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CCIT Feasibility Study

Vacuum vs. HVLD^{mc} on 1 & 2.25ml Syringes

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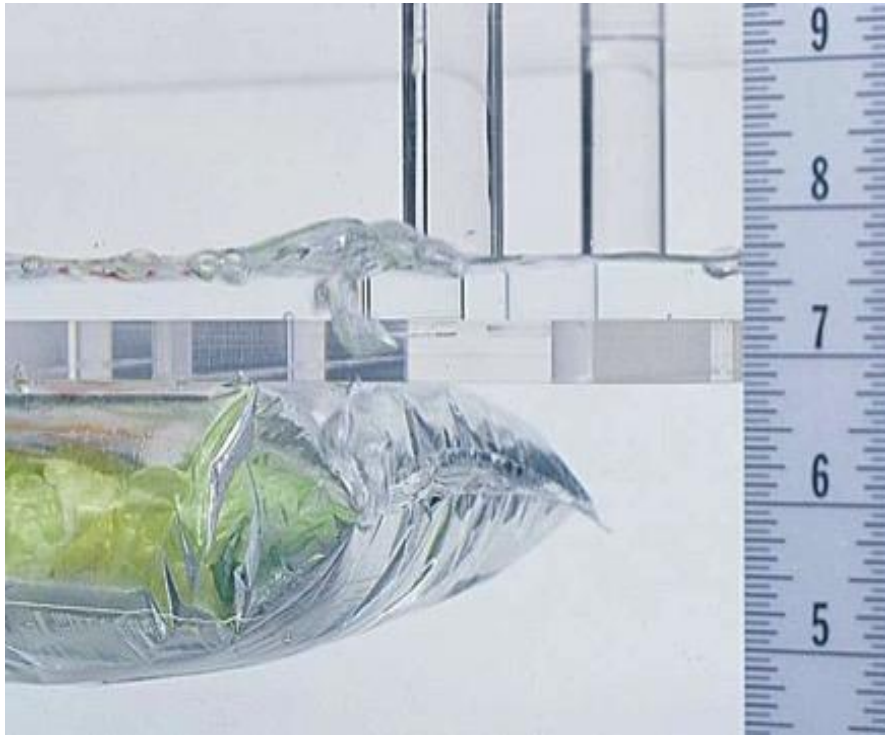
Common Package Inspection Methods

- **Manual / Vision Inspection (< 80% efficient)**
- **Destructive Testing**
  - Burst Test
  - Water Bath (20-50 microns)
  - Dye Test (20-30 microns)
  - Microbial ingress
- **Most are probabilistic**
- **Always depends on operator**



The Good News

- **You have now a regulatory guideline (USP 1207) of the best testing practices for a particular package**

- **You have a range of deterministic tests available to replace probabilistic tests**

CCIT - 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**

Vacuum Micro Leak Testing / CCIT

VeriPac®

- 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

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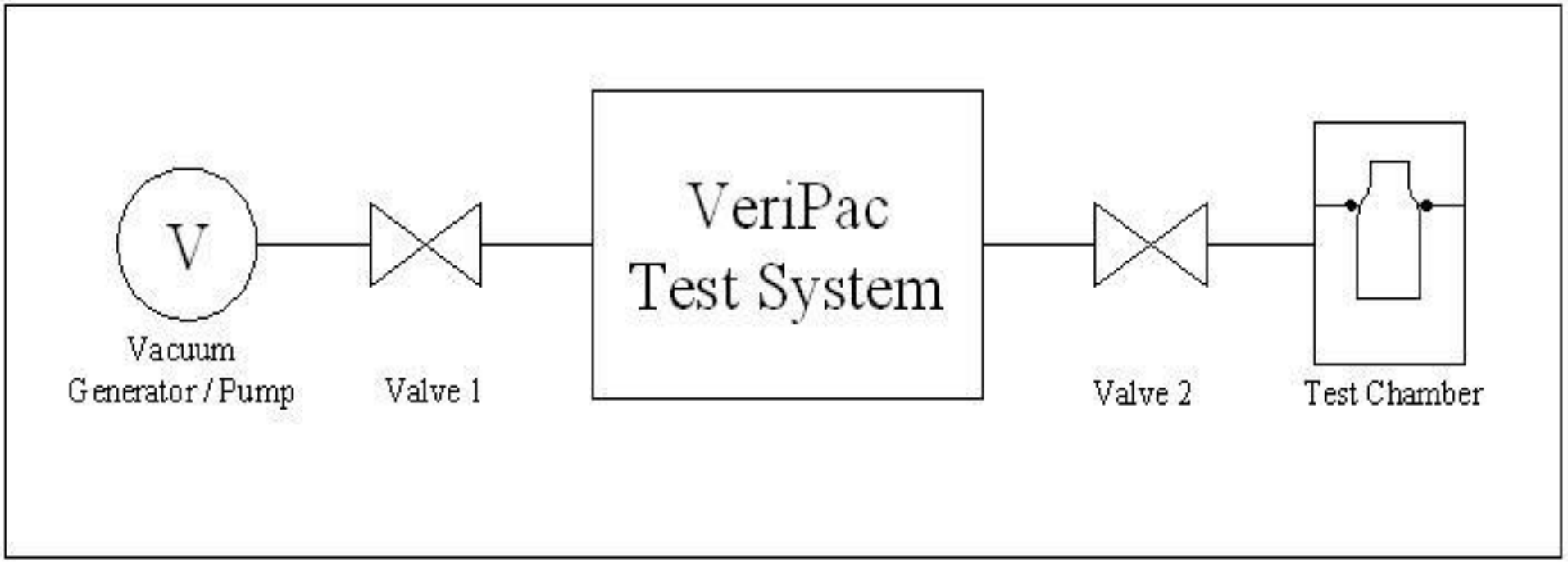
VeriPac Differential Vacuum Principle
(simplified schematics)

