CCIT - Container Closure Integrity Testing following USP 1207

Tony Stauffer/ Tatiana Simental CCIT s.a./Pti

St Prex, Switzerland

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CCIT - New USP 1207 guidance document

Documents specifies and differentiates acceptable test methods:

- **Deterministic Leak Test Methods**
  - **Vacuum (ASTM F2338-09)**
  - **Electrical Conductivity and Capacitance tests (HVLD)**
  - **Head Space analysis**

- **Seal Quality test methods**
  - **Airborne Ultrasound (ASTM F3004-13)**

- **Probabilistic leak test methods (not considered good practice)**
  - **Water bath**
  - **Blue Dye Ingress**
  - **Microbial ingress test**
  - **Burst test**

Positive Controls - Natural Vial Defects

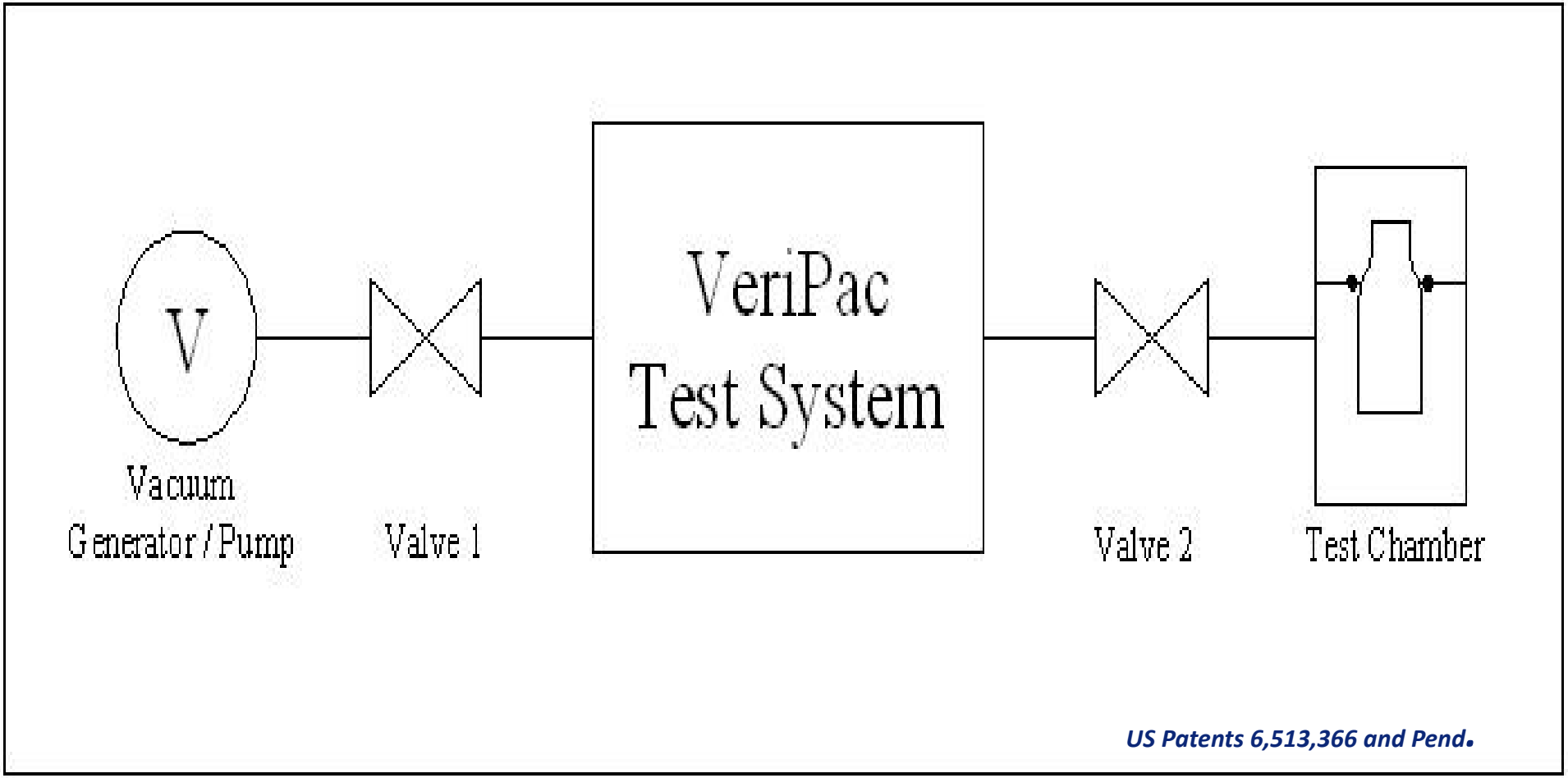
Vacuum Micro Leak Testing/CCIT

- Measures and verifies container closure integrity
- Detects vapor or gas release
- Test sensitivity down to 0.01 cc/min. (1 – 1.5 micron)
- Case studies prove more reliable than dye ingress
- ASTM F2338-09

