



CASE STUDY

Leak Detection of 1ml and 2.25ml Albumin PFS Vacuum Decay vs. HVLD^{mc} Test Methods

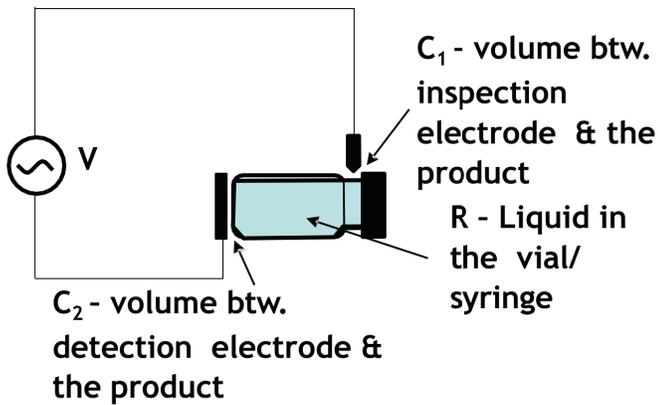
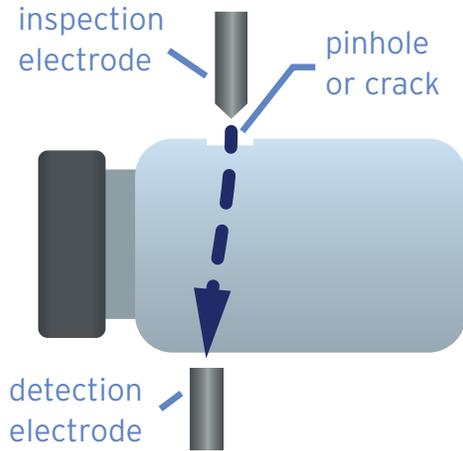
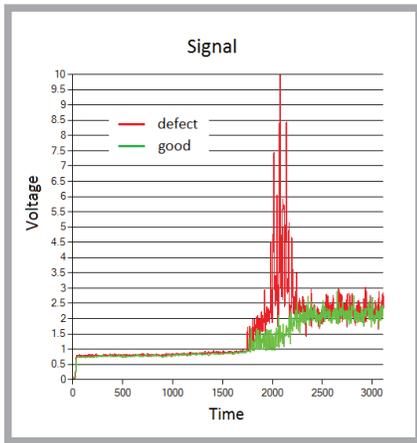
Container Closure Integrity (CCI) can be challenged using various test methods, not all of which are equally capable of detecting leaks in the package. Of the test methods listed as 'deterministic' in USP 1207, two methods for CCI commonly used for parenteral products are Vacuum Decay and High Voltage Leak Detection (HVLD). The following study focuses on CCI testing using the MicroCurrent HVLD technology, and tangentially addresses limitations of Vacuum Decay with protein filled products, and their clogging effects.

The study was done with 1 mL and 2.25 ml glass syringes containing either water or Albumin. The samples tested included a series of negative controls (non-leakers) and certified positive controls (leakers). The Vacuum Decay CCI test

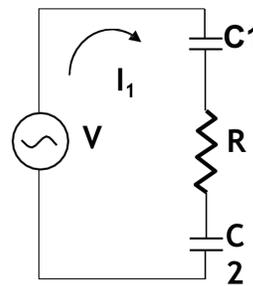
method shows a reduced probability in detecting positive controls containing water, and zero capability to detect positive controls with Albumin. The same sample set subjected to the E-Scan MicroCurrent HVLD technology showed nearly 100% detectability of either water or Albumin filled products.

The study addresses the common concern that Vacuum Decay is not a suitable test solution for detecting micro leaks in parenteral containers if the product contains large molecule or proteinaceous liquids. The data further supports and confirms that a wide range of liquid parenteral products can reliably be tested for CCI using MicroCurrent HVLD to detect micro leaks in the critical leak range.

