Container Closure Integrity: Regulations, Test Methods, Application - Test Method Development and Validation

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Outline

Test Method Development and Validation

A. Positive and negative controls, masters, blanks

B. Instrument/equipment qualification

C. Method development

D. Method validation

Introduction

WHY DEVELOP & VALIDATE?

- No CCIT method is appliable to all product-package systems.
- Same Package, Different Products → Separate Methods
- Different Packages, Same Product → Separate Methods
- Same Package, Same Product, Numerous Study Goals → Separate Methods
- Leak detection is an **Analytical Procedure**, not a **Standard Method**.

J. Young, B. Zurawlow. Optimized CCI Test Method Dev. and Val. Approaches, PDA Europe Parenteral Packaging Conference, Frankfurt, Germany, 4 March 2015.

Introduction

- Method development should commence according to:
- Defined method requirements
  - Leak location vs leak severity
  - Sensitivity level (MALL vs other study goals)
- According to a specific product-package system
  - With considerations for limitations imposed by product and package

Introduction to USP <1207>: Package Integrity Evaluation – Sterile Products

Leak tests, even many commonly recognized industry standard testing approaches, require optimization and validation for each product–package application. A science- and risk-based approach may allow some tests to be leveraged for broader application under certain circumstances. For example, small differences in product formulation or package design and materials may permit the use of one test for multiple product–packages. Package integrity verification plays an important role throughout the product life cycle, starting with product development and continuing through marketed product stability studies.

Controls, Masters, Blanks

CCIT development and validation requires appropriately designed and assembled product-package units

Negative controls – Product-packages **with no known leak**

- Used to demonstrate method performance with good packages
- Used in method development and validation studies

Positive controls – Product-packages **with intentional leak**

- Used to demonstrate method's ability to detect leaks
- Used in method development, validation studies
- Used in system suitability checks for some methods

Controls, Masters, Blanks

Master – **No-leak CC model**, OR a designated set of CC units

Used as a routine test system performance check

E.g., Such a model may be a replica of the CC in plastic or metal

Blanks are also included in some test methods

Used to establish method baseline performance

E.g., Liquid tracer leak detection by UV/Vis spec analysis employs a blank solution without tracer element as a standard

Blanks are <u>not</u> negative controls

Negative Controls

Population set should consider variations in:

- Component lot material
- Dimensions
- Component or finished product-package processing
- Assembly

Positive Controls

Small Defects

Sizes:

- Range from ≤ to ≥ the estimated detection limit for test method development.
- Range from detection limit to larger sizes for test method validation and routine test verification, as needed.

Creation Considerations:

- Package/seal type, dimensions, materials of construction.
- Defect creation technology limitations and challenges.

Positive Controls

Small Defects

Micro-tubes:

- Beware of using long wide-bore tubes to simulate smaller hole defects. Greatest application: gas mass flow behavior.
- Leaks around tube perimeter may influence results.
- Material may not be the same as the package.
- May be used to simulate channels through wide package seal.

Micro-pipettes:

- Most simulates “holes”
- Tips prone to damage
- Leaks around tube perimeter may influence results
- Long pipette air locks may block liquid leak detection
- Material may not be the same as the package

