Automated Deterministic Inspection Technologies:

Complete Quality Control for Vials and Syringes

Oliver Stauffer, CEO
PTI Inspection Systems

PDA Parenteral Drug Association

CONNECTING PEOPLE SCIENCE AND REGULATION®

Pharma's Future

- Antibody-Drug Conjugates (ADC's)
- Advanced gene therapy (RNA)
- Personalized therapy (CAR-T)
- Target therapy (mAbs)

LARGE MOLECULE PARENTERAL DELIVERY

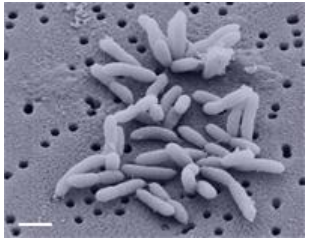
Shift in CCI

- FDA Guidance for Industry (2008)- Container and Closure System Integrity Testing in Lieu of Sterility Testing
- USP Chapter 1207 (2019)– Package Integrity Evaluation – Sterile Products
- EMA Annex 1 (2020)– Manufacture of Sterile Medicinal Products

Package Integrity

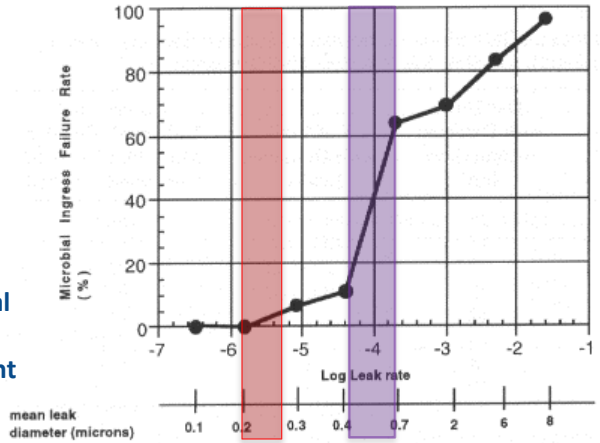
Smallest leak to allow ingress determination

Lee Kirsch, et al, PDA J Pharm Sci & Technol, Vol. 51, No. 5, 1997



108 to 1010 P. diminuta
From: MicrobeWiki

E. Coli
From Wikipedia



- **Glass micro-pipettes through wall of stoppered glass vial**
  - **0.1 to 10µm diameter** (Sized via helium mass spec)
- **Microbial challenge by immersion + liquid tracer element**
- **Challenge conditions**
  - Water bath immersion 60ºC 2hr, then 25ºC 1hr
    - 24 hr immersion, ambient pressure

Ingress Risk Dropped: Log -3.8 sccs (Leak < ~1µm)

No Ingress: Log -5 to -5.8 sccs (Leak ~0.3 to 0.2µm)

Most bacteria are **0.2 µm** in diameter and 2-8 µm in length. The three basic bacterial shapes are coccus (spherical), bacillus (rod-shaped), and spiral (twisted), however pleomorphic bacteria can assume several shapes.

A Complex System

- CCI and Component Performance
  - Dimensional tolerances
  - Stopper and tip-cap
  - Barrel barrier properties
- Barrel – Plunger(piston)
- Needle Shield - Needle Tip & Barrel
- Plunger Ribs
- Headspace Criticality

Dye Ingress Test Methods

Test Method	Ph.Eur. 3.2.9 USP 31 <381>	Modified USP/PhEur	ISO 8362-5 ISO	Modified ISO
Dye Solution	1 g/L (0.1% w/v) Methylene Blue Aqueous Solution	1 g/L (0.1% w/v) Methylene Blue Aqueous Solution	0.1% w/v Methylene Blue Aqueous Solution	0.1% w/v Methylene Blue Aqueous Solution
Vacuum	-27 kPa	-37 kPa	75 ± 5 kPa[1]	63 kPa[2]
Time Vacuum	10 minutes	10 minutes	30 minutes	30 minutes
Time Atmospheric Pressure	30 minutes	30 minutes	30 minutes	30 minutes

[1] equivalent to drawing a vacuum of about -25 kPa
[2] equivalent to drawing a vacuum of about -37 kPa

- Package characteristics
- Surfactant concentration
- Vacuum level
- Vacuum dwell time
- Ambient pressure dwell time
- Operator capability
- Operating conditions

Vacuum Decay Dye Ingress

Defect Type	ID Code[1]	Leak Test Results		Visual Inspection Results[2]		
		dP Pa	P/F	Inspector 4	Inspector 5	Inspector 6
Controls Tested for Ingress	B6	8	P	N	N	N
	B7	8	P	N	N	N
	B8	8	P	N	N	N
	B9	8	P	N	N	Y
	B10	8	P	N	N	N
5µm hole	111	64	F	Y	Y	Y
	112	54	F	N	N	Y
	113	88	F	Y	Y	Y
	114	56	F	N	N	N
	115	46	F	N	N	Y
10µm hole	126	192	F	Y	Y	Y
	127	184	F	Y	Y	Y
	128	186	F	Y		
	129	301	F	Y		
	130	194	F	Y		
15µm hole	141	352	F	Y		
	142	356	F	Y		
	143	346	F	Y		
	144	445	F	Y		
	145	371	F	Y		

[1] Holed syringes are identical to those used for Part 1, ASTM precision and bias studie
[2] Y = dye seen, N = No dye seen

Dye Ingress Research

Vacuum Decay Container/Closure Integrity Testing Technology. Part 2. Comparison to Dye Ingress Tests

Heinz Wolf, Tony Stauffer, Shu-Chen Y. Chen, Yoojin Lee, Ronald Forster, Miron Ludzinski, Madhav Kamat, Brian Mulhall and Dana Morton Guazzo; PDA Journal of Pharmaceutical Science and Technology September 2009, 63 (5) 489-498

Development of a Dye Ingress Method to Assess Container-Closure Integrity: Correlation to Microbial Ingress

Lana S. Burrell, Mary W. Carver, George E. DeMuth and William J. Lambert; PDA Journal of Pharmaceutical Science and Technology November 2000, 54 (6) 449-455

