CCIT Feasibility Study for Vials and Syringes Vacuum vs. HVLD^{mc} on PFS

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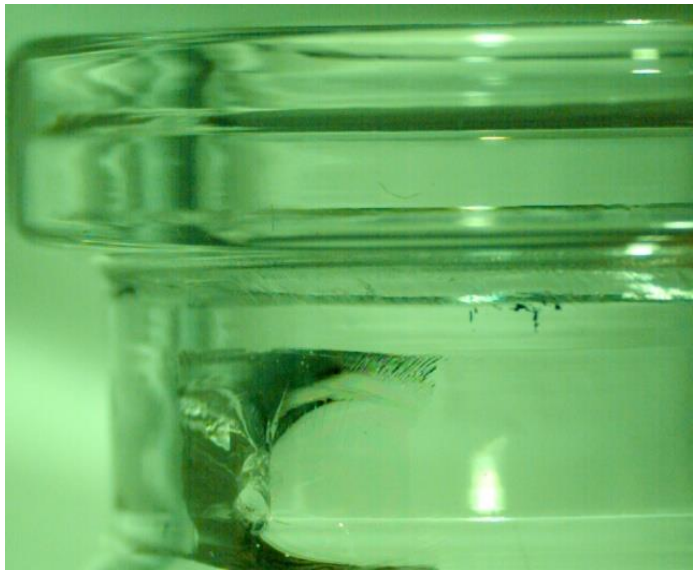
Natural Vial Defect –Cracks

mostly not visible – no liquid to vaporize

- Probabilistic in size, but can be measured and certified
- Similar to naturally occurring defects
- Cracks primarily detected by HVLD^{mc}
  - Liquid will not pass through cracks



Vacuum Micro Leak Testing / PTI VeriPac®

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

Modified USP/Ph.Eur. Dye Ingress Test vs. Vacuum Decay Leak Test – BMS Test Site

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	Y	Y
	129	301	F	Y	Y	Y
	130	194	F	Y	Y	Y
15µm hole	141	352	F	Y	Y	Y
	142	356	F	Y	Y	Y
	143	346	F	Y	Y	Y
	144	445	F	Y	Y	Y
	145	371	F	Y	Y	Y

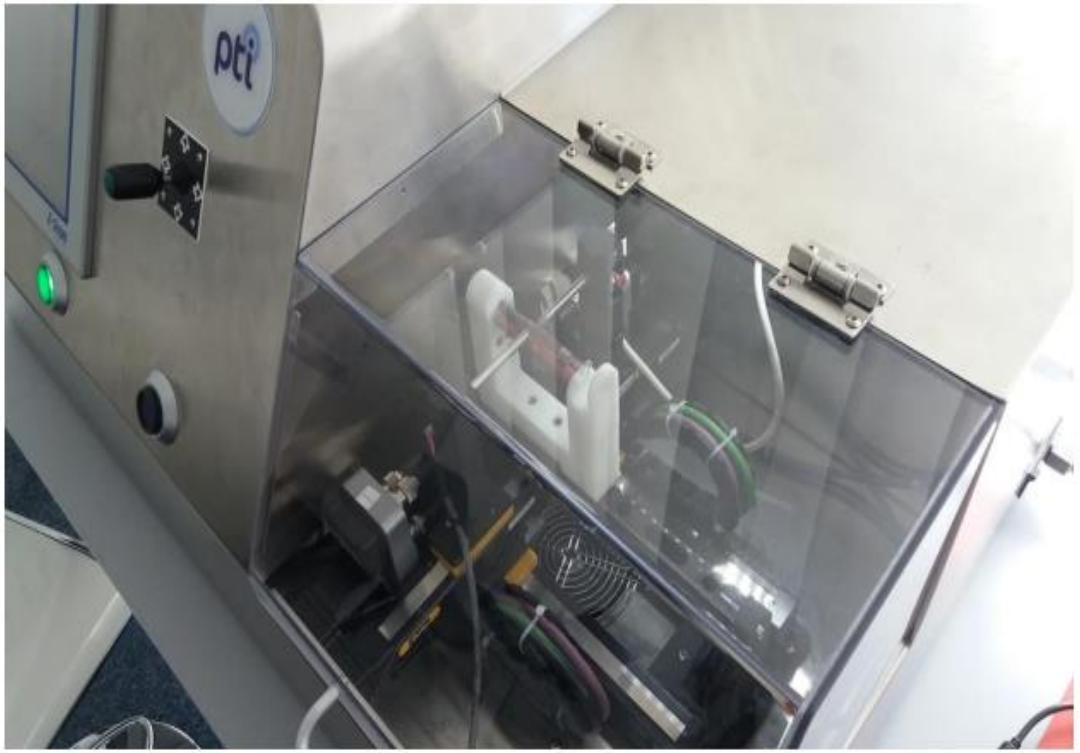
Holed syringes are identical to those used for Part 1, ASTM precision and bias studies.

[2] Y = dye seen, N = No dye seen

E-Scan - (HVLD^{mc})
High Voltage Leak Detection

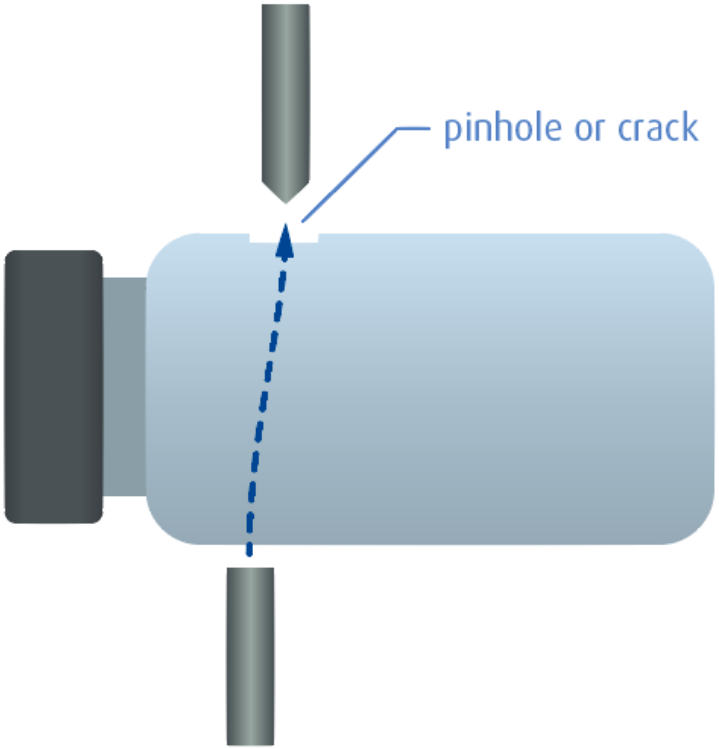
CCIT Leak Testing with HVLD^{mc} E-Scan®