VeriPac Differential Vacuum Test Method

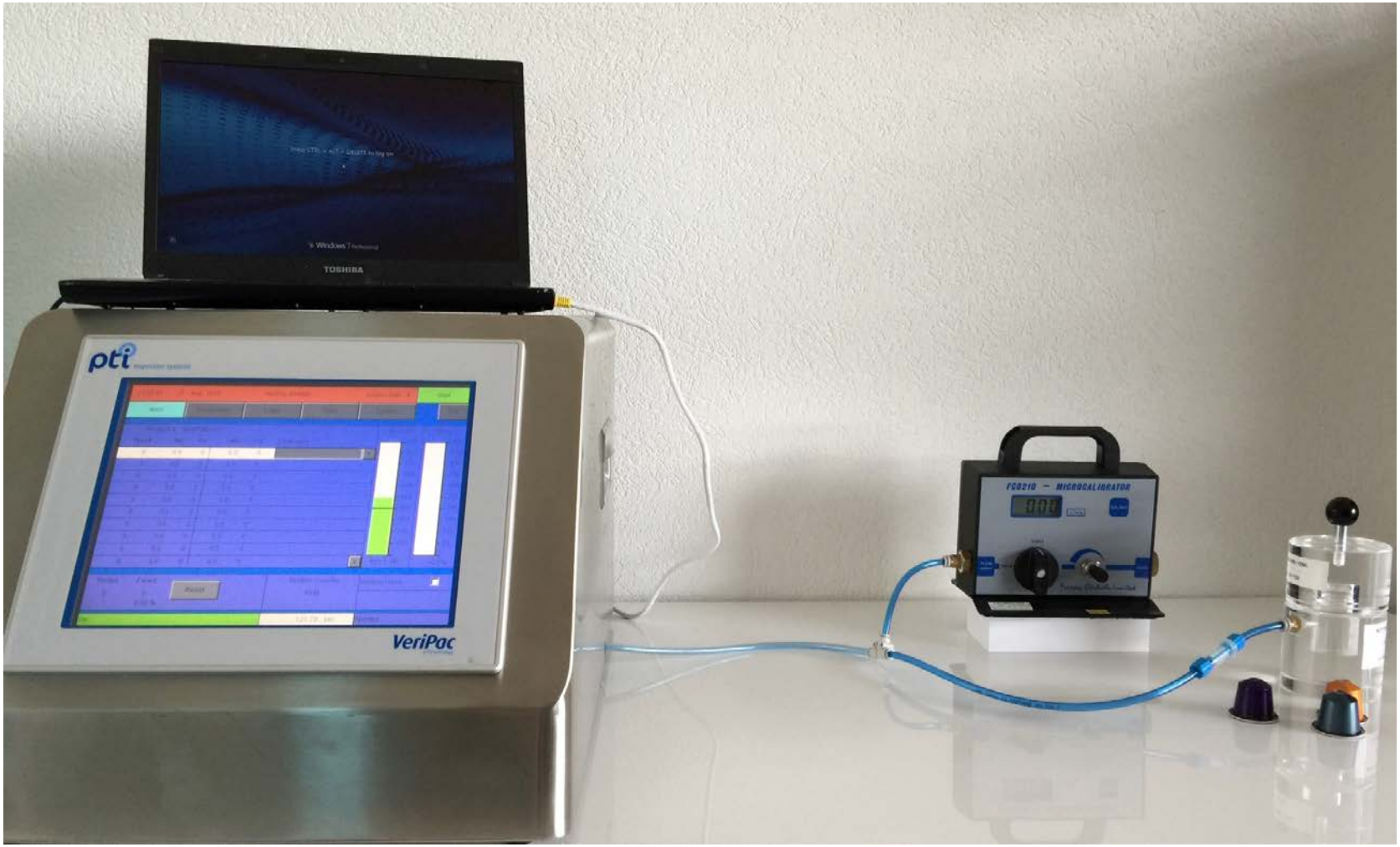
(simplyfied scPti hematics)

ASTM F2338-09

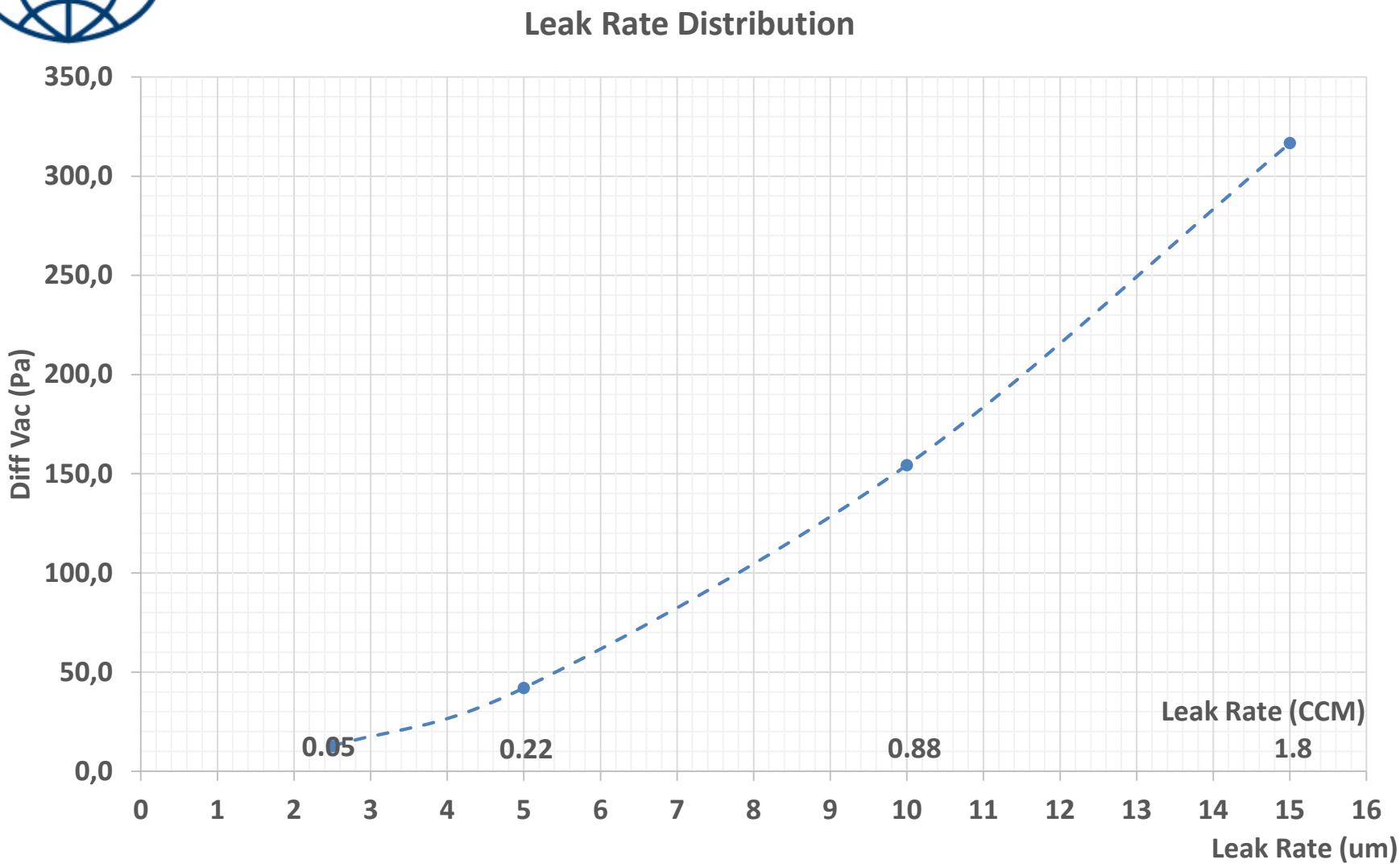


US Patents 6,513,366 and Pend.

