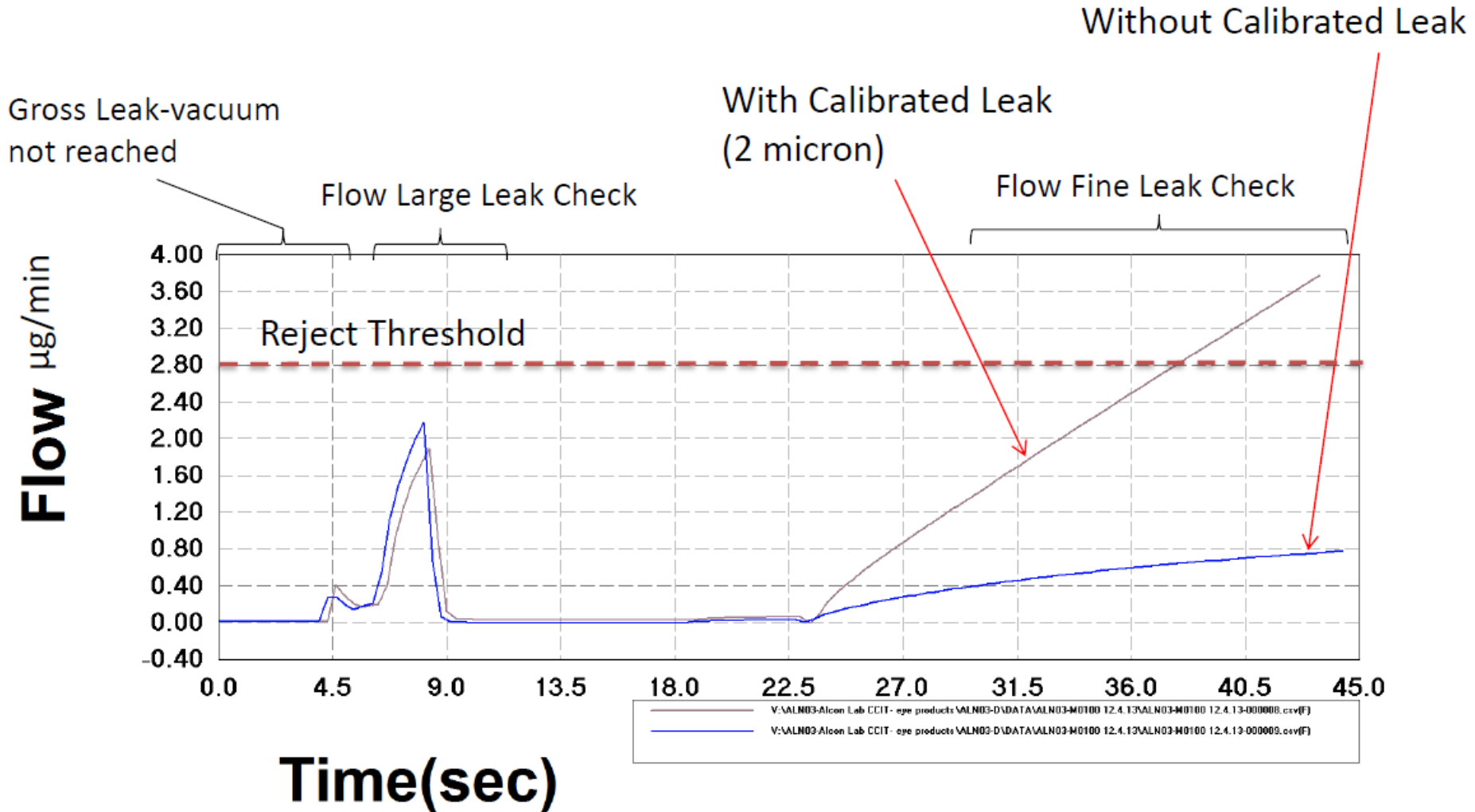
At a given test condition- Flow measurement is function of defect geometry (or Equivalent Micro-Geometry, EMG):

EXAMPLES:

Hagen-Poiseuille 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= $\frac{\overline{R}}{M}$

