PDA Training Course

Container Closure Integrity
Regulations, Theory, Test Methods, Application

Dana M. Guazzo Ph.D., RxPax, LLC
Email: dguazzo@rxpax.com
Web: www.rxpax.com

Outline

Container Closure Integrity
Regulations, Theory, Test Methods, Application

Part 2. Test methods

A. Introduction
B. Deterministic leak test methods
C. Probabilistic leak test methods
D. Seal quality test methods

Probabilistic leak test methods

- **Leakage event: Stochastic in nature**
  - Relies on a series of sequential and/or simultaneous events each associated with uncertainties
  - Results:
    - Associated with random outcomes (probability distributions)
    - Some uncertainty in findings

- **Examples**
  - Microbial challenge tests
  - Bubble emission tests
  - Tracer liquid tests (either qualitative or quantitative measurement)
  - Tacer gas tests by sniffer probe

Probabilistic leak test methods

- **If smaller or rarely occurring leaks to be detected**
  - Large sample sizes required
  - Rigorous test condition controls needed
- **More difficult to design, develop, validate, implement**
- **Test sample preparation required**

Deterministic leak test methods

- **Leakage event : Follows a predictable sequence**
  - Gas movement through an open leak path (at specific delta Pressure or partial pressure)
    - **E.g.,** tracer gas, laser-based gas headspace analysis, pressure decay, vacuum decay, and mass extraction
  - Liquid presence near or in a leak path
    - **E.g.,** electrical conductivity and capacitance test

Introduction

Deterministic leak test methods

- **Leak detection**
  - Based on physicochemical technologies readily controlled and monitored
  - Objective, quantitative data
- **Little or no test sample preparation**
- **Reliable detection of smaller leaks or rarely occurring leaks**
- **Less difficult to design, develop, validate, implement**

Deterministic or Probabilistic?

- **Deterministic**
  - For determining inherent CCI via definitive results
  - When a compatible method exists for a given product-package
- **Probabilistic**
  - When deterministic methods are incompatible with product-package
  - When a specific method outcome is required, e.g.,
    - Leak location detection
    - Microbial grow-through check

Introduction

Leak test methods included

- Described in relevant peer-reviewed publications
- ASTM test with supportive precision and bias data
- Significant variation w/in technologies is seen among vendors
- Other methods not included may be acceptable
- No method is appropriate for all product-packages
- All methods are valuable when used appropriately

Introduction

Seal Quality Tests

- Tests used to characterize and monitor the quality and consistency of a seal parameter providing some assurance of the package's ability to remain integral
- Parameters monitored may include
  - Seal quality or characteristic
  - Package materials
  - Package components
  - Sealing process
- **SQT are not leak tests**

Introduction

Seal Quality Tests

- **Passing SQT ≠ leak-free package**
- Examples
  - Heat seal strength
    - A pouch with a strong heat seal peel force may have a pinhole in the pouch face
  - Closure application force
    - A well-closed capped bottle may leak due to a scratch on the bottle finish

Seal Quality Tests

- **Failing SQT = package integrity risk**
- Examples
  - Heat seal strength
    - A pouch with a weak heat seal peel force is more likely to leak during product life cycle
  - Closure application force
    - A loosely capped bottle may leak during shipping
- **SQT and package leak tests work together to ensure package quality**

Introduction

Seal quality tests included

- Described in relevant peer-reviewed publications
- ASTM test with supportive precision and bias data
- Significant variation w/in technologies may be seen among vendors
- Other methods not included may be acceptable

Deterministic leak test methods

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

Deterministic leak test methods

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 Nonflammable

Deterministic leak test methods

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 sweeps over the test sample
    - Electrical current frequency is a vendor-specific proprietary parameter
    - Electrodes differ in design and material.
    - Most equipment employ electrodes that contact the test sample surface; Nikka Densok/PTI uses electrodes that pass near but do not contact
  - 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

Deterministic leak test methods

Electrical conductivity and capacitance test

aka High voltage leak detection (HVLD)

- **Application**
  - Whole package surfaces or single point inspection possible
  - Electrical probe may operate in direct contact with test sample or not (option for some vendors)
  - 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)

Deterministic leak test methods

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
- **Leak limit of detection**
  - 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
  - ≥ 2-5 µm may be possible

Deterministic leak test methods

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

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

Deterministic leak test methods

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, H_2O, and/or pressure reported.

