Mass Extraction Technology for Pharmaceutical Packaging CCIT

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Mass Extraction Technology

Presentation Scope

- How does Mass Extraction for CCIT work?
- Application data with various defect sizes and STERILE products-Limit of Detection for various products:
  - Vials
  - Syringes
  - LPDE bottles
  - IV Bags/pouches
  - Pens/Auto-Inject Devices
- Single use bag (pressure testing)- not part of USP1207.
- Applications considerations, challenges and potential solutions.
- Implementation examples (Videos):
  - High Speed Sampling
  - 100% Inspection

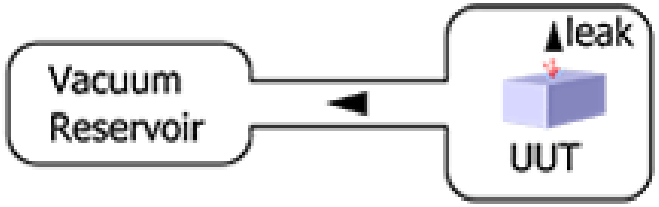
Mass Extraction Technology

Mass Extraction- Definitions and How Does it Work?

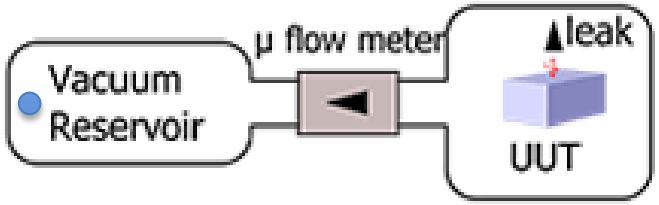
- Mass Extraction – Using Micro-Flow sensor measurement of the mass flow rate (µgram/min or scc/sec) or total mass extracted from a Closure while it is in a vacuum chamber to quantify and detect the presence of leaks equal to or larger than maximum allowed value.
  - The measured fluid is gaseous:
    - Air/Nitrogen.
    - At vacuum (for liquid filled containers: under the boiling point of water at room temperature ~ 18 torr)→ water vapor.

MASS EXTRACTION – BASIC CONCEPT

Mass Conservation Law:
Mass Extracted = mass leaked at steady state



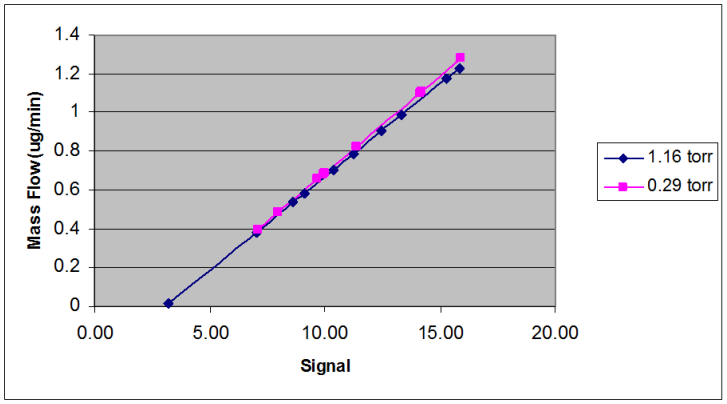
- Air path: Unit Under Test → Chamber → Reservoir



- Measure with *Micro-Flow Sensor*
  Gas (Mass) Extracted

ATC's Micro-Flow sensors: Flow sensors designed to measure very small flow rates, through small defects and can operate at multiple micro-flow regimes:

- Intelligent Molecular Flow Sensor (IMFS)- operates at hard vacuum, where flow is defined and controlled by molecular gas transport behavior. Measures from $7X10^{-7}$ scc/sec (0.05 µg/min AIR Flow-> IMFS with 0-1 µg/min flow range).
- Intelligent Gas Leak Sensor (IGLS)- operates at shallow vacuum to pressure where flow is defined and controlled by viscous and laminar effects (typically at shallow vacuum and pressure).



IMFS Calibration Curve-Measures 10^{-7} to 10^{-5} sccs range

FAQ: What is the difference between Mass Extraction and Vacuum Decay?

Note: Both are proven CCIT Test Methods.

Property	Mass Extraction	Vacuum Decay
Pass/fail decision based on Flow, using:	Flow Sensor (micro-flow sensor)	Common Pressure Transducer
How is flow rate established:	Independently calibrated, direct measurement flow.	Calculated based on pressure rise over time in known volume
Operating condition	Vacuum Chamber	Vacuum Chamber
Pressure measurement	Secondary function	Primary function

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= $\frac{R}{M}$

Defect Size (EMG) (Diameter Length)

↑

Flow (Q-volumetric flow, mass flow)

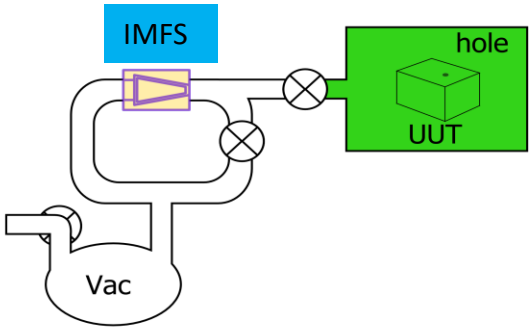
measured directly by mass extraction

↑

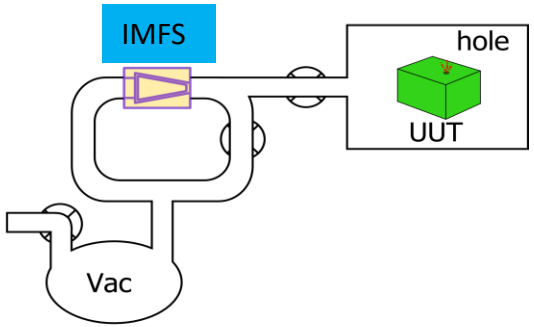
$\frac{\Delta P}{\Delta T}$

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

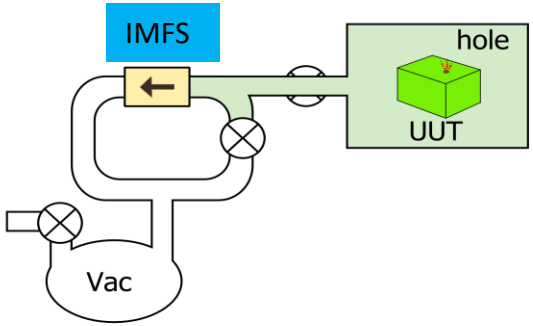
Method of Operation - Mass Extraction



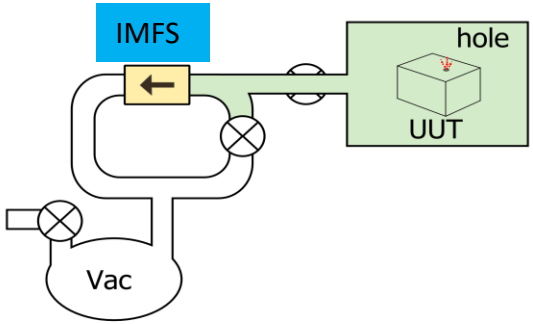
1 Standby - Vacuum Reservoir: P_0
- IGLS: no flow