ASTM F2338-09



US Patents 6,513,366 and Pend.

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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

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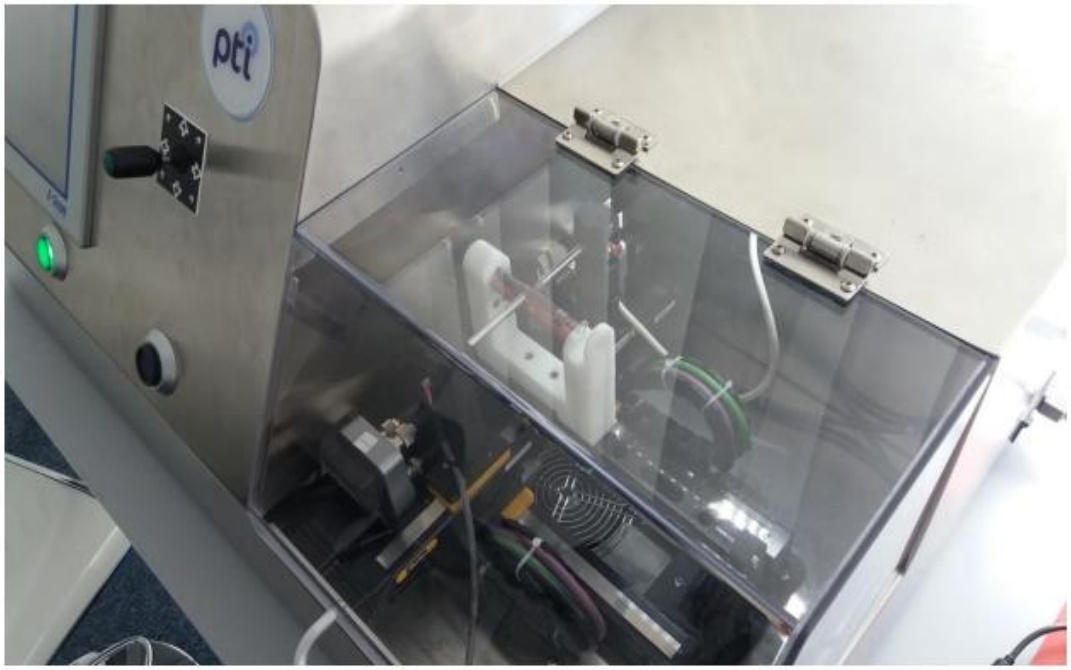
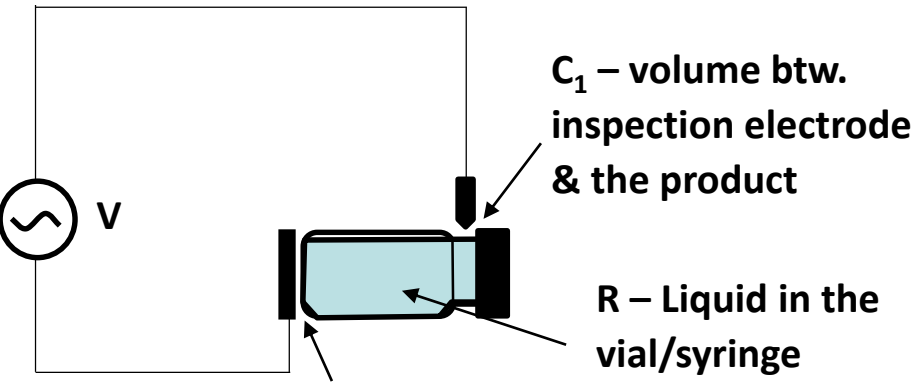
CCIT Leak Testing with HVLD^{mc} E-Scan®

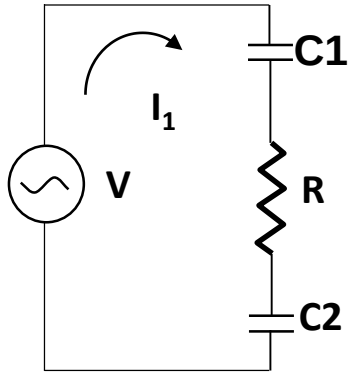
- Off-line laboratory system to inspect liquid filled
  - Vials
  - Syringes
  - Ampules
- DC with offset AC Voltage
- Lower HV application
- mc: micro current
- Improved SNR
- Negligible Ozone
- Product not exposed to HV
- Good for low conductivity liquids incl. distilled water