Deterministic leak test methods

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)

Deterministic leak test methods

Laser-based gas headspace analysis test

- **Nondestructive**
- **Leak limit of detection**
  - 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
  - <0.1µm to largest leaks

Deterministic leak test methods

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

Deterministic leak test methods

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

Deterministic leak test methods

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

Deterministic leak test methods

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

Deterministic leak test methods

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

Deterministic leak test methods

Mass extraction test

(aka mass flow test)

- **Nondestructive**
- **Leak limit of detection**
  - 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
  - ≥ 2-5 µm may be possible

Deterministic leak test methods

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

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

Deterministic leak test methods

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

Deterministic leak test methods

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

Deterministic leak test methods

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

Deterministic leak test methods

Vacuum decay test

- **Nondestructive**
- **Leak limit of detection**
  - 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
  - ≥ 2-5 µm may be possible

Deterministic leak test methods

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

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)

Deterministic leak test methods

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

Deterministic leak test methods

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

Deterministic leak test methods

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

Deterministic leak test methods

Pressure decay test

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

- **Leak limit of detection**
  - 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

  - ≥ 2-5 µm may be possible

Deterministic leak test methods

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

Deterministic leak test methods

Tracer gas detection (vacuum mode)

- **Detection**: Tracer gas leakage rate in mass flow units

- **Technology**
  - Quantitative measure of tracer gas leak rate from a gas-charged test sample into a vacuum chamber
  - Output analyzed by spectroscopic 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

Deterministic leak test methods

Tracer gas detection (vacuum mode)

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

Deterministic leak test methods

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

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

Deterministic leak test methods

Tracer gas detection (vacuum mode)

- **Leak limit of detection**
  - 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
  - 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
  - ≤ 0.01 µm to several µm

Deterministic leak test methods

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)

Probabilistic leak test methods

- Bubble emission
- Microbial challenge by immersion exposure
- Tracer liquid detection
- Tracer gas detection (sniffer mode)

Probabilistic leak test methods

Bubble emission test

- **Detection**: Bubble emission at leak site

- **Technology**
  - Qualitative measure by visual inspection of bubbles escaping test sample while sample is submerged and subject to differential pressure
  - Alternatively, sample surface may be coated with surfactant; leakage evidenced by foaming
  - Outcome judged by operators trained using no-leak and with-leak controls; indicates leak presence, location and relative size

Probabilistic leak test methods

Bubble emission test

- **Requirements**
  - Package
    - Nonporous, rigid
    - Porous material require masking to limit airflow through material
    - Flexible or non-fixed components may employ optional restraint mechanism
    - Must tolerate submersion or surfactant wetting
  - Product: Headspace gas only must be present at leak site

Probabilistic leak test methods

Bubble emission test

- **Test – Internal pressurization (ASTM F2096)**
  - Insert positive pressure source with monitor into test sample
  - Submerge test sample in water; apply air to target pressure; hold for pre-determined time
  - Observe for continuous stream of bubbles
- **Test – External vacuum (ASTM D3078)**
  - Submerge test sample in water or other suitable fluid in vacuum chamber
  - Evacuate chamber to target pressure; hold for pre-determined time
  - Observe for continuous stream of bubbles
- **Test - Alternative to submersion**
  - Apply surfactant to test sample surfaces. Observe for foaming

Probabilistic leak test methods

Bubble emission test

- **Application**
  - Packages must be able to tolerate submersion or wetting
  - Gas must be at leak path; product or debris can block leak path
  - Test fixture or restraint mechanism at test sample site of contact may block leak path
  - Outgassing of sorbed gas on test sample surface or release of entrapped air pockets may falsely simulate leakage
  - Submersion liquid boiling under vacuum may mask leakage
  - Used in all product life-cycle phases, often as a leak forensics test. Not recommended for inherent CCI verification
  - Off-line test; On-line testing used for aerosol products
  - Several minutes per test sample