Comparing Physical Container Closure Integrity Test Methods and Artificial Leak Methodologies

Sarah S. Peláez, Hanns-Christian Mahler, Christoph Herdlitschka, Toni Wertli, Matthias Kahl, Atanas Koulov, Anja Matter, Satish K. Singh, Martina Widmer, Oliver Germershaus and Roman Mathaes; PDA Journal of Pharmaceutical Science and Technology May 2019, 73 (3) 220-234

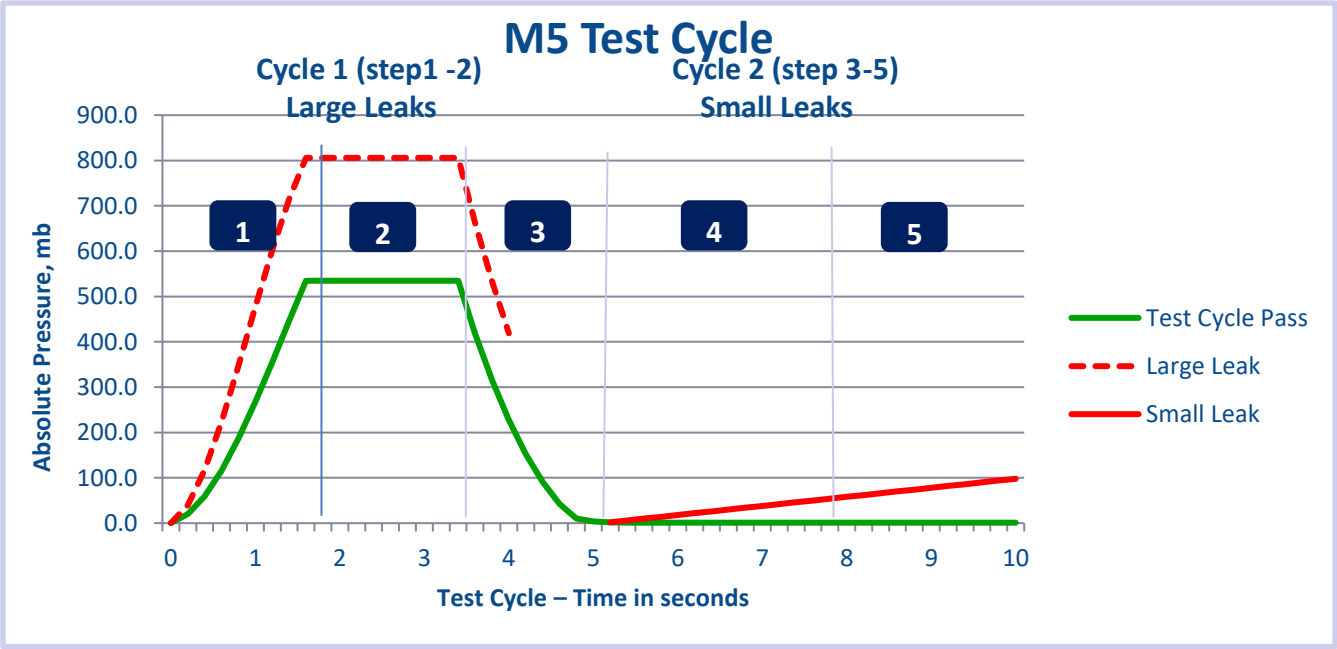
Container Closure Integrity Testing—Practical Aspects and Approaches in the Pharmaceutical Industry

Helen Brown, Hanns-Christian Mahler, James Mellman, Alejandra Nieto, Daniel Wagner, Matthias Schaar, Roman Mathaes, Juergen Kossinna, Franz Schmitting, Sascha Dreher, Holger Roehl, Markus Hemminger and Klaus Wuchner; PDA Journal of Pharmaceutical Science and Technology March 2017, 71 (2) 147-162