Functional principle of HVLD^{mc} test

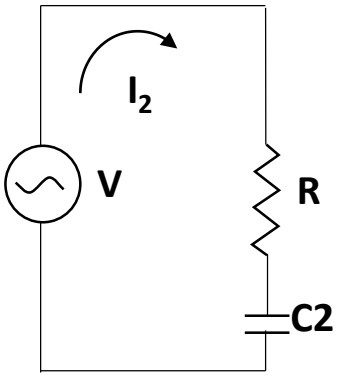


Good Sample



2 capacitors

Leak

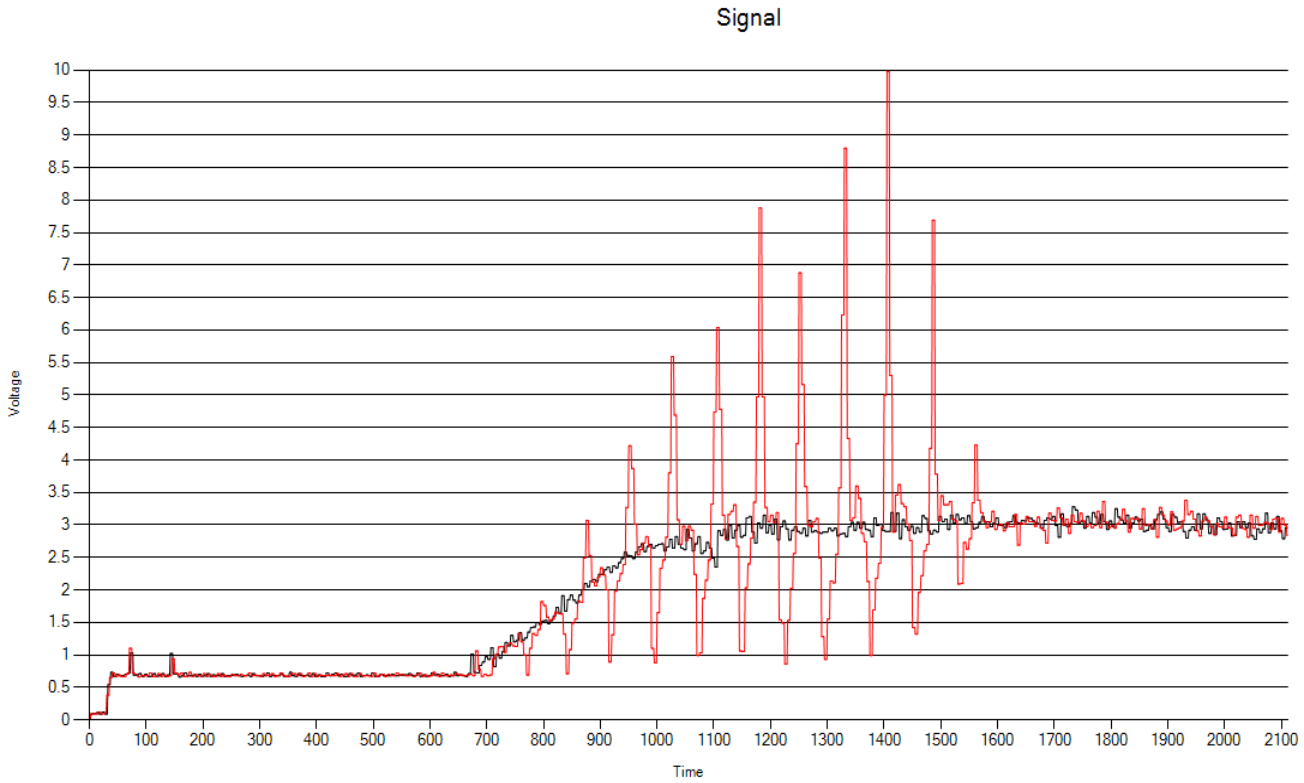


1 capacitor

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

HVLD^{mc} Test – Voltage Signal 1ml Syringe

- Signal Detection 1ml Syringe – Signal has amplitude changes
- High Voltage: 14kV
- Red - 3.6um hole size
- Black sample without defect
- Filled with distilled water (low conductivity)