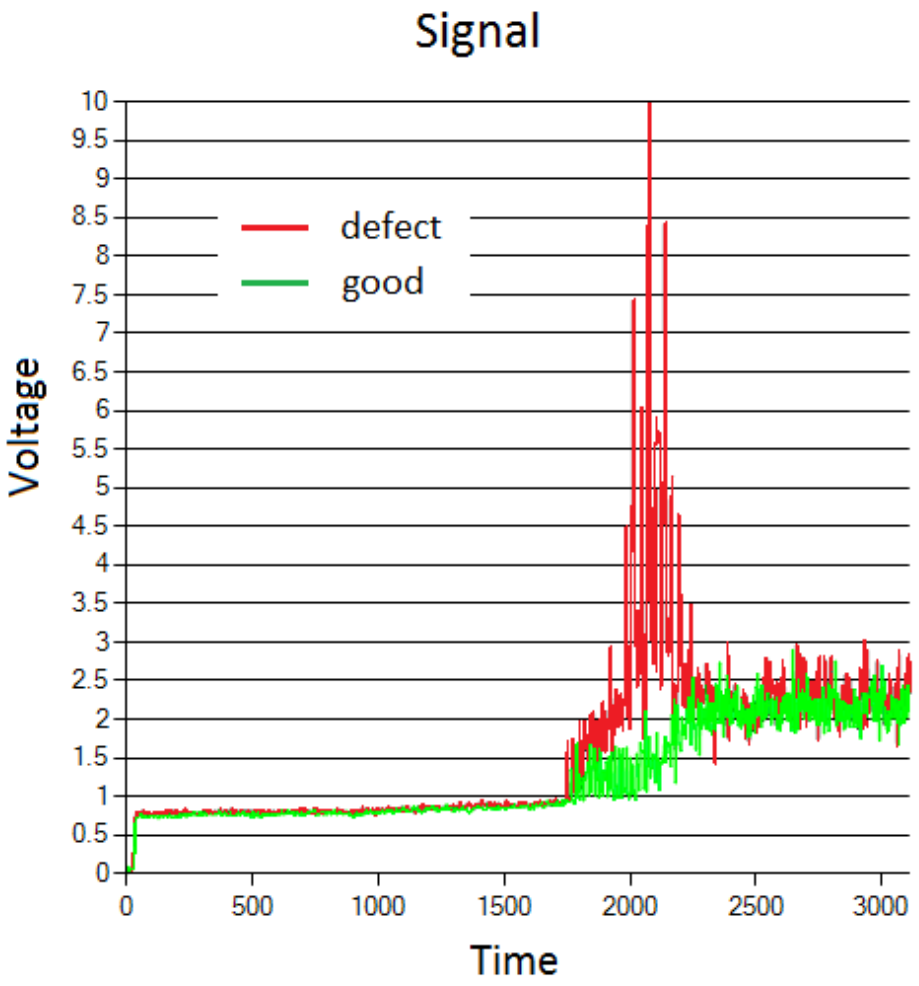
- Off-line laboratory system to inspect liquid filled
  - Vials
  - Syringes
  - Ampoules
- DC with offset AC Voltage
  - mc: micro current
- Product not exposed to HV
- Improved SNR
- Negligible Ozone



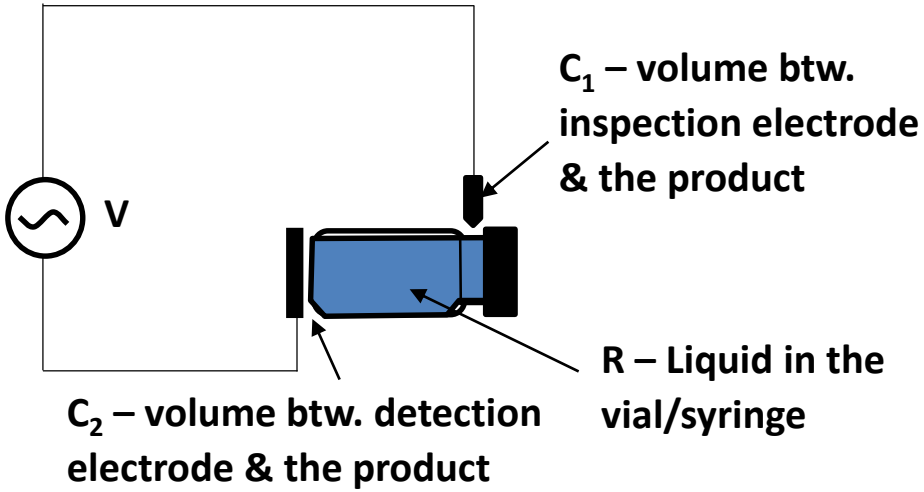
- Good for low conductivity liquids incl. distilled water

High Voltage Leak Detection (HVLD^{mc})

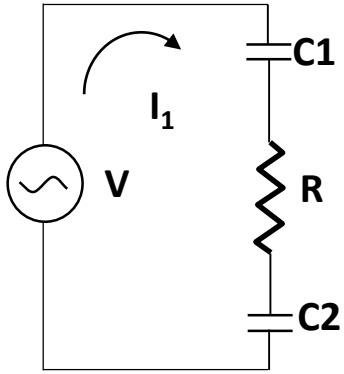




Functional Principle of HVLD^{mc} Test

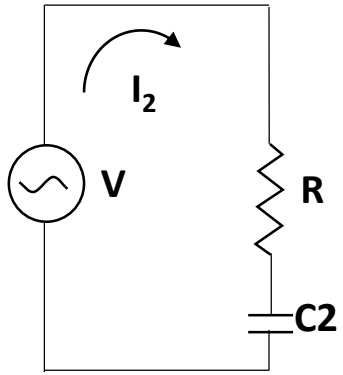


Good Sample



2 capacitors

Leak



1 capacitor

V – High Voltage Source

R – Electric Resistance of the product

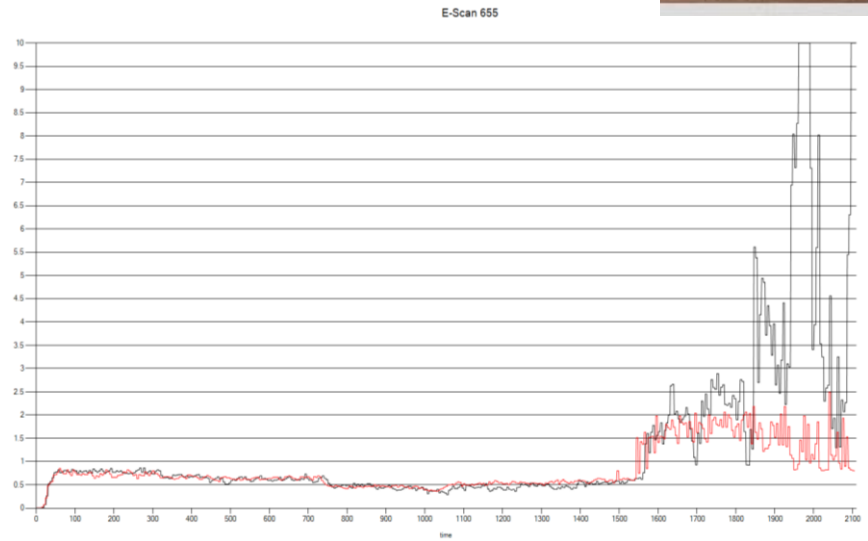
C_1 – Capacitor 1: Glass between the inspection electrode and product