Positive Controls

Small Defects

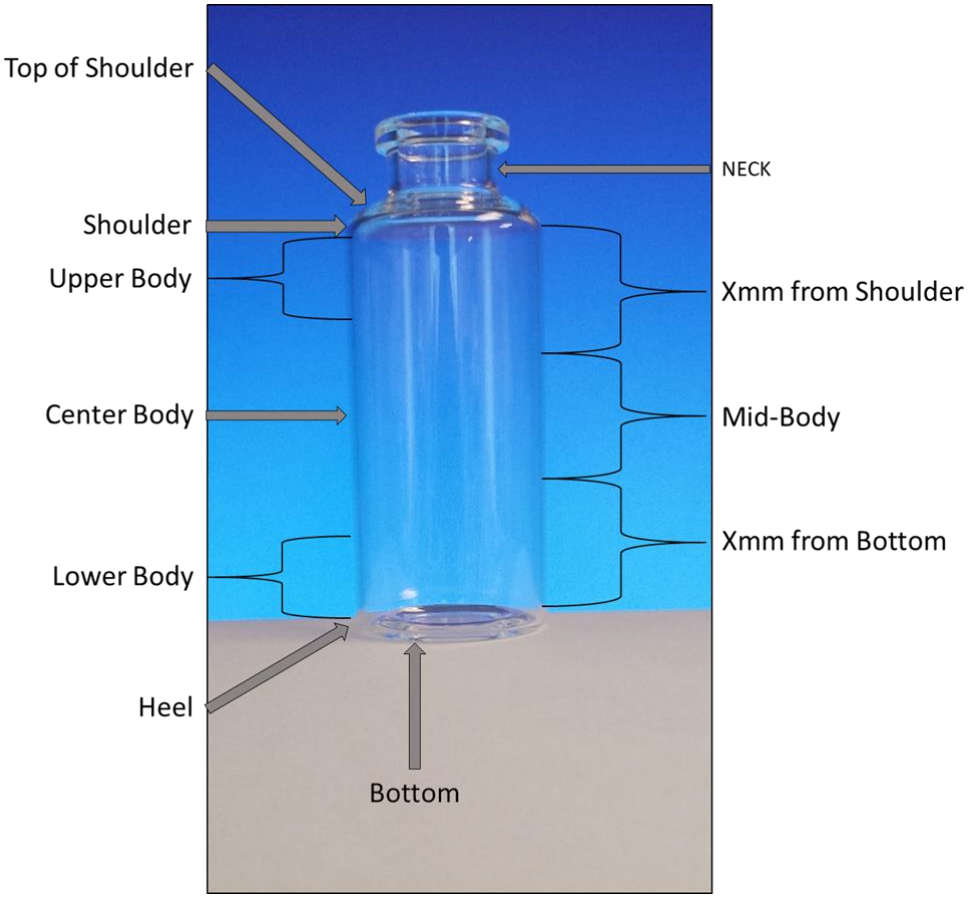
Laser-drilled Defects:

- Certified for nominal ‘hole’ size, although defect is not a hole.
- Morphology differs with vendor.
- Same material as package.

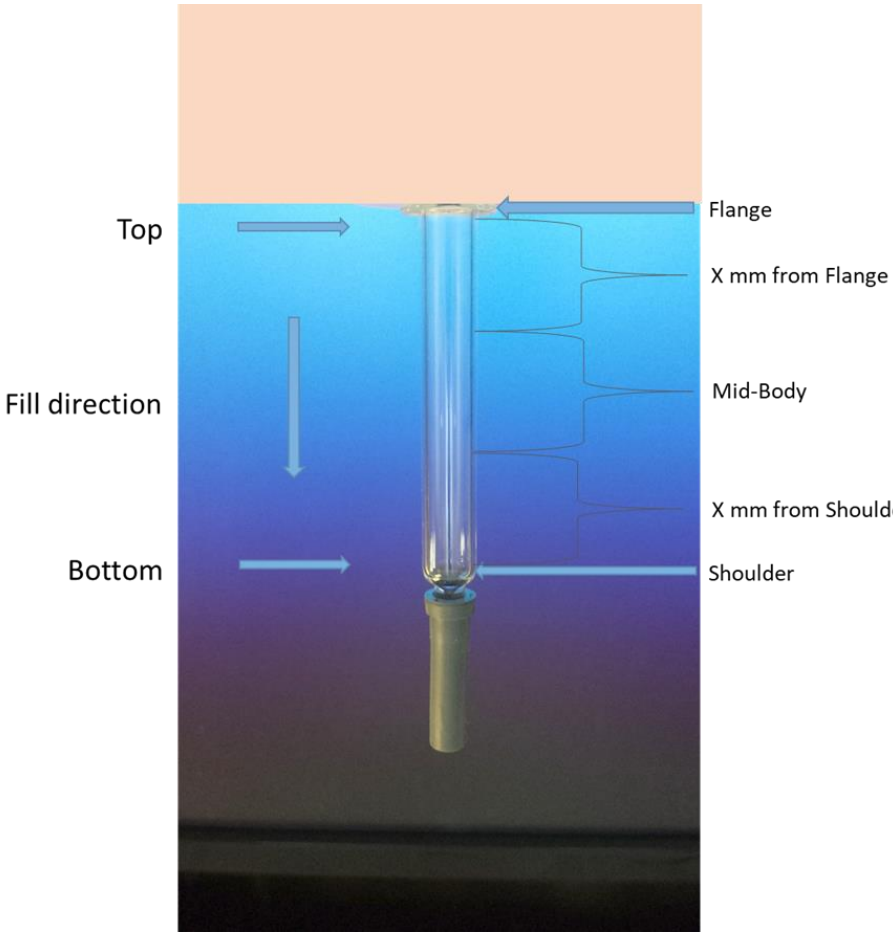
Wire or Other Material at Seal Interface:

- Leak path size unknown
- Appropriate if ‘other material’ represent a potential routine manufacturing defect