Typical VeriPac set-up with MicroCalibrator



Determining Leak Size



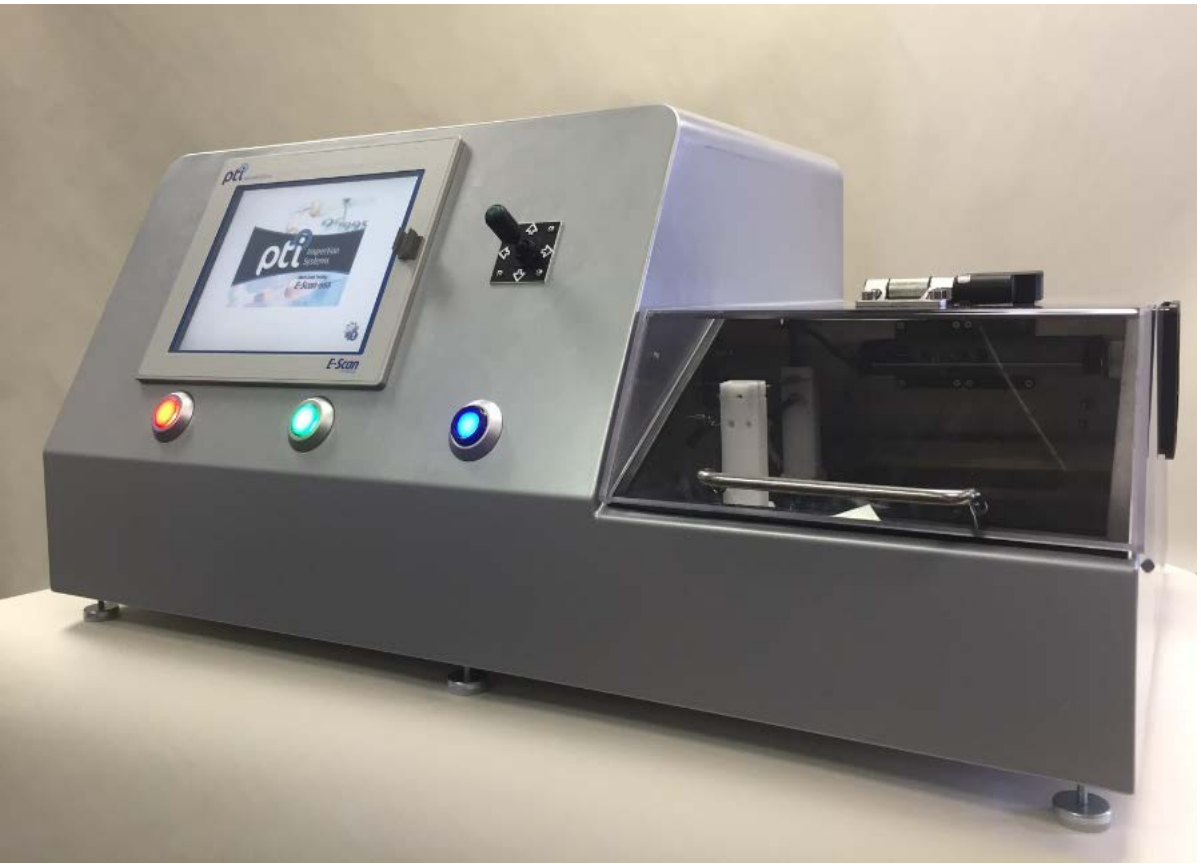
Test method for Tyvek® Lidded Trays (ASTM 2338-09)

Electrical Capacitance and High Voltage Detection also known as HVLD

- Pre-filled Syringes
- Vials & Ampoules
- BFS
- Bottles and Cups
- Pouches & IV Bags