2 Evacuate - All branches: P_0
- IGLS: no flow
- UUT: *leaks*

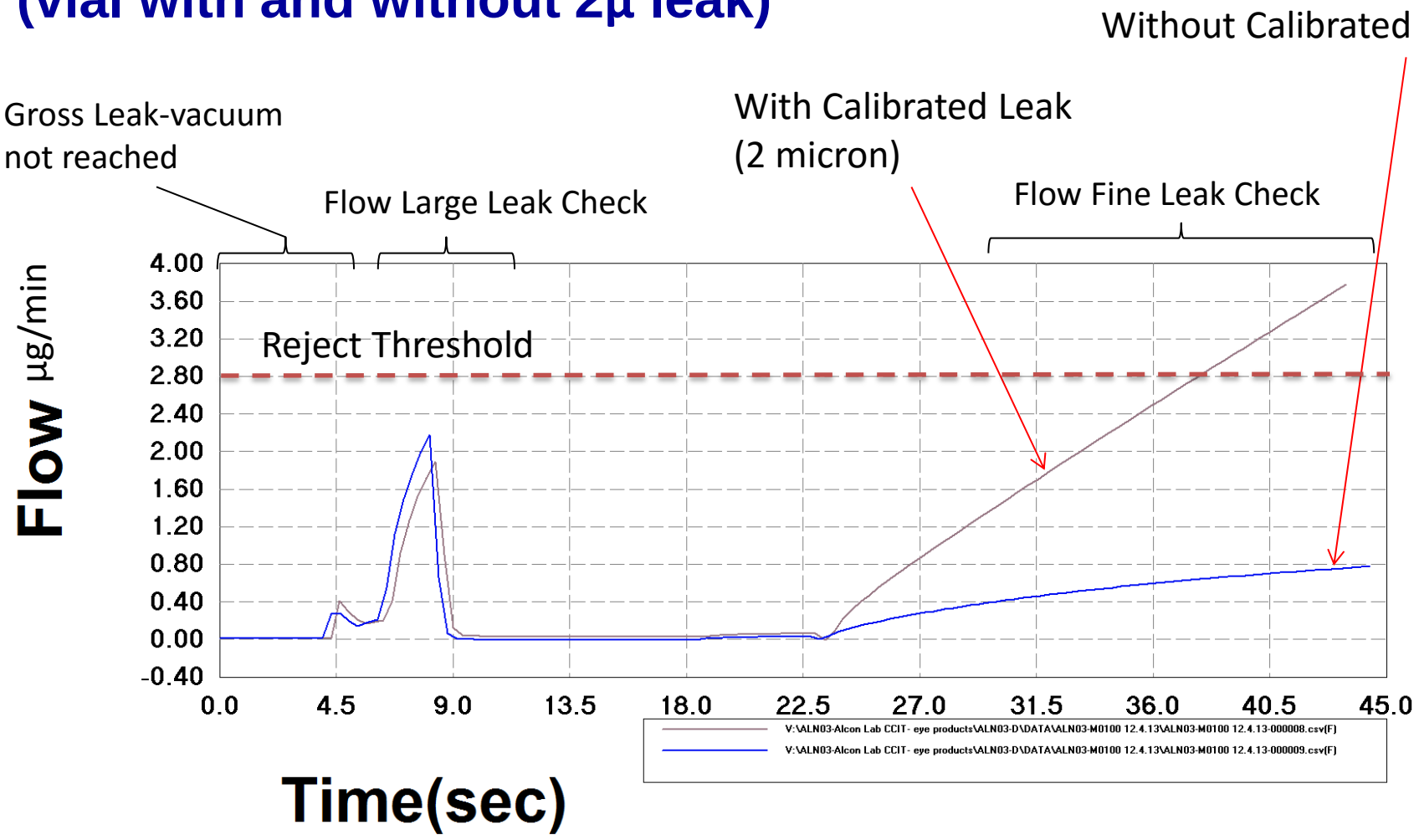


3 Stabilize - Leak: increases $P_{chamber}$
- IGLS: begins flow



4 Test - Steady flow thru leak
- IGLS: measures flow thru leak

Example: Flow Measurement- *Signature Test*
(vial with and without 2µ leak)