Common Hole Locations in Glass Vials



Common Hole Locations in Syringes



Positive Controls

Largest Size or 'Type' Defects

Should simulate various types of defects that could occur

- For TYPE defects, leak path **size is not determined**
- Defect is **described qualitatively**

For example

- Missing stopper in vial/stopper package
- Gap in pouch heat seal
- Product inclusion at seal interface (*E.g.*, lyophilized-powder on vial seal surface)
- Needle tip through syringe needle shield

Typically included in test method development only

Positive Controls

Largest Size or 'Type' Defects

- **Reasons** for investigating Type defect detection
- **Methods may miss larger leaks**
- **Product recalls** are often the result of larger leaks
- **Greater patient safety risk** possible from largely leaking packages
- **Instruments/equipment damage or contamination risk**
- Impact should be considered prior to test implementation
- Large defects may need to be culled out by other means, or prevented altogether

Instrument/ Equipment Qualification

Operational qualification - Functionality

- Performed using the instrument/equipment alone
- Calibration tools employed
  - Pressure or vacuum gauges/transducers
  - Temperature controllers
  - Timers
- Supported by instrument calibration certifications
- Plan for potential for instrument/equipment exposure to leaking product
  - Damage
  - Downtime for clean-up

Performance qualification – Detection limit & reliability

- Test sample 'master' plus test fixture(s) employed **Master:** A no-leak model of the container-closure

  E.g.,
  - A metal or plastic model of the container-closure
  - A small set of actual container-closures

- Leakage reference standards employed

  E.g.,
  - NIST certified helium gas leak standards
  - Calibrated micro-calibrator volumetric flow meter
  - Size-calibrated micro-orifice

Method Attributes

Test Method Development and Validation

Goal: Establish an optimal CCIT for a specific product-package that is

- **Accurate**
- **Specific**
- **Sensitive**
- **Precise**
- **Robust**
- **Quantitation limit***
- **Linear***

*method specific

Method Attributes

Accurate

Accuracy. The method's ability to differentiate:

- Packages that leak above the claimed detection limit
- Package that leak below this limit (i.e., do not leak)

Defined according to method outcome

- Leak presence
- Leak rate
- Leak location

When employing a highly quantitative method (e.g., helium mass spec or laser-based gas headspace analysis).

Accuracy is the closeness of the outcome to a **standard** (e.g., a NIST traceable leak rate standard).

Method Attributes

Specific

Specificity. The ability of the method to accurately differentiate between leaking and non-leaking packages, **despite interfering factors that may cause false detection.**

Examples

- **Helium mass spectrometry (vacuum mode).** Helium permeation through the package wall may mask small package leaks, or may be falsely interpreted as leakage
- **Bubble tests.** Trapped gas pockets or package surface gases may outgas and be falsely interpreted as leakage

Method Attributes

Sensitivity
(Detection Limit)

The smallest leak size (or rate) that is ***reliably*** **detected**. Specific for

- The product-package
- The leak test technology

Verified by testing positive/negative controls over multiple days by multiple operators (test application may also require multiple labs/instruments).

When expressing a test method's detection limit, include a full disclosure of:

- Test methodology
- Negative and positive control subsets used
- Test precision level
- Test results

Method Attributes

Sensitivity (Detection Limit) - Example

"The detection limit for method X was determined to be 7 ± 2 µm.

Validation studies found defects of this nominal size were detected 95% of the time; all larger defects were detected 100% of the time.

Studies included three replicate test series performed on multiple days by multiple operators in a single laboratory using one instrument.

Detection limit was determined using product-filled packages. Test units in each series included a negative control subset of 300 units (each without defect) and a positive control subset of 90 units (each having a laser-drilled defect ranging in nominal size from 7 ± 2 µm to 15 ± 3 µm).

Each defect was independently size-certified by comparing the dry air leakage rate at 1 atm differential pressure (leak inlet pressure of 1 atm versus outlet pressure of approximately 1 Torr) at 25°C to that of standard orifice leaks."

Method Attributes

Leak Detection Range

That interval between the smallest to largest leak size (or leak rate) that can be detected by a given leak test method with a suitable level of accuracy and precision.

Just because a leak test is sensitive (low detection limit) doesn't mean it will also detect larger leaks.

Method Attributes

Precise

Precision. The method's ability to yield reliable, repeatable data.