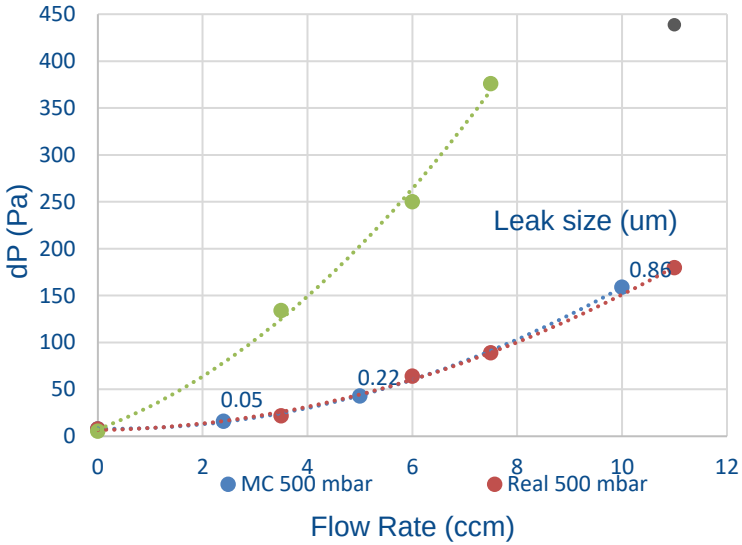
Vacuum Decay Leak Detection

Vacuum Decay Test Cycle

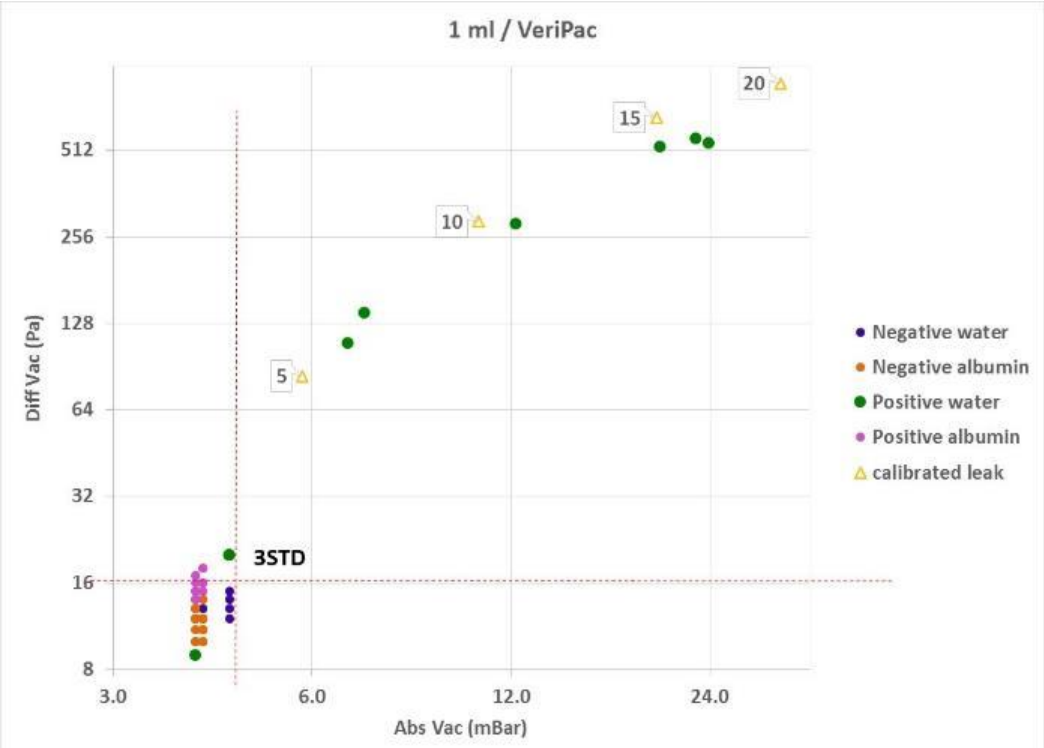
The gold standard for test method reliability.



Liquid Defect Amplification



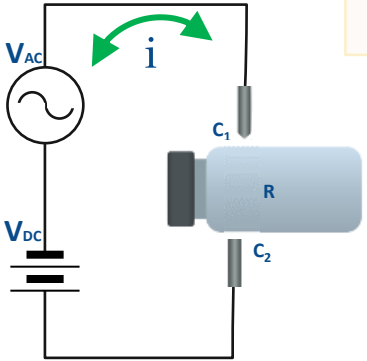
1mL Prefilled Syringe Case Study



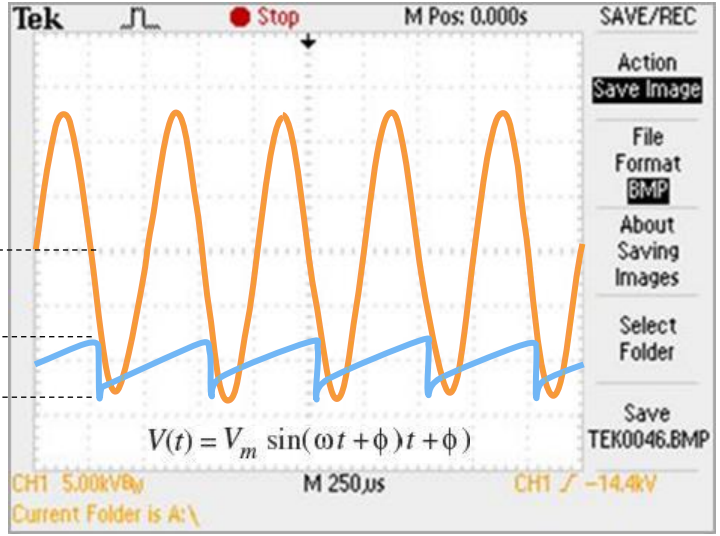
High Voltage Leak Detection (HVLD^{mc})

High Voltage Leak Detection (HVLD^{mc})

This new technology applies less than ***50% of the voltage*** used with conventional high voltage technologies and the product its exposed to less than a ***5% of the voltage exposure*** experienced when testing with comparable HVLD solutions.

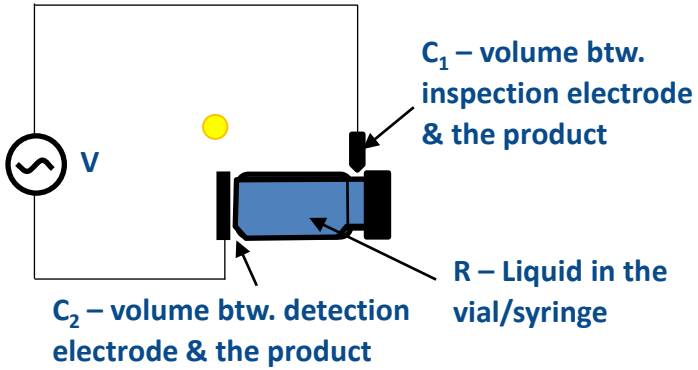


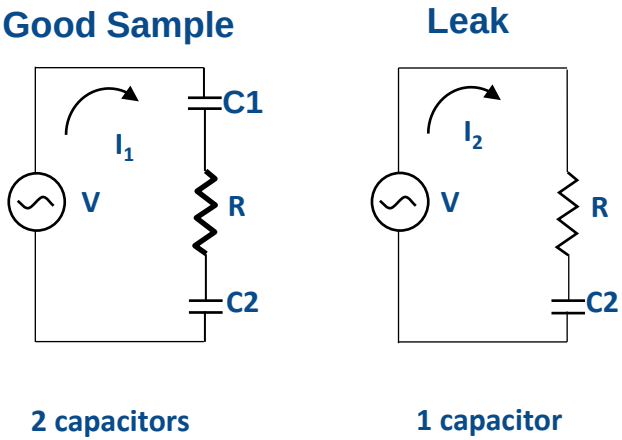
Conventional HVLD
Pure AC voltage:



MicroCurrent HVLD
AC + DC voltage:

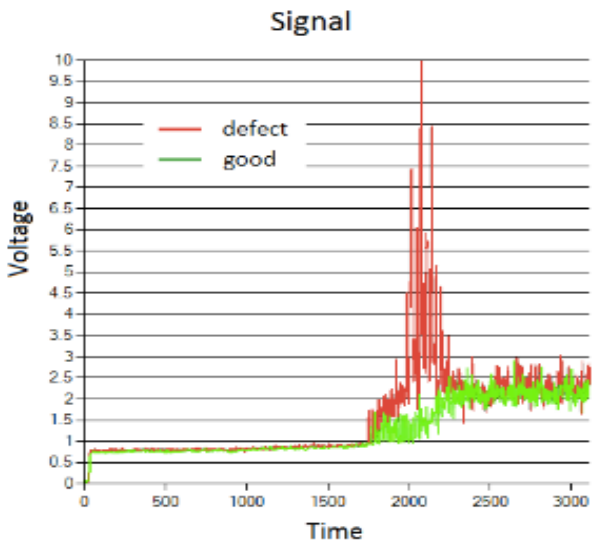
Functional Principle of HVLD^{mc} Test

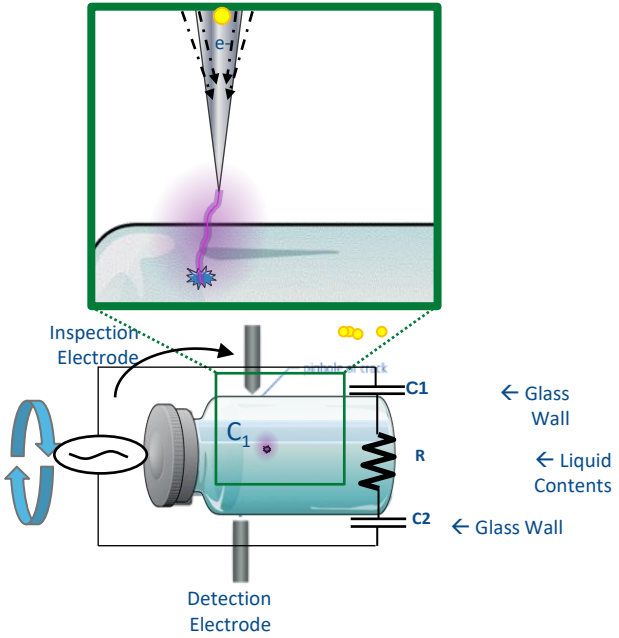




V – High Voltage Source
R – Electric Resistance of the product
C_1 – Capacitor 1: Glass between the inspection electrode and product
C_2 – Capacitor 2: Glass between the detection electrode and product
I_1 – current produced when product container is sealed
I_2 – current produced when product container is defective

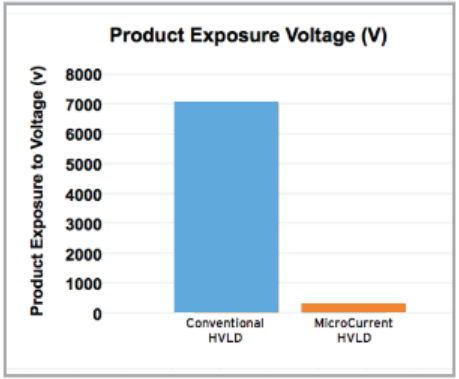
High Voltage Leak Detection (HVLD^{mc})