Functional Principle of HVLD^{mc} Test

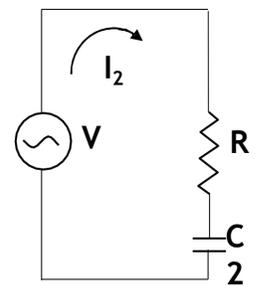


Good Sample



2 capacitors

Leak



1 capacitor

V - High voltage source

R - Electric resistance of the product

C₁ - Capacitor 1: Glass between the inspection electrode and product

C₂ - Capacitor 2: Glass between the detection electrode and product

I₁ - current produced when product container is sealed

I₂ - current produced when product container is defective

Feasibility Study - Samples Tested



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

Summary of Results (negative controls)

Negative controls		# samples	VeriPac VP-455		E-Scan 655 HVLD ^{mc}	
			Found negative		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)

Identified Positive Controls			#samples	VeriPac VP-455		E-Scan 655	
				Vacuum Decay		HVLD ^{mc}	
				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® identified all positive samples except one

Test Results Summary 1ml PFS w/ Water and Albumin

Vacuum Decay, VP-455					HVLD ^{mc} , E-Scan 655		
Test#	Water		Alb.		Test#	Water	Alb.
	Abs(mb)	Diff(Pa)	Abs(mb)	Diff(Pa)		Volt	Volt
1	4.3	13	41.	10	1	3.42	3.88
...
n	4.1	11	4.0	12	n	3.05	3.33
Average	4.2	12.2	4.0	11.4	Average	3.24	3.59
StD	0.2	1.4	0.1	1.2	StD	0.26	0.38
Noise (3Std)	0.6	4.3	0.2	3.5	Noise (3 Std)	0.78	1.14
Ref. 3Std	4.8	16.5	4.2	14.9	Ref. 3Std	4.02	4.73
Ref. 4Std	5.0	17.9	4.3	16.1	Ref. 4Std	4.28	5.11



Conclusion

The identical vacuum decay test method showed very similar results for negative control samples (good syringes) between the 1 ml and 2.25 ml syringes, with a range in absolute results from 3.8 to 4.2mbar and differential readings ranging from 10.7 to 13.9. When introducing positive (defects) controls with pure water, a discrepancy between detection of positive controls appears between the 1 ml and 2.25 ml syringe. While the vacuum test method is generally more capable of detecting samples with pure water content, the results show a greater detection capability with 1 ml syringes over the 2.25 ml syringes, all other things being equal. The discrepancy between 1 ml and 2.25 ml syringes in the

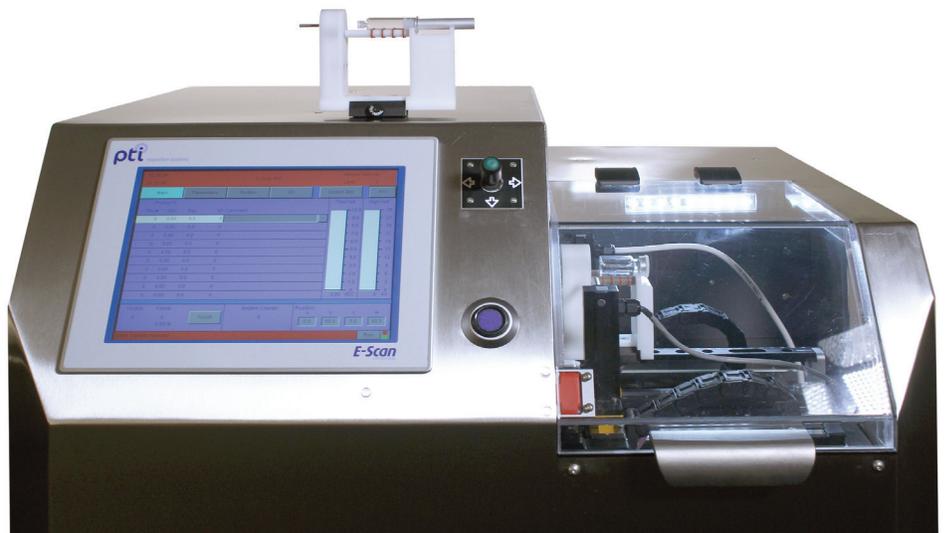
ability to detect the positive controls extends into the Albumin results, with the 1 ml syringe having a higher detection capability across all defect sizes for both water and Albumin.

The discrepancy in detection capability may be a result of defect geometry and flow rate. The positive controls are manufactured laser drilled defects, a process that is sensitive to material variations. In manufacturing the 1 ml and 2.25 ml syringe defects, a difference in characteristics of the positive control samples is evident. This difference in the quality and performance of the positive control samples may be the source of deviation when samples were tested using HVLD and the 5 micron defect in a 2.25 ml syringe sample (K2) was not detected.

