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 3. Test method selection and application

A. Product life cycle and CCI testing
B. Test method selection criteria
C. Test application examples

Product life cycle and CCI testing

Package integrity

- **IS NOT** the absence of ingress or product sterility
- **IS** the **absence of a gap/defect that risks product quality**
- **IS** the conformance of the package to the **maximum allowable leakage limit** (i.e., critical leak)
  - **Product quality requirements** define MALL
  - **May vary** during the **product life cycle**

Product life cycle and CCI testing

Product life cycle phases

1. **Package development and validation**
   a. Package development
   b. Package processing and assembly validation
2. **Product manufacturing**
3. **Commercial product stability**

Product life cycle and CCI testing

1a. Package development

- **Product-package profile is prepared (user-spec)**
  - Product end use
  - Stability requirements
  - Method of manufacture
  - Anticipated storage, distribution environments
- **Package is identified, CCI is assessed**
  - Design and critical dimensions
  - Materials of construction
  - Suppliers

Product life cycle and CCI testing

1a. Package development

- **Package processes ID'd, CCI is assessed**
  - Component cleaning, sterilization, other
  - Formation/assembly
- **Assess CCI considering extremes of process parameters and package dimensions**

Product life cycle and CCI testing

1a. Package development

Outputs: Final user requirement specs

- **Package component purchasing specs**
- **Equipment user requirement specs**
  - Component processing equipment
  - Package formation/assembly equipment
  - Allied materials supply and component feed systems
- **Equipment purchase and/or contract manufacturing direction**

Product life cycle and CCI testing

1b. Package processing & assembly validation

- **CCI to be part of larger process validation activity**
- **CCI testing scope and quantities of samples tested may vary** with experience, package complexity, and risk assessments
- **Consideration given to user requirement specs**
  - Sterilization; package formation, assembly processes
    - Extreme condition impact on CCI
      - E.g., resterilization, line speed max/min, assembly procedures
    - 2ndary, tertiary packaging impact on CCI
  - Technical transfer to final manufacturing site assessment

Product life cycle and CCI testing

1. Package development and validation

FINAL OBJECTIVE

- Package meets user requirement specs
- Quality product-package prepared by packaging processes that reliably and consistently run within specified operating parameters
- Critical package defects occur at satisfactorily low rate
- CCI in-process and end-product testing should complement, not replace package development and validation efforts

Product life cycle and CCI testing

2. Product manufacturing

- **CCI assurance starts with component quality specifications**
  - Component vendor evaluation
  - Incoming component AQL conformance
  - Vendor certification and corrective action
  - Change control

Product life cycle and CCI testing

2. Product manufacturing

- **Manufactured product CCI and SQ tests**
  - **Selection:** Based on earlier R&D and validation
  - **Goal:** Prevent or ID/remove defects of greatest concern
  - **100% nondestructive CCI tests**
    - Provides greatest quality assurance, but may not be appropriate or necessary
    - Increasingly considered as technologies become available
    - Recommended or required
      - Glass/plastic ampoules
      - Product with critical headspace (vacuum, inert gas)

Product life cycle and CCI testing

3. Commercial product stability

- **FDA 2008 recommended CCI tests replace sterility test** in stability studies to assure package integrity (initial sterility test still required)
  - Sterility test is a poor measure of integrity
  - CCIT more sensitive, reliable
  - Only CCIT able to confirm headspace gas maintenance requirements

3. Commercial product stability

- **CCI test method selection**
  - **CCIT should verify absence of leaks risking**
    - Product loss
    - Sterility loss
    - Gas exchange (if applicable)
  - **Product should not interfere with CCIT**
    - Proteinaceous ingredients or salts can block gas/liquid flow through leak paths
      - Impacting vacuum decay, mass extraction, tracer gas, tracer liquid