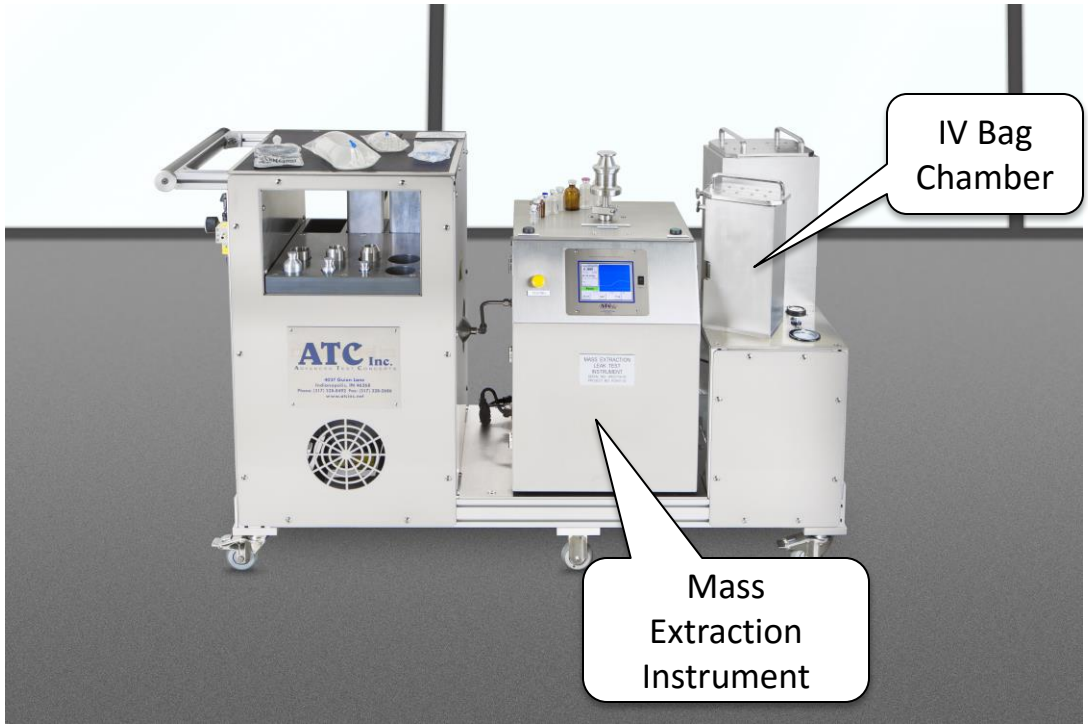


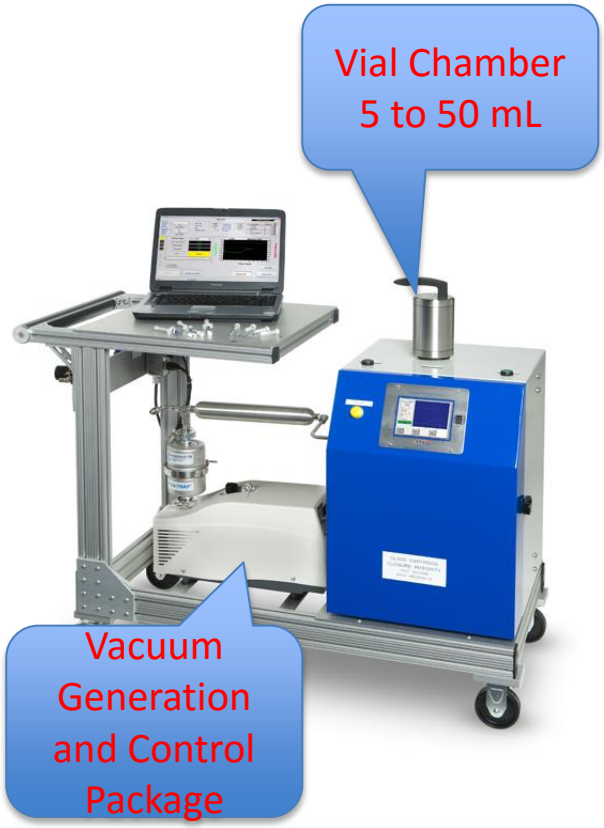
Note: The Smaller Defect Size Mass Extraction is set to detect (Limit Of Detection)- the lower is the customer risk.

Mass Extraction Technology

Applications- Sterile Products

CCIT Systems- Vial and IV Bags





CCIT Systems- Vial and Syringes

LABORATORIES' CORRELATION STUDY- VIALS, LDPE BOTTLES, SYRINGES

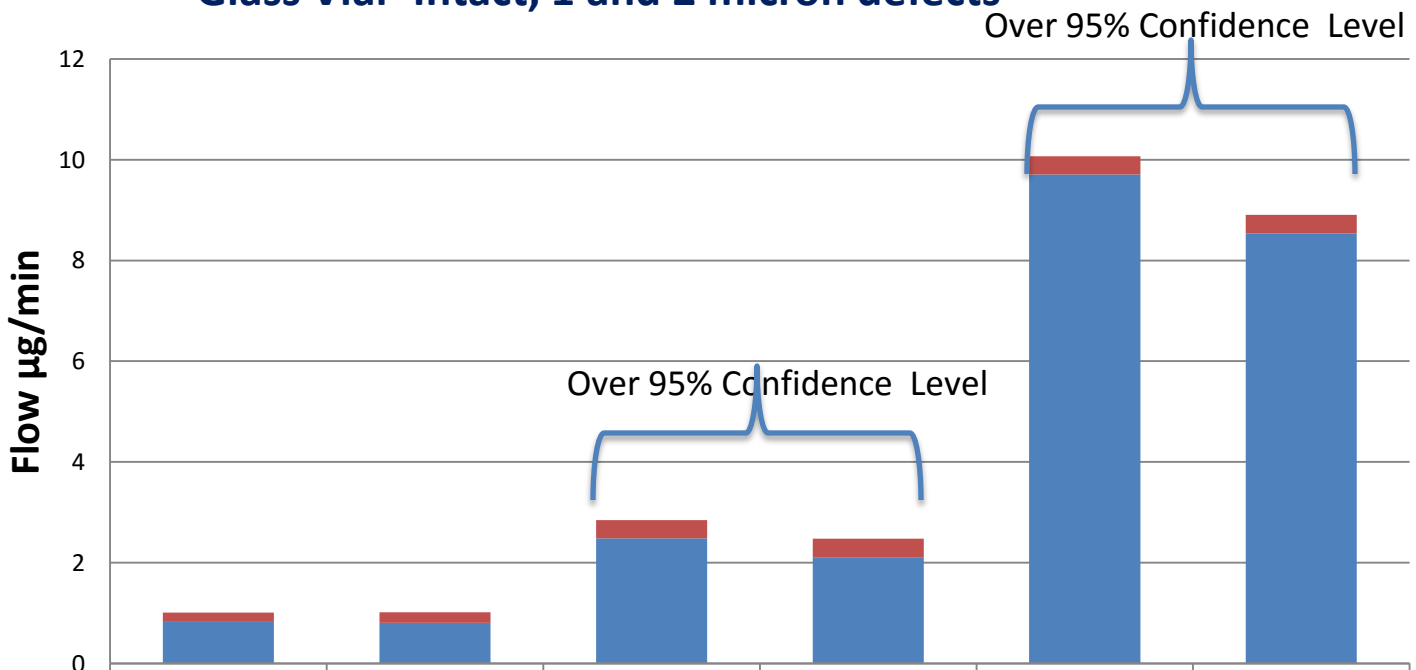
- Correlation Study testing:
  - Glass Vials
  - LDPE Bottles
  - Glass Syringes
- Four independent labs, each lab's operator tested over two days.
- Four different Mass Extraction Instruments - some 2 to 6 years in usage at the labs!
  - Calibration or calibration verification was completed prior to 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 or 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 1µ, 2µ, 5µ, 10µ.
  - All Micropipette were verified to be intact prior to testing.
  - Micropipette size was verified by ATC Flow Calibration Standards (ISO17025 Accredited Standards) as applicable.
- Total of 1069 tests.
- Each Lab submitted its results to an independent body (ASTM).
- Active ASTM standard is in balloting stage.

LABORATORIES' CORRELATION STUDY- Glass VIALS

All Negative samples passed. ALL Positives-Rejected.

5 and 10 micron- rejected for Large Leaks and exceeded sensor full scale (not shown)

