Container Closure Integrity: Regulations, Test Methods, Application

Deterministic Test Methods

Instructors

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Vienna Austria, 9-10 November 2017

Deterministic leak test methods

- Tracer gas detection (vacuum mode)
- Vacuum and pressure decay
- Mass extraction
- Laser-based gas headspace analysis
- Electrical conductivity and capacitance (High voltage leak detection)

Tracer gas detection (vacuum mode)

- **Detection**: Tracer gas leakage rate in mass flow units
- **Technology**
  - Quantitative measurement of tracer gas leak rate from a gas-charged test sample into a vacuum chamber
  - Output analyzed by spectrometric means
  - Leak rate calculated by normalizing results by the concentration of tracer gas in the test sample
  - Calibrated leak standards used to verify method accuracy

Reference ASTM F2391

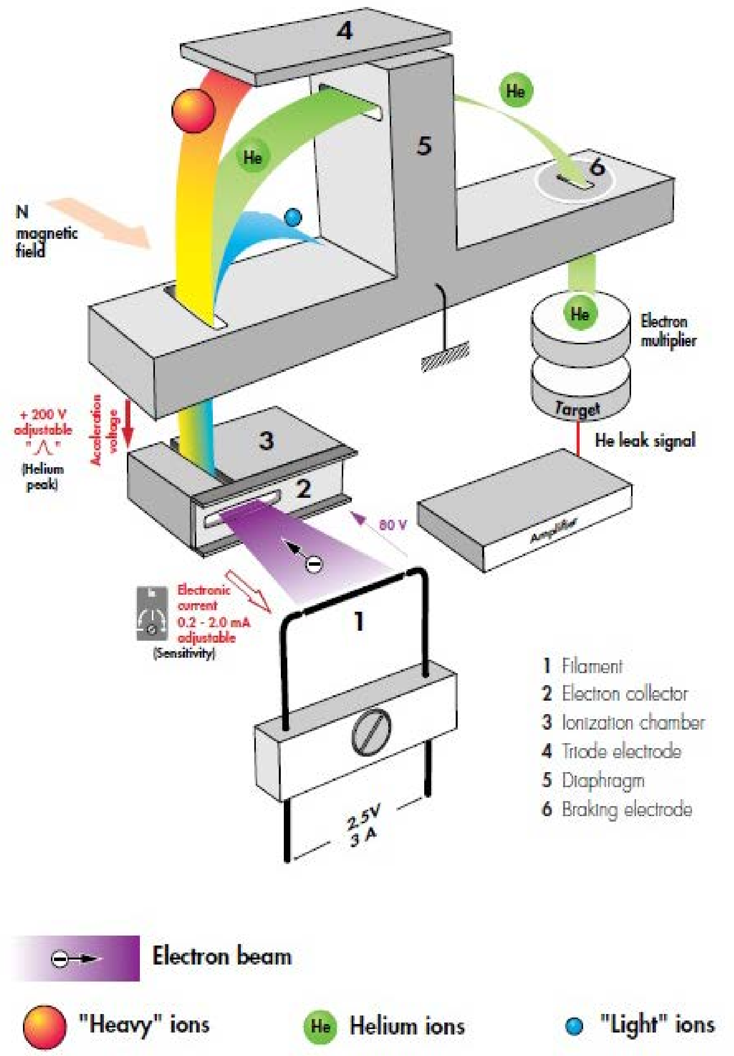
Tracer gas detection (vacuum mode)

- **Requirements**
  - Package
    - Nonporous, rigid
    - Flexible or non-fixed components may employ optional restraint mechanism
    - Ablility to tolerate high test vacuum
    - Limited tracer gas permeability
  - Product: Tracer gas only must be present at leak site

Tracer gas detection (vacuum mode)

- **Test**
  - Flood helium tracer gas (or perhaps hydrogen) into test sample. Use restraint mechanism for flexible package or package with non-fixed components as required
  - Place test sample in vacuum chamber connected to spectroscopic analyzer specific for tracer gas (for helium: mass spec analysis)
  - At test start, chamber is evacuated and tracer gas is drawn into analyzer; gas mass flow rate is reported. Normalize findings based on test sample tracer gas concentration

Deterministic leak test methods



Leak Detection Associates, Blackwood, NJ

Tracer gas detection (vacuum mode)

- **Application**
  - Best performed on empty test sample. Product drawn into analyzer may cause instrument damage.
  - Leakage may be masked by tracer gas permeation. Proper fixturing and test method optimization needed.
  - Generally performed off-line in R&D for inherent CCI verification.
    - Can be employed in manufacturing for line set-up.
  - Requires seconds to minutes per test sample.
- **Nondestructive**
  - IF tracer gas introduction into test sample poses no threat to product sterility/quality

Tracer gas detection (vacuum mode)

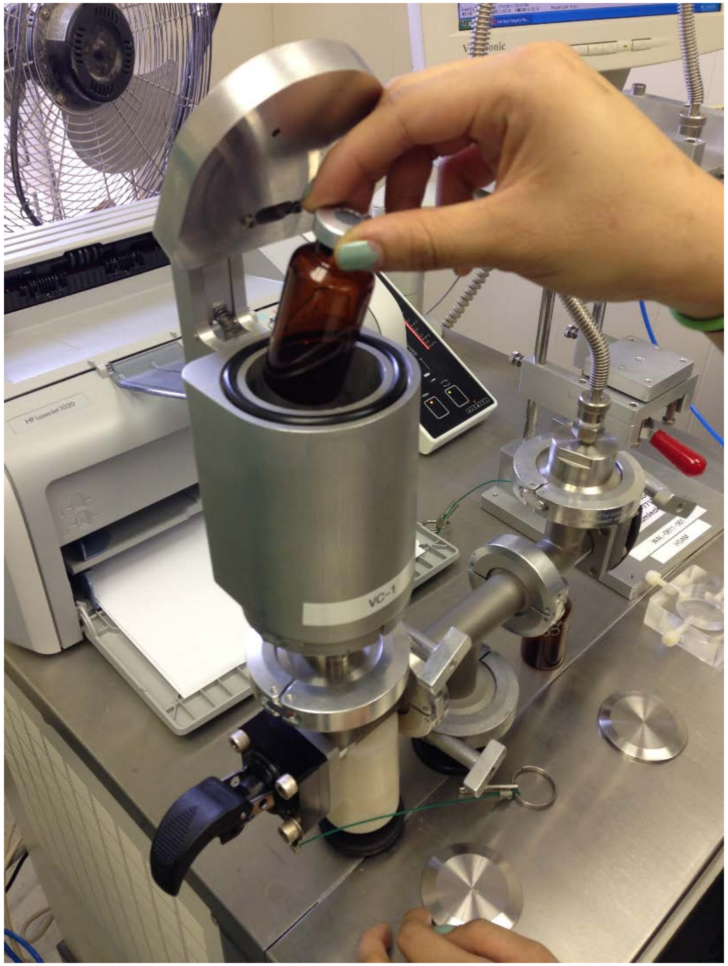
- **Detection limit**
  - Highly sensitive and quantitative method
  - Permeation of tracer gas through package can be mistaken for leakage
  - Tracer gas escape through large leaks before test performed can lead to false negatives
    - May be necessary to utilize headspace analyzer to adjust leak rate results
  - Tracer gas background in testing environment can influence test results
  - Proper fixturing is important to capture leakage site of interest
  - Even long, tortuous leaks can be detected; Blocked leak paths prevent detection

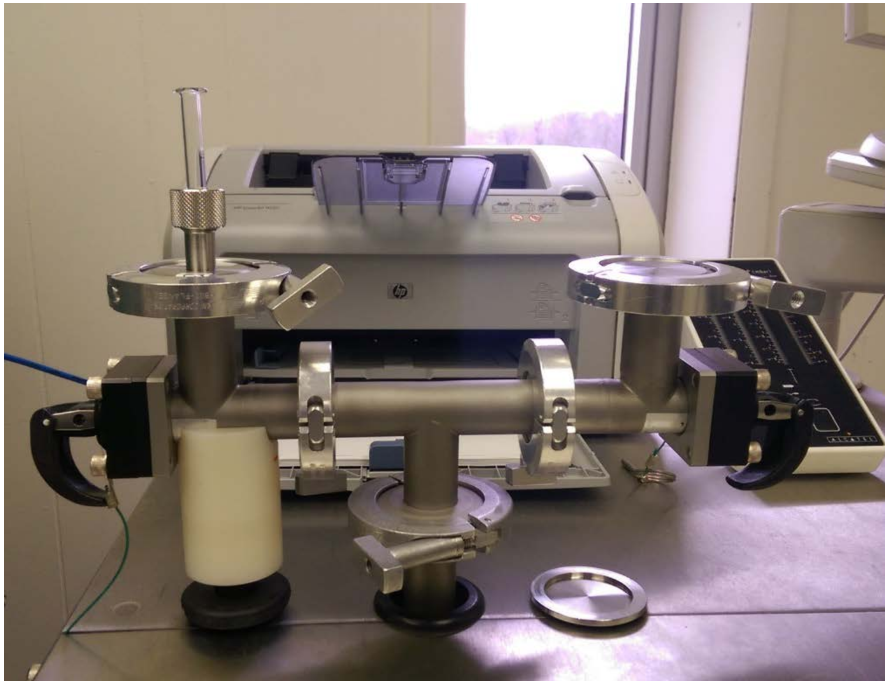
- **Detection range**: 0.01 µm to mm may be possible