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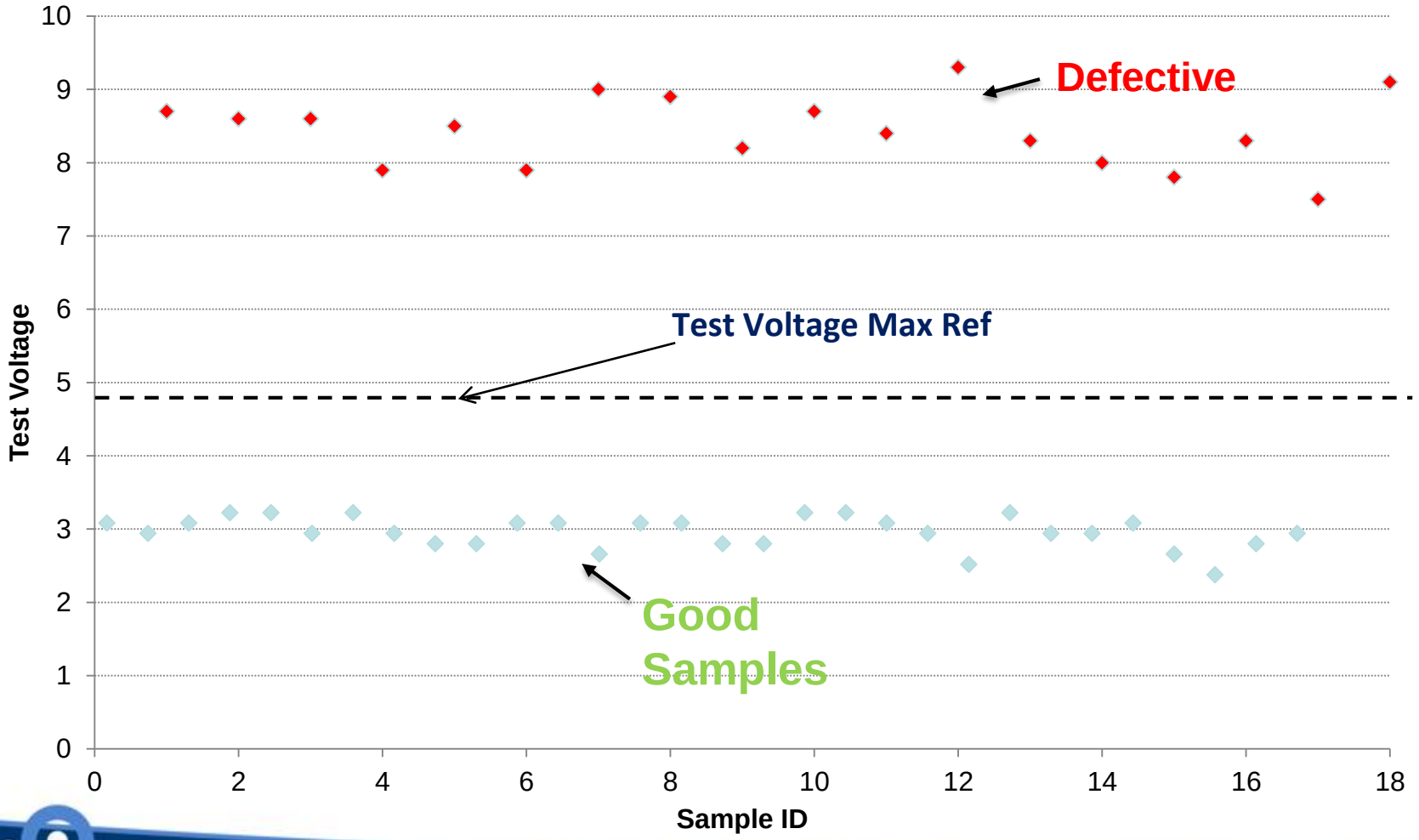
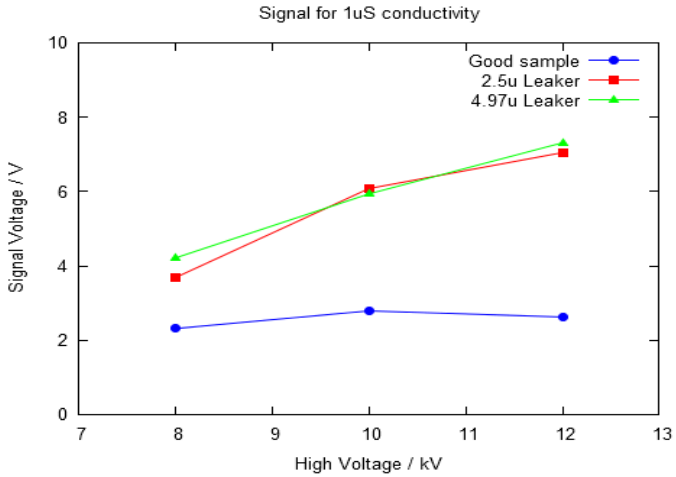
Voltage results for Negative and Positive Controls



High Voltage – Technology Comparison
(distilled Water with 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

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Feasibility Study - Samples tested

- 1 ml and 2.25 ml syringes
- Filled with H2O and Albumin (17.5%)

Sample Identification

	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)

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) 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

Tests with VeriPac®
(negative controls)

	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

Tests with VeriPac®
(positive controls)