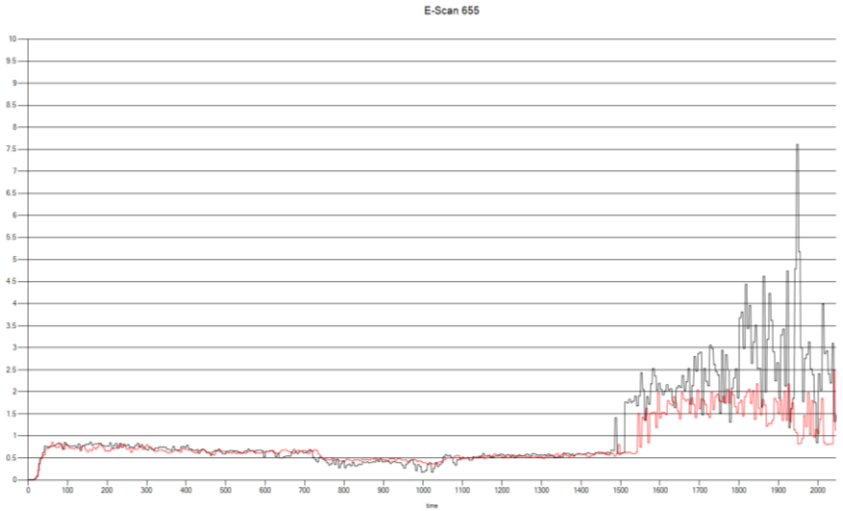
C_2 – Capacitor 2: Glass between the detection electrode and product

I_1 – current produced when product container is sealed

I_2 – current produced when product container is defective

MALL – What is detectable by the HVLD^{mc}





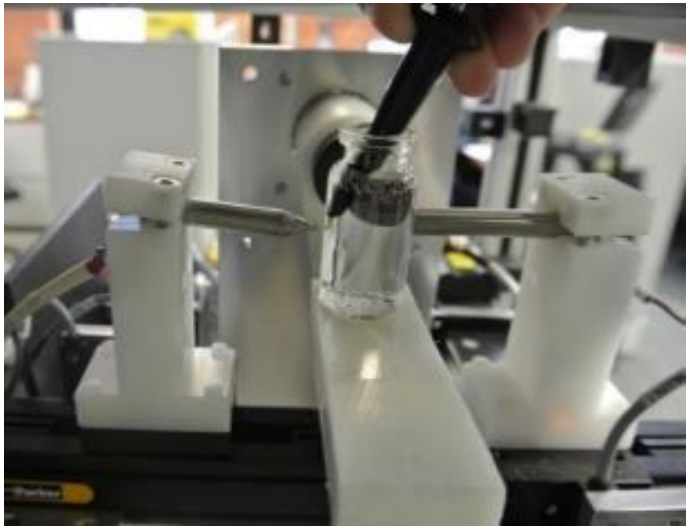
Sample	mbar*l/s	sccm
A2=10 VDC	0.0000021	0.000126

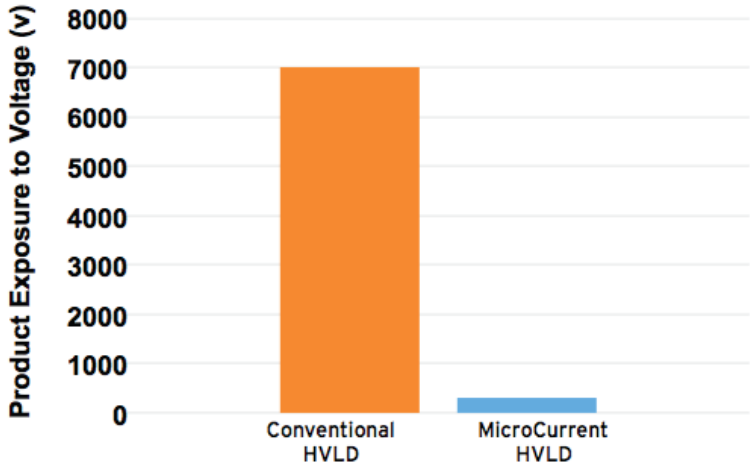
Sample	mbar*l/s	sccm
A3=7.6 VDC	0.000014	0.00084

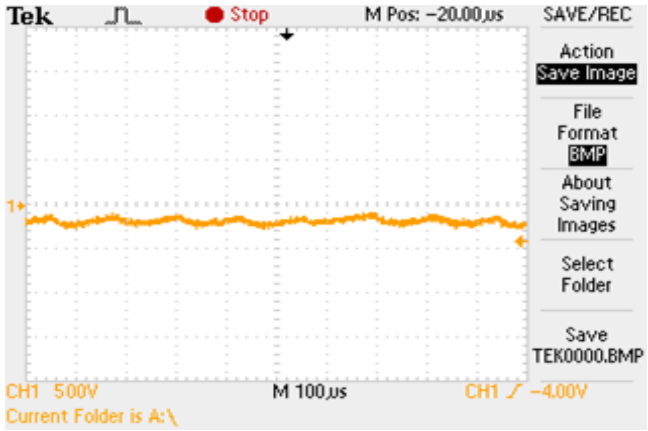
MicroCurrent HVLD^{mc} – Low Voltage

The MicroCurrent applied to the product during the test greatly reduces the voltage exposed to the product and environment.