E-Scan based on HVLD^{mc}

for liquid filled parenteral products



Off-line laboratory system to Inspect liquid filled

- **Vials**
- **Syringes**
- **Ampules**

Lower HV application

mc: micro current

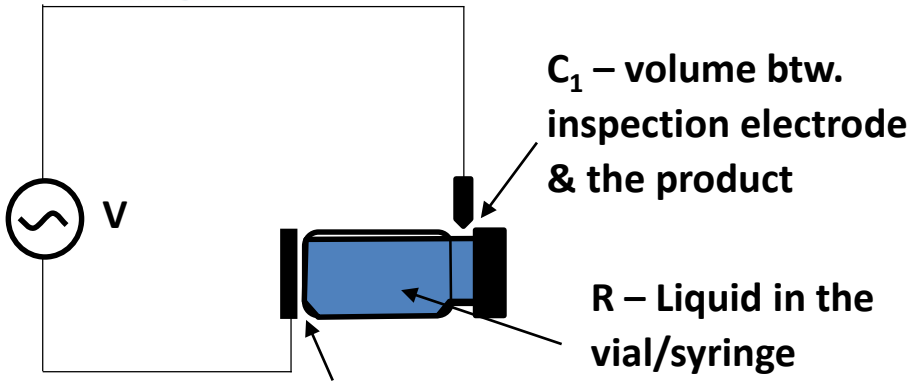
Improved SNR

Good for low conductivity liquids Incl distilled water

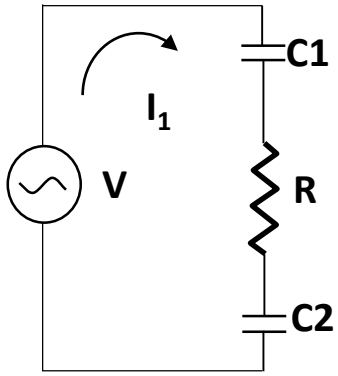
Product not exposed to HV

Negligable Ozone production

Functional principle of HVLD^{mc} test

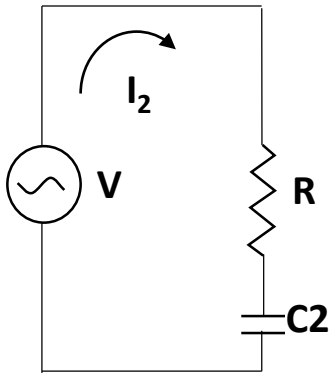


Good Sample



2 capacitors

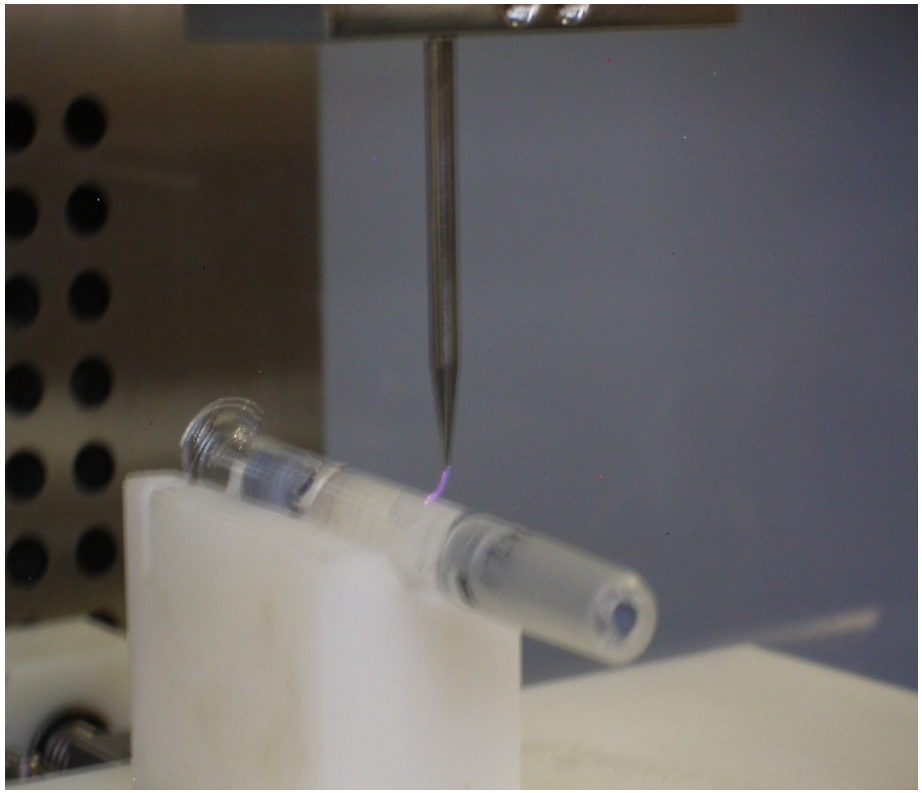
Leak

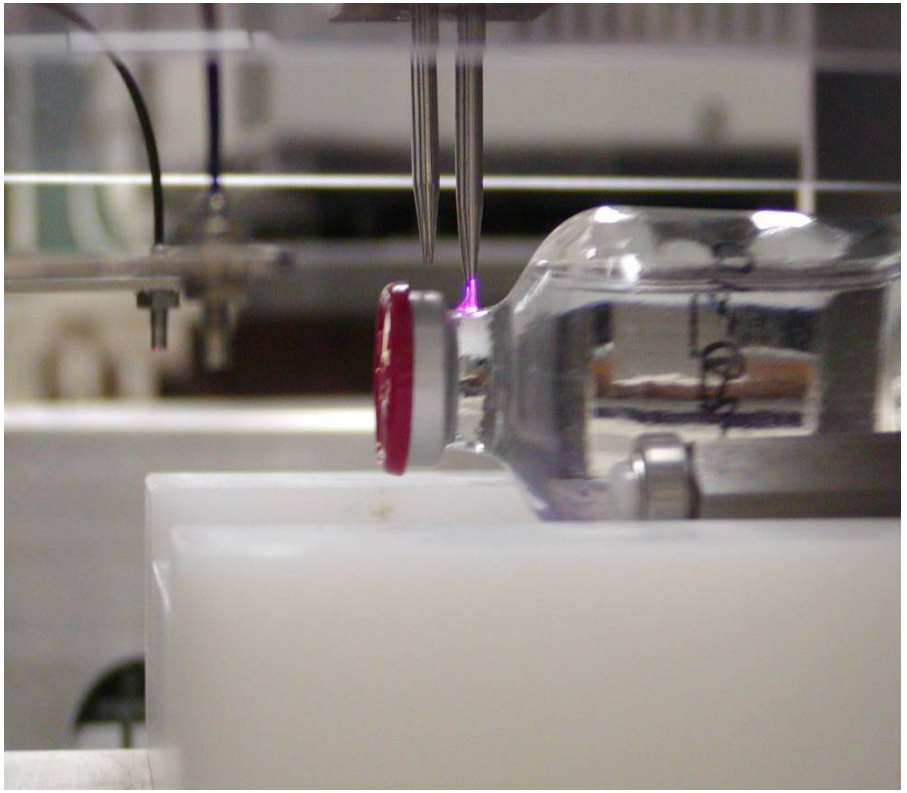


1 capacitor

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

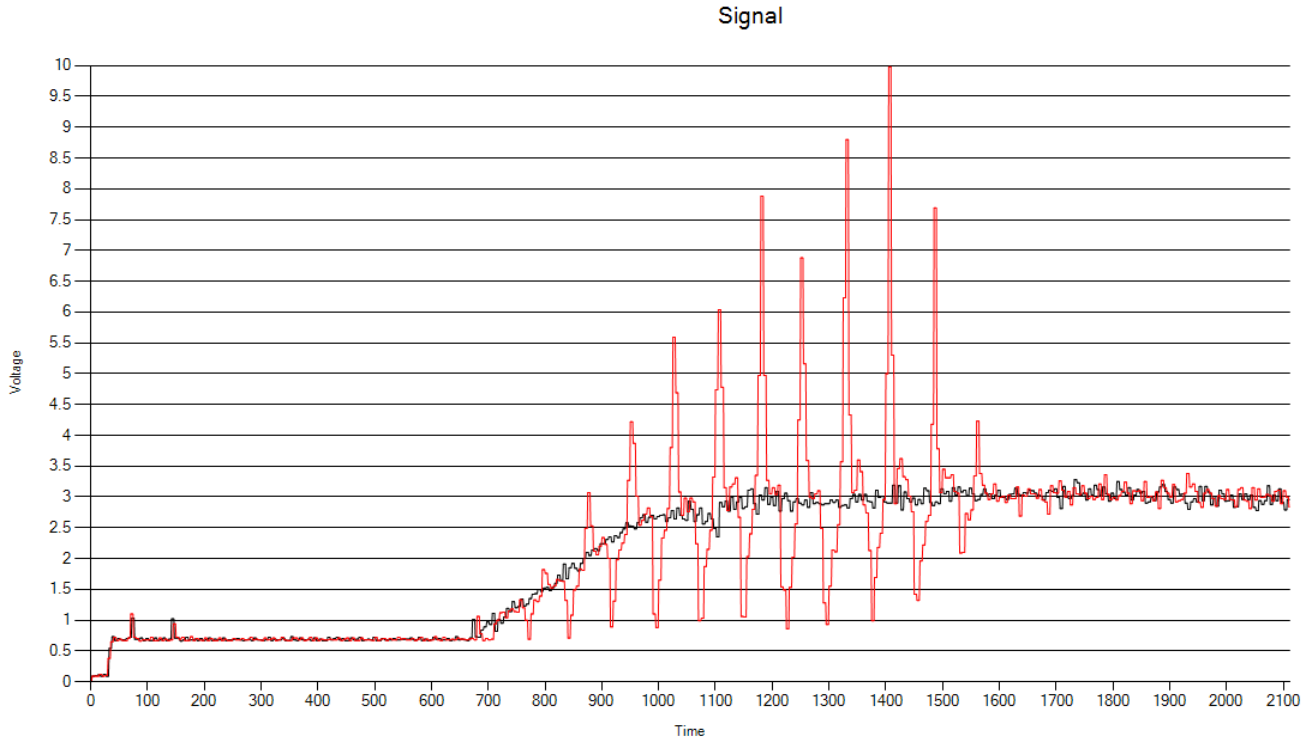
E-Scan – HVLD^{mc} - Electrical Conductivity and Capacitance Micro Leak Detection