		Positive 1 ml syringe			
		Water		Alb.	
Sample id.	Nominal	Abs (mb)	Diff (Pa)	Abs (mb)	Diff (Pa)
44	5	4.0	9		
41	10	7.2	139		
38	20	22.9	564		
39	20	23.9	543		
40	20	20.2	527		
42	10	12.2	285		
43	10	6.8	109		
45	5	4.5	20		
46	5	4.5	20		
23	5			4.1	18
35	10			4.0	17
7	20			4.0	15
8	20			4.1	18
9	20			4.1	16
10	20			4.1	16
11	20			4.0	14
31	10			4.0	16
32	10			4.0	15
33	10			4.0	17
34	10			4.0	14
19	5			4.0	15
20	5			4.0	14
21	5			4.1	15
22	5			4.0	14

		Positive 2.25 ml syringe			
		Water		Alb.	
Sample id.	Nominal	Abs (mb)	Diff (Pa)	Abs (mb)	Diff (Pa)
M2	5	4.1	22.0		
M3	10	3.8	7.0		
M	20	6.2	109.0		
N2	5	3.8	7.0		
O2	5	3.7	9.0		
N3	10	3.8	15.0		
O3	10	3.8	9.0		
N	20	7.2	133.0		
O	20	6.5	120.0		
G2	5			3.7	7.0
G3	10			4.1	10.0
G	20			3.8	8.0
H2	5			3.8	10.0
I2	5			3.7	9.0
J2	5			3.7	9.0
K2	5			3.8	9.0
H3	10			3.8	9.0
I3	10			3.8	8.0
J3	10			3.8	9.0
K3	10			3.8	10.0
H	20			3.8	8.0
I	20			3.8	9.0
J	20			3.8	10.0
K	20			3.8	8.0

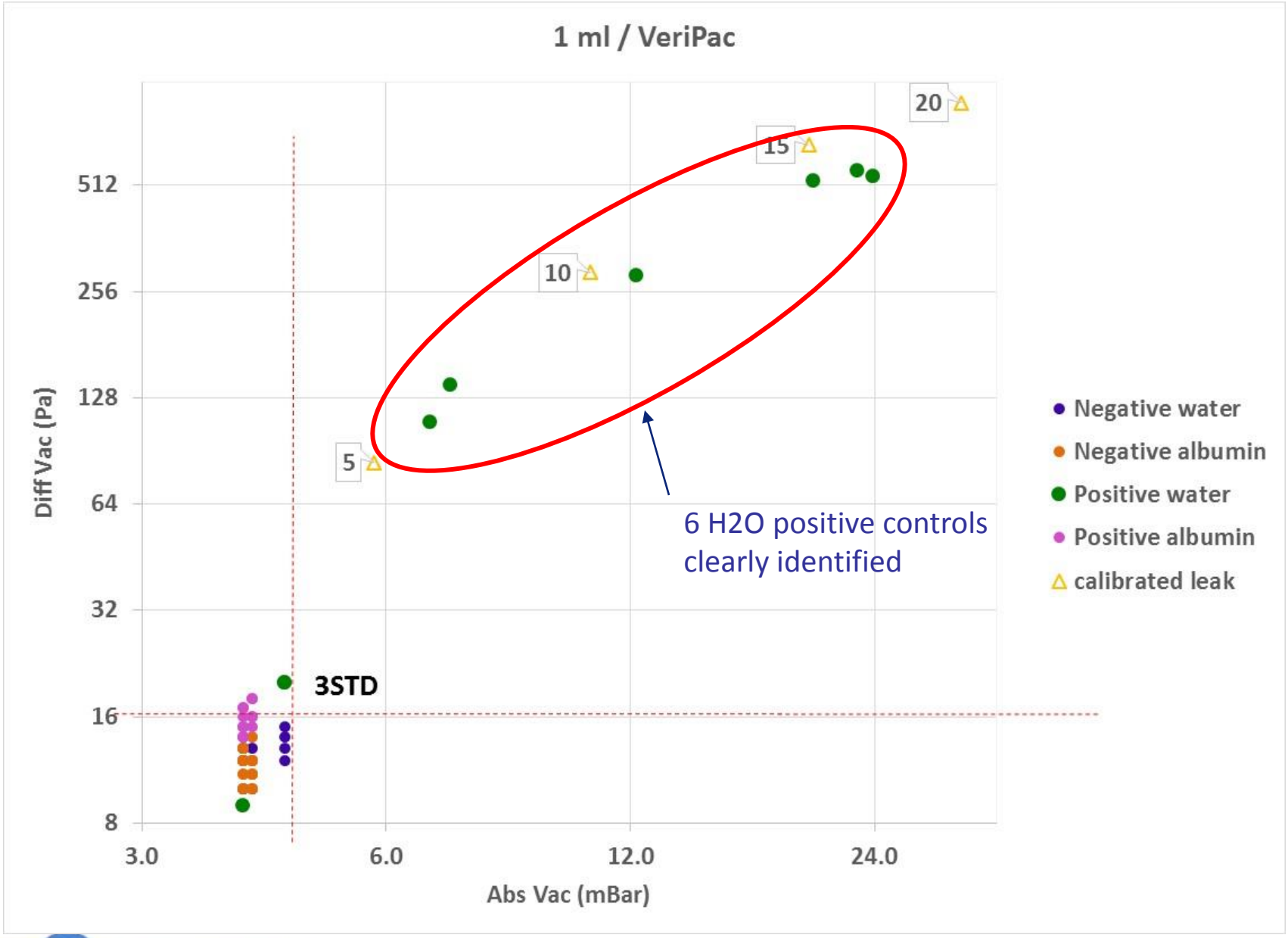
Tests with E-Scan®
(negative controls)