Probabilistic leak test methods

Bubble emission test

- **Destructive**
  - Internal pressurization results in test sample barrier breach
  - Submersion or surface wetting is destructive to test samples
- **Leak limit of detection**
  - Varies with
    - Leak size, type, length, blockage
    - Package material of construction, flexibility
    - Challenge conditions, including time, pressure, sample positioning, immersion fluid surface tension and gas saturation
    - Inspection conditions and operator technique/skill
  - ≥ 6-10 µm may be possible

Probabilistic leak test methods

Bubble emission test

- **Reported usage**
  - Formulations
    - Gas must be present at leak site
    - Best used for testing empty packages to prevent clogging of leak site
  - Packages
    - All types of vials, bottles, syringes, blisters, pouches, bags, etc.
    - Small volume generally (< few liters)
    - Plastics, glass, metal
    - Rigid to flexible to non-fixed components (restraint mechanism may be desirable)

Probabilistic leak test methods

Microbial challenge by immersion test

- **Detection**: Microbial growth in test sample resulting from passive ingress or active growth

- **Technology**
  - Qualitative measure by visual inspection of microbial growth inside incubated test samples filled with growth-supportive media or product, post immersion in heavily contaminated challenge media over a pre-determined challenge time.
    - Pressure and/or temperature cycling may be used to encourage ingress.
  - Outcome judged by visual inspection by trained operators; verified by other analytic means. Outcome indicates presence of leak path(s) capable of allowing passive or active microbial entry

Probabilistic leak test methods

Microbial challenge by immersion test

- **Requirements**
  - Package
    - Nonporous, rigid
    - Flexible or non-fixed components may employ optional restraint mechanism
    - Must tolerate submersion
  - Product
    - Must be demonstrated to be supportive of microbial growth; otherwise, test samples must contain sterile growth supportive media
    - Test sample headspace must include gas appropriate for microbial growth (e.g., oxygen for aerobic microorganisms)

Probabilistic leak test methods

Microbial challenge by immersion test

- **Test**
  - Fill test samples with sterile media (growth support capability must be verified). Incubate and inspect to confirm test sample content sterility.
  - Immerse test samples in media concentrated with challenge organisms for pre-determined time.
    - **Recommend**: Cycle pressure and/or temperature conditions and extend exposure time to encourage entry.
  - Remove and clean test samples. Incubate under growth-promoting conditions.
  - Examine test sample contents for evidence of growth by visual or other means. Compare to test sample blanks and no-leak/with-leak controls.

Probabilistic leak test methods

Microbial challenge by immersion test

- **Application**
  - Packages must be able to tolerate submersion
  - Liquid must fill leak path to allow microbes to be mechanically swept in (passive entry) or to allow microbial growth into package (active entry)
  - Debris or air-locks in leaks will prevent microbial ingress
  - Test fixture or restraint mechanism at test sample site of contact may block leak path
  - Off-line test, although often used as part of aseptic processing validation runs to verify processing conditions
  - Generally used in R&D to check inherent CCI (only recommended if deterministic methods are not applicable)
  - Weeks per test sample

Probabilistic leak test methods

Microbial challenge by immersion test

- **Destructive**
- **Leak limit of detection**
  - Varies with
    - Leak size, type, length, material of construction, blockage
    - Challenge organism type and concentration, media
    - Challenge conditions, including temperature/pressure cycling, time, sample positioning
  - ≥ 6-10 µm may be possible; actual LOD may be much larger

Probabilistic leak test methods

Microbial challenge by immersion test

- **Reported usage**
  - Formulations
    - Unless the product itself is growth-supportive, test samples are not filled with product
  - Packages
    - All types of vials, bottles, syringes, blisters, pouches, bags, etc.
    - Smaller volume generally (< 1 liter)
    - Plastics, glass, metal
    - Rigid to flexible to non-fixed components (restraint mechanism may be required)