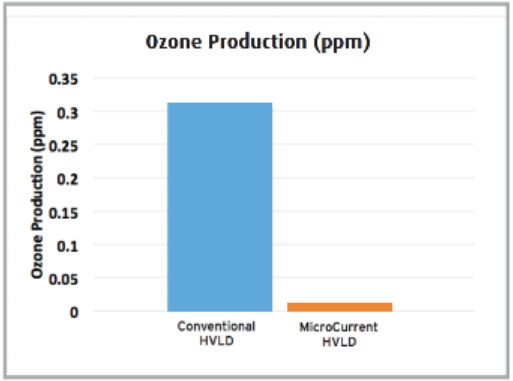


MicroCurrent HVLD - Benefits

Product HV Exposure



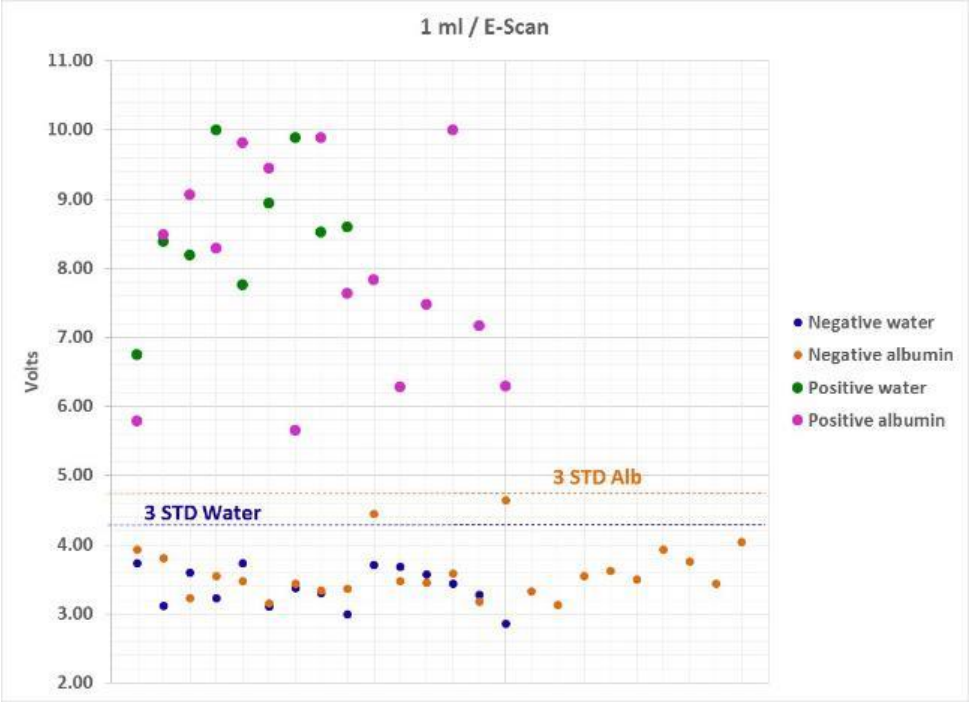
Ozone Creation



10 minutes test
Outside the product

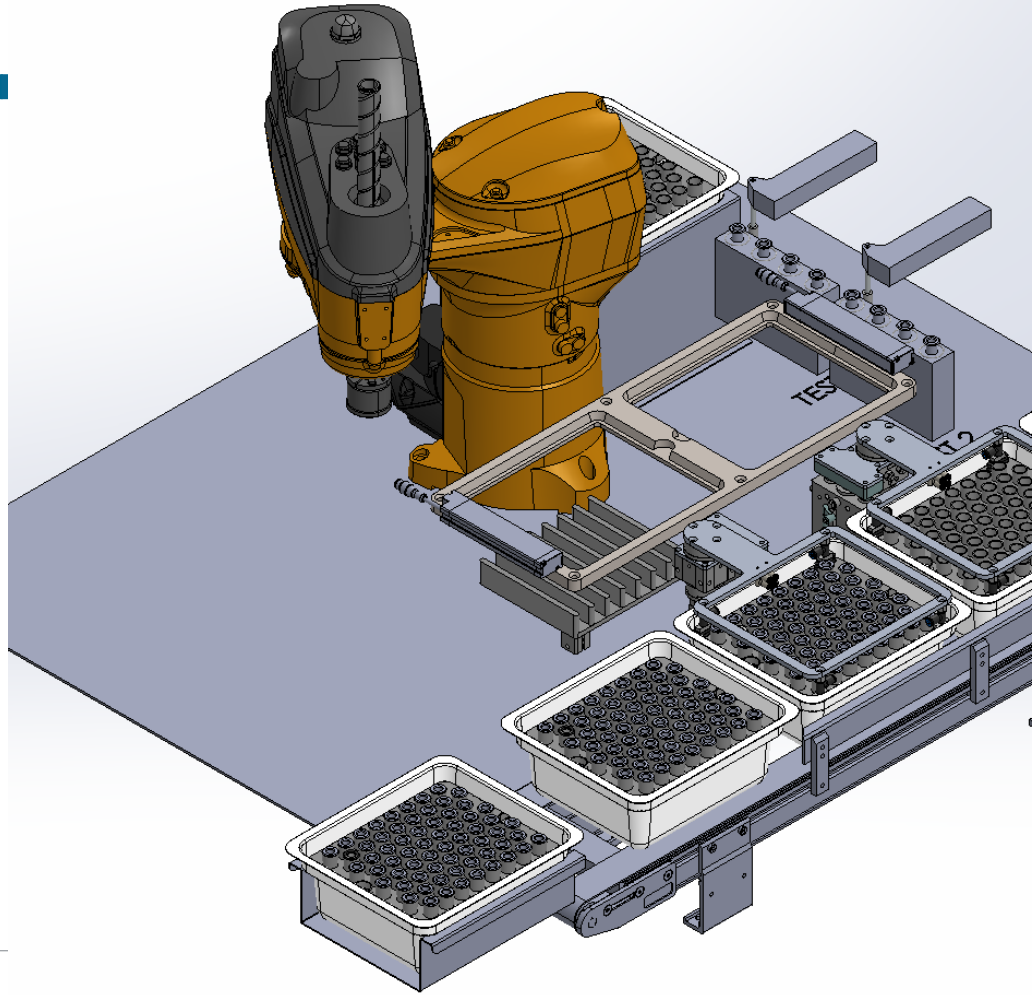
	Conventional HVLD	MicroCurrent HVLD
Exposure Voltage (V)	7000	300
Ozone Production (ppm)	0.305	0.006

1mL Prefilled Syringe Case Study



PTI's Robotic Platform

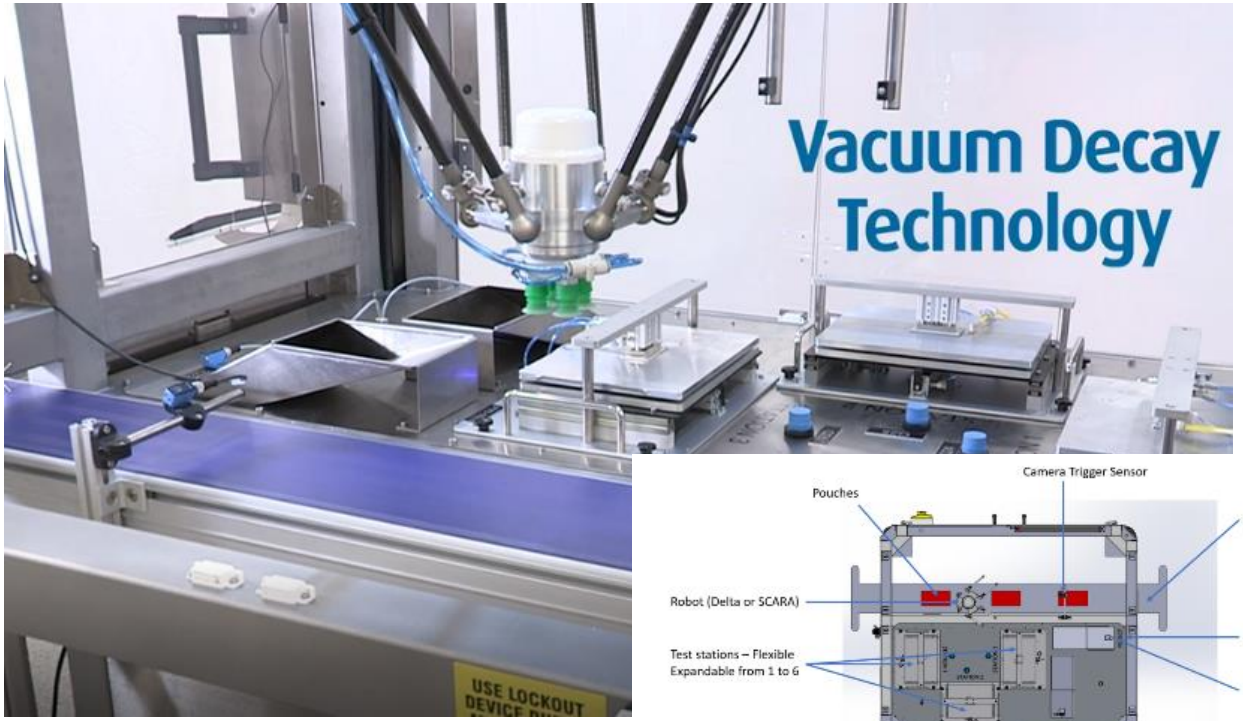
- Highly flexible
- Indexing accumulator
- Adaptive handling or nested presentations
- Multi-format rapid changeover
- Modular concept throughout
- Defects preserved
- HVLD^{mc} or Vacuum Decay

