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 5. Wrap-up

A. Current regulations: US, EU
B. Future direction
   1. USP <1207> proposed revision
   2. PDA TR 27 revision

Container Closure Integrity Testing Expectations from an FDA CBER Perspective

Presented by

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At the PDA 6th Global Conference on Pharmaceutical Microbiology, Bethesda, MD Oct 17, 2011

D. Sillivan of FDA Oct 17, 2011

Definitions

Limit of detection: Lowest level of analyte detected by a given assay, typically > 95% of the time

Critical Leak: Refers to the smallest defect size where ingress into or out of the container becomes possible, when considering container contents (e.g., protection against microbial ingress, protection against loss of headspace vacuum)

Primary packaging component: A packaging component that is or may be in direct contact with the dosage form. A secondary packaging component means a packaging component that is not and will not be in direct contact with the dosage form.

D. Sillivan of FDA Oct 17, 2011

Regulations

- **21 CFR § 600.11 (h)**

After filling, sealing shall be performed in a manner that will maintain the integrity of the product during the dating period. In addition, final containers and closures for products intended for use by injection shall be sterile and free from pyrogens.

- **21 CFR § 211.94 (b)**

Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.

D. Sillivan of FDA Oct 17, 2011

Regulations

- **Guidance for Industry**, **"**Container Closure Systems for Packaging Human Drugs and Biologics"

- **Guidance for Industry,** "Container and Closure System Integrity Testing in Lieu of Sterility Testing as a component of the Stability Protocol for Sterile Products"

- **Guidance for Industry,** "For the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products"

D. Sillivan of FDA Oct 17, 2011

Regulations

- **What is covered by**

  "Suitability for the Intended Use"

Every proposed packaging system should be shown to be suitable for its intended use: it should **adequately protect** the dosage form; it should be compatible with the dosage form; and it should be composed of materials that are considered safe for use with the dosage form and the route of administration.

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Submission requirements

- ***Test results from appropriate qualification and characterization tests*** should be provided. Adequate information regarding the tests, methods, acceptance criteria, reference standards, and validation information should be provided.

- To address protection, use of USP tests for light transmission, moisture permeation, microbial limits, and sterility are generally considered sufficient. ***Testing for properties other than those described in USP (e.g., gas transmission, solvent leakage, container integrity) may also be necessary*** (e.g. depending upon container and product considerations).

D. Sillivan of FDA Oct 17, 2011

FDA accepted methods

- ***There is no "gold standard" CCI test.*** Testing method selected should be appropriate for both the product and the final packaging configuration.

- ***Any validated container closure system integrity test method should be acceptable*** provided the method uses analytical detection appropriate to the method and is compatible with the product being tested. A test method is validated if it has been proven through scientifically accepted studies to be capable of detecting a breach in container closure system integrity.

D. Sillivan of FDA Oct 17, 2011

Microbial ingress

Procedure. Testing by liquid immersion of nutrient broth filled containers (i.e. vials, syringes) into a liquid concentration of microorganisms for a specified period of time, removing the units, rinsing them, incubating the units and examining them for microbial growth.

KEY COMMENTS OFFERED

- There is no FDA mandate or expectation for microbial challenge tests
- Years ago, the agency wanted to see microbial challenge testing. This is no longer the case
- Previously, use of other P-C methods required a comparison to microbial challenge tests. This is no longer the case.
- The agency prefers validated P-C leak test methods.

D. Sillivan of FDA Oct 17, 2011

Microbial ingress validation considerations

The FDA will not prohibit microbial ingress tests. HOWEVER, the FDA expects to see method validation.

- That adequate **concentration of microorganisms** are present in the challenge suspension *[initially and at the end of tests]*
- That **media** within the container adequately supports microbial growth.
- That **worst case conditions** were considered [extremes of pressure, worst case challenge organism(s)]
- **Positive controls** should demonstrate **microbial growth**, and should be designed using a defect **size** that approaches a **critical leak.**

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Documentation issues in submissions to CBER or FDA 483 observations

- **Failure to include positive controls** in the test plan.
- Failure to provide information regarding: **positive control defect size**, number of units tested, type of organism used in microbial ingress testing, or **limit of sensitivity** of the test.
- The microbial ingress test challenge employs a positive control using a defect generated with a **26-ga needle**; a 26 ga needle is slightly greater than 450µm. Microbial failure potentially occurs in the leak rate region of 10-4.5 to 10-3 scc/s, which roughly corresponds to leak diameters ranging from 0.4 to 2µm.

D. Sillivan of FDA Oct 17, 2011

Documentation issues in submissions to CBER or FDA 483 observations

- A chloride ingress test challenge employed a positive control using a defect generated by drilling a frozen stopper with a **1/16 drill bit**. Chloride ingress would occur at a much lower defect size. **The sensitivity of the method was not established.**

*[FDA would like to see defects, such as laser drilled holes, at least **8 to 10 µm** in diameter. Leaks made with needles are not acceptable.]*

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Documentation issues in submissions to CBER or FDA 483 observations

- Failure to use an **appropriate challenge organism** for a microbial ingress test (i.e., use of *Escherichia coli* vs. use of an organism that would represent a worst case challenge)

- Failure to establish that the microbial ingress bacterial challenge solution remained at a **sufficiently high population** throughout the test period. Failure to perform growth promotion testing on growth media used during microbial ingress testing.