Glass Vial- Intact, 1 and 2 micron defects

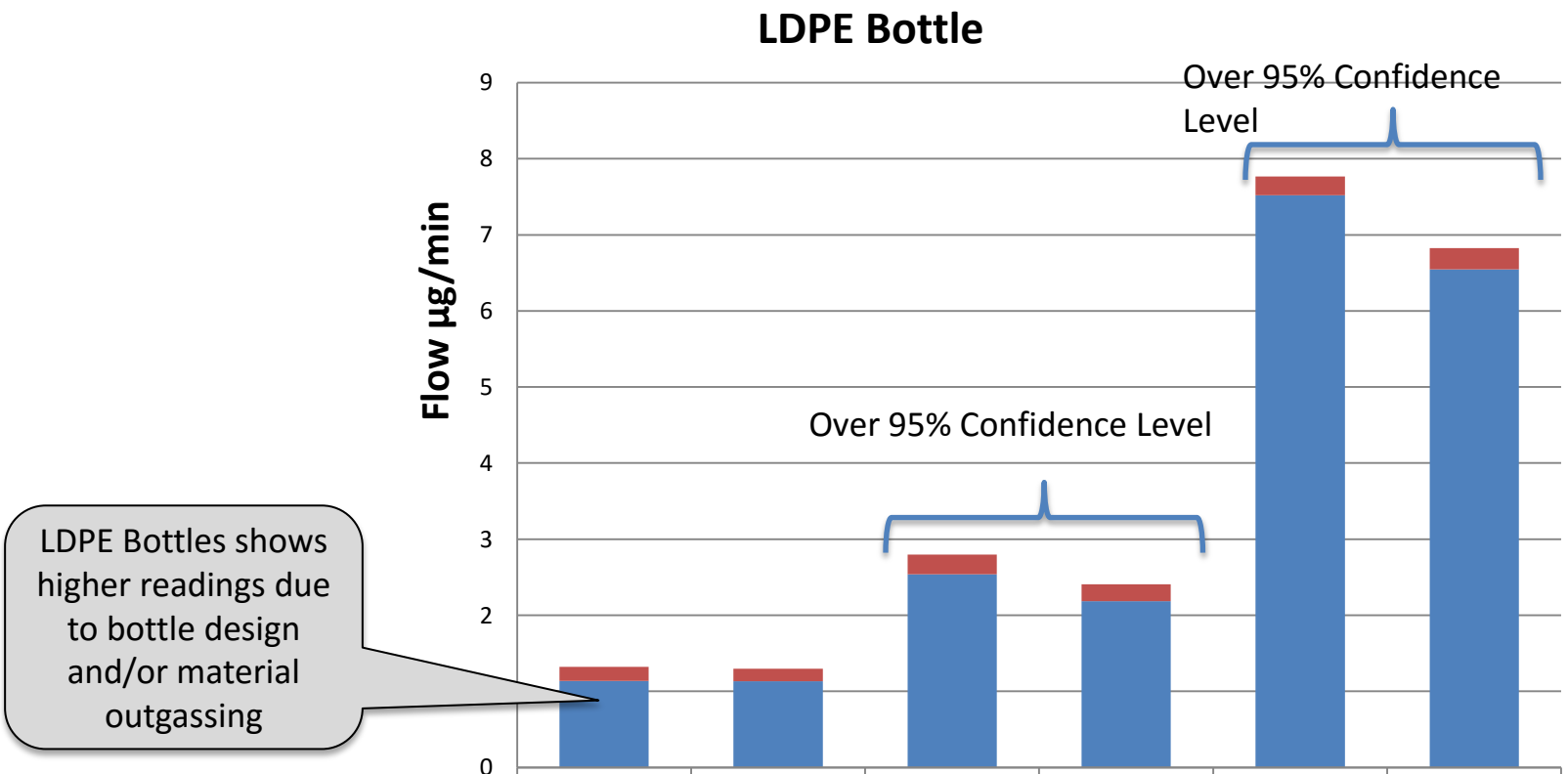


	0- air	0-liq	1µ-Air	1 µ-Liq	2µ-Air	2 µ-Liq
Combined STD Deviation	0.1850	0.2086	0.3619	0.3662	0.3651	0.3687
Vial-Average	0.827	0.81	2.484	2.111	9.704	8.537

LABORATORIES CORRELATION STUDY- LDPE BOTTLES

All Negative samples passed. ALL Positives-Rejected.

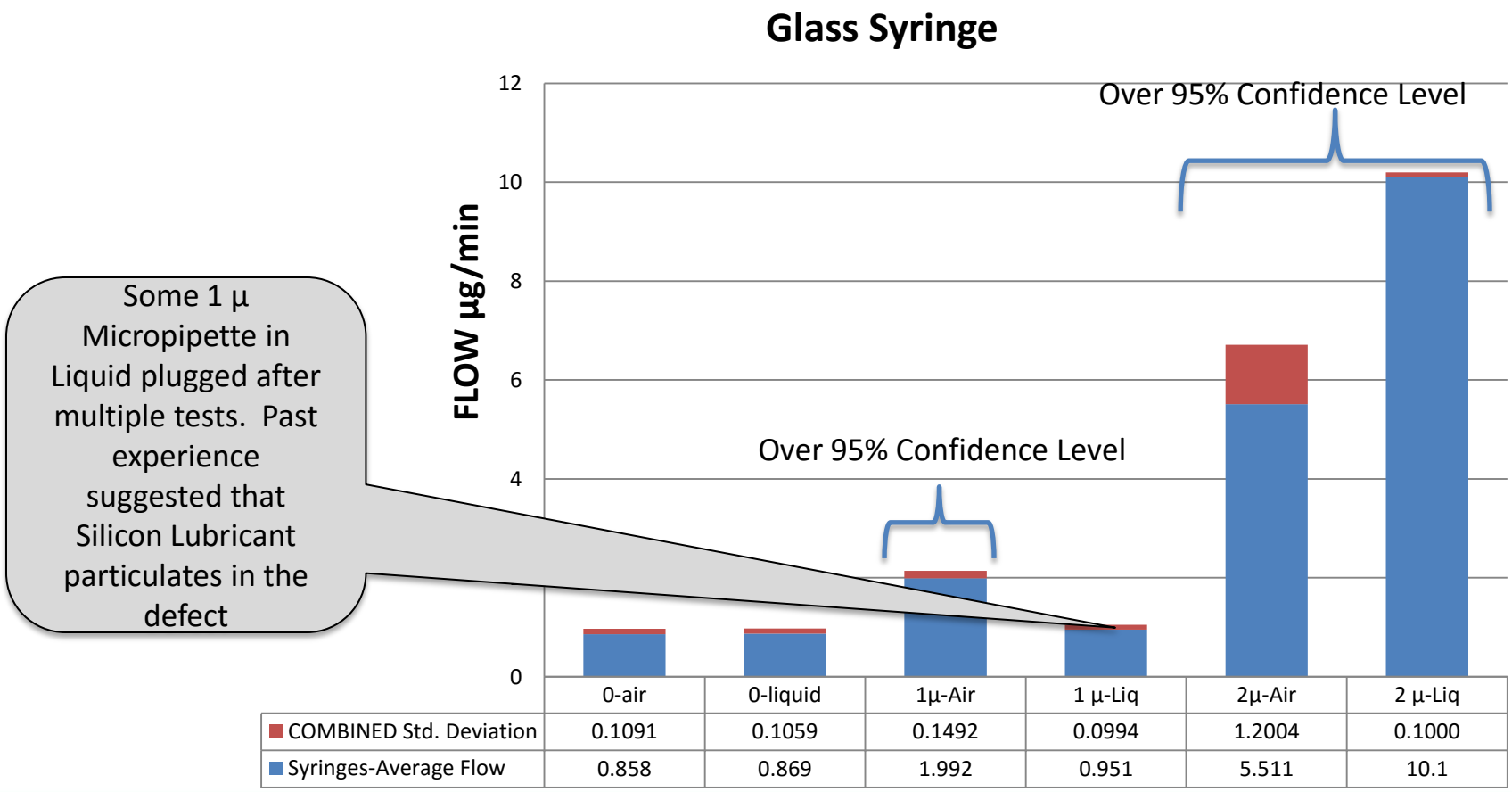
5 and 10 micron- rejected for Large Leaks and exceeded sensor full scale (not shown)



	air	liq	1µ-Air	1 µ-Liq	2µ-Air	2 µ-Liq
COMBINED Std. Deviation	0.1834	0.1670	0.2574	0.2240	0.2488	0.2795
LDPE Bottle-Average Flow	1.138	1.132	2.539	2.184	7.52	6.548

LABORATORIES' CORRELATION STUDY- SYRINGES

All Negative samples passed. Positives-Rejected-except plugged 1 micron with liquid.
5 and 10 micron- rejected for Large Leaks and exceeded sensor full scale (not shown)



	0-air	0-liquid	1µ-Air	1 µ-Liq	2µ-Air	2 µ-Liq
COMBINED Std. Deviation	0.1091	0.1059	0.1492	0.0994	1.2004	0.1000
Syringes-Average Flow	0.858	0.869	1.992	0.951	5.511	10.1