Probabilistic leak test methods

Tracer liquid test

- **Detection**: Tracer liquid migration into (or out of) test sample
- **Technology – Qualitative measurement**
  - Visual inspection of tracer liquid inside test samples post immersion in tracer liquid while exposed to differential pressure conditions over a pre-determined time
    - Alternatively, test samples may be filled with tracer liquid and submerged in tracer-free fluid
  - Outcome judged by trained operators using blank standards and no-leak/with-leak controls
- **Technology – Quantitative measurement**
  - Appropriate analytical means (e.g., UV/Vis spectrophotometry for dye tracer) of test sample contents post immersion, as above
    - Alternatively, tracer-free submersion fluid is analyzed for tracer.
  - Outcome judged by appropriate analytical means, versus blank solution standard and no-leak/with-leak controls
- **Outcome**: Indicates presence of leak path(s) capable of allowing tracer liquid entry

Probabilistic leak test methods

Tracer liquid test

- **Requirements**
  - Package
    - Nonporous, rigid
    - Flexible or non-fixed components may employ optional restraint mechanism
    - Must tolerate submersion
  - Product
    - Liquids: If used, product must be compatible with tracer liquid; otherwise, test samples are to contain placebo solution
    - Powders: Product must be compatible with tracer liquid. For smallest leak detection powders will required constitution with tracer-free liquid for analysis or inspection

Probabilistic leak test methods

Tracer liquid test

- **Test – Tracer ingress**
  - Immerse test samples in tracer liquid for pre-determined time and temperature
  - Remove and clean test samples. Control and limit time to inspection
  - Examine test sample contents for evidence of tracer liquid by visual or analytical means. Compare findings to test sample blanks, no-leak and with-leak controls
- **Test – Tracer egress**
  - Fill test samples with tracer liquid
  - Immerse test samples in tracer-free liquid for pre-determined time and temperature
  - Examine immersion liquid for evidence of tracer liquid by visual or analytical means Compare findings to test sample blanks, no-leak and with-leak controls

- **Recommended for both methods**
  - Minimize volume of tracer-free liquid per test sample. Liquids should be clean and of low surface tension
  - Cycle temperatures and/or pressure conditions and extend exposure time to encourage tracer migration
  - Control/limit time and conditions of sample storage prior to examination

Probabilistic leak test methods

Tracer liquid test

- **Application**
  - Packages must be able to tolerate submersion
  - Liquid must be able to migrate through leak path
  - Debris or air-locks in leaks will block liquid migration
  - Test fixture or restraint mechanism at test sample site of contact may block leak path
  - Off-line test
  - Used in R&D or stability to check CCI (only recommended if deterministic methods are not applicable). May be used in package forensics analysis
  - Minutes to hours per test sample
- **Destructive**

Probabilistic leak test methods

Tracer liquid test

- **Leak limit of detection**
  - Varies with
    - Leak size, type, length, material of construction, blockage
    - Tracer concentration, surface tension, cleanliness
    - Tracer compatibility with product (ingress test) or immersion fluid (egress test)
    - Challenge conditions of time, temperature, pressure, sample positioning
    - Inspection conditions and operator training/skill
    - Analytical detection sensitivity and test sample preparation
  - ≥ 6-10 µm may be possible; actual LOD may be much larger

Probabilistic leak test methods

Tracer liquid test

- **Reported usage**
  - Formulations
    - Ingress test: Test samples are filled with placebo unless the product itself is compatible with tracer liquid
    - Egress test: Test samples are filled with tracer liquid
  - Packages
    - All types of vials, bottles, syringes, blisters, pouches, bags, etc.
    - Smaller volume generally (< 1 liter)
    - Plastics, glass, metal
    - Subject to visual inspection if applicable
    - Rigid to flexible to non-fixed components (restraint mechanism may be required)

Probabilistic leak test methods

Tracer gas detection (sniffer mode)

- **Detection**: Tracer gas leakage rate in mass flow units
- **Technology**
  - Quantitative measure of tracer gas leak rate from a gas-charged test sample into the atmosphere captured using a sniffer probe connected to a spectroscopic analyzer
  - Output analyzed by spectroscopic means
  - Leak rate above a baseline pass/fail limit indicative of leak presence and relative size
  - Calibrated leak standards used to verify method accuracy and reliability