Tracer gas detection (vacuum mode)

- **Reported usage**
- Formulations
  - Tracer gas must be present at leak site
  - Best used for testing empty packages to prevent product contamination of gas analyzer
- Packages
  - All types of vials, bottles, syringes, blisters, pouches, bags, etc.
  - Small volume to large volume
  - Plastics (with limited helium permeability), glass, metal
  - Rigid to flexible to non-fixed components (restraint mechanism may be required)

Deterministic leak test methods





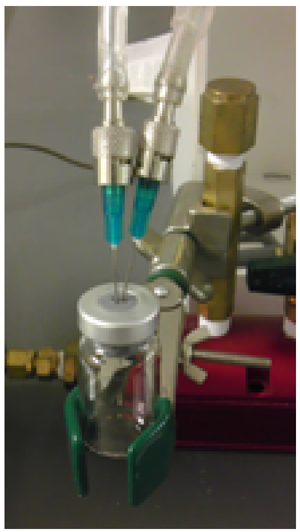
Helium leak detection utilizing a Leak Detection Associates SIMS 1282+. Images from Whitehouse Labs, NJ, USA

Deterministic leak test methods

2014 PDA ANNUAL MEETING
Biopharmaceutical and Sterile Manufacturing – Embracing Innovation to Meet Global Challenges
April 7-9, 2014 | JW MARRIOTT SAN ANTONIO HILL COUNTRY | SAN ANTONIO, TEXAS

Initial Development

He Leak



Stack-up
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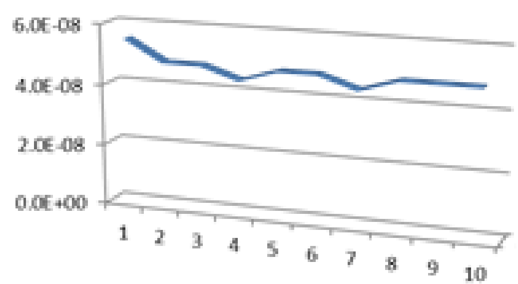


Images by West READY PACK®

Component fit • Component material • Component processing

D. Paskiet, R. Asselta, "Qualifying Integral Container Closure Systems Employing Advanced Measurement Techniques"

Helium leak detection of foil blister packages

Images from www.heliumleak.com, Leak Detection Associates, accessed May 7, 2014

Deterministic leak test methods

Helium mass spectrometry has been reported to be found useful for detecting leaks in single-use bags prior-to-use

V. Pethe, Microleak detection in flexible containers and its correlation to microbial ingress probability, PDA Europe Parenteral Packaging Conference, Brussels, Belgium, March 12, 2014

Vacuum decay test

- **Detection**: Gas or volatilized product leakage rate in pressure rise units
- **Technology**
  - Quantitative measure of pressure rise (vacuum decay) typically within an evacuated test chamber housing a test sample, resulting from test sample headspace leakage or liquid product volatilization
  - Output compared to that of leak rate standards, plus pre-determined limits using no-leak and with-leak controls

Reference ASTM F2338

Vacuum decay test

- **Requirements**
  - Package
    - Nonporous, rigid
    - Flexible or non-fixed component package requires restraint mechanism
    - Porous material requires masking to limit gas flow
  - Product
    - Gas headspace of sufficient volume at leak site required, OR
    - Liquid (capable of volatilization) must be present at leak site

Vacuum decay test

- **Test**
  - Place test sample in test chamber. Use restraint mechanism for flexible/moveable package
  - At test start, test chamber is evacuated to target vacuum (target pressure can be varied to suit product-package)
  - Pressure increase as a function of time is monitored and compared to pre-determined limits; indicative of leaks

Vacuum decay test

•Application

- Solidified product or debris in leak path may block leak detection
- Test fixture or restraint mechanism at test sample site of contact may block leak path
- Volatiles or liquids drawn into test system can cause damage
- Generally performed off-line in R&D and stability for CCI verification
- May be performed on-line in manufacturing on-line (larger leak detection)
- Requires several seconds to minutes per test sample

Vacuum decay test

- **Nondestructive**

- **Detection limit**
  - Varies with
    - Leak size, type, length, blockage
    - Package internal volume, flexibility, outgassing
    - Test system volume, test system outgassing, sensitivity of pressure transducers
    - Test time, target vacuum

- **Detection range**: 2-5 µm to mm may be possible

Vacuum decay test

•Reported usage

- **Formulations**
  - For gas at leak site, sufficient headspace volume required
  - For liquid at leak site, solution formulations capable of volatilization at test pressure required

- **Packages**
  - All types of vials, bottles, ampoules, syringes, blisters, pouches, bags, etc.
  - Small volume to large volume
  - Plastics, glass, metal
  - Rigid to flexible (with restraint mechanism)
  - Porous if mechanism for blocking porous structure employed

Deterministic Leak Test Methods

Vacuum decay leak test

PTI VeriPac 325/LV

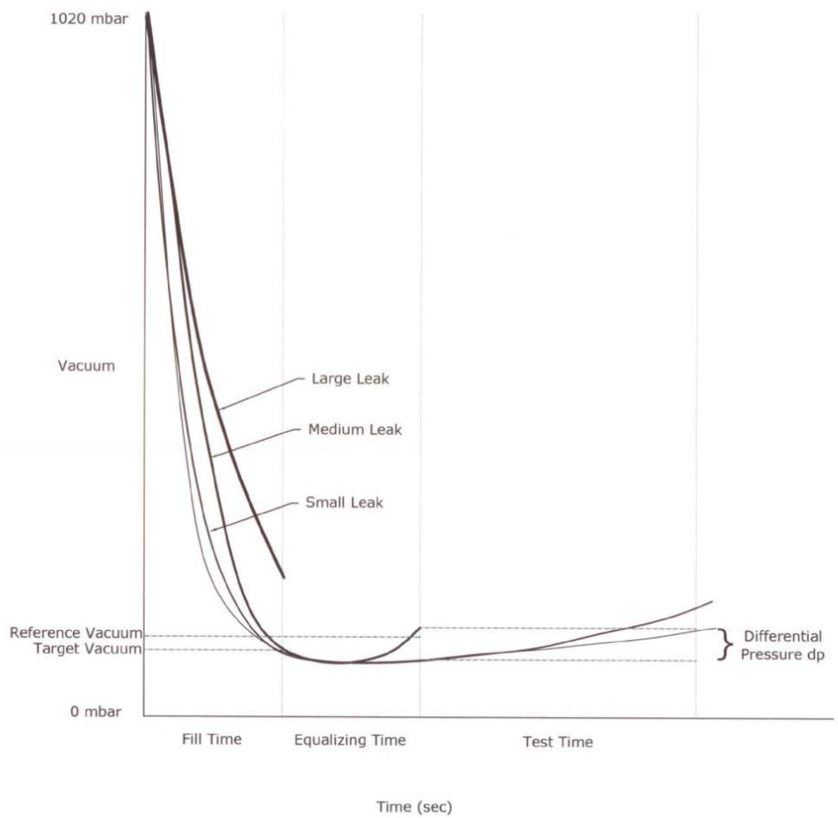
Test chamber

PDA PSIG meeting, Mar 2010, Orlando, FL 22

S. Orosz, D. Guazzo, Glass vial finish defects - Leak detection and product risk assessment, PSIG session of the PDA Annual Meeting, Orlando, FL, March 16, 2010

Deterministic Leak Test Methods

ASTM F2338-09



Test Method Sequence of Events
1a. Vacuum drawn during FILL Time 1000 Torr Transducer (mbar) **1b. Vacuum source is shut OFF**
2. Pressure rise monitored during EQUALIZATION and TEST Times 1000 Torr Transducer (mbar)
3. Pressure rise monitored during TEST Time 10 Torr Transducer (Pa)

Vacuum decay leak test method

Capped lyo-style vial package with ambient pressure air headspace

Package description	Test packages	Total test count	Test count passed (no leak detected)	Test count failed (leak detected)
Negative controls	70	210	210	0
Positive controls, Holes 2.39 – 3.17 µm	10	30	21	9
Positive controls, Holes 4.36 – 6.02 µm	**10**	**30**	**0**	**30**
Positive controls, Holes 12.08 – 15.04µm	**10**	**30**	**0**	**30**

J. Patel, B. Mulhall, H.Wolf, et al, PDA J Pharm Sci & Tech, 65, Sep/Oct 2011 p. 486 – 505

Deterministic Leak Test Methods

M. Whitlow, CCIT flexible foil packaging, PDA Europe Parenteral Packaging Conference, Brussels, Belgium, March 12, 2014

Deterministic Leak Test Methods

Vacuum Decay
coupled with an inflated package
Force Decay Leak Test

LARGE POUCH

- Product in a large flexible foil pouch was introduced to the market after successfully completing all requirements/validations.
- Manual inspection.
- Within months, a recall was initiated due to defect in body of the pouch.
- Defect was created by a shift in the manufacturing process.

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CORRECTIVE ACTION

1. Modified the process to mitigate risk.
2. Investigated various CCIT options.
   - Vacuum decay test method identified as best fit technology.
3. Deployed PTI's VeriPac 425 series equipment with flexible test chamber technology due to the shape of the package.
4. Implemented 100% in process CCIT.

