PDA Training Course

Container Closure Integrity
Regulations, Theory, Test Methods, Application

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Outline

Container Closure Integrity
Regulations, Theory, Test Methods, Application

Part 4. Test method development and validation

A. Positive and negative controls, masters, blanks
B. Instrument/equipment qualification
C. Method development
D. Method validation

Positive and negative controls, masters, blanks

Controls, masters, blanks

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

- **Negative controls** – product-packages **with no known leak**
- **Positive controls** – product-packages **with intentional leak**
- **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
  - 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 and negative controls, masters, blanks

Negative control units

- **Quantities** chosen for testing should consider
  - **Extremes** anticipated in routine manufacturing
  - **Probabilistic vs. deterministic** methodology
    - Probabilistic methods require considerably more units
  - **Destructive methods**
    - New set of units required per each test
  - **Nondestructive methods**
    - **Impact of repeated test exposure**

      E.g.,
      - Many 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
    - **Recommend**
      - ≥ 300 units for deterministic test method development
      - ≥ 30 units for deterministic test method validation

Positive and negative controls, masters, blanks

Positive control units

Small defect sizes

- **Sizes**: Include sizes that bracket intended LOD
- **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

Continued…

Positive and negative controls, masters, blanks

Positive control units

Small defect sizes

- **Microtubes**
  - Beware of using long wide-bore tubes to simulate smaller hole defects. Only relevant to 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**
  - Tips prone to damage
  - Leaks around tube perimeter may influence results
  - 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 and negative controls, masters, blanks

Positive control units

Large size or 'Type' defects

- **Simulate various types of defects** that could occur
  - 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

- **Included in test method development only**

Positive and negative controls, masters, blanks

Positive control units

Large size or 'Type' defects

- **Reasons** for investigating Type defect detection
  - **Methods may miss larger leaks**
    - All methods have both an upper and lower LOD
  - **Product recalls** are often the result of larger leaks
  - **Greater patient safety risk** possible from largely leaking packages that enter commercial or clinical distribution
  - **Instruments/equipment damage or contamination** possible from larger leaks
    - Impact should be considered prior to test implementation
    - Large defects may need to be culled out by other means, or prevented altogether

Positive and negative controls, masters, blanks

Positive control units

Small and Type defects

- **Quantities** chosen for testing should consider
  - **Probabilistic versus deterministic method**
    - Probabilistic tests require more units
  - **Nondestructive methods** – Impact of test exposure on defect

    E.g.,
    - 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
  - **Destructive methods** – Units must be replaced per each test
  - **Risk to instrument/equipment**
    - Damage
    - Downtime for clean-up

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**

Instrument/equipment qualification

- **Performance qualification - Limit of detection & 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

Test method development

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

- **Sensitive**
- **Accurate**
- **Reproducible** - A measure of precision
  - **Repeatability**
  - **Ruggedness** (aka intermediate precision)
  - **Reproducibility**
- **Robust**

Test method development

- **Sensitive** – Able to detect smallest to largest leaks of concern, given the method's reported detection capabilities and intended outcome
- **Accurate** – Able to correctly identify leaking packages ; size or locate leaks (depending on intended method outcome)
- **Reproducible** - A measure of precision
  - **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
- **Robust** – Method accuracy is demonstrated at test conditions bracketing optimal
  - E.g., The robustness of a vacuum decay leak test with cycle time of 30s might by verifying by performing tests at 28s and 32s

Test method validation

Goal: Verify final method accuracy, limit of detection and reproducibility

- **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 limit of detection (leaks are detected)

Test method validation

Deterministic vs. probabilistic methods

- **Probabilistic methods**
  - **Require greater quantities of controls**
  - **Demonstrate variability in smaller leaks detection (LOD)**
    - Acceptance criterion proposed states LOD is based on the smallest leak that is ALWAYS detected
    - Routine testing may require the incorporation positive controls to demonstrate day-of-test LOD
    - As more data are generated, a LOD may be established, eliminating need for positive control incorporation

Test method validation

Comparison to microbial ingress

- **Current USP <1207> and the PDA Technical Report 27**
  - **State that use of methods other than microbial challenge tests require a comparison to a microbial challenge test be performed**
    - Comparison can be direct side-by-side study
    - Comparison can be indirect using published study data
  - **Experience shows such a comparison is no longer required by the FDA although still some regulatory reviewers still ask**
    - A well developed and validated method using positive controls having leak sizes that approach smallest sizes of concern is sufficient to support CCIT use

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**
  - Final method to be sensitive, accurate, reproducible, robust
  - Positive controls of small leaks and larger 'type' leaks employed
- **Method validation**
  - Final method to be accurate, reproducible, meet defined LOD
  - Positive controls of small leaks employed
  - Comparison to microbial ingress not required

End of Part 4