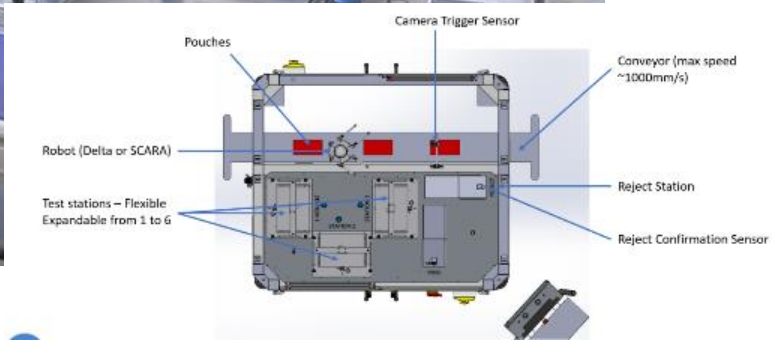


Advanced Applications

- Auto-injectors
- Cartridges
- Combination devices
- Complex geometries

Vacuum Decay Platform





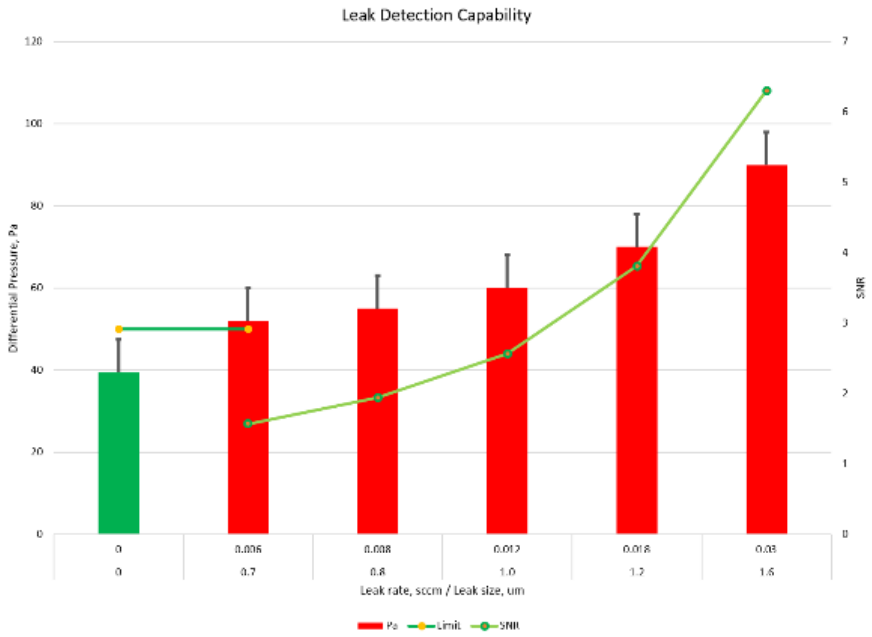
MicroCurrent HVLD

- Liquid fill
- MALL Sensitivity (<1 micron)
- Low exposure voltage
- Dynamic product range
- No Ozone generated
- Defect position ID
- Detects clogged defects
- 0.2mL to 500mL containers

Vacuum Decay

- Small molecule liquid and lyophilized
- MALL Sensitivity (<1 micron)
- Large leak capture, no contamination
- Quantifies leak size
- Adaptive leak testing capabilities
- Any size container

Next Generation Sensitivity



Conclusions

- Dye ingress is not effective for many parenteral applications
- Understanding product and package dynamics is critical
- Next generation technologies: Reliability, Sensitivity, Practicality
- Robotic automation provides distinct advantages
- Vacuum Decay and HVLD are powerful technologies for parenteral CCIT

Uncompromised flexible quality assurance.

Thank you!

o.stauffer@ptiusa.com

Best Practices: CCIT In Manufacturing

A Webinar Series by PDA Asia Pacific

8 July 2020 (Wednesday)
10:00-11:00 hours (GMT+8)

How to Better Understand Automated Deterministic Inspection Technologies for Complete Quality Control of Prefilled Syringes

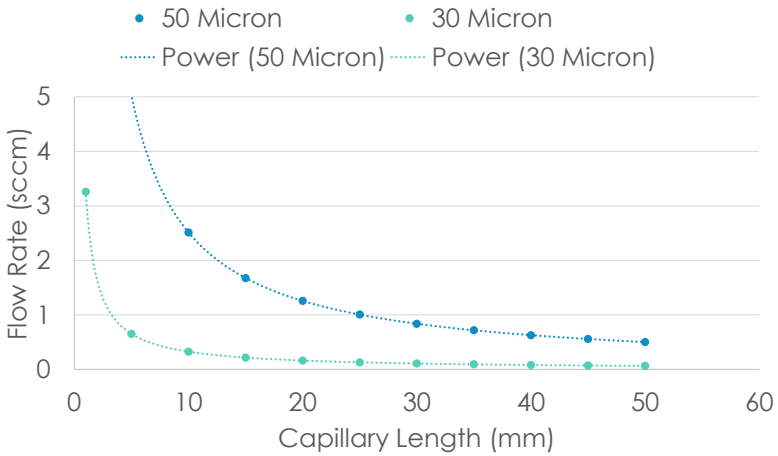
Oliver Stauffer

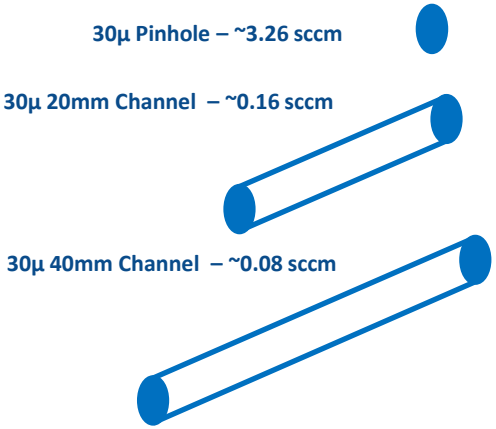
CEO of PTI - Packaging Technologies & Inspection
United States