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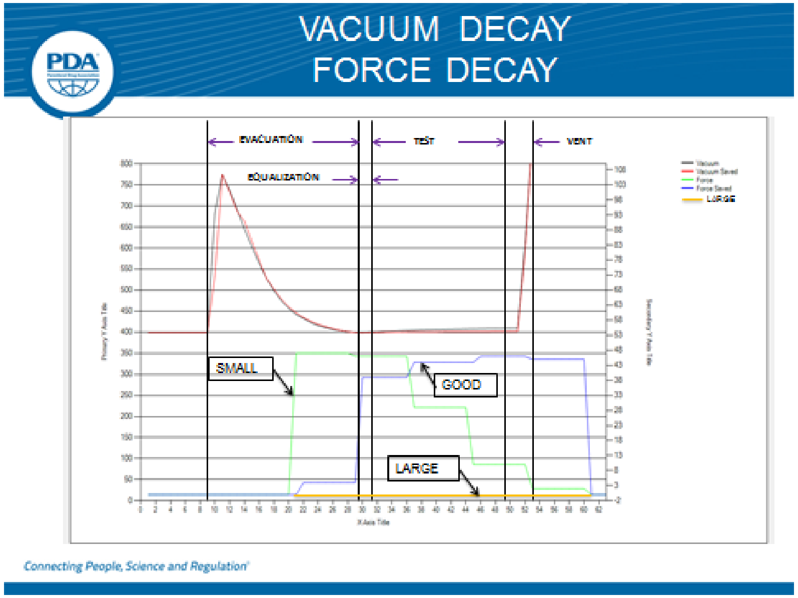
M. Whitlow, CCIT flexible foil packaging, PDA Europe Parenteral Packaging Conference, Brussels, Belgium, March 12, 2014

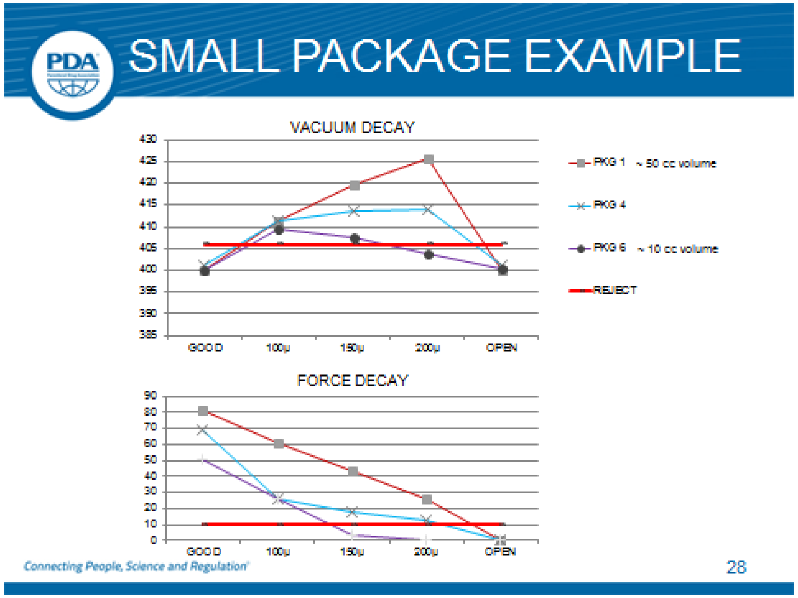
Deterministic Leak Test Methods



Vacuum Decay

coupled with an inflated package

Force Decay Leak Test



M. Whitlow, CCIT flexible foil packaging, PDA Europe Parenteral Packaging Conference, Brussels, Belgium, March 12, 2014

Pressure decay test

- **Detection**: Gas leakage rate in pressure decay units

- **Technology**
  - Quantitative measure of pressure decay within a pressurized test sample
  - Output compared to that of leak rate standards, plus pre-determined limits using no-leak and with-leak controls

Reference ASTM F2095 (for flexible packages)

Pressure decay test

- **Requirements**
  - Package
    - Nonporous, rigid
    - Flexible or package with non-fixed components may employ optional restraint mechanism
  - Product: Gas only must be present at leak site

Pressure decay test

- **Test**
  - At test start, pressurizing gas (air or inert gas) is introduced into test sample to target pressure.
    - Option: Use restraint mechanism for flexible package (required for packages with non-fixed components)
  - Pressure decay as a function of time is monitored; indicative of leaks

Pressure decay test

Application

- Solidified or liquid product or debris in leak path may block leak detection
- Generally performed off-line in R&D for inherent CCI verification
- Can be performed on packages on-line in manufacturing (e.g., empty bottle test)
- Can be performed in manufacturing to check equipment/line integrity
- Test requires several seconds (small volume test samples) to days (largest volume samples), depending on test sample volume and leak limit of detection required

Pressure decay test

- **Nondestructive:** If gas introduction into test sample poses no threat to product sterility/quality

- **Detection limit**
  - Varies with
    - Leak size, type, length, material of construction, blockage
    - Package internal volume, flexibility
    - Test time; target pressure; gas temperature and humidity control; pressure sensor sensitivity

- **Detection range**: 2-5 µm to mm may be possible

Pressure decay test

Reported usage

- Formulations
  - Gas must be present at leak site
  - Product must not obstruct leak path

- Packages
  - All types of vials, bottles, syringes, pouches, bags, etc.
  - Small volume to large volume to bulk containers
  - Plastics, glass, metal
  - Rigid to flexible to non-fixed components (restraint mechanism may be required)
  - Manufacturing equipment, incl. tanks, aseptic isolation systems

Mass extraction test

(aka mass flow test)

- **Detection**: Gas or volatilized product leakage rate in mass flow rate units

- **Technology**
  - Quantitative measure of gas mass flow rate within an evacuated test chamber housing a test sample, resulting from test sample headspace leakage or liquid product volatilization
  - Output compared to that of leak rate standards, plus pre-determined limits using no-leak and with-leak controls

Mass extraction test

(aka mass flow test)

- **Requirements**
  - Package
    - Nonporous, rigid
    - Flexible or package with non-fixed components; restraint mechanism required
    - Porous material - requires masking to limit gas flow
  - Product
    - Gas headspace of sufficient volume at leak site required, OR
    - Liquid (capable of volatilization) must be present at leak site

Mass extraction test

(aka mass flow test)

- **Test**
  - Place test sample in test chamber. Use restraint mechanism for flexible package or package with non-fixed components
  - At test start, test chamber is evacuated to target pressure (multiple stages may be required)
  - Pressure increase as a function of time (or gas mass flow) is monitored and compared to pre-determined limits; indicative of larger leaks
  - Gas mass flow post final high vacuum draw is monitored and compared to pre-determined limits; indicative of smaller leaks

Mass extraction test

(aka mass flow test)

Application

- Solidified product or debris in leak path may block leak detection
- Test fixture or restraint mechanism at test sample site of contact may block leak path
- Volatiles or liquids drawn into test system can cause damage
- Generally performed off-line
- Used in all product life cycle phases
- Requires several seconds to minutes per test sample

Mass extraction test

(aka mass flow test)

- **Nondestructive**
- **Detection limit**
  - Varies with
    - Leak size, type, length, blockage
    - Package flexibility, size, outgassing
    - Test system volume, test system outgassing, sensitivity of pressure transducers and mass flow meter
    - Test time, target vacuum
- **Detection range**: 2-5 µm to mm may be possible

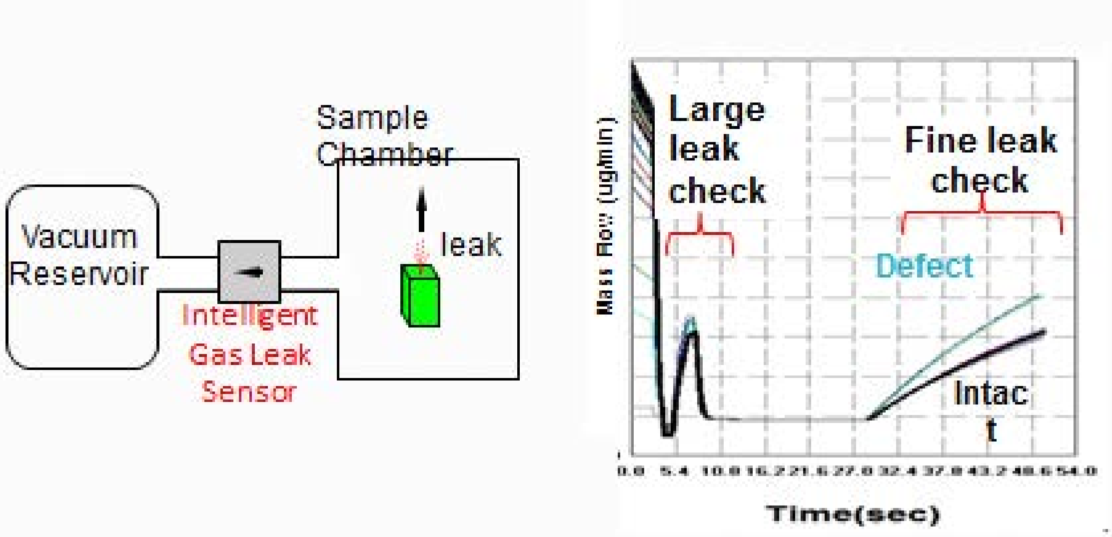
Mass extraction test

(aka mass flow test)

- **Reported usage**
- Formulations
  - Gas headspace of sufficient volume at leak site required, OR
  - Liquid (capable of volatilization) must be present at leak site
- Packages
  - All types of vials, bottles, ampoules, syringes, pouches, bags, etc.
  - Small volume to large volume
  - Plastics, glass
  - Rigid to flexible (with restraint mechanism)
  - Porous if mechanism for blocking porous structure employed