1 ml Syringe - HVLD^{mc} Test

- Signal Detection 20ml Vial – Integrator – Signal has amplitude changes
- High Voltage:16kV
- Red - 3.6um leakage
- Black sample without defect
- 350 RPM, 5mm/s, filled with distilled water

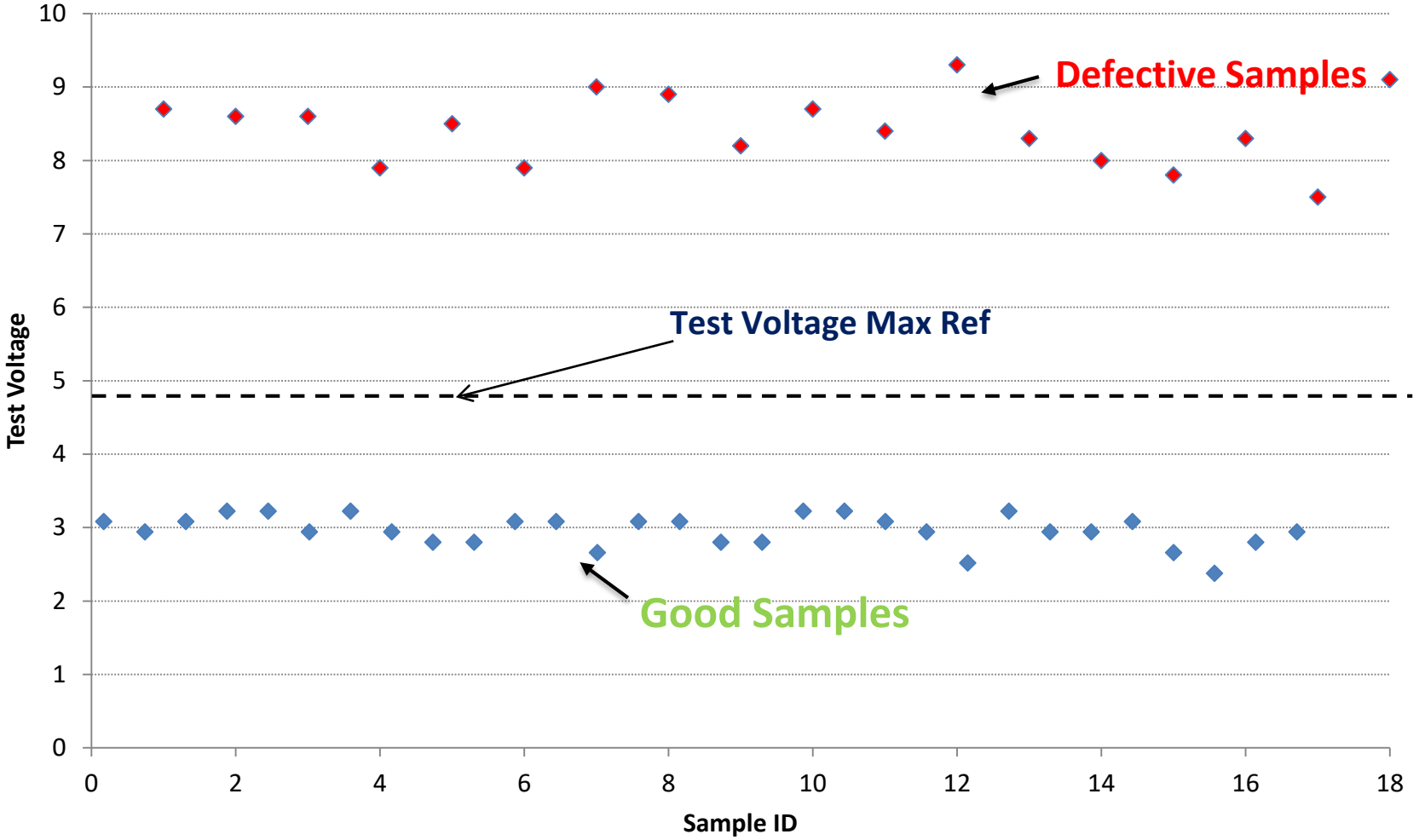


Test with E-Scan®
(positive controls)