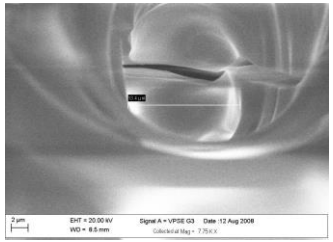
PDA®
Parenteral Drug Association
Asia Pacific

Supplemental Slides

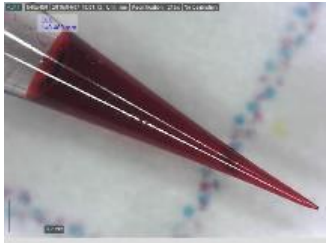
Tortuous Defects







"Proteinaceous product may interfere with defect detection."[1]



- Naturally occurring defects and laser defects are susceptible to blockage when testing.
- Solutes may be deposited internal to the defect passage during testing due to liquid vaporization.

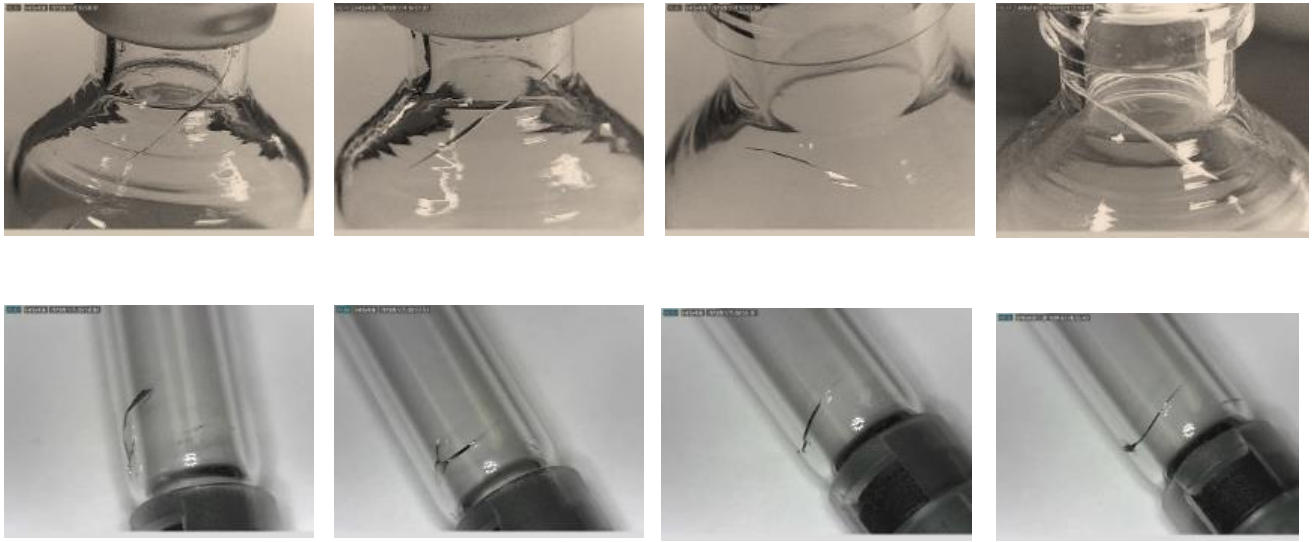
- Pipettes draw liquid through the calibrated defect into the pipette cavity ahead of test.
- Volume of liquid exposed to vacuum with low potential for solute blockage before test.
- **Ideal condition for detection.**
- **Not representative of naturally occurring defects.**

[1] Li, Lei. American Pharmaceutical Review. February 20, 2013. *Container Closure Integrity Testing Method Development and Validation for Prefilled Syringes*.

Statistical Quality Limits

Reject Limit Set Point	% Known good will Pass	% Known good will Fail	# of good samples that will fail per 10,000	1 False Reject Per
Avg +1 Std Dev	84.13%	15.87%	1587	6
Avg +2 Std Dev	97.72%	2.28%	228	44
Avg +3 Std Dev (1x Noise)	99.87%	0.13%	13	769
Avg +4 Std Dev	99.99%	0.0033%	.33	31,574
Avg +5 Std Dev	99.9972%	0.000028%	.0028	~3,500,000
Avg +6 Std Dev (2x Noise)	99.999%	0.00001%	.001	~10,000,000

Realistic Defects



Naturally Occurring Defects

Sample	leak rate			Visual	Size
	mbar·l/s	10^{-5} mbar·l/sec	sccm		um
1	0.00095	95	0.05700	Large crack	2.67
2	0.0000021	0.21	0.00013	Medium crack	0.13
3	0.000014	1.4	0.00084	Medium crack	0.32
4	0	0	0.00000	Small Scratch	0.00
6	0.00067	67	0.04020	Large crack	2.24
7	0.015	1500	0.90000	Large crack	10.61
9	0.00000029	0.029	0.00002	Small crack	0.05
10	0.00029	29.0	0.01740	Large crack	1.47
11	0.074	7400	4.44000	Large crack	23.56
12	0.055	5500	3.30000	Large crack	20.31
16	0.0014	140	0.08400	Small crack	3.24
18	0	0	0.00000	Small Scratch	0.00
19	0	0	0.00000	Small Scratch	0.00
20	0.016	1600	0.96000	Large crack	10.95