HVLD^{mc} (E-Scan 655) technology performed the CCI test satisfactorily and is the recommended CCIT inspection method as per USP 1207 for liquid prefilled syringes, ampoules and vials. 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.

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

- Off-line laboratory system to inspect liquid filled:
 - Vials - Syringes - Ampoules
 - Cartridges - BFS
- DC with offset AC Voltage
- Lower HV application
- mc: MicroCurrent
- Improved SNR
- Negligible Ozone
- Product not exposed to HV
- Good for low conductivity liquids including distilled water



Micro Leak Testing of Parenteral Products

The E-Scan 655 is a revolutionary deterministic offline micro leak test instrument that utilizes a new class of HVLD technology to inspect vials, syringes, and other liquid filled parenteral products for container closure integrity. The E-Scan 655 technology is a MicroCurrent conductivity test method, HVLD^{mc}, that is completely non-destructive to the container and product; exposing the package and product to lower voltage than other conductivity based solutions. The technology uses a non-contact and non-invasive test method that requires no sample preparation. E-Scan 655 can be used with a wide range of liquid based products including low conductivity sterile water for injection (WFI) and proteinaceous products with suspensions. The E-Scan 655 features a fast test cycle and simple operation. Additional benefits include quick changeover and easy recipe setup to accommodate a wide range of products and applications. The offline E-Scan 655 method can be migrated from laboratory to 100% inline testing applications at high production speeds.



E-Scan 655

TECHNOLOGY

The E-Scan testing process uses a set of electrode probes to scan a non-conductive container that is sealed. The container material can be glass, plastic, or poly laminate. The container or package must contain liquid (minimum fill 30%). If a pinhole, crack, or other defect is present, there is a resistance differential and change in current flow indicating a breach in the container. The approximate defect location can be identified. PTI's E-Scan 655 patent pending technology uses a unique mode of MicroCurrent HVLD, applying less than 50% of the voltage used with conventional high voltage technologies. The nature of this solution allows for testing packages with extremely low conductivity liquids such as sterile water (WFI). The MicroCurrent applied to the product during the test greatly reduces the voltage exposed to the product and environment. In fact, using PTI's MicroCurrent HVLD reduces voltage exposure to the product to less than 5% of the voltage exposure experienced when testing with comparable HVLD solutions. MicroCurrent HVLD technology is the optimal solution for all parenteral and biologic products.

SPECIFICATIONS

E-Scan 655

Application	Non-destructive micro leak detection for parenteral products (liquid fill)
Inspection Criteria	<ul style="list-style-type: none">• Detection of pinholes, cracks, and defective seals• Measures & verifies container closure system integrity
Package Type	Pre-filled syringes, vials, cartridges, ampoules, BFS, bottles, pouches
Package Materials & Combinations	Glass, plastic, poly laminate
Contents	<ul style="list-style-type: none">• Liquids including products with suspensions, emulsions and proteins• Sterile Water for Injection (WFI)
Test Configuration	<ul style="list-style-type: none">• Offline laboratory• Technology is scalable to 100% online inspection
Test Method	MicroCurrent HVLD (HVLD ^{mc})
Operator Interface	Color Touch Screen
Test Parameter Storage	Up to 20 Products
Test Sensitivity	Approximate hole size < 1 micron* (MALL)
Test Results	Voltage Reading 0 - 10 Volt analog measure
CFR Security Capability	Yes (21 CFR, Part 11)
Remote Internet Access	Yes
Data Collection	View on touch screen and electronic
Test Instrument Enclosure	Stainless steel with Lexan safety panels
System Dimensions	29" w x 23.1" D x 23.4" H
Weight	160 lbs.
Power	100-240 VAC; 50/60 cycles
Options	Validation Qualification Package (IQ/OQ/PQ)
Certifications	CE

*Test results may vary according to application and package specifications.

BENEFITS

MicroCurrent HVLD

- Non-destructive, non-invasive, no sample preparation
- High level of repeatability and accuracy
- Effective across all parenteral products, including extremely low conductivity liquids (WFI)
- Low voltage exposure to the product and environment
- Listed in USP Chapter <1207> as recommended method for parenteral liquid package inspection
- Robust method and approximate 3x Signal-Noise-Ratio for a wide range of product classes and package formats
- Simplifies the inspection and validation process
- Offline and 100% online inspection at high production speeds
- Low voltage exposure to the product and environment



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