Deterministic Leak Test Methods

Mass Extraction Method: Principles



- Leak detection based on measuring gas/vapor egress flow rate from defective samples

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L. Li, Container Closure Integrity Testing Method Development and Validation for Pre-filled Syringes, PDA Universe of Pre-filled Syringes and Injection Devices, Las Vegas, NV, Oct 16, 2012

Deterministic Leak Test Methods

Mass Extraction CCI Testing: Merits and Limitations

Merits

- Simple and fast (1-2min/sample)
- Sensitive: 2 µm capable; typically 5-10 µm
- Flexible
  - Containers of various sizes and geometries
  - Applicable to injection devices

Limitations

- Potential instrument contamination by liquid leaks
- Elastomeric components may deform under pressure differential
- Limited applicability to proteinaceous product-filled samples
  - Protein concentration
  - Storage duration

Yoon et al. *PDA Journal of Pharmaceutical Science and Technology*, Sep/Oct 2012

61

L. Li, Container Closure Integrity Testing Method Development and Validation for Pre-filled Syringes, PDA Universe of Pre-filled Syringes and Injection Devices, Las Vegas, NV, Oct 16, 2012

Laser-based gas headspace analysis test

- **Detection**: Gas headspace content
- **Technology**
  - Quantitative measure by laser-based analysis of oxygen concentration, water vapor concentration, and/or low absolute pressure
  - Output compared to that of standard gas mixtures
  - To determine leak rate, change in headspace is measured over time

Laser-based gas headspace analysis test

- **Requirements**
  - Package: nonporous, transparent or translucent, amber or colorless
  - Product: headspace gas volume, path length and content must be compatible with instrument capability

- **Test**
  - Place test sample in holding fixture
  - At test start, near-IR diode laser light passes thru headspace
  - Light absorption is measured by frequency-modulated spectroscopy
  - Findings analyzed, compared to gas standards. O_2, CO_2, H_2O, and/or pressure reported.

Laser-based gas headspace analysis

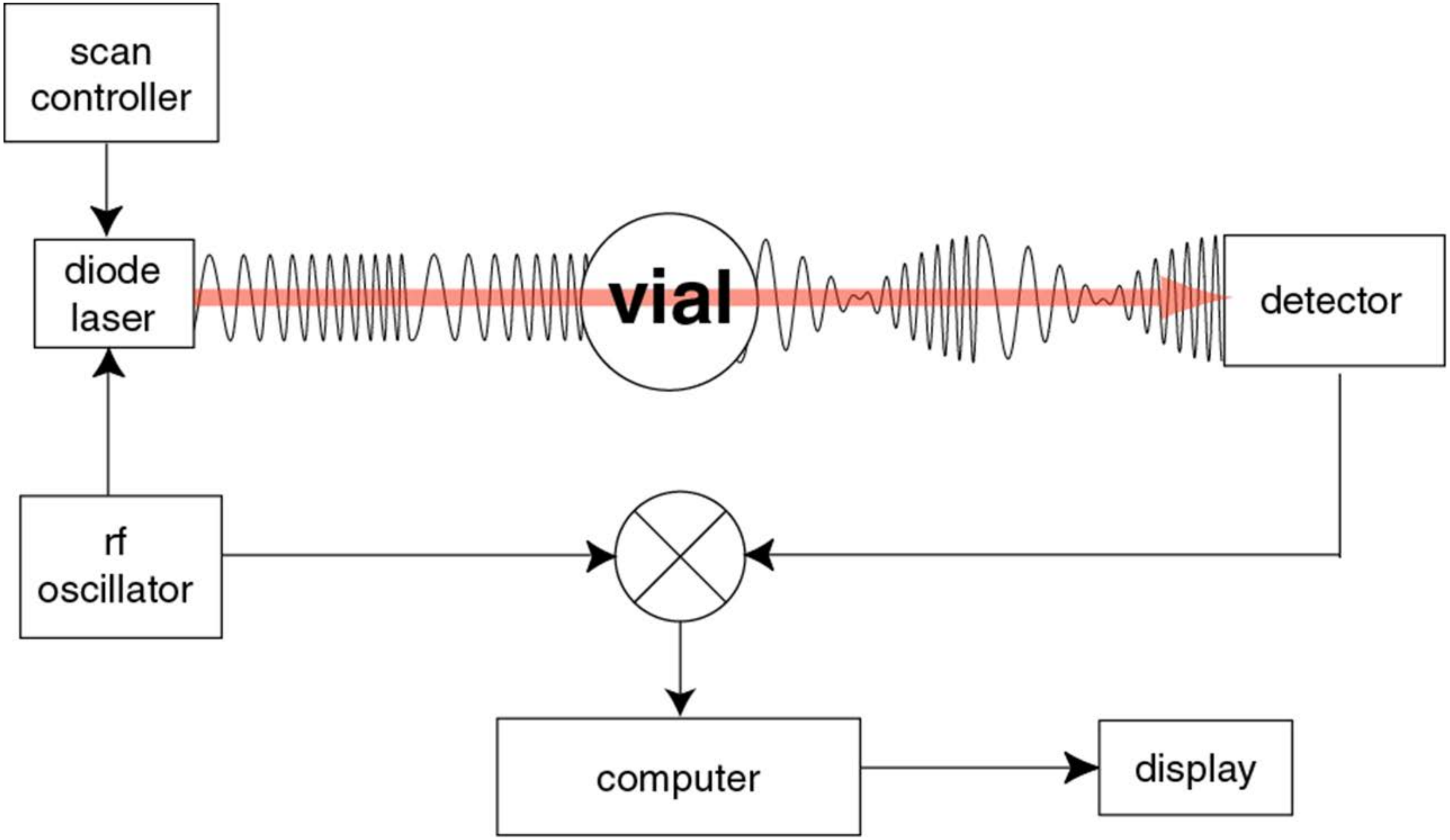


Image property of Lighthouse Instruments

Laser-based gas headspace analysis test

- **Test continued**
  - Laser passes through container headspace
  - Laser frequency is tuned to match internal absorption frequency of target molecule
    - **Absorption is proportional to pressure**
    - **Amplitude is proportional to concentration**
  - Differential absorption and phase sensitive detection techniques employed to enhance sensitivity

Laser-based gas headspace analysis test

•Application

- Vendors vary in capability of gases and package materials/designs that can be tested
- Faster test speed can raise standard deviation of findings
- Test sample outer surface moisture may hamper test performance
- Test sample temperature influences gas pressure and moisture readings
- Can be performed on- or off-line
- Can provide just-in-time headspace content analysis
- Used in all product life cycle phases
- Extremely rapid test (<1s to a few seconds per test sample)

Laser-based gas headspace analysis test

- **Nondestructive**
- **Detection limit**
  - Not a direct measure of leakage
    - Leakage can be calculated by analysis of sample headspace change as a function of time
      - Change of headspace due to permeation should be considered
    - Longer time between replicate sample tests allows detection of smaller leaks
- **Detection range**: <0.1µm to largest leaks are possible

Laser-based gas headspace analysis test

•Reported usage

•Formulations

- Liquids of all formulation types
- Lyophilized or dry powder dosage forms
- All API and ingredient types

•Packages

- Vials, bottles, ampoules, syringes
- Small volume to large volume
- Plastics, glass
- Transparent, translucent, amber, colorless

Laser-based headspace analysis

Rise in oxygen content over time

ambient headspace pressure

10 mL vial container

Predicted rise in package oxygen content		Time to reach predicted oxygen levels (Days)	
Partial pressure (atm)	Oxygen concentration (% atm)	5 µm Hole	2 µm Hole
0	0	0	0
0.005	0.5	<1	4
0.01	1	1	8
0.02	2	3	17
0.04	4	6	36
0.08	8	13	81

Initial oxygen partial pressure = 0 Torr

Hole path length assumed to be 0.1 mm

(Courtesy of Lighthouse Instruments, Inc., Charlottesville, VA)

Deterministic Leak Test Methods

Laser-based headspace analysis

Vacuum loss over time

10 mL vial container

Time post package closing	Package headspace pressure (Torr)	
	5 µm Hole	2 µm Hole
0 minutes	0	0
1 minute	13	2.4
5 minutes	63	12
10 minutes	126	24
60 minutes	756	144
5 hours	760	720
8 hours	760	760