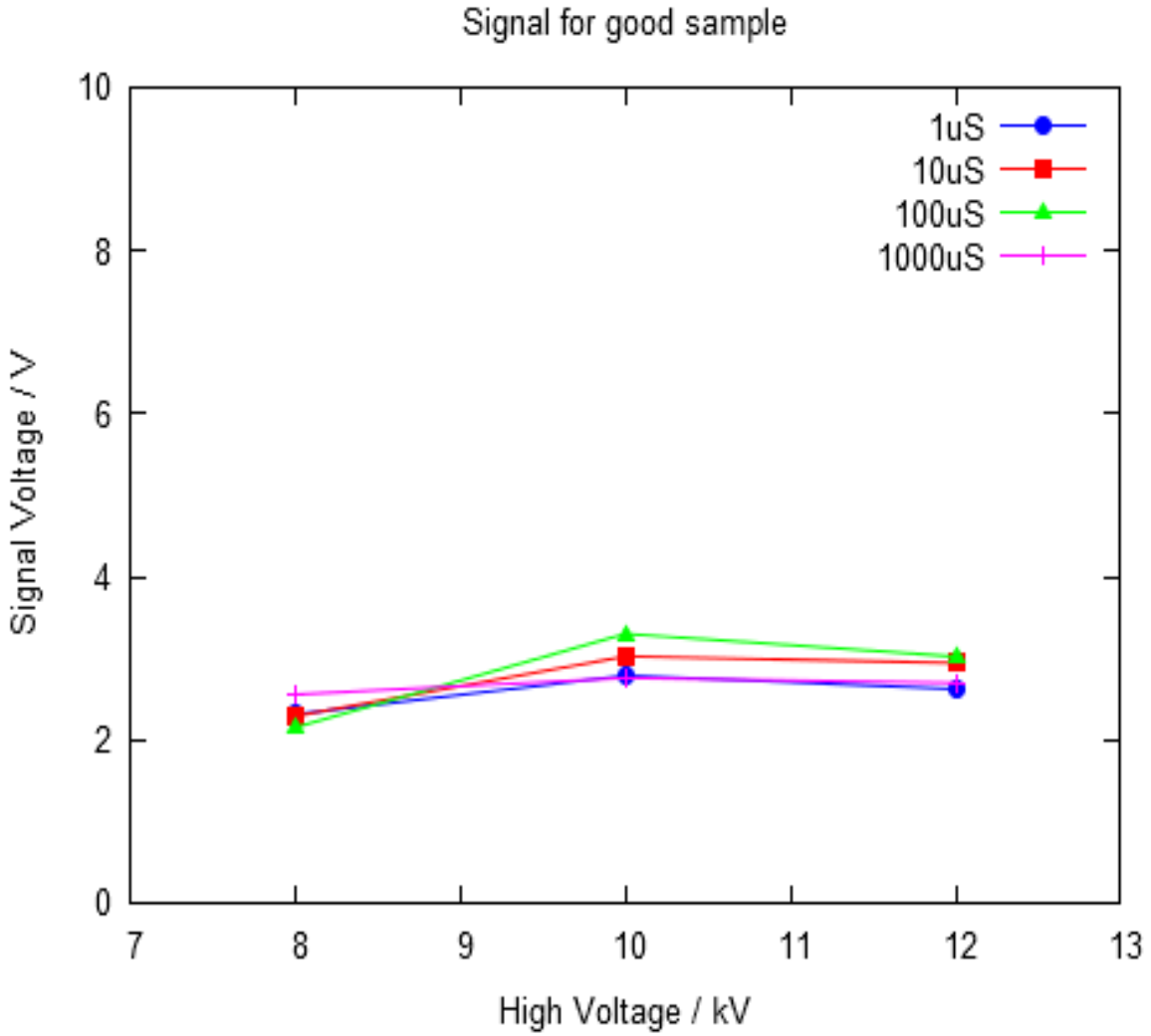
		Positive 1 ml syringe	
		Water	Alb.
Sample id.	Nominal leak	Volt	Volt
44	5	6.75	
41	10	8.38	
38	20	8.19	
39	?	10.00	
40	?	7.76	
42	?	8.94	
43	?	9.89	
45	?	8.52	
46	?	8.60	
23	5		5.79
35	10		8.48
7	20		9.06
8	?		8.29
9	?		9.82
10	?		9.45
11	?		5.65
31	?		9.89
32	?		7.64
33	?		7.83
34	?		6.28
19	?		7.47
20	?		10.00
21	?		7.17
22	?		6.29

		Positive 2.25 ml syringe	
		Water	Alb.
Sample id.	Nominal leak	Volt	Volt
M2	5	8.19	
M3	10	9.46	
M	20	10.00	
N2	?	9.22	
O2	?	10.00	
N3	?	9.22	
O3	?	7.95	
N	?	10.00	
O	?	10.00	
G2	5		5.38
G3	10		6.08
G	20		9.71
H2	?		7.09
I2	?		4.70
J2	?		5.45
K2	?		3.38
H3	?		7.06
I3	?		4.87
J3	?		5.83
K3	?		6.35
H	?		7.77
I	?		9.03
J	?		8.74
K	?		8.60