Defect Size (EMG) (Diameter Length)
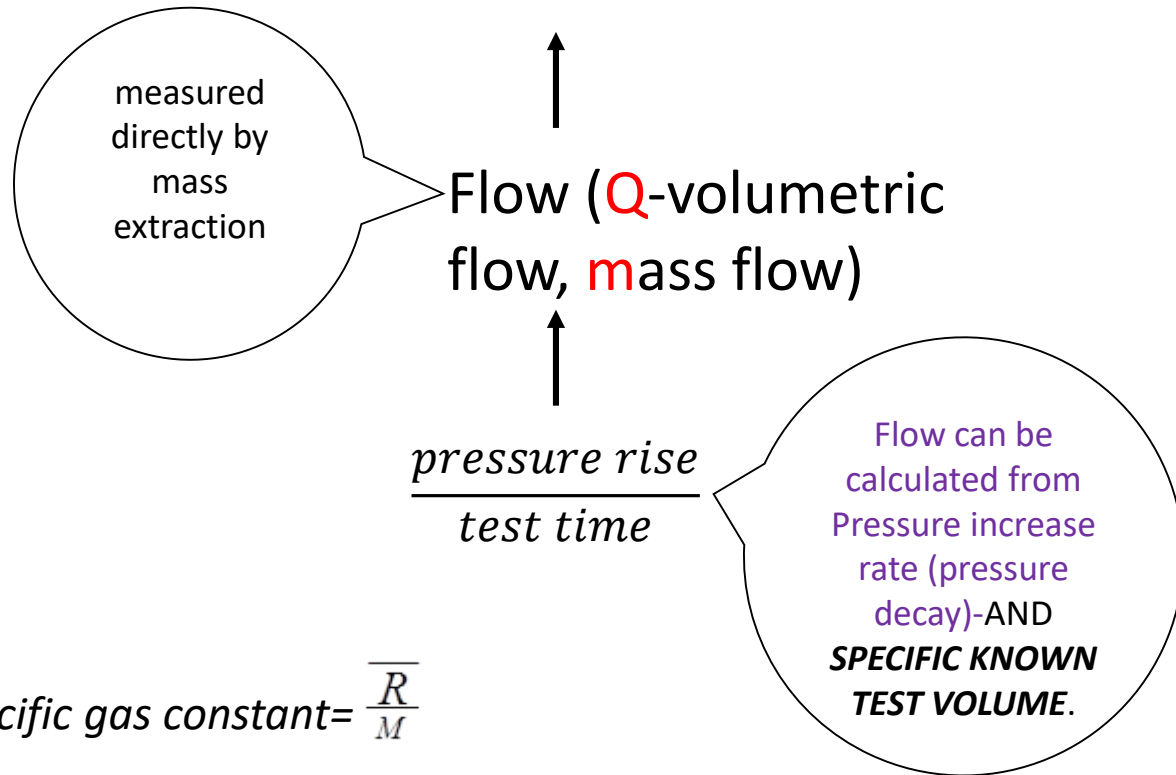
measured directly by mass extraction

Flow (Q-volumetric flow, mass flow)

$$\frac{pressure\ rise}{test\ time}$$

Flow can be calculated from Pressure increase rate (pressure decay)-AND **SPECIFIC KNOWN TEST VOLUME**.