Initial headspace pressure = 0 Torr

- hole path length 1.5 mm
- air viscosity 1.8 x 10^{-7} Pa·s

Viscous flow kinetics assumed

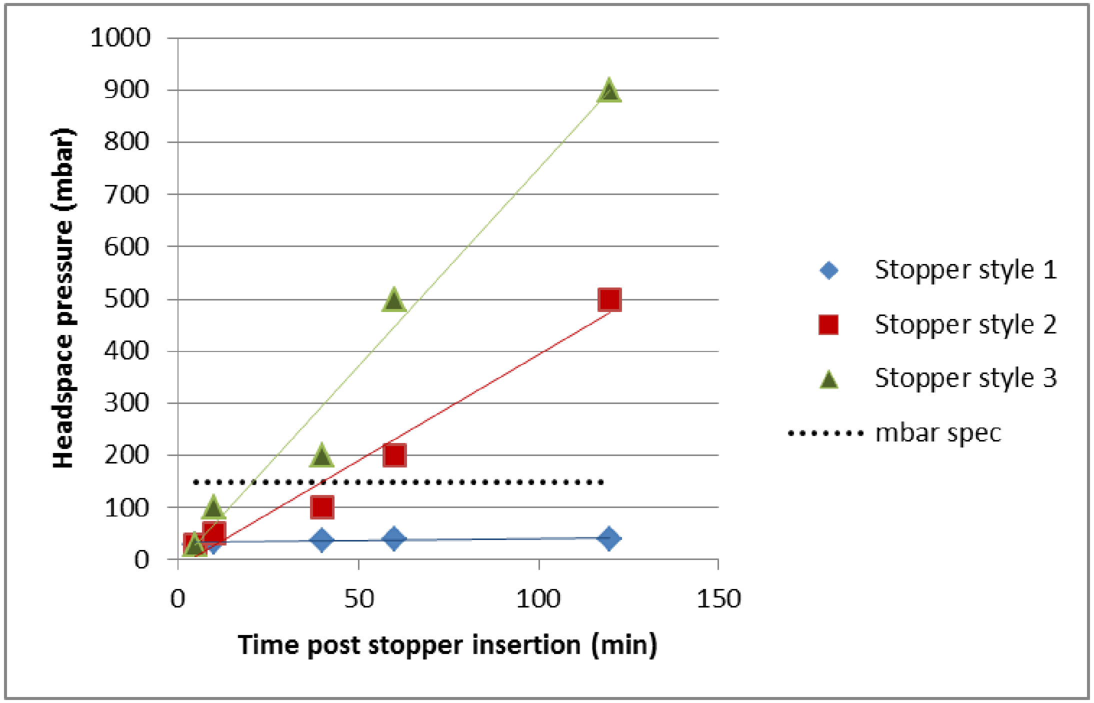
(Courtesy of Lighthouse Instruments, Inc., Charlottesville, VA)

Laser-based headspace analysis

Vacuum loss over time

Stoppered lyo-vial

Stopper type 1 maintained vacuum in vial below mbar spec limit for up to 2 hours post stopper insertion



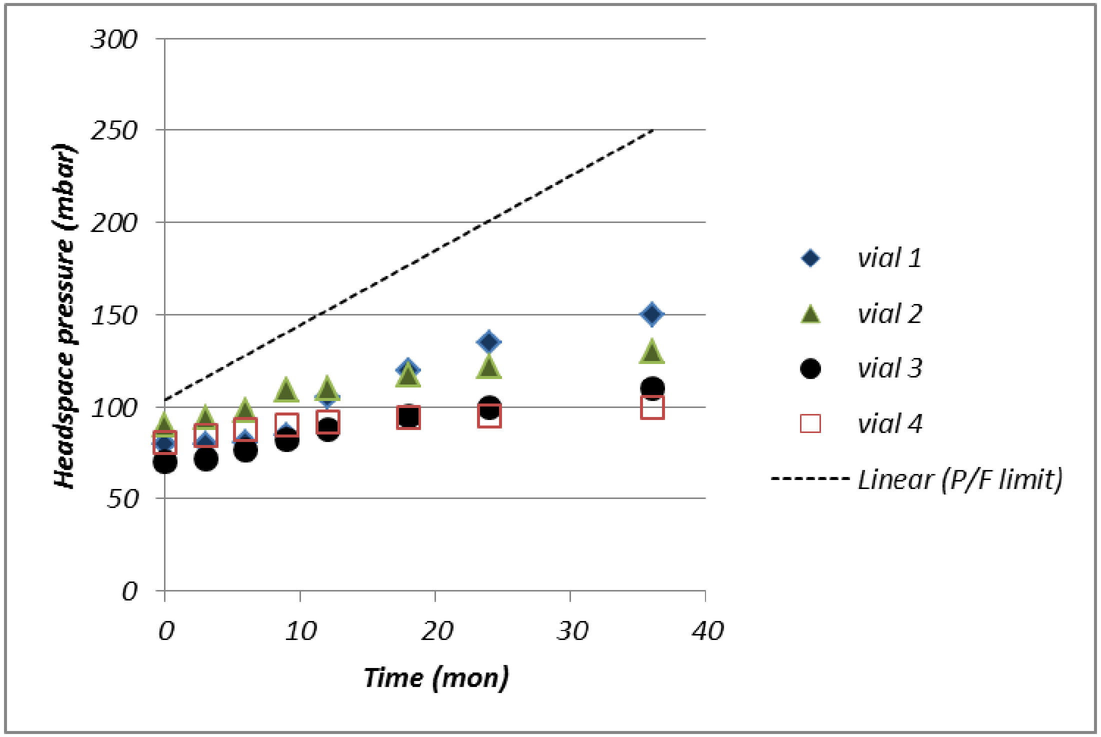
Fictional data for illustration only

Laser-based headspace analysis

Vacuum loss over time

Capped lyo vial package

Test sample headspace pressures remained below the pressure rise predicted given a 0.2µm leak



Fictional data for illustration only

Electrical conductivity and capacitance test

aka High voltage leak detection (HVLD)

- **Detection**: Liquid presence in or near leak path
- **Technology**
  - Quantitative electrical conductance and capacity measurement
  - Measured current output judged against pre-set Pass/Fail limit
- **Requirements**
  - Package: nonporous, rigid or flexible
  - Product: liquid or gel, more electrically conductive than package. Must be nonflammable

Electrical conductivity and capacitance test

aka High voltage leak detection (HVLD)

- **Test**
  - Place test sample on electrically grounded platform
  - At test start, sample is exposed to hi-frequency, hi-voltage, low-amperage (AC) current via an electrode that passes the test sample
    - Electrical current frequency is a vendor-specific proprietary parameter
    - Electrodes differ in design and material.
    - Electrodes either contact or pass near the test sample surface;
  - Current flows from the electrode, through and around the test sample to the ground
  - Spike in current at ground (converted to DC) indicates leak presence

Electrical conductivity and capacitance test

aka High voltage leak detection (HVLD)

- **Application**
  - Whole package surfaces or single point inspection possible
  - Probe types include carbon brushes, metal probes, metallic beaded strands
  - Samples may be tested while tested in place or during on-line transport
  - Can be performed on- or off-line
  - Used in all product life cycle phases
  - Extremely rapid test (<1s to a few seconds per package)

Electrical conductivity and capacitance test

aka High voltage leak detection (HVLD)

- **Nondestructive**
  - Although product exposure to HVLD has been found to cause product degradation in rare cases (e.g., ozone build-up in package headspace may trigger active oxidation)
  - If used as a nondestructive method, HVLD impact on product stability recommended

- **Detection limit**
  - Varies with
    - Leak size, length, presence of product (liquid to solid) near or in leak
    - Test scan speed
    - Probe design and material of construction, proximity of probe to leak/liquid
    - Ground design, material of construction, position relative to the test sample
    - Current voltage/amperage/frequency setting
    - Ground sensitivity setting
    - Product vs. package conductivity

- **Detection range**: 2-5 µm to mm size leaks may be possible

Electrical conductivity and capacitance test

aka High voltage leak detection (HVLD)

- **Reported usage**
  - Formulations
    - Solutions, liquids, gels
    - Proteinaceous or small molecule active ingredients
  - Packages
    - Flexible IV bags
    - Stoppered vials or bottles
    - Form, fill, seal ampoules (glass or plastic)
    - Form, fill, seal small volume bags
    - Syringes
    - Large volume bulk bags

Deterministic Leak Test Methods

High voltage leak test

Nikka Densok HVLD Model HDT1

Positive leak detection

PDA PSIG meeting, Mar 2010, Orlando, FL 25

S. Orosz, Guazzo, Glass vial finish defects - Leak detection and product risk assessment, PSIG session of the PDA Annual Meeting, Orlando, FL ,March 16, 2010

Deterministic Leak Test Methods

Leak detection vs. Defect size & type

- Purpose
  - To determine the ability of HVLD and vacuum decay to identify leaks in with-defect and without-defect packages

- Test samples
  - Packages included
    - Negative control, no defect packages
    - Natural defect vials
    - Laser-drilled holes through glass vial neck
    - Channels cut along seal surfaces
  - Package contents
    - 1/2 were active product-filled, 1/2 were placebo-filled
      - Exception: All natural defects were active product-filled

PDA PSIG meeting, Mar 2010, Orlando, FL 35

S. Orosz, D. Guazzo, Glass vial finish defects - Leak detection and product risk assessment, PSIG session of the PDA Annual Meeting, Orlando, FL, March 16, 2010

Deterministic Leak Test Methods

Leak detection vs. Defect size & type

Hole size (μ)	Package contents	# Packages tested	# Packages ID'd as LEAKING	
			Vacuum decay	HVLD
15	Placebo	10	10	10
	Active	10	8	10
25	Placebo	10	10	10
	Active	10	9	10
50	Placebo	10	10	10
	Active	10	10	10

No helium leak tests were performed on holed vial packages post vacuum decay tests.