Reference ASTM F2391

Probabilistic leak test methods

Tracer gas detection (sniffer mode)

- **Requirements**
  - Package
    - Nonporous, rigid, limited gas permeability
    - Flexible or non-fixed components may employ tooling to restrain and/or compress package
  - Product: Tracer gas only must be present at leak site

Probabilistic leak test methods

Tracer gas detection (sniffer mode)

- **Test**
  - Flood tracer gas into test sample. Use tooling to restrain and/or compress flexible package or package with non-fixed components as required
  - At test start, scan test sample surfaces with sniffer probe connected to spectroscopic analyzer specific for tracer gas (for helium: mass spec analysis)
  - Gas mass flow rate is continually reported. Reading above a pre-determined baseline is indicative of leak presence (pass/fail test). Reading magnitude may correlate to relative leak size

Probabilistic leak test methods

Tracer gas detection (sniffer mode)

- **Application**
  - Best performed on empty test sample.
    - Product or debris can block leak path
    - Test sample fixture or compression tooling can block leak path
    - Product drawn into analyzer or probe may damage instrument
  - Used in all product life-cycle phases
    - Not recommended for inherent CCI verification
    - Useful for leak forensics analysis
  - Generally performed off-line
  - Requires minutes per test sample

Probabilistic leak test methods

Tracer gas detection (sniffer mode)

- **Nondestructive**
  - If tracer gas introduction into test sample poses no threat to product sterility/quality
- **Leak limit of detection**
  - Tracer gas permeation through package may be mistaken as leakage
  - Tracer gas background in testing environment can influence test results
  - Varies with operator technique and sniffer probe design
  - ≤ 0.01 µm to several µm

Probabilistic leak test methods

Tracer gas detection (sniffer 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 and test probe
  - 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 (tooling for package restraint and/or compression may be required)

Seal Quality Tests

- Tests included
  - Closure application and removal force
  - Package burst
  - Package seal strength
  - Residual seal force
  - Airborne ultrasound
  - Vision inspection (including x-ray)

Seal quality test methods

Closure application and removal force

- **Description**
  - **Application force:** The torque required to apply a screw-cap onto a threaded closure
  - **Removal force:** The torque required to initiate screw-cap removal

- **Correlation to package integrity**
  - Well-closed caps are less likely to back-off during product life-cycle and leak
  - Over-closed caps may distort components causing damage and leakage

Reference : Numerous ASTM methods for various closure types

Seal quality test methods

Closure application and removal force

- **Application**
  - Test results are impacted by
    - Instrument automation (automatic, not manual, recommended)
    - Tooling to lock bottle/cap in position (use recommended)
    - Testing speed (controlled, constant speed recommended)
- **Examples of reported usage**
  - Ophthalmic solution dropper tip bottles with screw-caps

Seal quality test methods

Package burst

- **Description**: The pressure at which a package ruptures during exposure to increasingly greater internal air pressure forces

- **Correlation to package integrity**
  - Low burst strength packages
    - More likely to rupture during product life-cycle
    - Indicative of sealing process failure or material changes
  - The mode of rupture can indicate seal failure risks
    - E.g., seal bond rupture vs. seal edge rupture

Reference : ASTM F2054, F1140

Seal quality test methods

Package burst

- **Application**
  - A restraining plate is used to limit test sample expansion and ensure uniform stress is applied to seal areas
  - No restraining plate is used to understand sample strength if exposed to typical conditions of sterilization, shipping, etc.
  - Test results are impacted by
    - Air pressure rise rate
    - Pressure sensing mechanisms
    - Tooling dimensions (including restraining plate gap height)

- **Examples of reported usage**
  - Flexible pouches or bags

Seal quality test methods

Package seal strength

aka Peel test

- **Description**: The forces required to peel apart two bonded surfaces, including maximum and average force

- **Correlation to package integrity**
  - Low seal strength packages
    - More likely to open during product life-cycle
    - Indicative of sealing process failure or material changes
  - The mode of rupture can indicate seal failure risks
    - E.g., seal bond rupture vs. seal edge rupture