Exposure Voltage	
Conventional HVLD	MicroCurrent HVLD
7,000 V	300 V
4.3%	



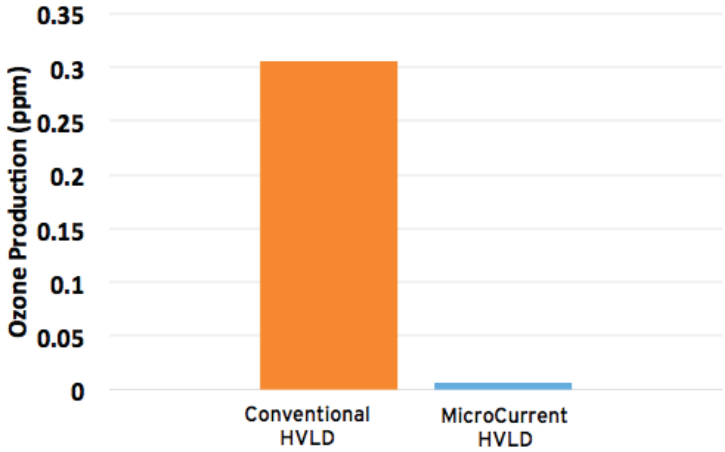




MicroCurrent HVLD^{mc} – Negligable Ozone

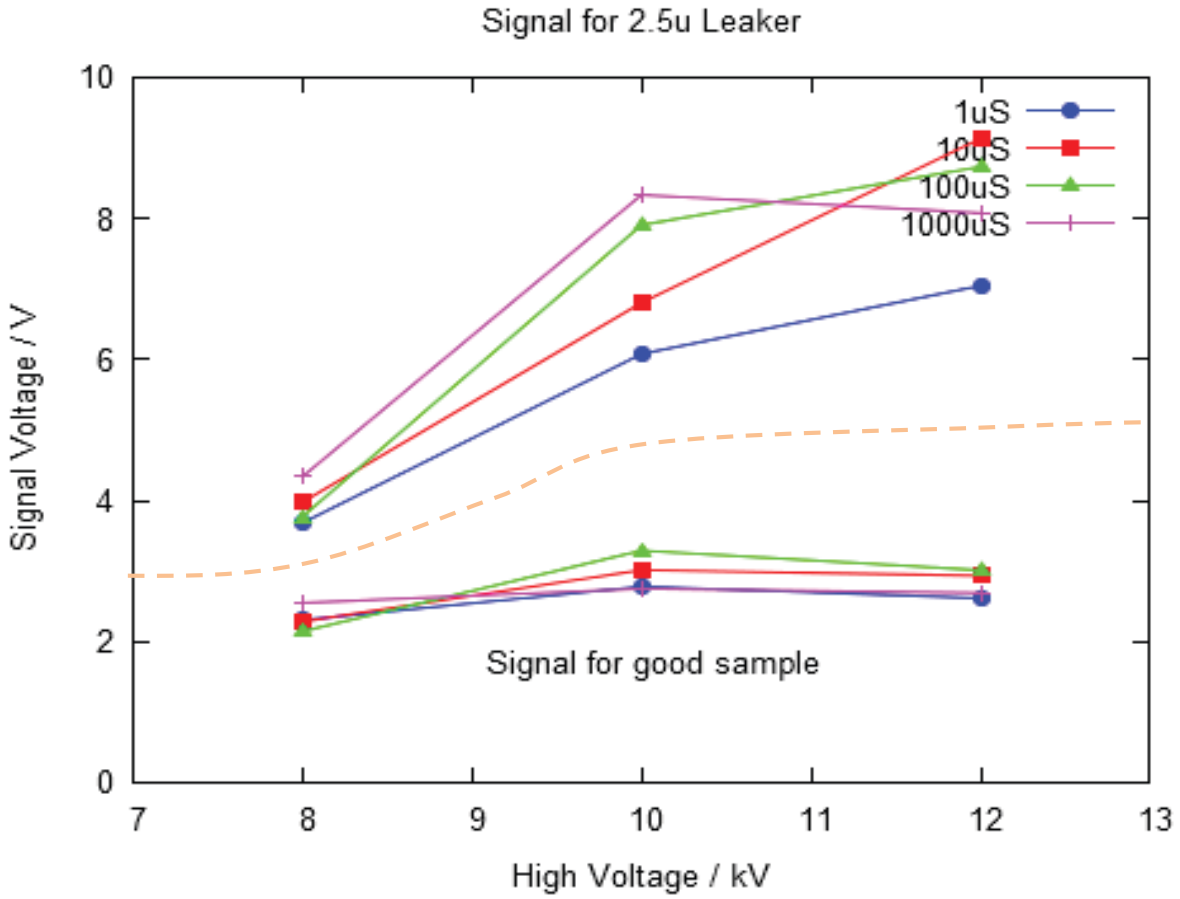
The MicroCurrent applied to the product during the test greatly reduces the voltage exposed to the product and environment.

Ozone Production	
Conventional HVLD	MicroCurrent HVLD
0.305 ppm	0.006 ppm
2.0%	



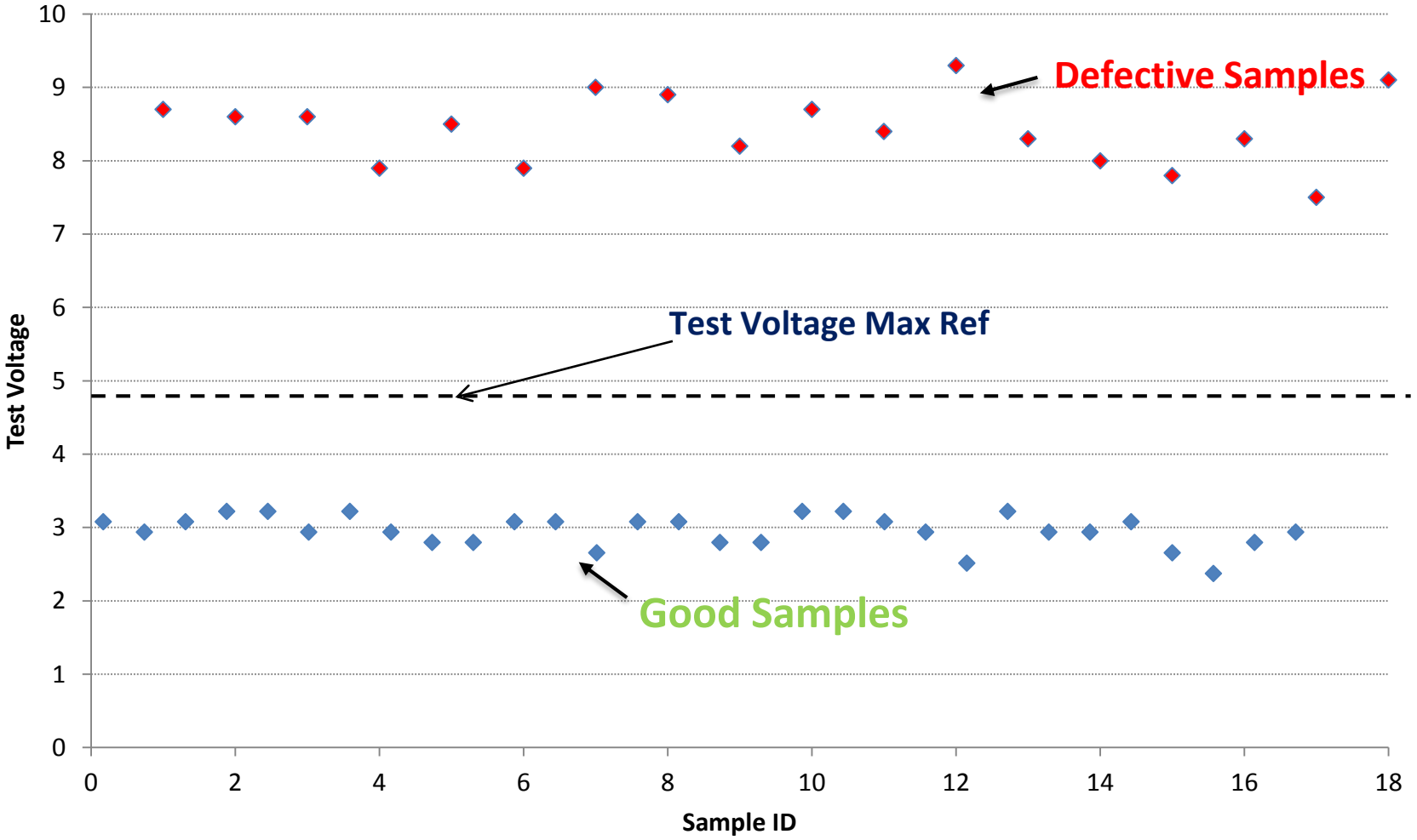
MicroCurrent HVLD^{mc} - Low Conductivity