Storage area for laptop, packaging

Test chambers for different vials

additional chambers for other packaging

Vacuum System

ME2 Integrity Test Unit

ME3 For in-line testing

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

IMFS* – Sensor Calibration (for operation in molecular flow regime)
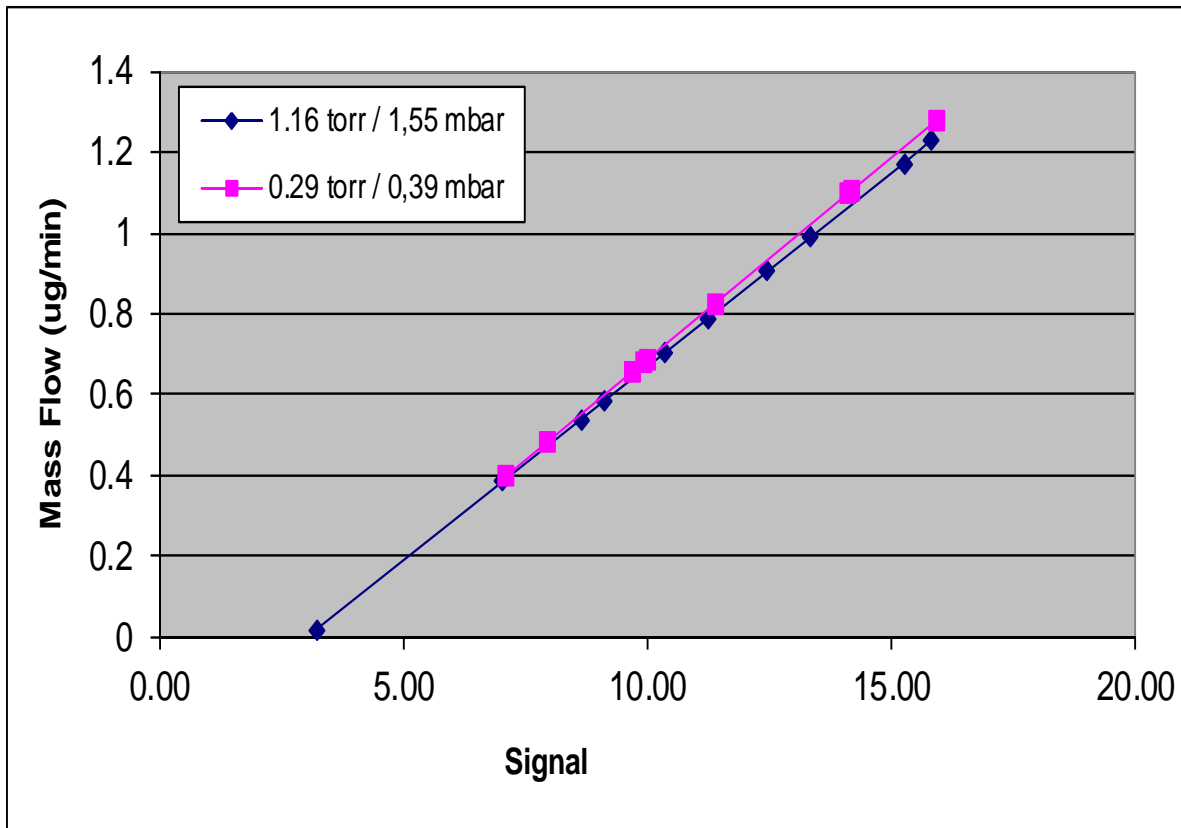
MEASURES MASS FLOW
at Transitional /
Molecular Flow

Note:

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

$1\mu g/min = 1.3*10^{-5}$ mbar*l/s at STP

*Intelligent Molecular Flow Sensor

- 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.

- 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 based on official standards. This gives Mass Extraction the increased capability in regards to sensitivity.
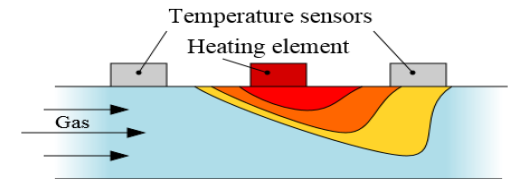
ASTM Definition and Application Study

- 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)
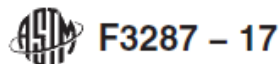
ASTM F3287 – 17

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]	Repeatability Standard Deviation	Reproducibility Standard Deviation	Repeatability Limit	Reproducibility Limit
		$\bar{x}$	s_r	s_R	r	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

- 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

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*

Primary Seal

Secondary /temporary Seal
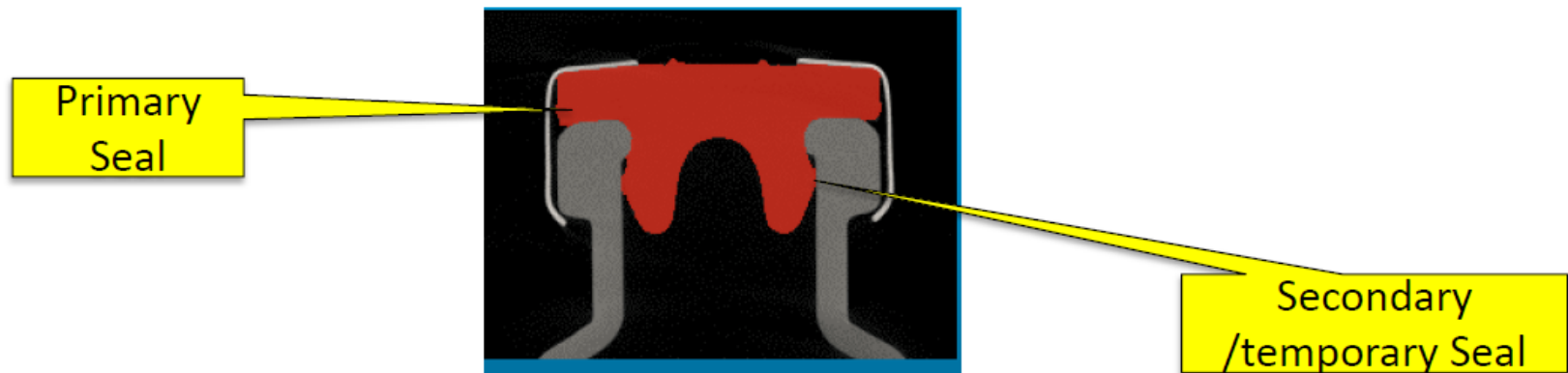
Mass Extraction: Failed Large Leak Check, due to air trapped between primary and secondary seal.