PDA PSIG meeting, Mar 2010, Orlando, FL 37

S. Orosz, D. Guazzo, Glass vial finish defects - Leak detection and product risk assessment, PSIG session of the PDA Annual Meeting, Orlando, FL, March 16, 2010

Deterministic Leak Test Methods

Leak detection vs. Defect size & type

Channel location	Package contents	# Packages tested	# Packages ID'd as LEAKING	
			Vacuum decay	HVLD
None	Placebo	50	0	0
	Active	51	0	2*
Valve	Placebo	10	0	0
	Active	10	0	0
Land + Valve	Placebo	10	10	10
	Active	10	10	10

* - *Helium leak rate was elevated for 1 of 2 HVLD failures (2E-6 std cc/s).*
[No-defect package leak rate ~ E-8 std cc/s.]
- *Second HVLD failure was confirmed for a total of 5 HVLD tests.*
- *Both packages demonstrated* ***HVLD char marks*** *across vial and stopper land surfaces.*

continued

S. Orosz, D. Guazzo, Glass vial finish defects - Leak detection and product risk assessment, PSIG session of the PDA Annual Meeting, Orlando, FL, March 16, 2010

Deterministic Leak Test Methods

Leak detection vs. Defect size & type

Channel location	Package contents	# Packages tested	# Packages ID'd as LEAKING	
			Vacuum decay	HVLD
Land *No change between vacuum decay and HVLD*	Placebo	9	8	8
	Active	12	12	12
Land *Re-stoppered/capped between vacuum decay and HVLD **	Placebo	7	2	7
	Active	3	0	2
TOTAL Land defects	Placebo	16	10	15
	Active	15	12	14
	TOTAL	31	22	29

** - After vacuum decay test, these packages were punctured and helium flooded for helium mass spec leak test. Each package was re-stoppered and capped before HVLD to eliminate potential false positive HVLD results due to stopper puncture.*

- This re-packaging process may have contributed to differences noted between vacuum decay and HVLD.

PDA PSIG meeting, Mar 2010, Orlando, FL 40

S. Orosz, D. Guazzo, Glass vial finish defects - Leak detection and product risk assessment, PSIG session of the PDA Annual Meeting, Orlando, FL, March 16, 2010

Deterministic Leak Test Methods

Leak detection vs. Defect size & type

SUMMARY

- HVLD and Vacuum decay are effective leak detection methods

- However,
  - HVLD detected a larger % of potential leaking packages

PDA PSIG meeting, Mar 2010, Orlando, FL 43

S. Orosz, D. Guazzo, Glass vial finish defects - Leak detection and product risk assessment, PSIG session of the PDA Annual Meeting, Orlando, FL ,March 16, 2010

Deterministic Leak Test Methods

Leak detection vs. Product formulation and storage time

- Purpose
  - To determine the impact of product formulation and product storage time on the leak detection capability of HVLD and vacuum decay
- Test samples
  - Vials had laser drilled holes (15, 25, 50 µ)
  - Packages contained either
    - **Proteinaceous active product solution**
    - **Placebo solution**
- Experiment
  - Samples were leak tested in random order on day 1 and day 29
  - Vacuum decay performed first, then HVLD on each test day

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S. Orosz, D. Guazzo, Glass vial finish defects - Leak detection and product risk assessment, PSIG session of the PDA Annual Meeting, Orlando, FL ,March 16, 2010

Deterministic Leak Test Methods

Leak detection vs. Product formulation and storage time

Vial hole size (μ)	Packages tested (#)	# Packages ID'd as LEAKING DAY 1		# Packages ID'd as LEAKING DAY 29	
		Vacuum decay	HVLD	Vacuum decay	HVLD
PRODUCT-FILLED					
15	10	8	10	2	10
25	10	9	10	2	10
50	10	10	10	3	10
PLACEBO-FILLED					
15	10	10	10	10	10
25	10	10	10	10	10
50	10	10	10	10	10

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S. Orosz, D. Guazzo, Glass vial finish defects - Leak detection and product risk assessment, PSIG session of the PDA Annual Meeting, Orlando, FL ,March 16, 2010

Deterministic Leak Test Methods

Leak detection vs.
Product formulation and storage time

SUMMARY

- Vacuum decay FAILED to find all defects in product-filled packages
  - Protein blockage of defect leak path is suspected
- HVLD is not influenced by protein presence
- Protein blockage risk increases over time

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S. Orosz, D. Guazzo, Glass vial finish defects - Leak detection and product risk assessment, PSIG session of the PDA Annual Meeting, Orlando, FL ,March 16, 2010

References from PDA Journal

Volume 67 2013

High-Voltage Leak detection of a Parenteral Proteinaceous Solution Product Packaged in Form-Fill-Seal Plastic Laminate Bags:

- Part 1. Method Development and Validation
- Part 2. Method Performance as a Function of Heat Seal Defects, Product-Package Refrigeration, and Package Plastic Laminate Lot
- Part 3. Chemical Stability and Visual Appearance of a Protein-Based Aqueous Solution for Injection as a Function of HVLD Exposure

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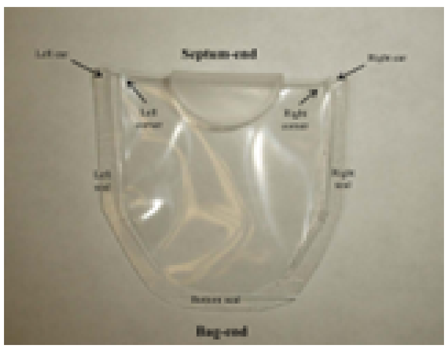
P. Buus, R. Damgaard, High voltage leak detection (HVLD) of flexible container, PDA Europe Parenteral Packaging Conference, Brussels, Belgium, March 12, 2014

Deterministic Leak Test Methods

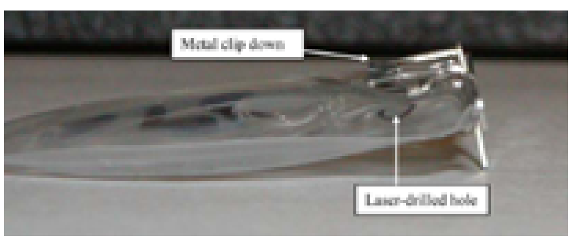
Project

- Container



The package consisted of a flat plastic laminate bag roughly 4 cm long by 4 cm wide, heat-sealed on three sides, and folded along the fourth edge. The fourth edge included an elastomeric disc or septum heat-welded in place.

The product is the aqueous solution formulation of the rapid acting insulin analogue, insulin aspart (NovoRapid/NovoLog) by Novo Nordisk A/S



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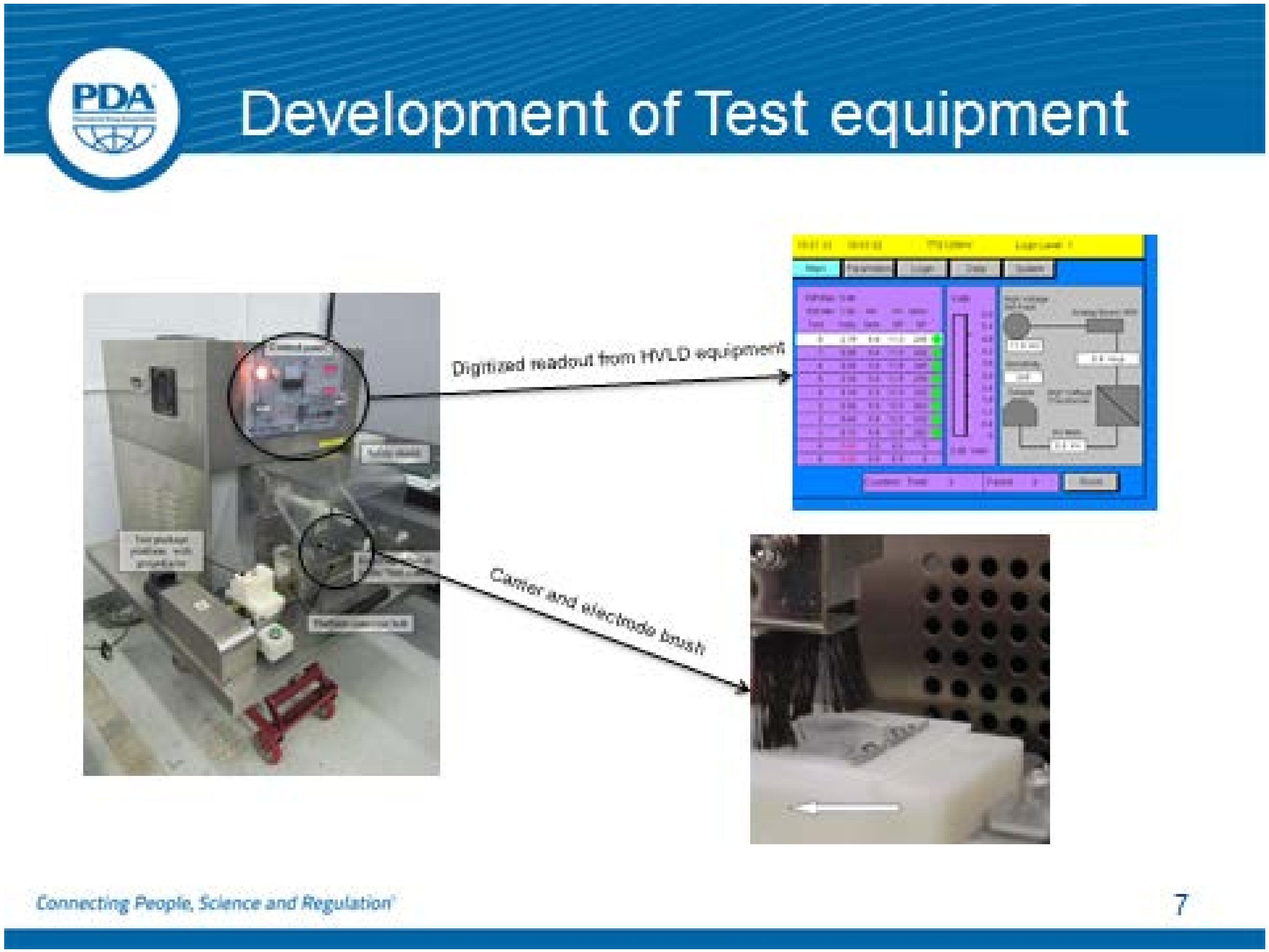
P. Buus, R. Damgaard, High voltage leak detection (HVLD) of flexible container, PDA Europe Parenteral Packaging Conference, Brussels, Belgium, March 12, 2014