The nature of this solution allows the testing of packages with extremely low conductivity liquids such as sterile water (WFI).



Source: PTI / Packaging Technologies and Inspection

Voltage results for Negative and Positive Controls



CCIT - New USP 1207 guidance document

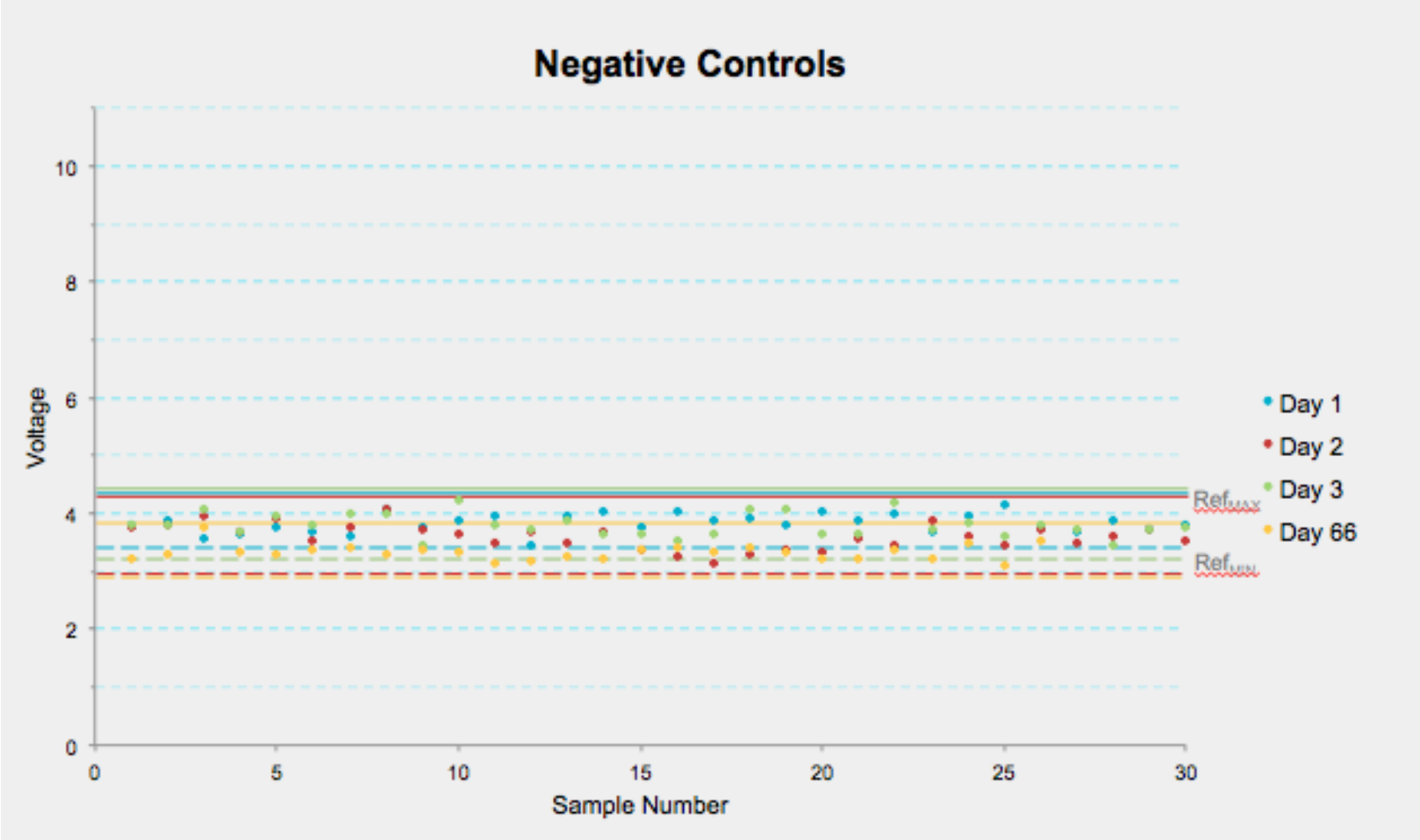
Case Study 1

- 2R (4ml capacity) glass vials
- 13mm Teflon faced stopper, Flip Off Seal 13 mm
- Positive Controls: 5, 10 und 15 µm laser drilled holes, neck and bottom
- 3 positive control samples of each hole size and position
- 4 rounds of testing; 3 consecutive days, and one round 66 days later.

Fill volume was 3ml 20% Albumin solution for both PC and NC groups. Vials were filled prior to testing, stoppered and crimped.