Repeatability

- Within the same lab within a short time period
- Same analyst, Same equipment

Ruggedness (aka intermediate precision)

- Within the same lab , Different days
- Within the same lab , Different analysts or equipment

Reproducibility

- Different labs, as in a collaborative study

NOTE: Degree of precision to which a leak test method is validated is often a function of resource availability (e.g., one instrument versus multiple instruments) and intended test method application (use of the method at one test site only versus across multiple test sites).

Method Attributes

Robust

Robustness. The method's ability to accurately identify leaking versus non-leaking packages **despite small but deliberate variations** in procedural parameters, providing an indication of the method's suitability during normal usage

Example:

Vacuum decay

- NORMAL test time: 30sec
- ROBUSTNESS verification test times: 28sec and 32sec

Method Attributes

Linear

Linearity. The method's ability to elicit test results mathematically proportional to leak path size or leakage rate.

Examples

- Laser-based gas headspace analysis
- Tracer gas analysis (vacuum mode)
- Vacuum / pressure decay, mass extraction also produce results that correlate to leak size/rate; however, outcome seeks to ID leak presence and perhaps relative leak size.

Method Attributes

Quantitation Limit

Quantitation limit is that lowest leakage rate or leak size that can be determined with **accuracy and precision.**

Example: Laser-based gas headspace analysis

For most methods, **detection limit** is more meaningful

Test Method Validation

Protocol

- Use random population mix of negative and positive controls.
- Test multiple days by multiple operators, and when possible, using multiple test instruments.

Acceptance criteria

- All* negative controls pass (no leaks are identified)
- All* positive controls fail with leaks at or above the designated detection limit (leaks are detected)

or **essentially all,** e.g., ≥ 95%.

Test Method Validation

CONTROL UNIT QUANTITIES

Destructive Methods – New set of units required per each test

Non- Destructive Methods – Consider repeated test impact

- **Effects on Positive Control Defects**
  - HVLD exposure may enlarge glass wall laser-drilled defect
  - HVLD exposure may close plastic wall laser-drilled defect
  - Vacuum or pressure exposure may clog leaks with product, debris

- **Effects on Control and Test Packages**
  - Repeated HVLD exposures may weaken plastic pouch heat seals
  - Vacuum exposure may cause outgassing of polymeric or elastomeric materials, impacting vacuum decay or mass extraction results

Test Method Validation

CONTROL UNIT QUANTITIES

DETERMINISTIC methods

- More clearly defined, reliable detection limit
  - **Fewer controls** are typically required in **development/validation**
  - **Positive controls** may not be needed for **routine testing**

PROBABILISTIC methods

- Less reliable, especially when testing smaller leaks near LOD
  - **More controls** typically required in **development/validation**
  - **Positive controls** may be needed to verify LOD in **routine testing**
  - As more data are generated, a more confident detection limit may be established

Positive Control Utilization

- Gas based methods where measurement is direct indicator of leakage (He leak, Laser based headspace as function of time)
  - Positive controls used to prove leaks at specific package locations can be detected and to determine the impact of product presence and other factors on leak detection

- OTHER CCI methods in which the measurement signal is a direct indicator of leakage (Liquid tracer leak tests, Microbial challenge leak tests)
  - Positive controls are used to prove leaks at specific package locations can be detected, to determine the impact of product presence and other factors on leak detection and to confirm limit of detection

- For physicochemical CCI methods in which the measurement signal is an indirect indicator of leakage (Vacuum decay/pressure decay/mass extraction, Electrical conductivity/capacitance test (HVLD))
  - Positive controls are used to verify that the measurement signal is a function of leak presence/size/rate vs. other interfering factors and to confirm limit of detection

Microbial Ingress Comparison

Comparison to Microbial Ingress

ORIGINAL USP <1207> states that use of methods other than microbial challenge tests require a comparison to a microbial challenge test

- Direct side-by-side study

OR

- Indirect by referring to relevant published study data

Some FDA reviewers still request a comparison study

Summary

Positive and Negative Controls, Masters, Blanks
Population set of product-packages controls needed

- **Negative controls**: no known leak
- **Positive controls**: with intentional leak
  - **Small leaks** used for LOD, method development, validation
  - **Larger type leaks** used to understand upper performance limits during method development
- **Master** is used to simulate a no-leak standard for checking system performance
- **Blanks** are not negative controls or masters, but are needed for some test analytical test methods

Instrument/Equipment Qualification

- **Operational qualification** – instrument/equipment functionality
- **Performance qualification** – test system verification using master and leak standard

Method Development and Validation

- Final method to be **accurate, specific, sensitive, precise, robust**, and in some cases, **linear, quantitative**
- **Positive controls** of small and larger 'type' leaks employed

Leak detection is an analytical procedure, NOT a standard method