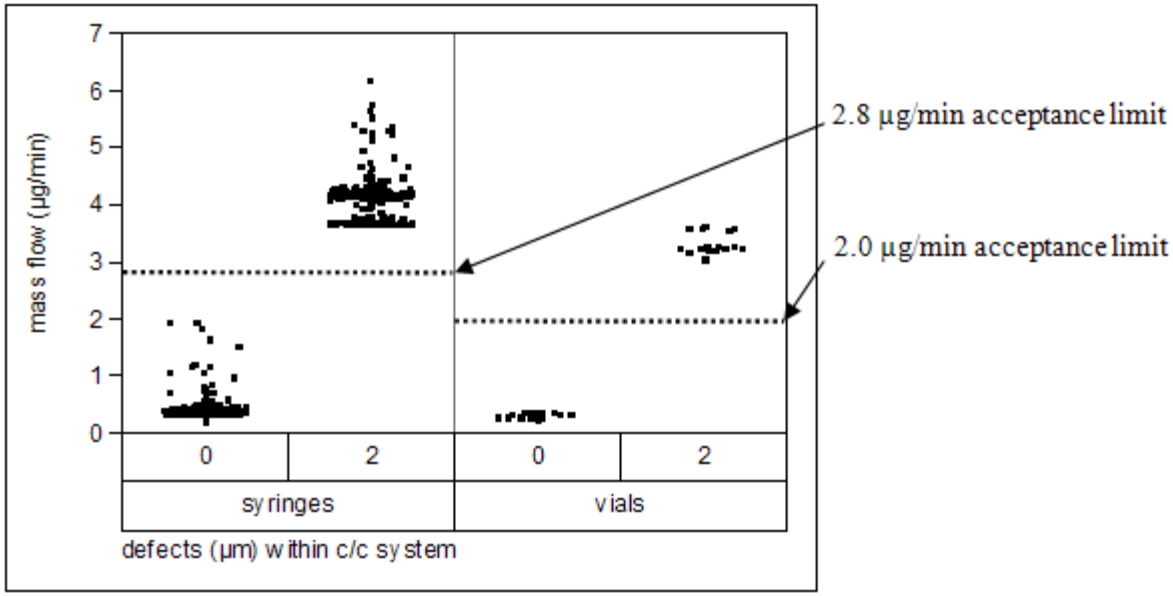
Conclusion from Mass Extraction Correlation Study

- Standard draft to ASTM is in a balloting process.
- 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.

Mass Extraction Robustness Test

Robustness study is an indicator for long term reliability. Study included multiple operators, testing days, and two stand-alone instruments were used to understand variations of the method. A total of 12 different combinations including two extreme vial sizes (2 and 50 mL) were incorporated into the design and 6 vials per combination were tested. For the syringe study, a total of 8 combinations were incorporated into the design and 90 syringes per combination were tested.



***Reference**: PDA J Pharm Sci and Tech* **2012**, *66* 403-419

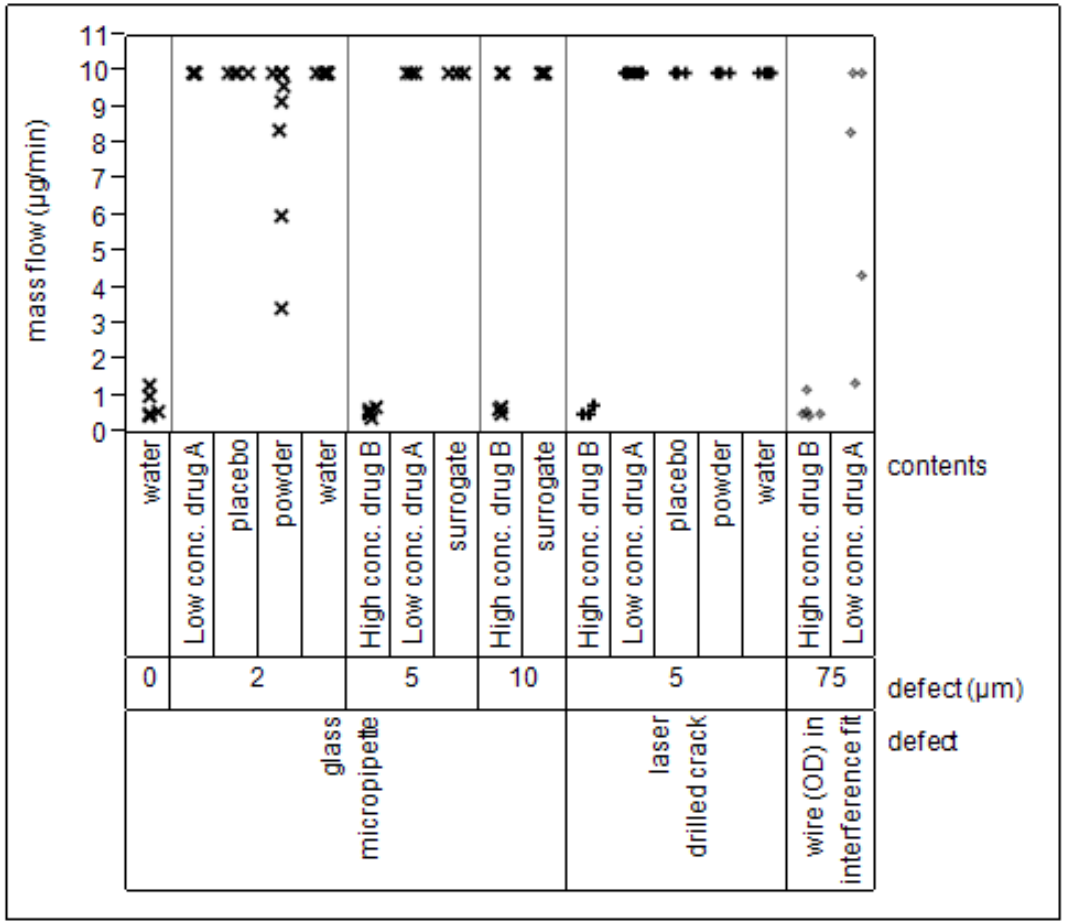
Mass Extraction Container Closure Integrity Physical Testing Method Development for Parenteral Container Closure Systems; by: SEUNG-YIL YOON, HEMI SAGI, CRAIG GOLDHAMMER, and LEI LI

Products Tested with 100% detection for 2 micron in the study:

- Small molecules drugs.
- Water base solutions.
- Dry products (Powder, Lyophilized)
- Low concentration protein drug
- Placebo and high viscosity surrogate
- Vials and Syringes

Types of positives:

- Laser drilled glass crack.
- Micropipettes



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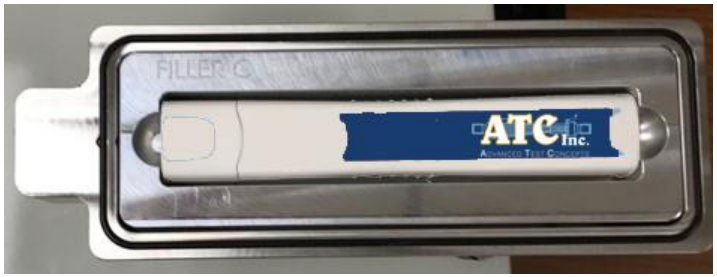
High Concentration Protein Drugs and Hole Plugging Effects:

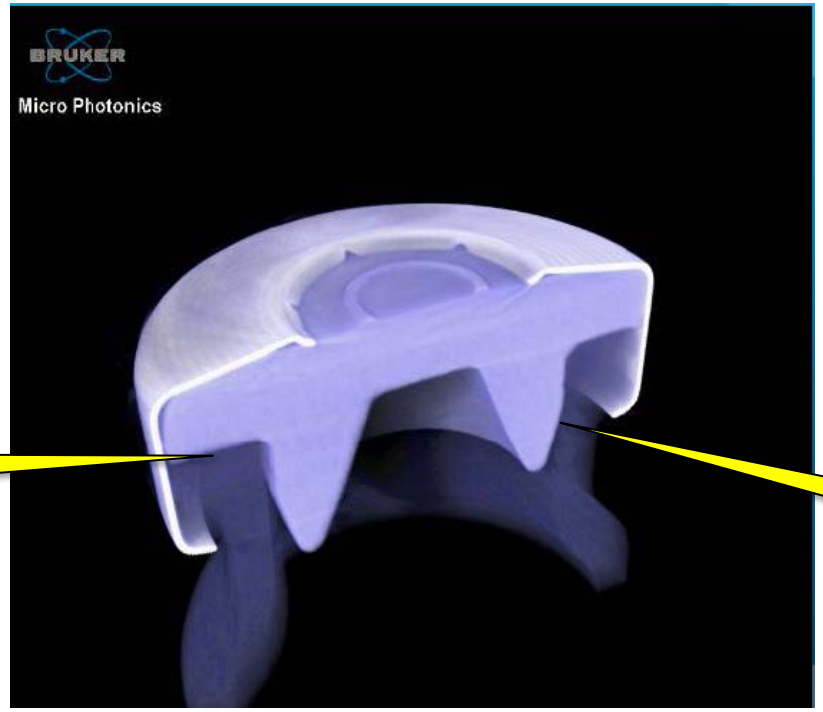
- Small defects (0.2-3 micron range) can get plugged due to handling, particulates in liquid (e.g: silicon lubricant of syringes, rubber components, etc).
  - The bigger the defect the less likelihood of plugging (e.g: 10 micron).
- Some high concentration protein drugs will self plug under long exposure to air or vacuum.
  - As long as the plugging skin is moisturized – Mass Extraction with *short evacuation and large leak* steps will likely to detect this reject.
  - A fully plugged dry defect will not transport air/gases. Therefore no method based on gas transport (or diffusion) would be reliable.
- Micro-defects plugging is not fully understood; multiple research studies has been published (for other industries).
- Best practice for high concentration protein based drug is done on a case by case analysis of specific CCIT test method and set-up.

CCI TESTING STERILE PENS/AUTO-INJECT DEVICES

- Two steps approach:
  - Testing primary package (cartridge, syringe type) as mentioned before for tight spec.(e.g: 1-2 micron)
  - Testing complete assembly for assembly error. Can be for a larger defect (e.g: 5 micron) as assembly errors are typically large defects.
- Considerations: Complete assembly may experience higher background due to virtual leaks or plastic outgassing (product dependent).
- Test at higher pressure (less vacuum) to reduce outgassing.



Challenge: Vial Testing for Lyophilized Products:



Primary Seal

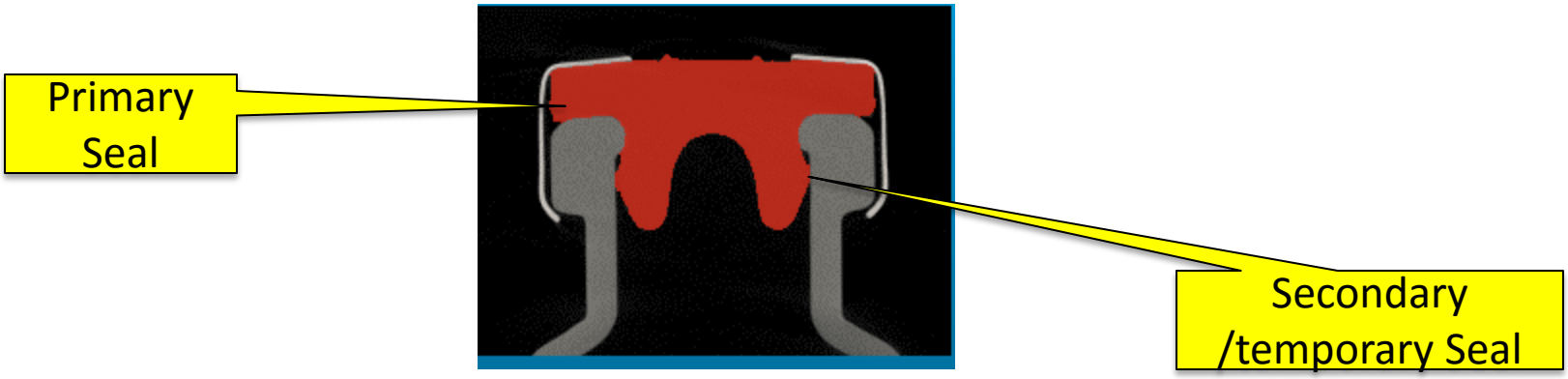
Secondary or temporary Seal

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*

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

Challenge –Vial Testing for Lyophilized Products:

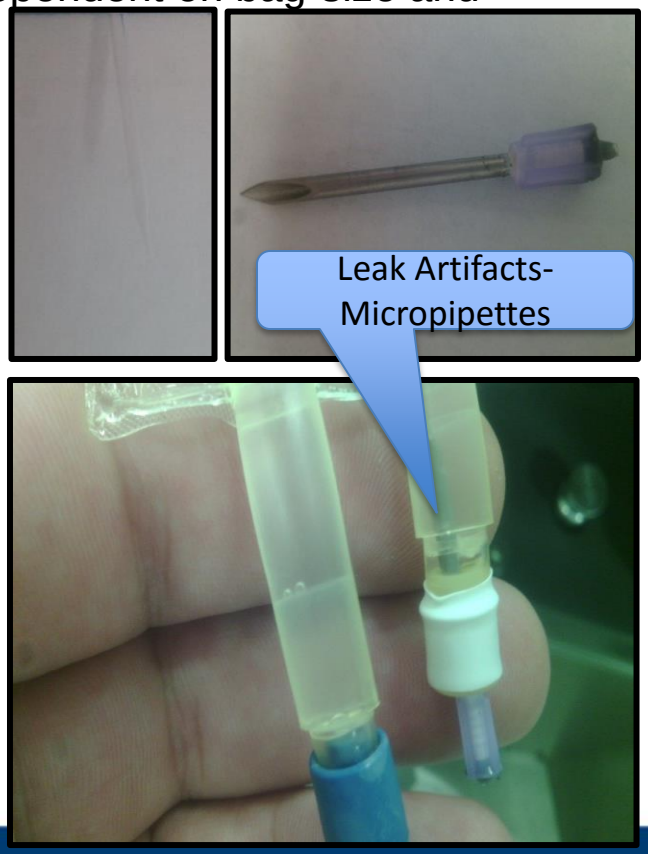
From X-Ray Tomography- no obvious defect