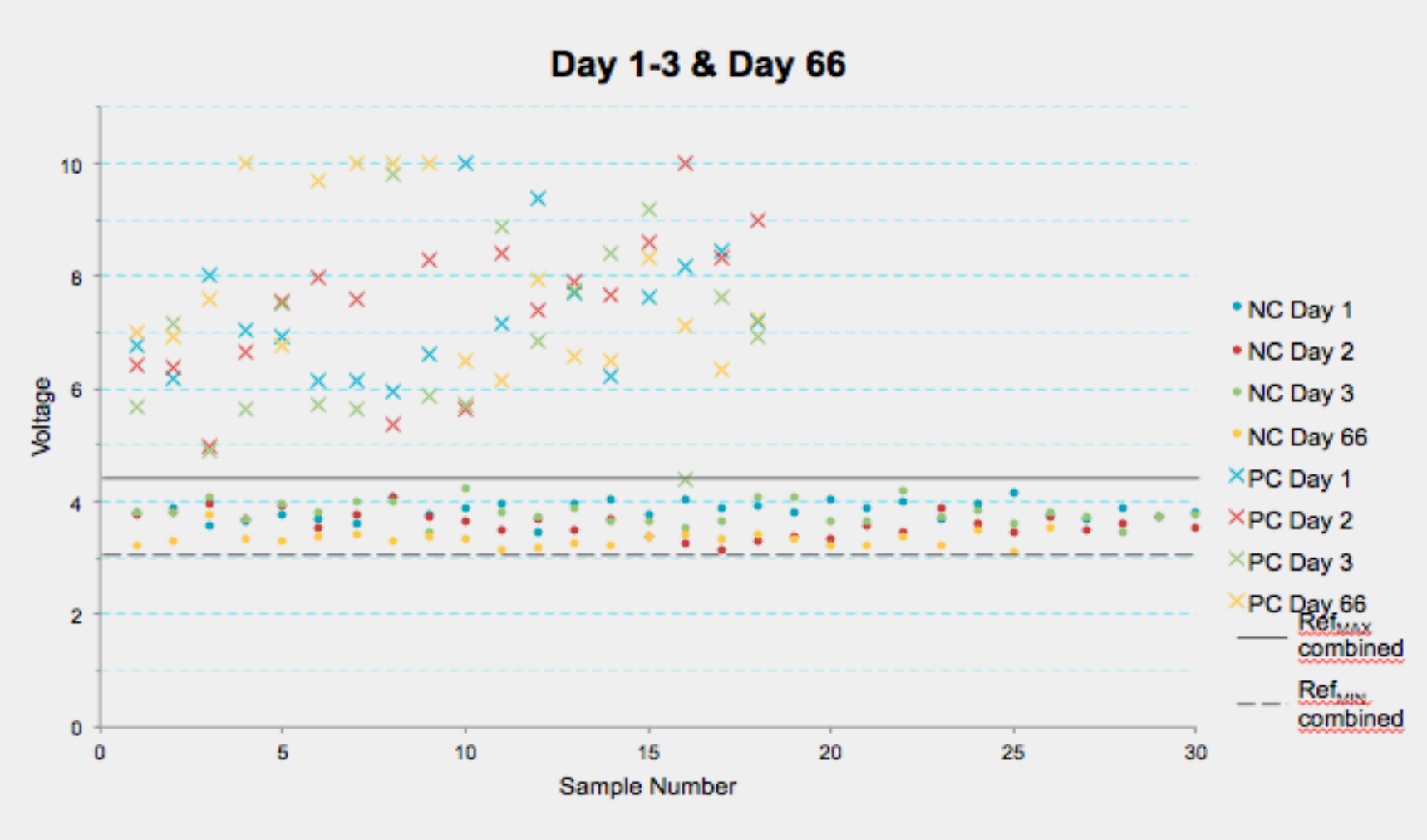
Negative Controls - Baseline

Case Study 1



Combined Test Results

Case Study 1



Vacuum vs. HVLD^{mc} for PFS

Case Study 2

- 1mL and 2.25 mL Syringe
- Positive Controls: 5, 10 und 20 µm laser drilled holes, barrel and shoulder
- 3 positive controls with water for each size
- 5 positive controls with Albumin for each size
- Albumin concentration of 17.5%
- Two test methods: Vacuum Decay and HVLD^{mc}

PFS - Sample identification

Case Study 2

	Number of Samples tested			
	1 ml		2.25 ml	
	Water	Albumin	Water	Albumin
Negative Controls unidentified	15	24	15	24

Positive Controls				
5 µm	3	5	3	5
Idendified as	44, 45, 46	19, 20, 21, 22, 23	M2, N2, O2	G2, H2, I2, J2, k2
10 µm	3	5	3	5
Identified as	41, 42, 43	31, 32, 33, 34, 35	M3, N3, O3	G3, H3, I3, J3, K3
20 µm	3	5	3	5
Identified as	38, 39, 40	7, 8, 9, 10, 11	M, N, O	G, H, I, J, K

Summary of results (negative controls)

Case Study 2

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)

Case Study 2

Positive Controls			# samples	VeriPac VP-455 (vacuum decay) Found positive		E-Scan 655 (HVLD) 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

Test with E-Scan® HVLD^{mc} (negative controls)

	Negative			
	1 ml syringe		2.25 ml syringe	
	Water	Alb.	Water	Alb.
Test #	Volt	Volt	Volt	Volt
1	3.73	3.93	3.11	3.26
2	3.11	3.80	3.02	3.66
3	3.59	3.23	3.22	3.51
↓	↓	↓	↓	↓
13	3.44	3.58	3.47	3.22
14	3.28	3.18	3.12	3.30
15	2.86	4.64	3.33	3.16
16		3.32		3.26
↓		↓		↓
23		3.44		3.20
24		4.04		3.51
Average	3.38	3.59	3.23	3.29
STD	0.28	0.38	0.19	0.19
Noise (3 x STD)	0.85	1.14	0.56	0.56
Ref. 3STD	4.23	4.74	3.79	3.85
Ref. 4 STD	4.52	5.12	3.97	4.04
Ref. 6STD	5.09	5.88	4.34	4.41

Test with E-Scan® (HVLD^{mc}) (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	20	10.00	
40	20	7.76	
42	10	8.94	
43	10	9.89	
45	5	8.52	
46	5	8.60	
23	5		5.79
35	10		8.48
7	20		9.06
8	20		8.29
9	20		9.82
10	20		9.45
11	20		5.65
31	10		9.89
32	10		7.64
33	10		7.83
34	10		6.28
19	5		7.47
20	5		10.00
21	5		7.17
22	5		6.29