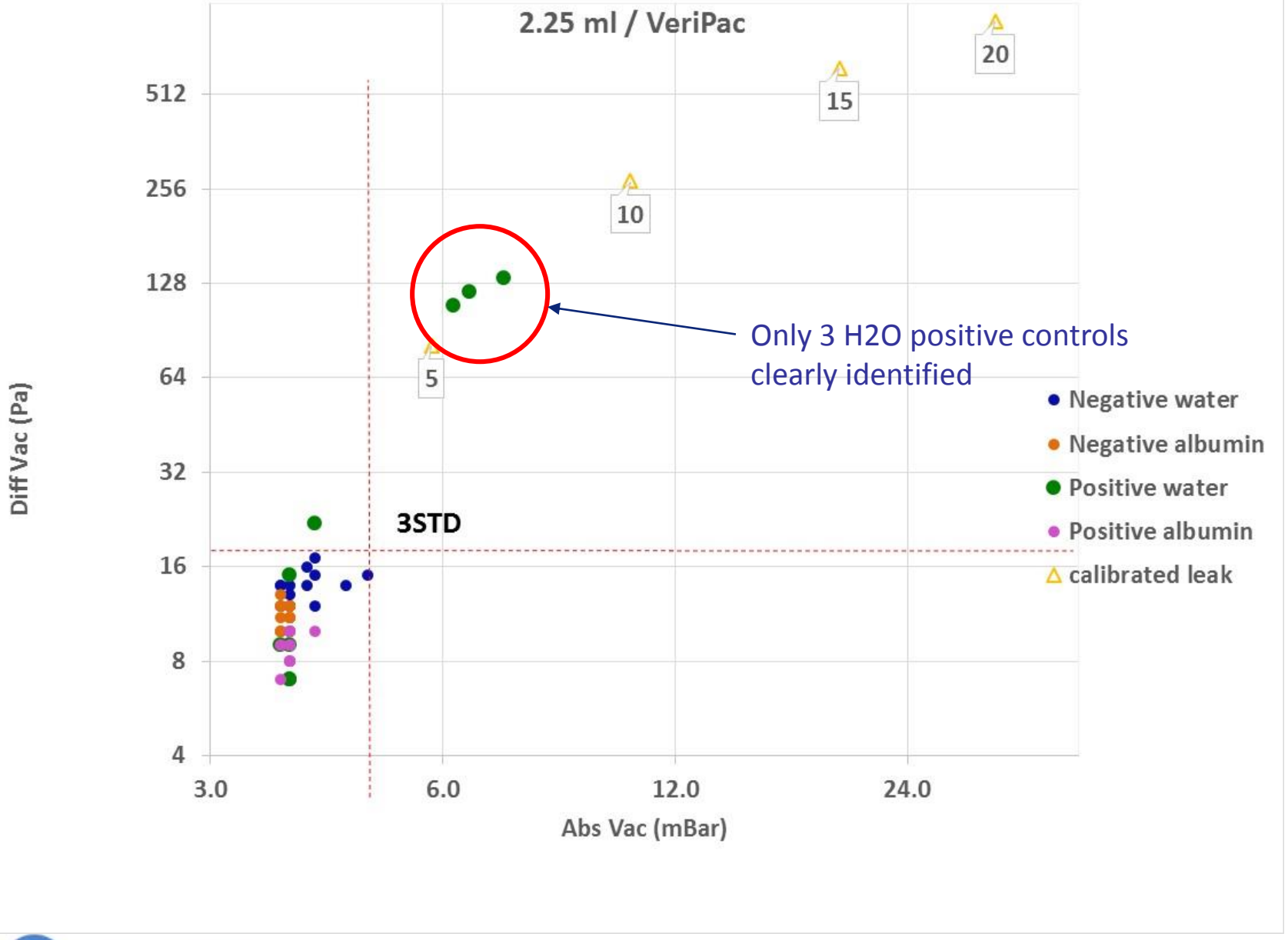
	Negative			
	1 ml syringe		2.25 ml syringe	
	Water	Alb.	Water	Alb.
Test #	Volt	Volt	Volt	Volt
1	3.73	3.93	3.11	3.26
2	3.11	3.80	3.02	3.66
3	3.59	3.23	3.22	3.51
↓	↓	↓	↓	↓
13	3.44	3.58	3.47	3.22
14	3.28	3.18	3.12	3.30
15	2.86	4.64	3.33	3.16
16		3.32		3.26
↓		↓		↓
23		3.44		3.20
24		4.04		3.51
Average	3.38	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