3. Commercial product stability

- **CCI testing considerations**
  - **Storage:** Marketed product labelled storage conditions
  - **Test quantities per time point:** Undefined
    - Consider prior R&D and validation data
    - If nondestructive tests used
      - All samples may be tested prior to stability storage
      - Samples tested by CCIT may be used for other tests at same stability time point

Part 3. Test method selection and application

Test method selection criteria

Leak test selection factors	Options
1. Package contents	Liquid, solid, gas, vacuum
2. Package materials of construction	Metal, glass, plastic, composite
3. Package design	Flexible/rigid Closure mechanism
4. How much leakage can the product tolerate, and still meet specs?	Gas headspace preservation Liquid content preservation Microbial ingress prevention
5. What does the leak test measure?	Gas leak rate Liquid migration/presence Microbial growth
6. Sensitivity (leak size detection range)	<<0.01 microns to several mm
7. Test sample preservation	Destructive vs. nondestructive
8. Test method application	High speed vs. Slower speed Product life cycle phase

Test method options

Deterministic methods	Probabilistic methods
Electrical conductivity and capacitance test (HVLD)	Microbial challenge
Laser-based headspace analysis	Liquid tracer tests (e.g., dye)
Pressure decay	Bubble tests
Tracer gas (vacuum mode)	Tracer gas (sniffer mode)
Vacuum decay	---
Mass extraction	---

Part 3. Test method selection and application

Example – Product 1

Single-dose liquid packaged in a stoppered vial. Low O_2 headspace

Stage	Closure system	Critical leakage	Leak tests, Other
Pre-capping	• Closure inserted, not capped • Seal at **plug/neck**	**Nitrogen content** loss	• **R&D/stability/manufacturing** • **Laser-based H.A.,** vision system

Post capping	• Closure capped
	• Seal at **closure/vial flange**
		Nitrogen content loss thru expiry	• **R&D/Manufacturing**
			  • **Laser-based H.A.** as a function of RSF
			• **Stability**
			  • **Laser-based H.A.**

Upon use	• **Puncture site**	**Product loss**	• **R&D/stability** • Dose delivery

Summary: 2 package seals, 2 critical leakage scenarios, **1 leak test**

Part 3. Test method selection and application

Example – Product 2

Multi-dose liquid product in a stoppered vial. Air headspace

Stage	Closure system	Critical leakage	Leak tests, Other
Pre-capping	• Closure inserted, not capped • Seal at **plug/neck**	**Airborne microbial ingress**	• **Manuf:** Media fill, vision system
Post capping	• Closure capped • Seal at **closure/vial flange**	**Liquid product loss** and **microbial ingress** thru expiry	• **R&D**: **Tracer gas (vacuum mode)** as a function of RSF • **Stability**: **HVLD** • **Manuf**: **HVLD**, RSF
Upon use	• **Puncture sites**	**Product loss**	• **R&D/stability**: **HVLD,** dose delivery

Summary: 3 package seals, 3 critical leakage scenarios, **2 leak tests**

Part 3. Test method selection and application

Example – Product 3

Lyo product in a stoppered vial; cryo-storage. Vacuum headspace

Stage	Closure system	Critical leakage	Leak tests, Other
Pre-lyo	• Closure in 'lyo' position • Seal at **plug-lug/vial-neck**	Closure kept in **open-leak-path** position; vial upright	• **Manuf**: Media fill, vision system
Post-lyo Pre-capping	• Closure inserted, not capped • Seal at **plug-top/vial-neck**	**Vacuum headspace loss**	• **R&D/Manuf**: **Laser-based H.A.**
Post capping	• Closure capped • Seal at **closure/vial flange**	**Vacuum headspace** loss thru expiry • At RT • At cryo-temps	• **R&D**: **Laser-based H.A.** as a function of RSF and Temp • **Stability**: **Laser-based H.A.** • **Manuf**: **Laser-based H.A.**, RSF
Upon use	• **Puncture site**	**Product loss**	• **R&D/stability**: dose delivery