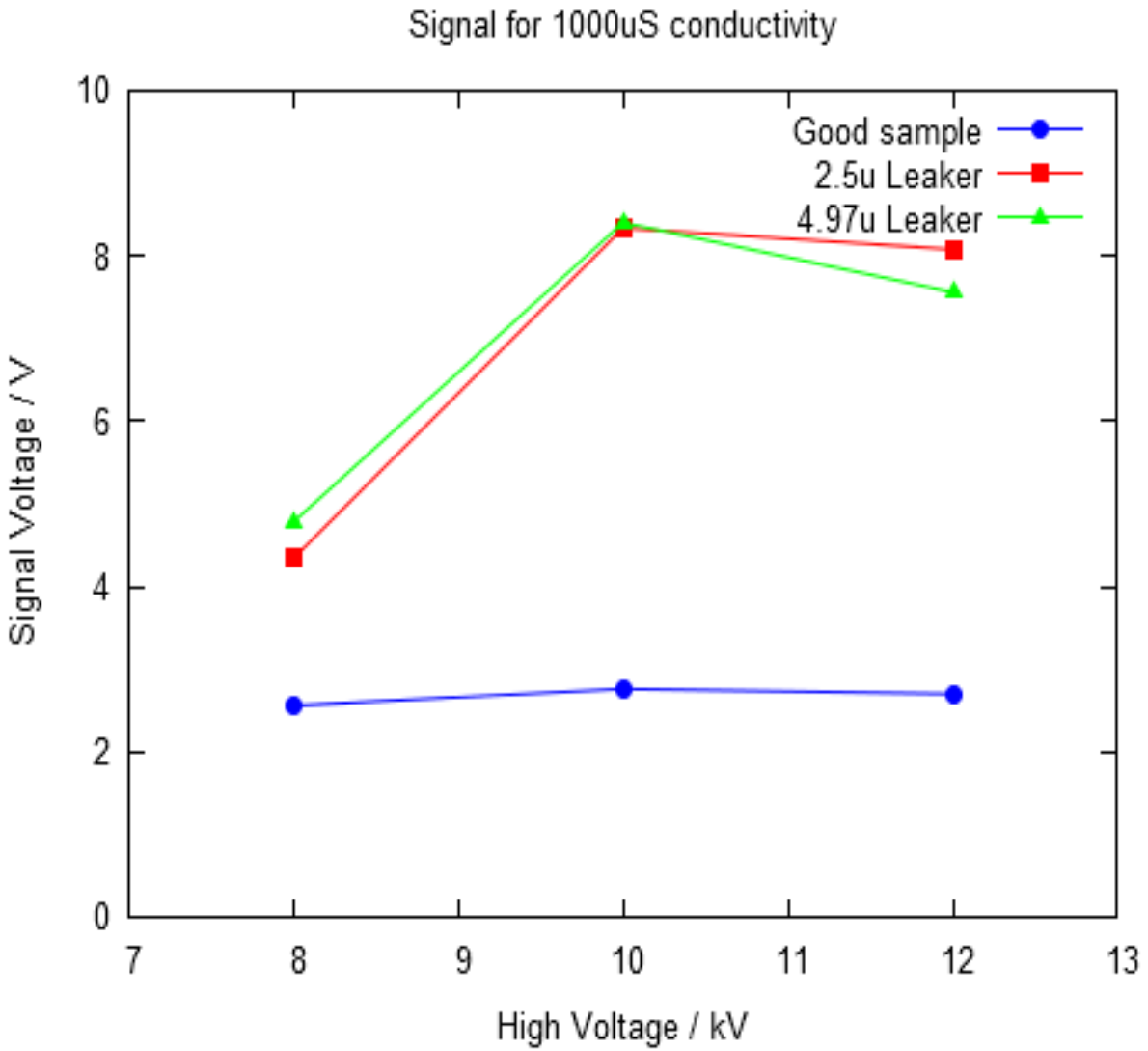
Voltage for Good and Defective samples



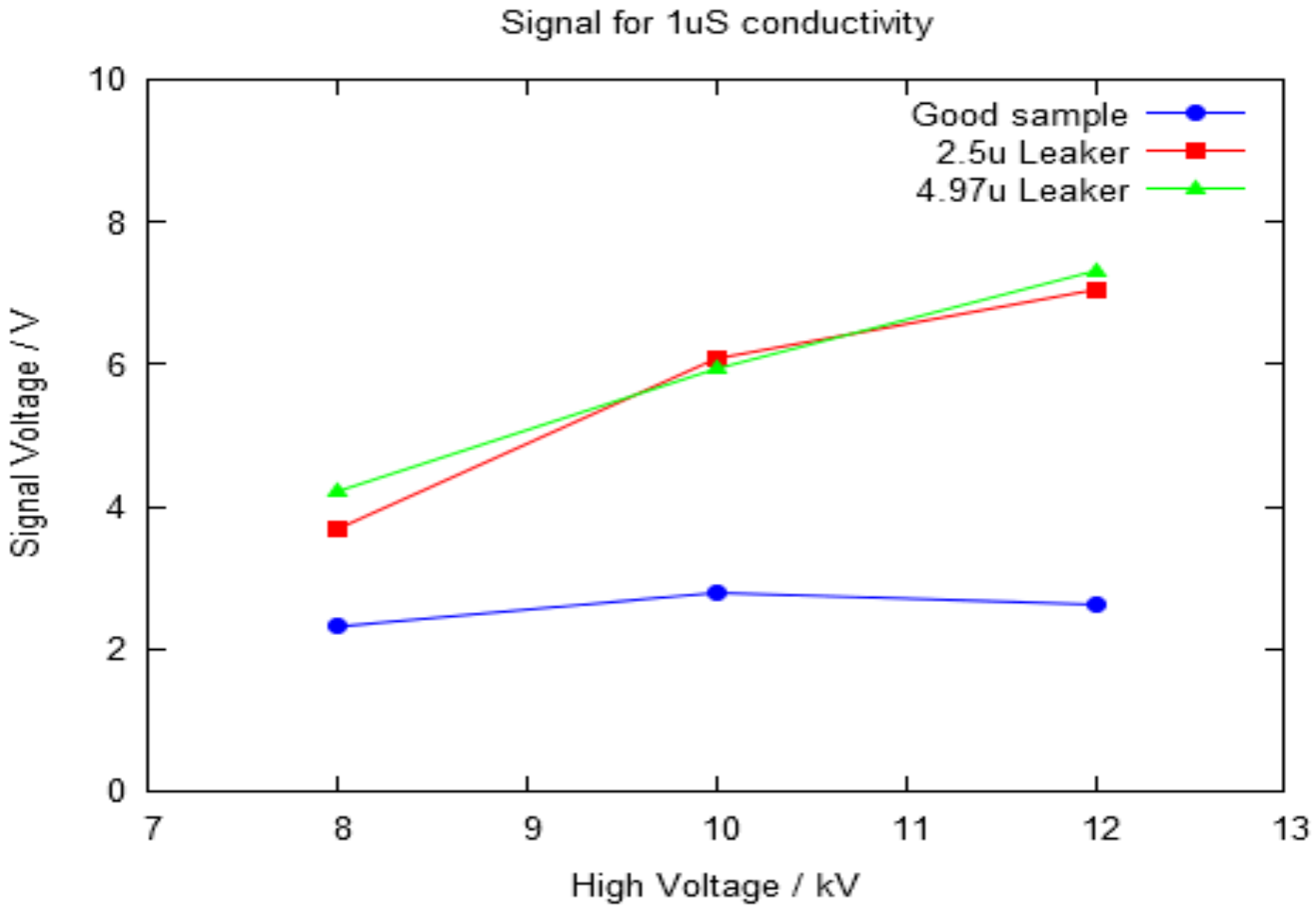
Negative Control Samples



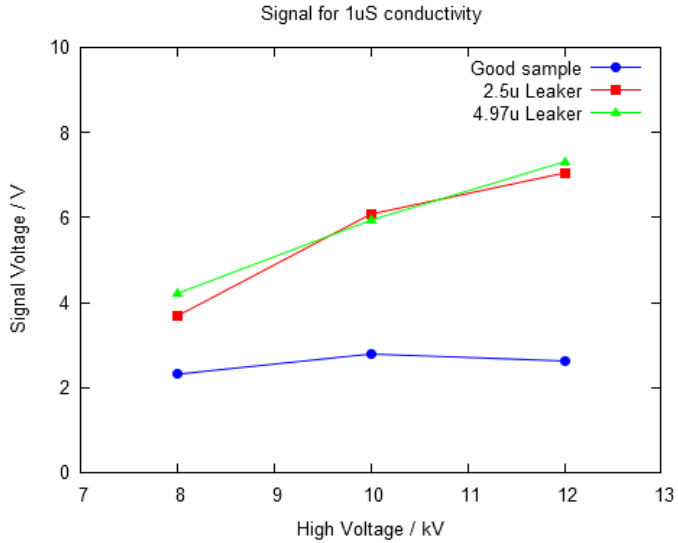
High Conductivity Liquid 1’000uS



Low conductivity Liquid 1uS



High Voltage - Technology Comparison
(distilled Water w/ 1ml Syringe)



	Conventional HVLD	E-Scan 655 (HVLD^{mc})
Product Exposure	7,000V with 18.5kV input	300V with 18.5kV input
Ozone production	0.305ppm ozone in 1 minute	0.004ppm ozone in 10 minutes

Ozone Creation

HVLD - 0.305ppm Ozone after 1 min

HVLD^{mc} – 0.001ppm Ozone after 6 minutes

Feasibility Study – PFS Samples tested

- 1 ml and 2.25 ml syringes
- Prefilled with H2O and Albumin (175 mg/ml, Cp $\simeq$ 2.5)

Summary of results
(negative controls)

Negative controls		# samples	VeriPac VP-455 (vacuum decay) found negative		E-Scan 655 (HVLD) found negative	
1 ml	Water	15	15	100 %	15	100 %
	Albumin	24	24	100 %	24	100 %
2.25 ml	Water	15	15	100 %	15	100 %
	Albumin	24	24	100 %	24	100 %