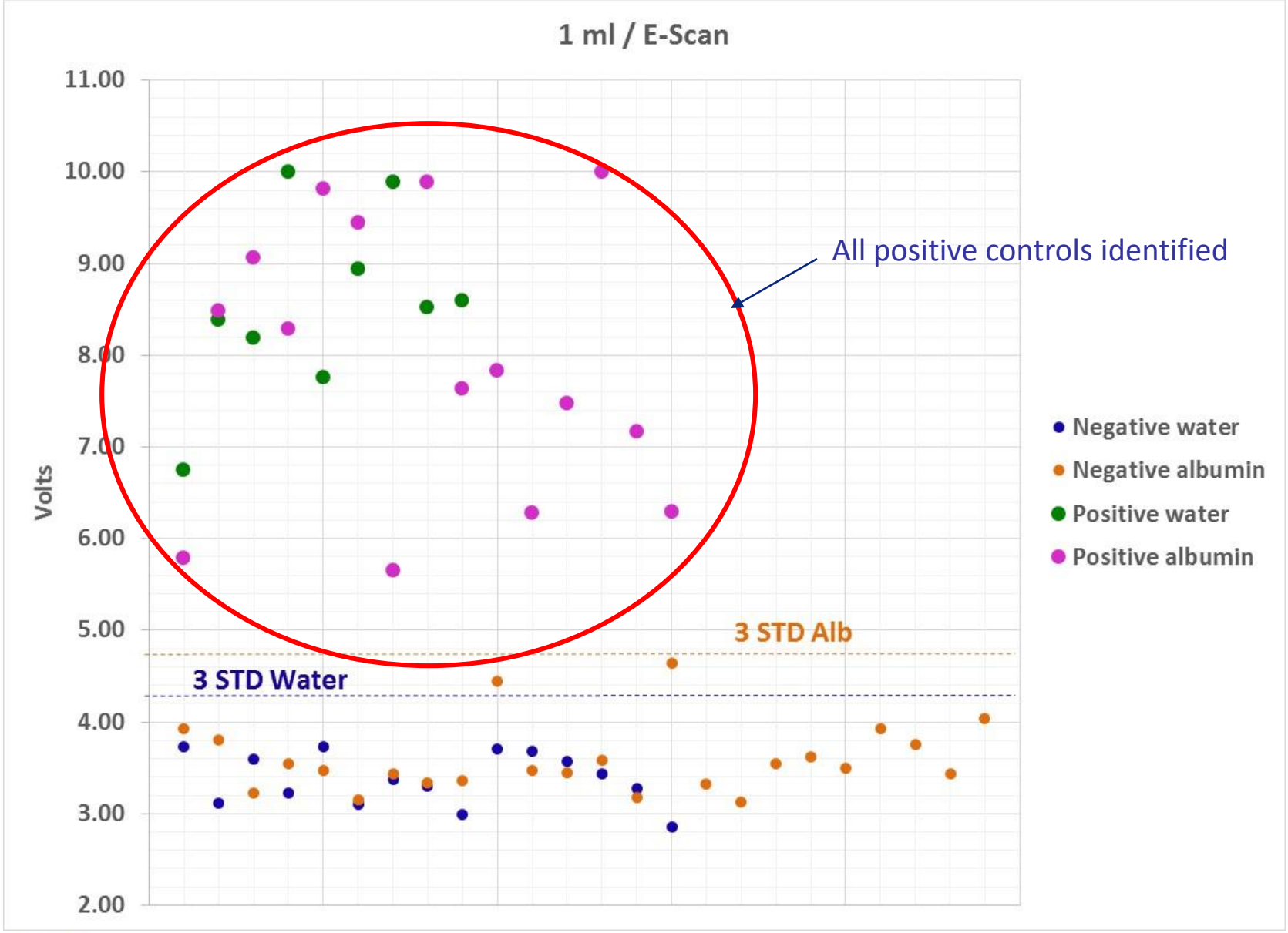
Tests with E-Scan®
(positive controls)