Summary: 3 package seals, 4 critical leakage scenarios, **1 leak test**

Part 3. Test method selection and application

Example – Product 4

Liquid in a stoppered LV vial, terminally sterilized. Air headspace

Stage	Closure system	Critical leakage	Leak tests, Other
Pre-capping	• Closure inserted, not capped • Seal at **plug-top/vial-neck**	Closure insertion maintenance; vial upright. Airborne **microbial ingress**	• **Manuf**: Media fill, vision system

Post capping	• Closure capped
	• Seal at **closure/vial flange**
		Liquid product loss and **microbial ingress** thru expiry
		• Pre-sterilization
		• During sterilization
		• Post sterilization
			• **R&D**:
			  • **Tracer gas (vac) (empty) & HVLD (filled)** as a function of RSF, pre/post sterilization.
			  • **Liquid tracer** as a function of RSF during sterilization
			• **Stability**: **HVLD**
			• **Manuf**: **HVLD,** RSF

Upon use	• **Spike insertion** site	• **Product loss**	• **R&D/stability**: **HVLD,** dose delivery

Summary: 3 package seals, 5 critical leakage scenarios, **3 leak tests**

Example – Product 5

Lyo product in a stoppered vial; 2-8°C storage. Air headspace

Stage	Closure system	Critical leakage	Leak tests, Other
Pre-lyo	• Closure in 'lyo' position • Seal at **mid-plug/vial-neck**	Closure kept in open-leak-path position; vial upright **Airborne microbial ingress**	• **Manuf.:** Media fill, vision system
Post-lyo Pre-capping	• Closure inserted, not capped • Seal at **plug-base/vial-neck**	**Airborne microbial ingress**	• **Manuf:** Media fill, vision system
Post capping	• Closure capped • Seal at **closure/vial flange**	**Airborne microbial ingress** thru expiry	• **R&D**: **Tracer gas (vac)** & **Vac decay** as a function of RSF • **Stability**: **Vac decay** • **Manuf:** **Vac decay**, RSF
During use	• Puncture site	**Product loss**	• **R&D/stability**: dose delivery

Summary: 3 package seals, 4 critical leakage scenarios, **2 leak tests**

Example – Product 6

Liquid in a staked needle syringe. Air headspace

Stage	Closure system	Critical leakage	Leak tests, Other
All	Needle shield seal at **needle tip**	**Product loss** and **microbial ingress**	• **R&D**: **Vacuum decay (empty)** • **Stab/Manuf:** **HVLD**, X-ray

All	Needle shield seal at **needle base**	**Airborne microbial ingress**	• **R&D/Stab.:**
			  • **Vacuum decay**
			  • Shield removal force
			• **Manuf:** Vision system

Continued…

Example – Product 6

Continued. Liquid in a staked needle syringe. Air headspace

Stage	Closure system	Critical leakage	Leak tests, Other

All	**Plunger/barrel seal**	• **Product loss**
		• **Product ingress into ribs**
		• **Microbial ingress**
			• **R&D**:
			  • **Tracer gas (vac mode) (empty)**
			  • **Tracer liquid (for ribs leakage)**
			  • **HVLD (filled)**
			• **Stability**:
			  • **HVLD**
			  • Vision (for ribs leakage)
			• **Manuf**: **HVLD**, vision

Upon use	**Plunger/barrel seal**	• **Product loss**
		• **Product ingress into ribs**
			• **R&D/stability:**
			  • **HVLD**
			  • Vision (for ribs leakage)
			  • Dose delivery
			  • Breakloose/extrusion forces

Summary: 3 package seals, 5 critical leakage scenarios, **6 leak tests**

Summary

- **CCIT selection considerations**
  - **1st** consider the **product and the package**
  - **2nd** consider the **leakage of concern**
  - **3rd** examine **method options**
    - Method outcome and sensitivity
    - How the method is to be applied
  - **4th** employ **other 'non-leak' tests** to ensure seal quality

End of Part 3