- **All negative samples are identified as such with both VeriPac® and E-Scan® instruments**
- **No false positives**

Summary of results
(positive controls)

Positive Controls			# samples	VeriPac VP-455 (vacuum decay)		E-Scan 655 (HVLD)	
				Found positive		Found positive	
5 µm	1 ml	Water	3	0	0 %	3	100%
		Albumin	5	0	0 %	5	100%
	2.25 ml	Water	3	0	0 %	3	100 %
		Albumin	5	0	0 %	4	80 %
10 µm	1 ml	Water	3	3	100 %	3	100%
		Albumin	5	0	0 %	5	100%
	2.25 ml	Water	3	0	0 %	3	100 %
		Albumin	5	0	0 %	5	100 %
20 µm	1 ml	Water	3	3	100 %	3	100%
		Albumin	5	0	0 %	5	100%
	2.25 ml	Water	3	3	100 %	3	100 %
		Albumin	5	0	0 %	5	100 %

- **No albumin prefilled positive sample could be detected with Vacuum Decay**
- **E-Scan® allows to identify all positive samples except one**

The Ideal Test Method

Non-Destructive, Non-Invasive, No Sample preparation

Follows USP 1207 Guidelines

ASTM test method > ISO/FDA recognized

Repeatable as well as Reproducible

Deterministic Quantitative (Informative)

Accurate and Reliable

Simple and Robust

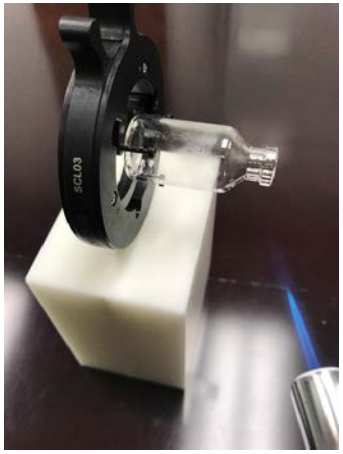
Cost Effective

Zero Waste

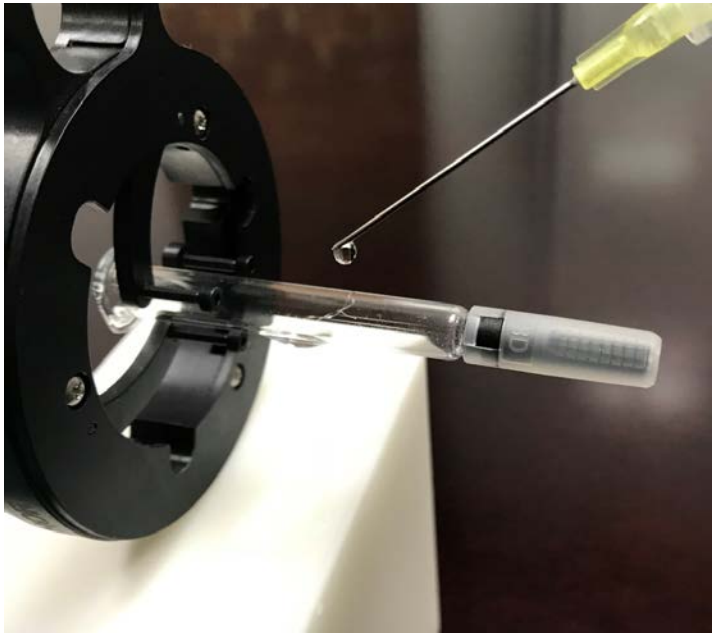
Case study 3 (Extra)

Scratch

Heat



Water Cool

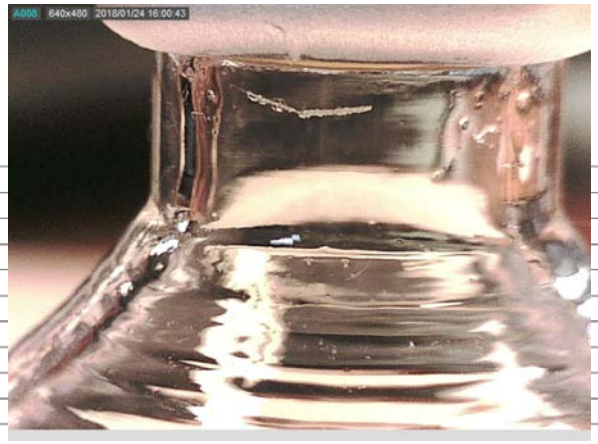









- 16kV
- Sensitivity 50%
- Speed 15mm/sec
- 250RPM
- Exposure voltage ~300V
- Negligible Ozone creation



Control sample includes surface scratch (Crack starting point), no leak.

Controlled crack produced.

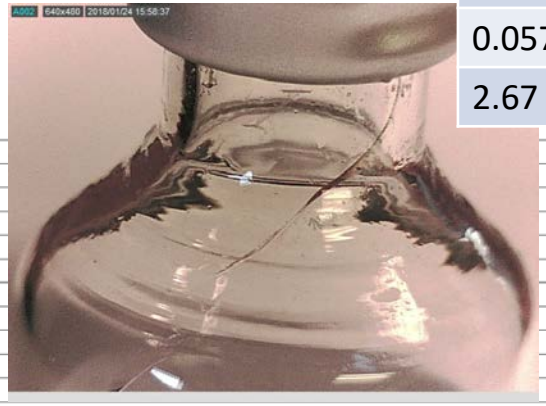
Certified flow measurement with Helium mass spec.

Peak signal response is recorded.

Voltage signal response with each rotation.

He Certified Leak Rate	
95.0	10^{-5} mbar·l/s
0.05700	sccm
2.67	~µm

Sample 1



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

2 He 2
Helium
4.002602

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

CCIT methodology requires consideration of multiple factors.

Wide range of positive control methods; use them responsibly.

HVLD is not time critical (time zero vs. day 66).

MicroCurrent HVLD generally effective for wide range of product conductivities.

Naturally occurring defects below the 1µm level can be readily detected using HVLD.

If a technology can accurately and reliably test for defects below the MALL, the debate over the MALL becomes negligible.

Global Quality Solutions

Thank You!

Tony Stauffer/Tatiana Ponce-Simental

contact@ccit.com

USA: +1 914 337 2005

Switzerland: +41 21 805 0020

www.ptiusa.com

www.ccit.com

a PTI affiliate

CCIT Laboratory – Pti-Europe

Address:

CCIT s.a.
Chemin du Glapin 4
1162 St-Prex
Switzerland

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