Deterministic Leak Test Methods

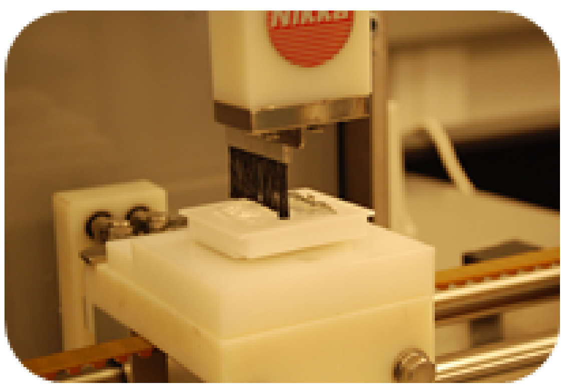


P. Buus, R. Damgaard, High voltage leak detection (HVLD) of flexible container, PDA Europe Parenteral Packaging Conference, Brussels, Belgium, March 12, 2014

Deterministic Leak Test Methods

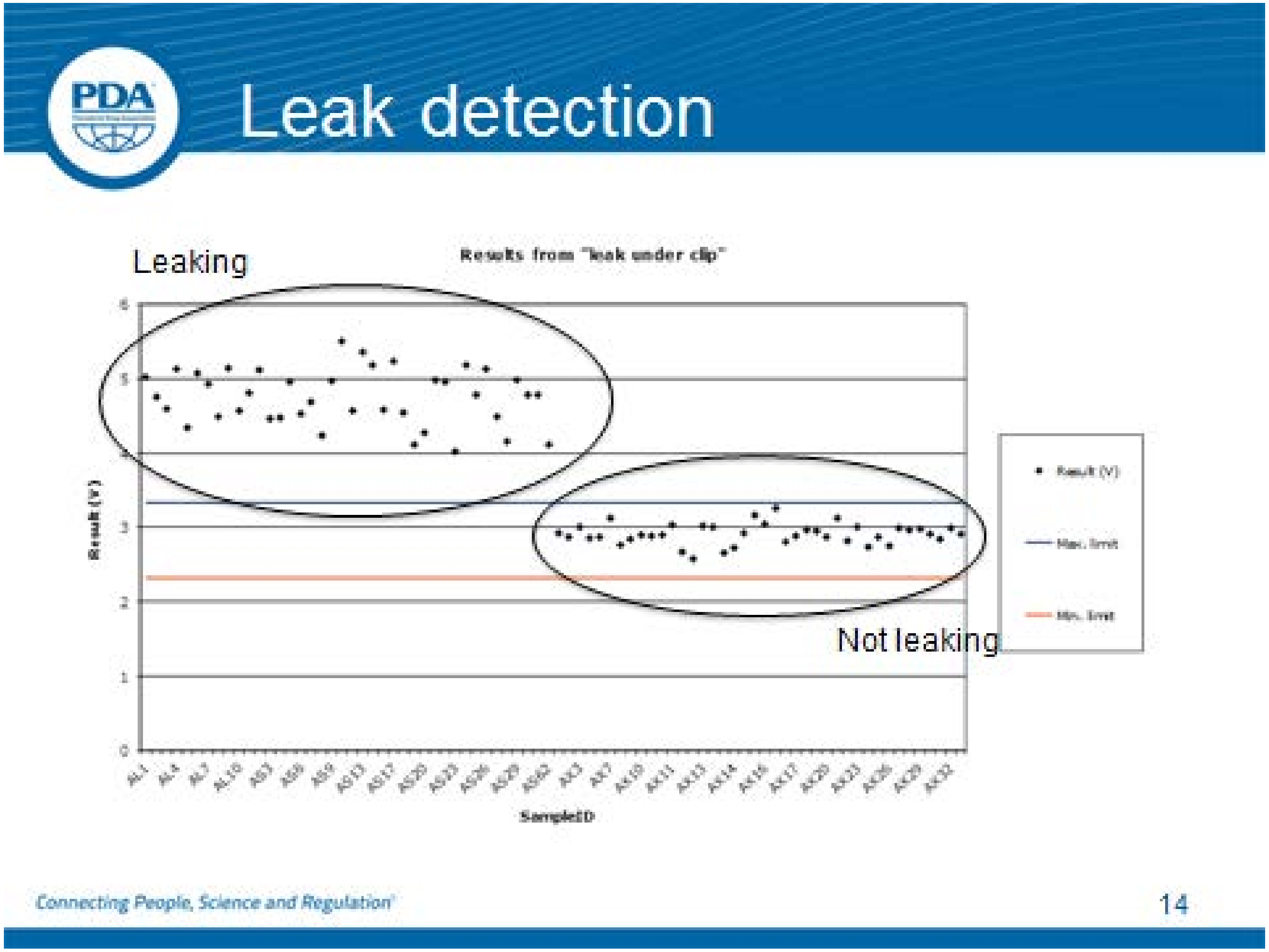
High Voltage Leak Detection (HVLD) method

- The package is "flat" and flexible. A customized set-up is developed, with a carrier and a fiber electrode. The ground electrode is placed in the carrier under the flexible package.



P. Buus, R. Damgaard, High voltage leak detection (HVLD) of flexible container, PDA Europe Parenteral Packaging Conference, Brussels, Belgium, March 12, 2014

Deterministic Leak Test Methods



P. Buus, R. Damgaard, High voltage leak detection (HVLD) of flexible container, PDA Europe Parenteral Packaging Conference, Brussels, Belgium, March 12, 2014

Impact on product stability

- Bags were tested twice to stress the product more than normal
- Results found no statistically significant differences in active, impurities, or degradation products assays.
- No statistically significant differences in all other stability indicating parameter results were reported.
- All data remained within commercial product specification limits.

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Deterministic Leak Test Methods

Summary

- HVLD can find small leaks in the container
- Larger leaks was not detected due to collapsed bags because the brush did touch the bag.
- Some negative controls failed due to narrow limits ($\pm 3\sigma$ from mean)
- The container material has a influence on the results
- HVLD can detect leak even if the protein has clogged the hole.
- Presence of liquid in the leak path increases the likelihood of detection
- Test imply that orientation of bag has an influence of leak detection
- No influnece on product quality by exposing the product twice with High Voltage