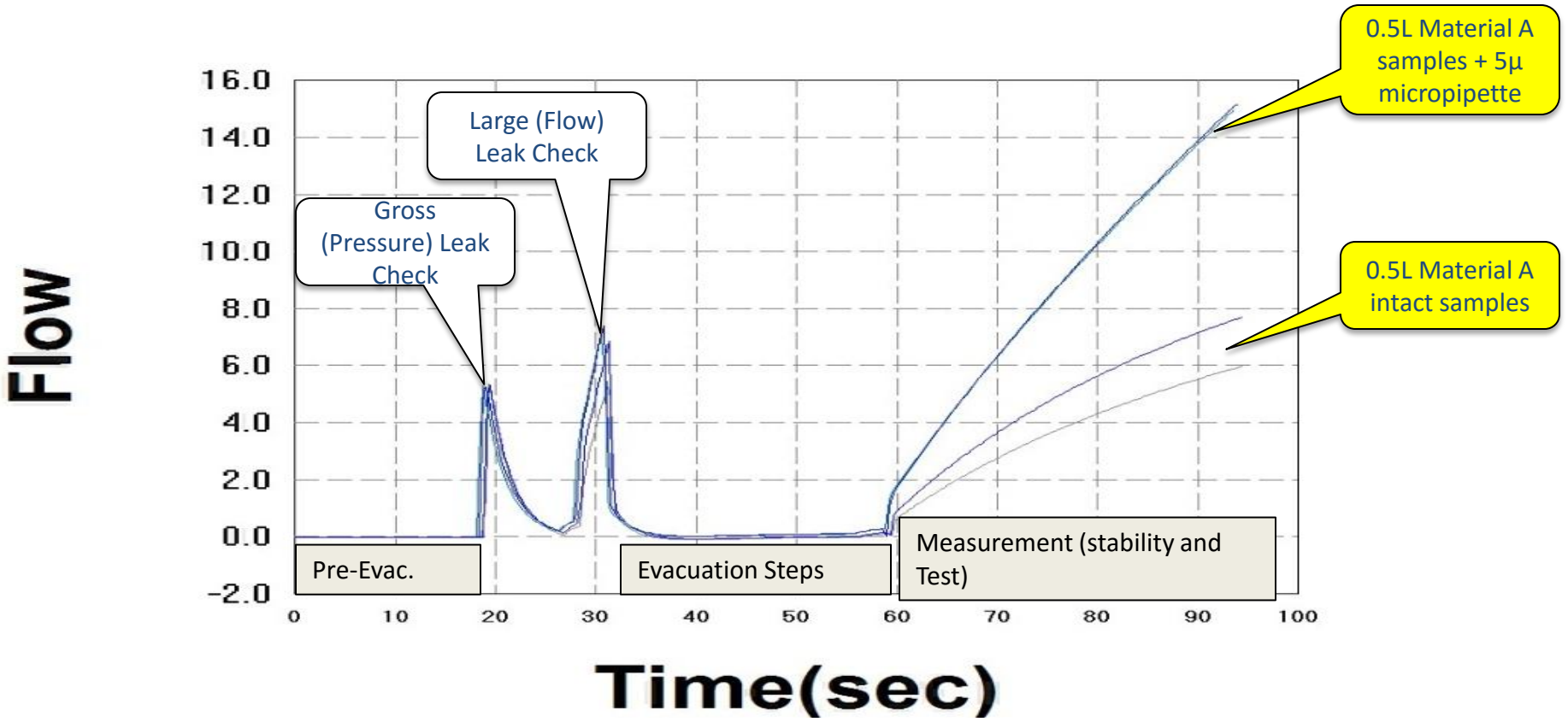
Mass Extraction: Failed Large Leak Check, due to air trapped between primary and secondary seal.
Oxygen Ingress as well as vacuum pressure: showed no seal breach as secondary seal is still sealing!!

IV Bags Testing With Mass Extraction

- IV Bags tested with 3 instruments, 0.25L to 3L in size. (Commercially purchased).
- Two main material types shows difference in intact samples due to material properties resulting in permeation, outgassing and surface wetness.
- Leak Artifacts (Micropipettes) from 5µ can be detected (dependent on bag-size and material)



IV Bags Testing With Mass Extraction



IV Bags- Two materials, 0.25L to 1L test on THREE Mass Extraction Machine- Negative and Positive Control

Accepted

Rejected

LLC-Large Leak Check Reject (Flow failure)
GRL- Gross Leak Check Reject (pressure failure)

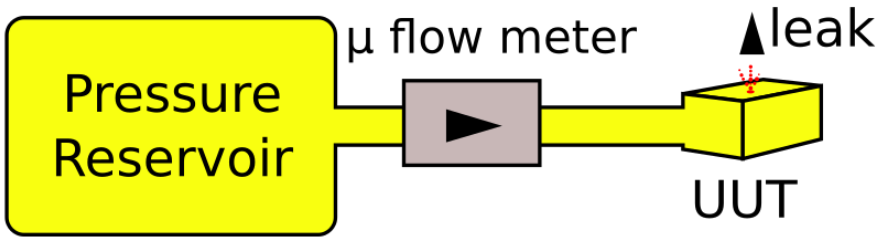
Bags Type	Orifice size, micron	FDA01-ME2-01	FDA01-ME2-02	FDA01-ME2-03	Suggested Fail Limit (µg/min)
A-1L	Negative	7.62; 7.87;	7.64; 7.49	8.95; 11.3	14
A-1L	5	18.02; 18.37	18.49;17.89	19.84; 19.86	
A-1L	10	LLC	LLC	LLC	
A-1L	Artif 5	LLC	LLC	LLC	
A-1L	Artif 10	GRL	GRL	GRL	
B-1L	Negative	26.72;23.92	23.36; 21.58	25.01;26.91	32
B-1L	5	38.67; 35.61	39; 40	40.29;39.9	
B-1L	10	LLC	LLC	LLC	
B-1L	Artif 5	GRL/LLC	LLC	LLC	
B-1L	Artif 10	GRL	GRL	GRL	
A-0.5L	Negative	7.65; 10.8;	7.14; 7.33	6.84;7.9	12
A-0.5L	5	17.5	18.27; 17.63;19.27	20.22; 19.63	
A-0.5L	10	LLC	LLC	LLC	
A-0.5L	Artif 5	LLC	LLC	LLC	
A-0.5L	Artif 10	GRL/LLC	GRL/LLC	GRL	
B-0.5L	Negative	15.50; 16.1	19.38; 18.35	16.0; 18.27	25
B-0.5L	5	29.3;30.1	33.44; 31.79	32.62; 32.18	
B-0.5L	10	LLC	LLC	LLC	
B-0.5L	Artif 5	LLC	LLC	LLC	
B-0.5L	Artif 10	GRL	GRL	GRL	
A-0.25L	Negative	5.12:5.48	5.8; 5.36; 5.2	5.973; 7.68	9
A-0.25L	5	13.11	13.1;13.27	14.92; 15.18; 14.98	
A-0.25L	10	LLC	LLC	LLC	
A-0.25L	Artif 5	LLC	LLC	LLC	
A-0.25L	Artif 10	GRL	GRL	GRL	
B-0.25L	Negative	14.25; 14.61	15.6; 14	10.82;11.03; 13.4	18
B-0.25L	5	20.96;	21; 22.33	23.36; 22.27	
B-0.25L	10	LLC/FS	LLC	LLC	
B-0.25L	Artif 5	LLC	LLC	LLC	
B-0.25L	Artif 10	GRL	GRL	GRL	

Design Consideration and Challenges

- Chamber design is critical for consistency and repeatable results.
  - New design allows to catch portentous drugs leakages from 5-10 micron defect during FAST large leak check using water evaporation.
- 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.