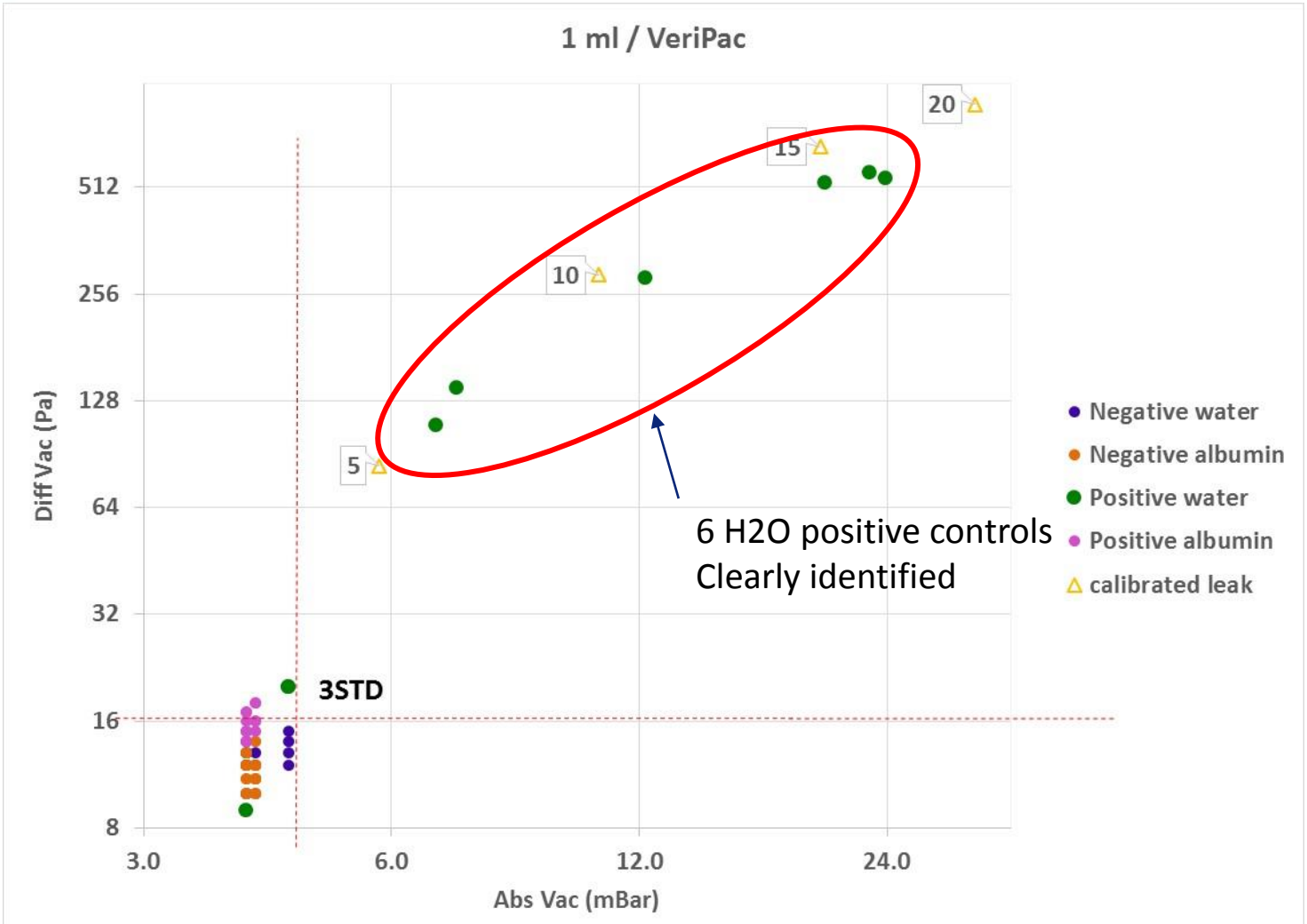
Vacuum Decay - Baseline

Case Study 2

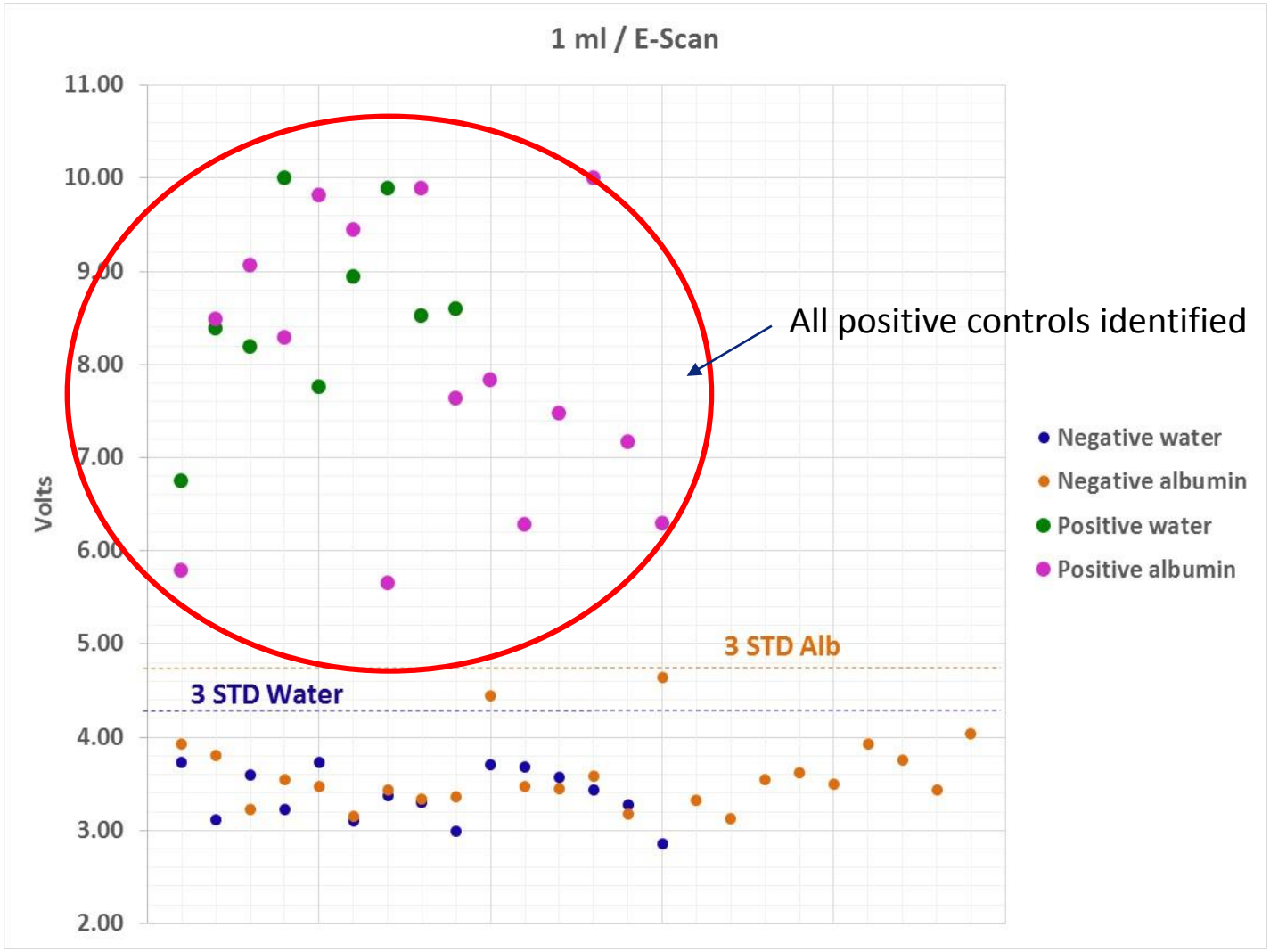
	Negative							
	1 ml syringe				2.25 ml syringe			
	Water		Alb.		Water		Alb.	
Test #	Abs (mb)	Diff (Pa)	Abs (mb)	Diff (Pa)	Abs (mb)	Diff (Pa)	Abs (mb)	Diff (mb)
1	4.5	15	4.1	10	4.8	15	3.7	13
2	4.5	13	4.0	11	4.0	16	3.8	11
3	4.5	12	4.1	11	3.8	15	3.8	12
↓	↓	↓	↓	↓	↓	↓	↓	↓
13	4.0	12	4.0	12	3.7	12	3.8	9
14	4.0	12	4.0	10	3.8	12	3.8	10
15	4.0	10	4.1	12	3.8	12	3.8	9
16			4.1	12			3.8	10
↓			↓	↓			↓	↓
23			4.1	10			3.8	10
24			4.0	12			3.7	10
Average	4.2	12.2	4.0	11.4	4.0	13.9	3.8	10.7
STD	0.2	1.4	0.1	1.2	0.3	1.5	0.0	1.1
Noise (3 x STD)	0.6	4.3	0.2	3.5	0.9	4.6	0.1	3.4
Ref. 3STD	4.8	16.5	4.2	14.9	4.9	18.5	3.9	14.1
Ref. 6STD	5.5	20.7	4.3	18.4	5.9	23.1	4.1	17.4