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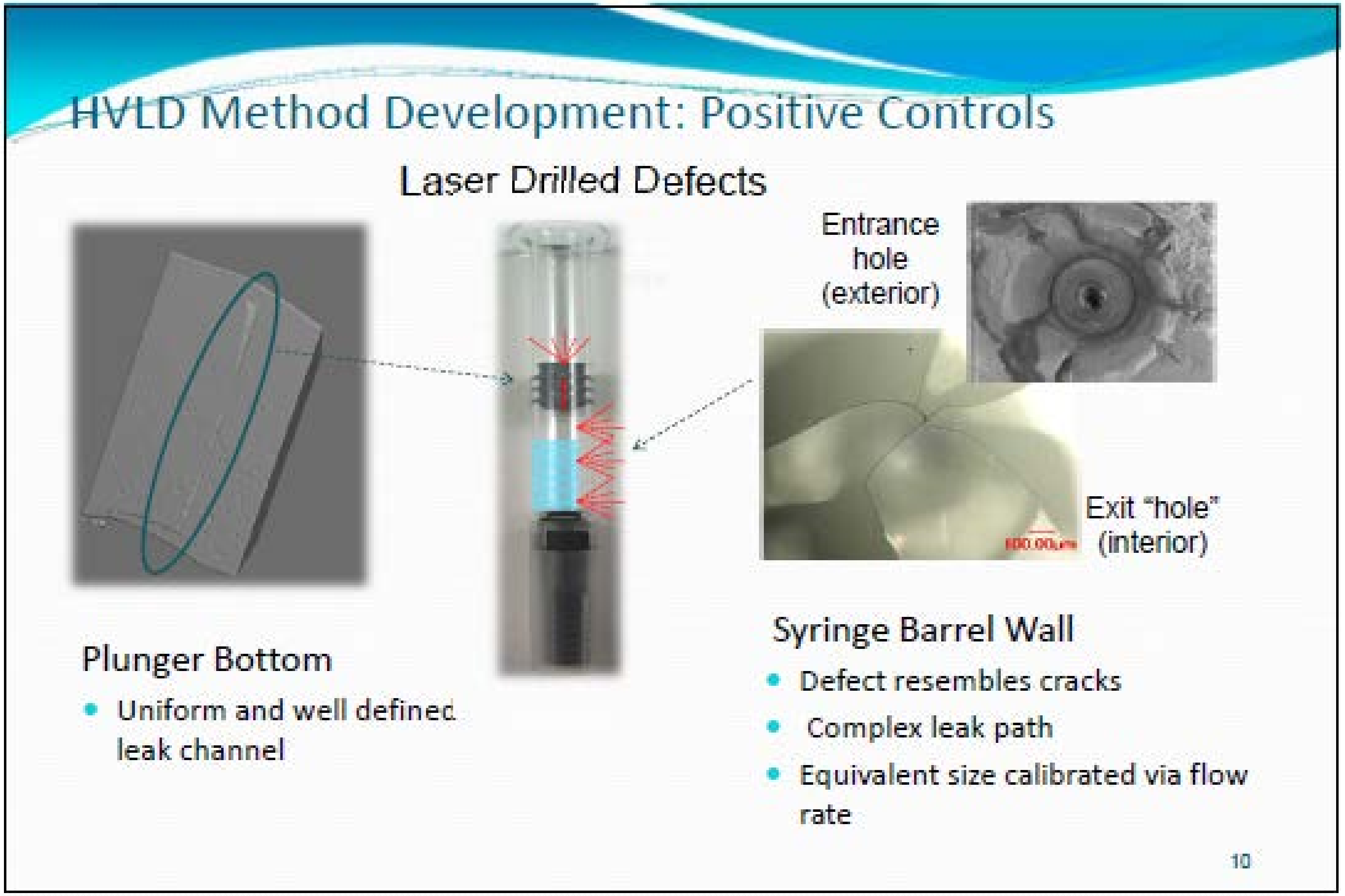
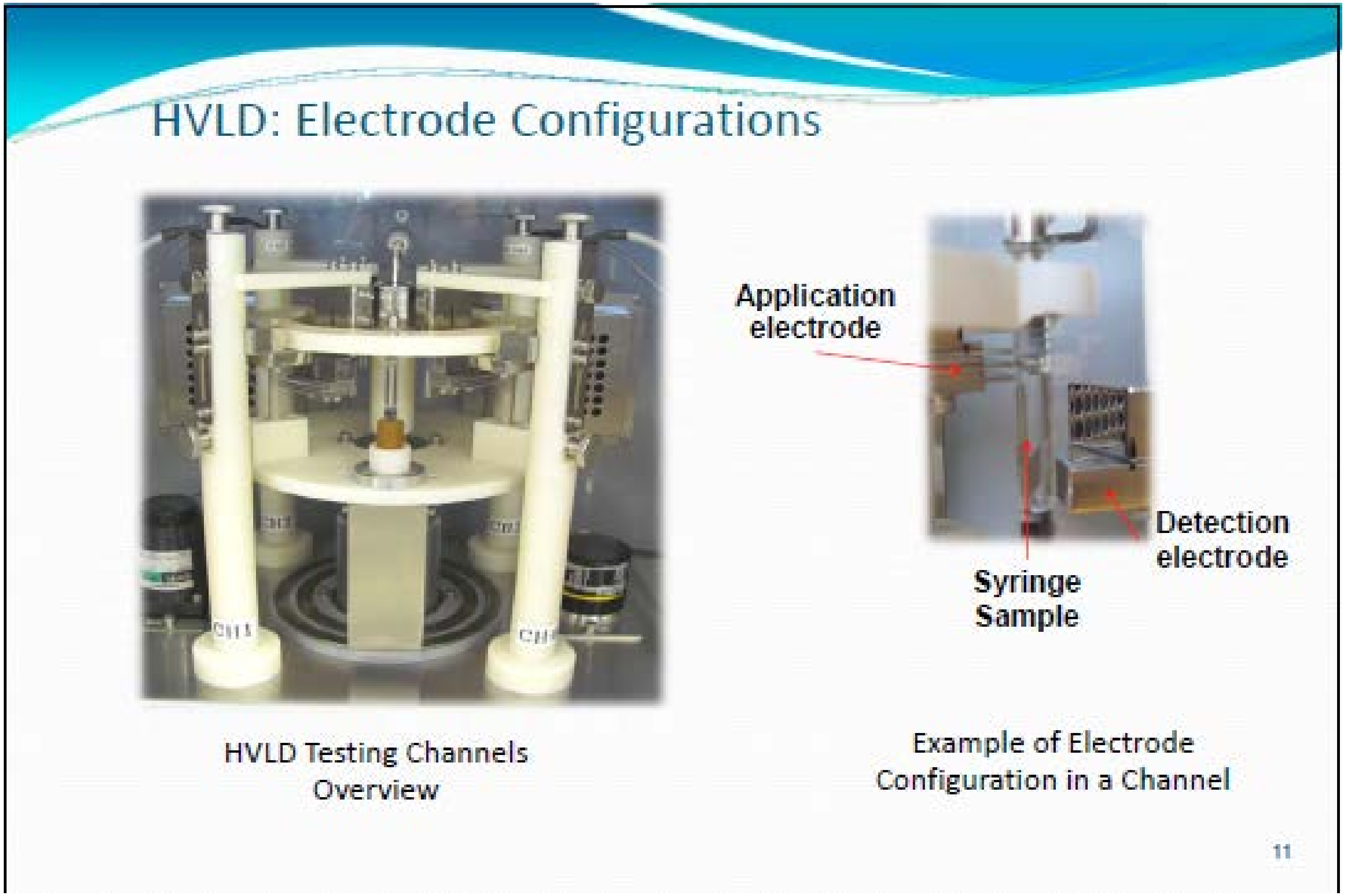
Deterministic Leak Test Methods



L. Li, Container Closure Integrity Testing Method Development and Validation for Pre-filled Syringes, PDA Universe of Pre-filled Syringes and Injection Devices, Las Vegas, NV, Oct 16, 2012

Deterministic Leak Test Methods



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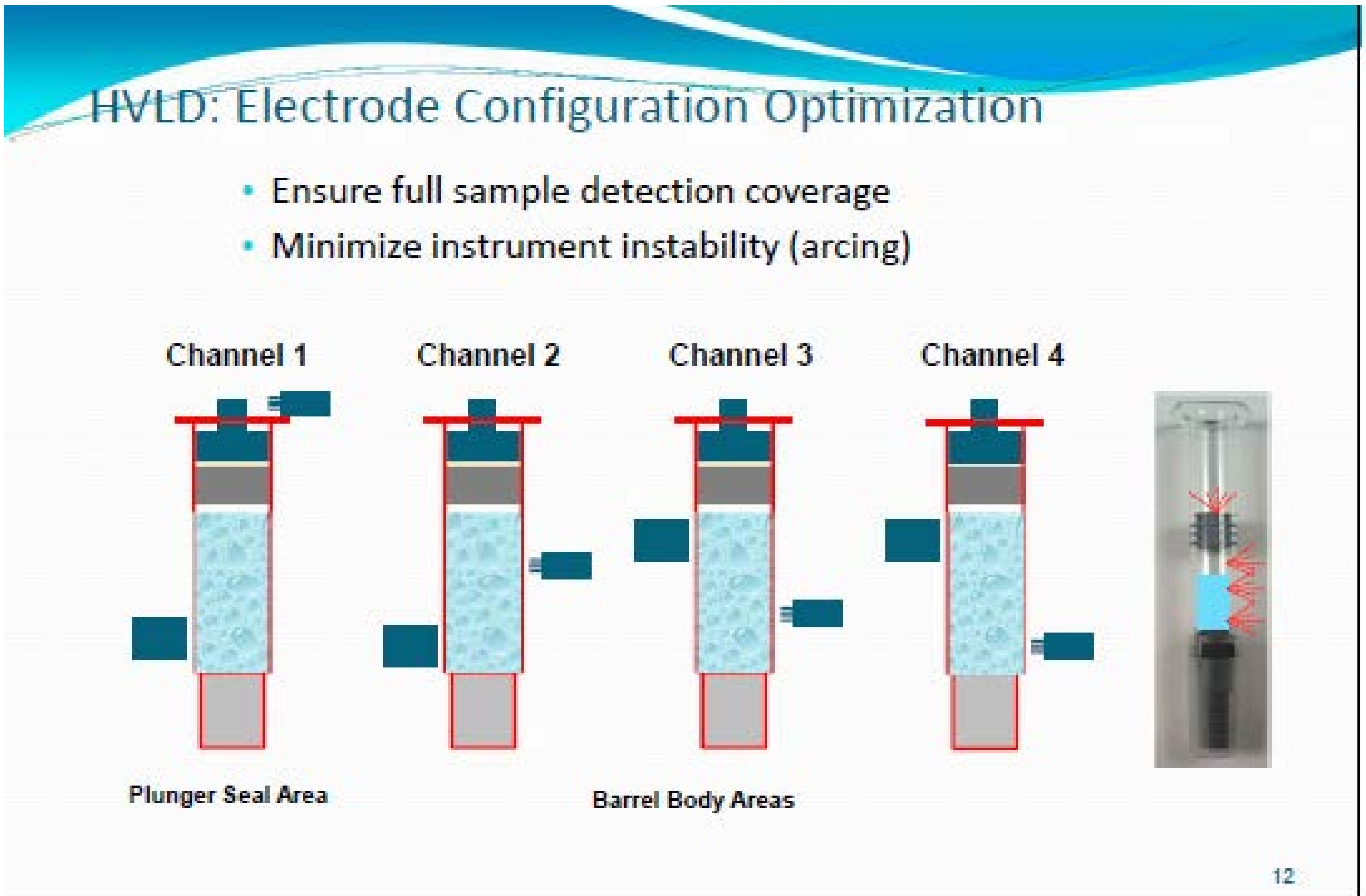

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