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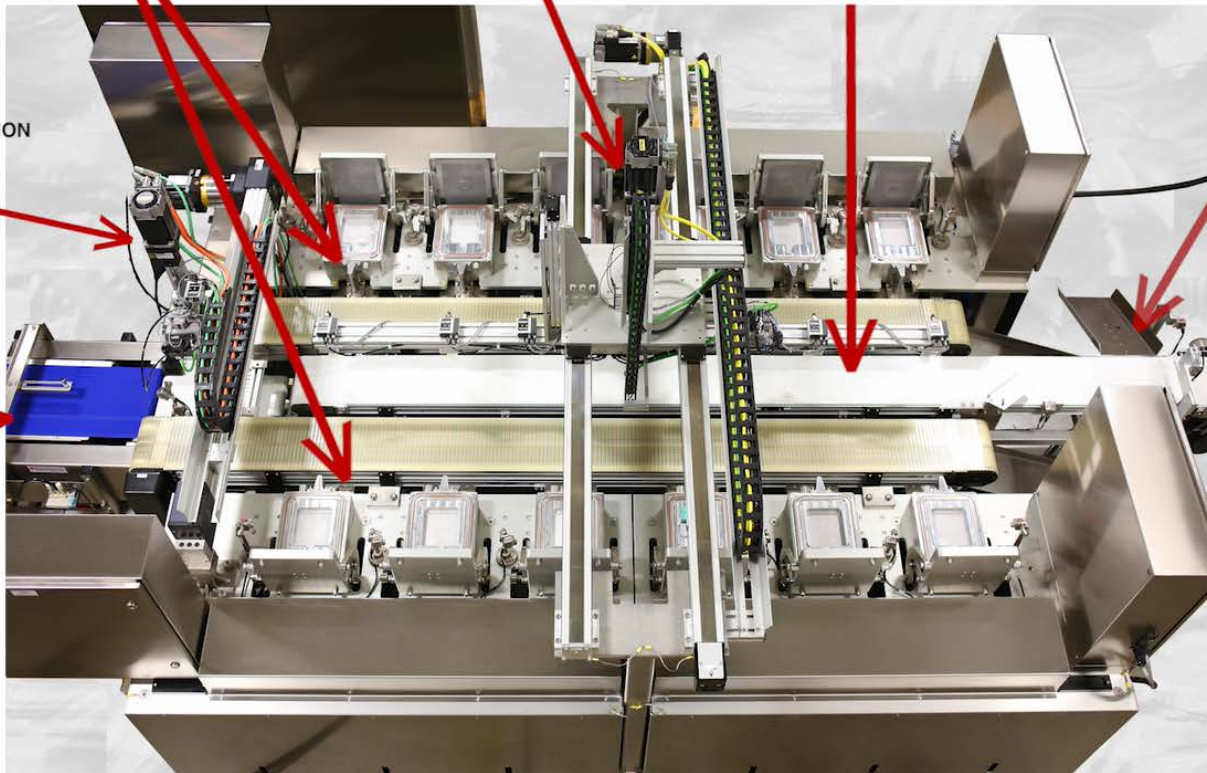
Summary

- Mass Extraction is a USP 1207 recognized DETERMINISTIC test method for different kinds of pharmaceutical packages
  - It is based on official calibrations in ISO 170265 certified Labs
- Compared to similar technologies it has significant benefits in regards to sensitivity and accuracy
  - Furthermore one equipment can be used for multiple type of packages without change of settings and recalibration
  - The systems can also perform fast Go/NoGo results for production processes and can thereby 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

Enlarged **Sensitivity** combined with high **accuracy and repead-ability** for quantitative measurement results

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

Yearly ISO calibration of sensors with **traceable leaks** and **verification option** on the equipment for check up

→ **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