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 and Validate

- No CCIT method is applicable 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

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

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

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 control units

Population set should consider variations in

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

Positive control units

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

Laser-drilled defects

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

Positive control units

Small defects

Microtubes

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

Positive control units

Small defects

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

Wire or other material at seal interface

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

Positive control units

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.,* lyo-powder on vial seal surface
- Needle tip through syringe needle shield

Typically included in test method development only

Positive control units

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**
  - For example,
  - 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

Instrument/equipment qualification

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 microcalibrator 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

Group Exercise: Method Development and Validation

Method Development Group Exercise

Objective:

Design a validation study

Instructions:

Each team will be assigned one method attribute

Team will work as a group to design an approach to confirming the given method attribute

- Define method attribute
- Experimental Design
- Sample population
- Acceptance criteria

Each team will present findings at the conclusion of Day 2

Attribute	Attribute Definition	Experimental Design	Acceptance Criteria
Accuracy			
Range			
Robustness		<table><tr><th>Parameter</th><th>Target</th><th>Low</th><th>High</th></tr><tr><td>Evacuation (s)</td><td></td><td></td><td></td></tr><tr><td>Equalization (s)</td><td></td><td></td><td></td></tr><tr><td>Test (s)</td><td></td><td></td><td></td></tr></table>	
Precision			
Detection Limit			

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)

Specific

Specificity. The ability of the method to accurately differentiate between leaking and nonleaking 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

Sensitive
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)

Sensitive
Detection Limit

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

For example….

Method Attributes

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."

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

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).

Robust

Robustness. The method's ability to accurately identify leaking versus nonleaking 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 : 30s

ROBUSTNESS verification test times: 28s and 32s

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

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%

Control unit quantities

DESTRUCTIVE methods – **New set of units required per each test**

NONDESTRUCTIVE 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

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

For gas-based CCI methods in which the measurement signal is a direct indicator of leakage

Tracer gas leak detection (e.g., He mass spec – vac mode)
Laser-based headspace analysis as a function of time

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

Positive controls are NOT used

To confirm **limit of detection**
Positive control defect sizes are much larger than these methods' LOD
LOD is a function of instrument capability and can be determined with gas standards

Positive control utilization

For OTHER CCI methods in which the measurement signal is a direct indicator of leakage

Liquid tracer leak tests (e.g., dye ingress)

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
- To confirm **limit of detection**

Positive control utilization

For physico-chemical 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**

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

Summary

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