Vacuum Decay - Baseline

Case Study 2

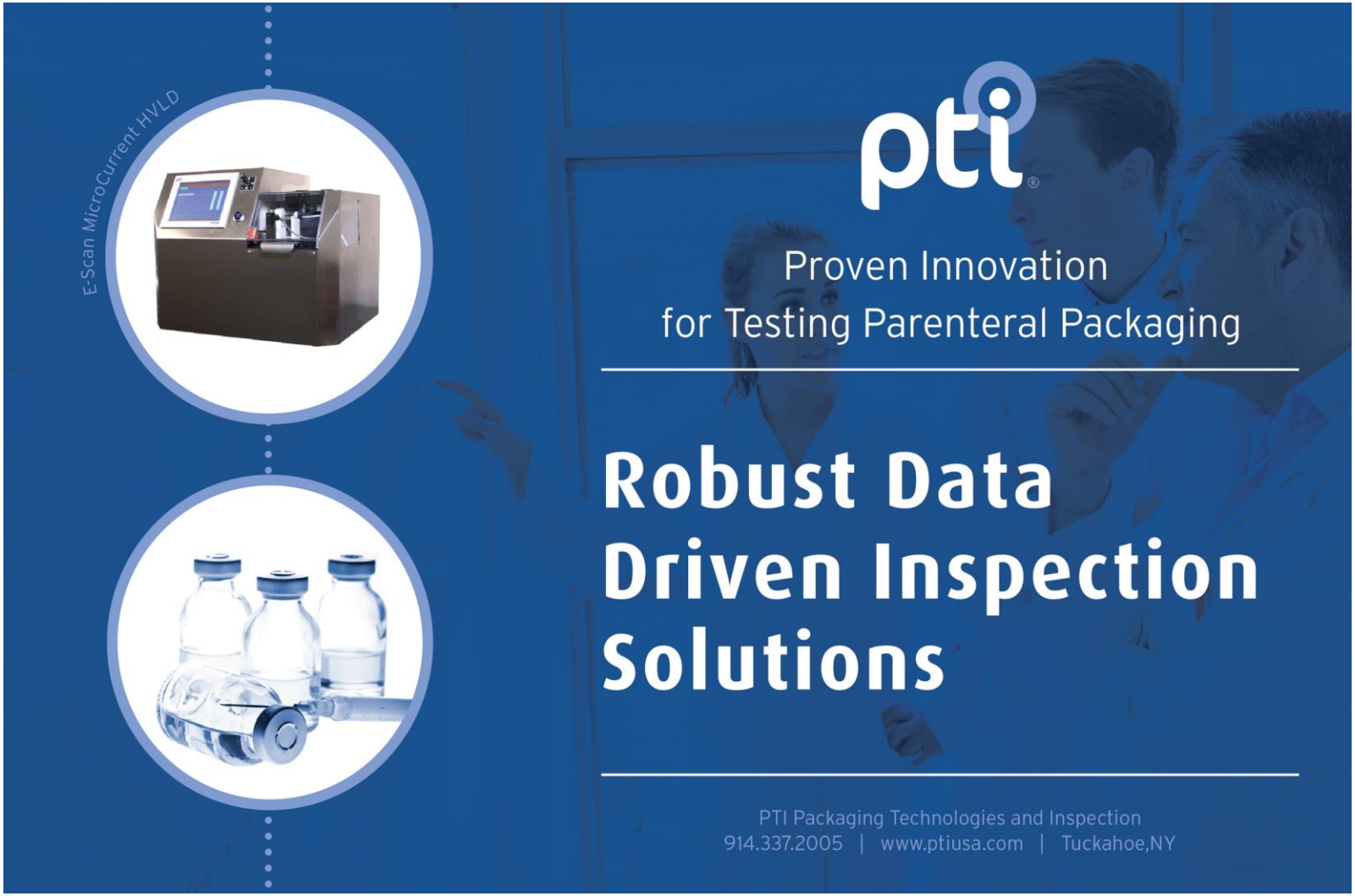


E-Scan HVLD^{mc} - Baseline



Conclusions

- Vacuum decay is a sensitive and reliable test method for gas applications
- Reliability and capability of Vacuum decay is adversely affected by large molecule products such as Albumin, producing a low to zero detection capability for proteinacious solutions
- MicroCurrent^{mc} High Voltage Leak Detection (HVLD^{mc}) is capable of detecting micro cracks to micro holes for all tested liquid protein based solutions – including low conductivity liquids
- HVLD^{mc} (E-Scan 655) technology is the recommended CCIT inspection method as per USP 1207 for liquid prefilled syringes, ampules and vials.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