Reference : ASTM F88

Seal quality test methods

Package seal strength

aka Peel test

- **Application**
  - Performed using a universal stress-strain instrument in the extension force mode
  - Special tooling required to position/hold test sample.
  - Test results are impacted by
    - Tooling design
    - Peel angle
    - Pull direction
    - Pull speed
- **Examples of reported usage**
  - Flexible bags or pouches
  - Lidded trays

Seal quality test methods

Residual seal force

- **Description**: An indirect measure of the compressive force (lb-f or newtons) exerted by an elastomeric closure onto a parenteral vial finish post package assembly (capping)

- **Correlation to package integrity**
  - Low RSF
    - Loosely capped vial more likely to leak during product life-cycle
  - High RSF
    - Overly compressed vial more likely to leak due to vial scoring or closure/seal distortion
  - Low or High RSF
    - Indicative of possible sealing process failure
    - Indicative of possible component changes

Seal quality test methods

Residual seal force

- **Application**
  - Performed using a universal stress-strain instrument in the compression force mode. Test sample top is fitted with a cap anvil tool
  - RSF is calculated by the stress-strain response curve 2nd derivative
  - Supplier: Genesis Packaging Technologies
  - Test results are impacted by
    - Test sample flip cap (no cap recommended)
    - Cap anvil tooling design
    - Test speed
    - Mode of calculating RSF
- **Examples of reported usage**
  - Vials, bottles, cartridges with stoppers having a land-seal flange, closed with aluminum caps

Seal quality test methods

Airborne ultrasound

- **Description**: An ultrasound signal is passed through the sealed area of a test sample. The magnitude of the transmitted signal through the seal is compared to that through so-called 'good' seals.

- **Correlation to package integrity**
  - Low signal
    - Loosely bonded seal more likely to leak during product life-cycle
    - May be indicative of product inclusion in seal
  - High signal
    - May be indicative of damage to bonded surfaces, materials
  - Low or High signal
    - Indicative of possible sealing process failure
    - Indicative of possible component changes

Reference : ASTM F88

Seal quality test methods

Airborne ultrasound

- **Application**
  - This non-contact test is performed using an airborne ultrasound instrument equipped with
    - A transducer to provide US signal
    - Fixturing to hold and move the test sample
    - A detection transducer to capture intensity of transmitted US signal
  - Test sample is scanned in either a single x-y linear mode or a full surface x-y-z scanning mode
  - Supplier: Packaging Technologies & Inspection
  - Test results are impacted by
    - Air gap between sample and transducers
    - US signal strength
    - Scanning speed
    - Test sample material of construction and surface topography

- **Examples of reported usage**
  - Pouches, bags
  - Blister packaging

Seal quality test methods

Vision and X-ray inspection

- **Description**:
  - **Vision systems** are used to inspect test samples for visibly evident dimensional nonconformities and defects
  - **X-ray** is used to detect those nonconformities hidden from view
- **Correlation to package integrity**
  - May or may not be indicative of package leakage
    - Depends on the type and extent of nonconformity

Seal quality test methods

Vision and X-ray inspection

- **Application**
  - A wide variety of inspection systems are available
  - Test results are impacted by
    - Instrumentation capabilities
    - Test sample inspection angle, design, size, material of construction, contents
    - Inspection speed

- **Examples of reported usage**
  - Vision: All product-package types
  - X-ray: vials, syringes

Summary

Leak test methods

- **Deterministic and Probabilistic methods**
  - Significant variation w/in technologies is seen among instrument vendors
  - Outcome varies based on test variables chosen
  - Other methods not included may be acceptable
  - **No method is appropriate for all product-packages**
  - **All methods are valuable when used appropriately**

Summary

Seal quality test methods

- Significant variation w/in technologies may be seen among vendors
- Outcome varies based on test variables chosen
- Other methods not included may be acceptable
- **SQT ≠ leak tests**
  - Passing SQT ≠ leak-free package
  - Failing SQT = package integrity risk
- **SQT and package leak tests work together** to ensure package quality

End of Part 2