Testing In Process Single use Bags

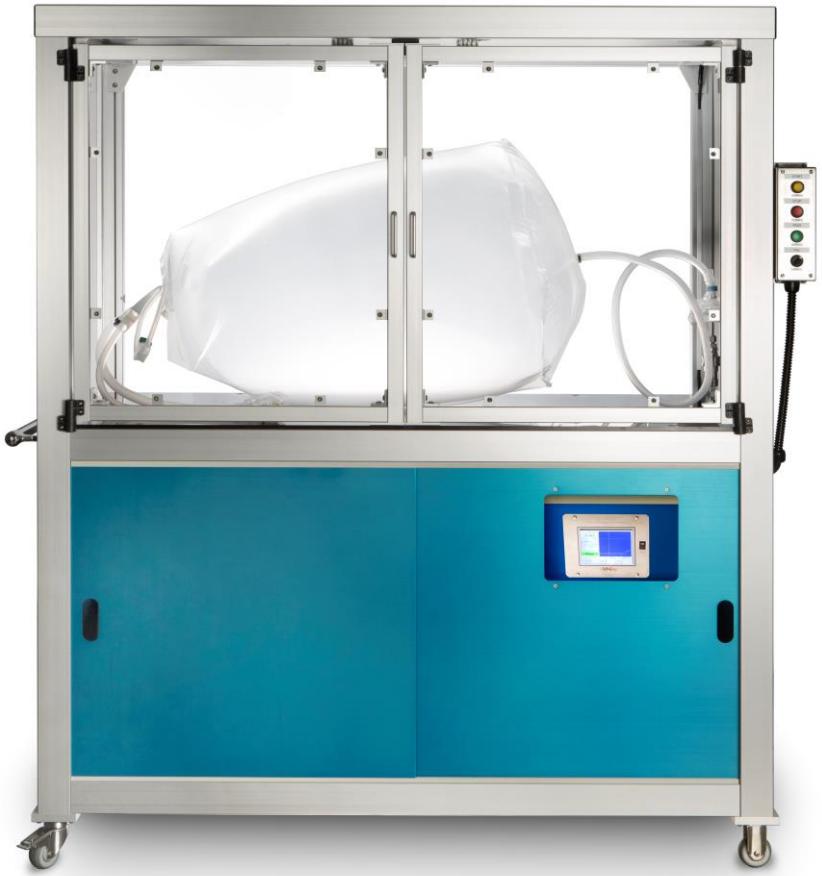
- Although not part of USP 1207, recent conferences showed interest in this topic.
- Testing with ATC's patented Micro-Flow sensors (work in pressure not vacuum)
- Two cases:
  - Bags are contained in a constraining fixture- GOOD FOR 2D Bags, not recommended for 3D Bags.
  - Bags are in free condition or at a point of use (in a process container)- applicable to all bags designs



- Measure with *Micro-Flow Sensor* Gas (AIR) Make Up Flow

PDA
Parenteral Drug Association

UN-CONSTRAINED



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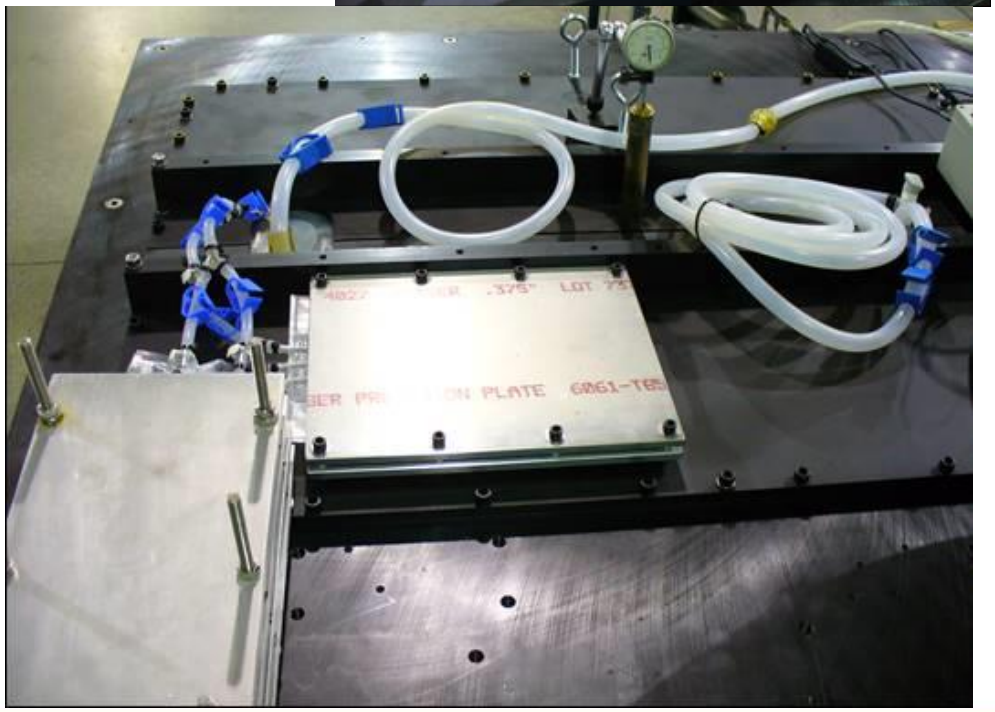

Limit of Detection-Single Use Bags

- Constrained bags: Bags to 200 L demonstrated 10 micron (sharp edge orifice) LOD.
  - Limited to 2D bags
  - For complete system-complicated and heavy set up
    - Specially design fixture with porous surfaces to avoid blocking a leak
- Unconstrained bag- 50L to 1000 L from 25 micron to 100 micron depends on bag size and test pressure. (The higher test pressure the lower is the LOD).
  - Higher test pressure at the point of use.
  - Simple flexible set up.

Applications Consideration-Mass Extraction

- **Mass Extraction Instruments are a DETERMENISTIC method; remote data collection may be considered**.
- Data collection can be done by PC (pass/fail and measurement values by instrument): requires FDA-CFR21 part 11 compliant software
- **Setting the Limit of Detection:**
  - **The smaller the defect size that Mass Extraction is set to detect, the lower the risk the user takes.**

COMMON APPLICATIONS:

- R&D , Stability and Quality Control Labs. (Manual systems, operator manually loads samples).
- High Speed Instruments enable higher speed applications:
  - Robotic (automatic) sampling: few tests per minute, in-line set up.
  - High speed 100% inspection in-line testing.

Application VIDEOS

Application videos:

CCIT of Flexible Pouch and Glass Vial- see http://atcinc.net/videos/

In-line (100%) CCIT system-please contact ATC

Acknowledgements

- ATC Engineering Research Team
- Our Pharmaceutical Customers collaborating and allowing the multiple lab. Correlation study.