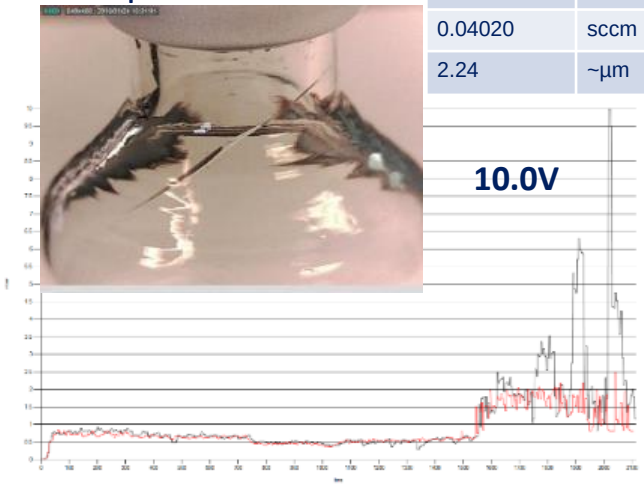
Sample 2

Sample 6

Sample 3

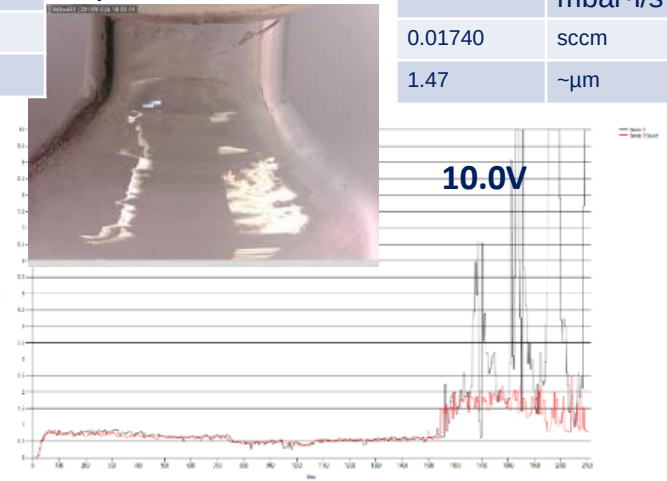
Sample 16

Sample 6



He Certified Leak Rate	
67.0	10^{-5} mbar·l/s
0.04020	sccm
2.24	~µm

Sample 3



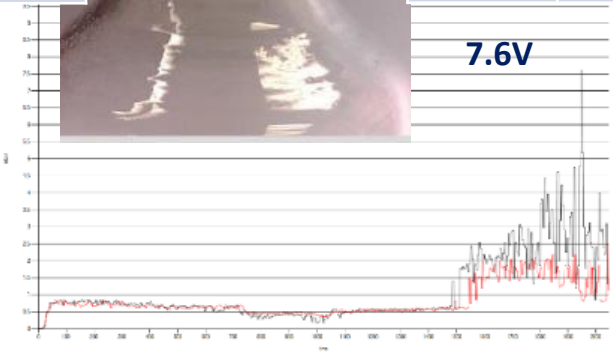
He Certified Leak Rate	
29.0	10^{-5} mbar·l/s
0.01740	sccm
1.47	~µm

Sample 2

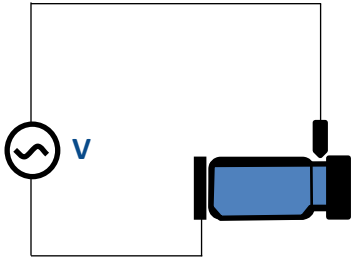
He Certified Leak Rate	
0.21	10^{-5} mbar·l/s
0.00013	sccm
0.13	~µm

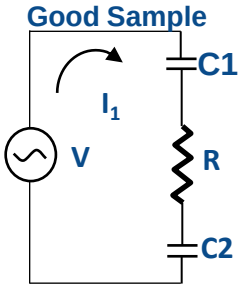
Sample 3

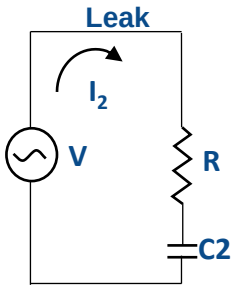
He Certified Leak Rate	
1.40	10^{-5} mbar·l/s
0.00084	sccm
0.32	~µm

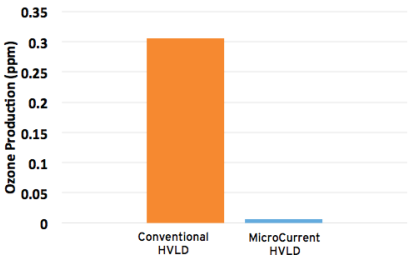


MicroCurrent HVLD

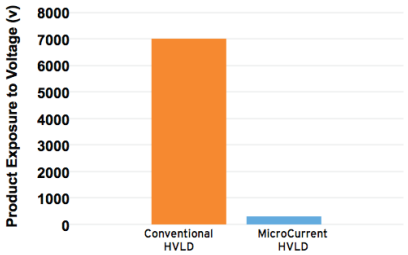




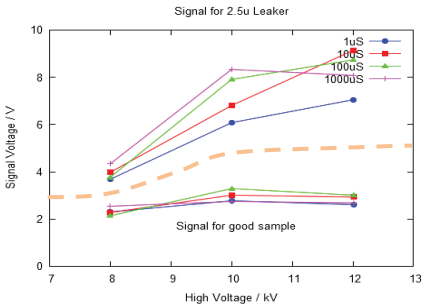




Ozone Creation



Exposure Voltage



Product Range

Deterministic CCI

- A package's ability to ***prevent product loss***, maintain ***product sterility***, and in some cases, prevent oxygen ingress or maintain sub-atmosphere headspace pressures.
- **Not defined as absence of microbial ingress, liquid ingress, or loss of sterility.**

Deterministic: the leakage event is based on phenomena that follow a ***predictable*** chain of events, and leakage is ***measured*** using ***physicochemical technologies*** that are readily ***controlled*** and ***monitored***, yielding objective ***quantitative data***.

Deterministic methods

- Electrical Conductivity and Capacitance (HVLD)
- Laser-Based Gas Headspace Analysis
- Mass Extraction
- Pressure Decay
- Tracer Gas Detection, Vacuum Mode
- Vacuum Decay