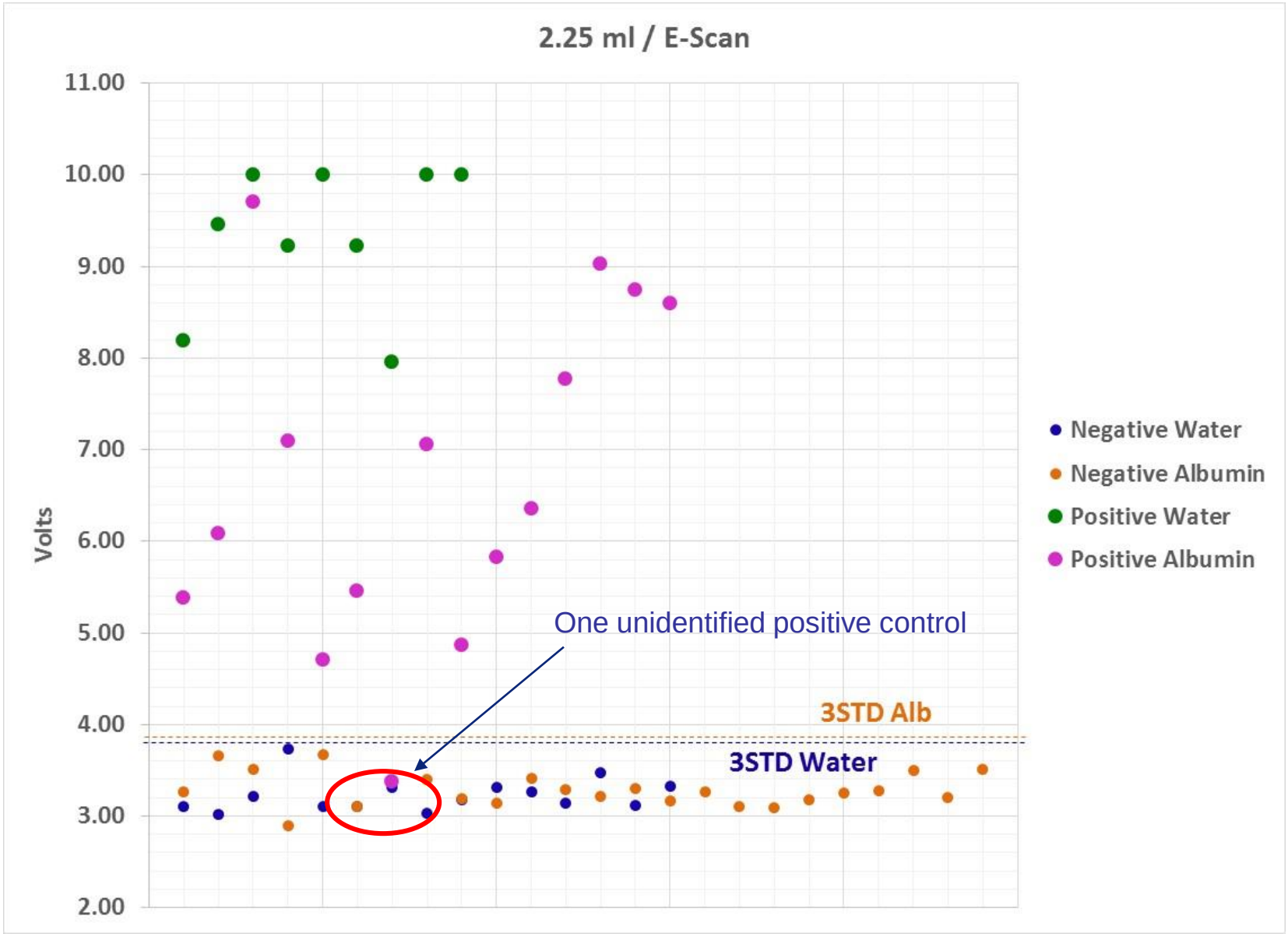
		Positive 1 ml syringe	
		Water	Alb.
Sample id.	Nominal leak	Volt	Volt
44	5	6.75	
41	10	8.38	
38	20	8.19	
39	20	10.00	
40	20	7.76	
42	10	8.94	
43	10	9.89	
45	5	8.52	
46	5	8.60	
23	5		5.79
35	10		8.48
7	20		9.06
8	20		8.29
9	20		9.82
10	20		9.45
11	20		5.65
31	10		9.89
32	10		7.64
33	10		7.83
34	10		6.28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

		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	5	9.22	
O2	5	10.00	
N3	10	9.22	
O3	10	7.95	
N	20	10.00	
O	20	10.00	
G2	5		5.38
G3	10		6.08
G	20		9.71
H2	5		7.09
I2	5		4.70
J2	5		5.45
K2	5		3.38
H3	10		7.06
I3	10		4.87
J3	10		5.83
K3	10		6.35
H	20		7.77
I	20		9.03
J	20		8.74
K	20		8.60









Conclusion

- The Vacuum Decay method fails to detect leaks on Albumin filled syringes, or has a reduced probability of detection on Water, because small leaks easily get plugged
- PTI's HVLD^{mc} technology will be able to perform the CCIT test satisfactorily, and detect the positive prefilled samples, regardless of liquid content
- Only one 2.25 ml positive sample was not identified as such. Deeper evaluation of the size of the leak should be done in order to find an explanation.
- HVLD^{mc} (E-Scan 655) technology is the recommended CCIT inspection method as per USP 1207 for liquid prefilled syringes, ampules and vials.

The ideal Test Method

Non-Destructive, Non-Invasive, No Sample preparation

USP/ASTM test method > ISO/FDA recognized

Repeatable as well as Reproducible

Deterministic - Quantitative (Informative)

Accurate and Reliable

Simple and Robust

Cost Effective

Zero Waste

CCIT Laboratory – Pti-Europe

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Global Quality Solutions

Thank You!

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