D. Sillivan of FDA Oct 17, 2011

Documentation issues in submissions to CBER or FDA 483 observations

- Failure to **challenge the container** under worst case conditions and for routine usage (i.e., extremes of pressure, and routine handling, shipment, and storage conditions)

- Confirmation of dye ingress is performed using a visual inspection process that has not determined the **limit of dye detection** operators/inspectors are capable of.

Current direction: US

Summary

- **Test method selection**
  - Consider regulations, regulatory guidance, and compendia during selection of CCI testing
  - Evaluate your chosen materials/product to determine suitability, and then decide on a suitable CCI test.
- **Test method validation**
  - Assure that you have submitted complete and appropriate validation information to CBER to allow a substantive review.
- **Most common issues** with testing have involved
  - Absent or inappropriate positive controls
  - Failure to determine the limit of sensitivity of the chosen test/assay.

Current direction: EU

2008 revision to Annex 1 of the European Union Good Manufacturing Practices (GMPs) for sterile products

- "**Containers closed by fusion**, e.g., glass or plastic ampoules should be subject to **100% integrity testing**.
- **Samples of other containers** should be checked for integrity according to **appropriate procedures**"
- "**Containers sealed under vacuum** should be tested for **maintenance of that vacuum** after an appropriate, pre-determined period."

Current direction: EU

2008 revision to Annex 1 of the European Union Good Manufacturing Practices (GMPs) for sterile products

- **Concerning stoppered vials**, "Vials with **missing or displaced stoppers** should be rejected prior to capping."

- "**Filled containers of parenteral products** should be **inspected individually** for extraneous contamination or other defects."
  - Direction is given for **human inspection**, and
  - "where other methods of inspection are used, the **process should be validated** and the performance of the equipment checked at intervals."

Excepts from

Sterile Product Packaging - Integrity Evaluation

Current Status and Future Direction

USP Packaging, Storage and Distribution EC

Oct 4-5, 2012 Meeting, Chicago, IL*

***Inserts per PDA Workshop March 2014 noted**

The Evolution of Leak Testing

- Evolution of sterile product package leak testing
- USP <1207> revision
  - Reasons for revision
  - Proposed revisions
  - Issues raised
- Future direction

The Evolution of Leak Testing

- A key function of packaging is to protect the product from loss and contamination – i.e., the package must not leak.

- In earlier days, leak testing was performed in response to large scale package failure crises.
  - **1950s, '60s** Glass ampoule tip crack concerns
  - **1971** Glass bottle LVP contamination caused by closure integrity failure lead to thousands of deaths and nation-wide product recall

The Evolution of Leak Testing

Time frame	Current events	Physical leak tests	Microbial leak tests
1950s 1960s	Ampoule tip crack concern	Methods published: • Dye ingress • Radionuclide liquid tracer • Helium spark	---
1971	Glass LVP global recall – microbial contamination due to CCI failure	---	Microbial ingress risk described in several publications.

The Evolution of Leak Testing

- Over time, leak tests (especially physical methods) began to be better understood and more widely employed.
  - **1980s**
    - Microbial challenge tests became a mainstay for leak testing, generally used by microbiologists.
    - Physical test methods were explored and published.
  - **1980s to present**
    - Various guidance documents were created
      - To explain the importance of package protection
      - To list and describe leak test options
      - To propose how and when such tests are to be performed.

The Evolution of Leak Testing

Time frame	Publications, Guidances	Physical leak tests	Microbial leak tests
1983	PDA Bulletin No. 4, *Aspects of CCI*	Bulletin names: • Vacuum retention • Vacuum chamber • Internal pressure • Dye immersion • Seal force	Bulletin names: • Static challenge • Aerosol challenge • Immersion challenge
1998	USP <1207> *Sterile product packaging – Integrity evaluation*	Physical tests are named. No details are given.	Microbial challenge tests are named. No details are given.
1998	PDA Technical Report 27 *Pharmaceutical package integrity*	Numerous physical test options are described.	Microbial challenge tests are described.

The Evolution of Leak Testing

Time frame	Publications, Guidances	Physical leak tests	Microbial leak tests
2008	FDA guidance: *Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products*	Encouraged using *properly validated physical or chemical integrity tests …*	*…or microbiological container and closure system integrity tests*
		…instead of sterility tests to demonstrate the potential for product contamination.	
		Validated tests should • Use analytical detection techniques appropriate to the method • Be compatible with the specific product being tested. • Be proven capable of finding leaks	

1998: USP <1207> and PDA TR 27

- **State physical tests are OK to use…**

  …as long as the physical method is shown to be "comparable" to microbial ingress.

2008: FDA Guidance

- **<u>Does not</u> require a comparison of physical methods to microbial ingress risk.**

  Instead, validation data are required demonstrating test method container closure defect detection capability.

Revision of USP Packaging Integrity Tests

- ***WHY?***

  The world of packaging and leak testing has rapidly evolved, and greater guidance is needed

- **RESEARCH DATA AND EXPERIENCE SHOW**
  - All leak test methods have pros/cons.
  - No one method works for all applications.
  - Probabilistic methods (e.g., microbial ingress and dye tests) are no longer preferred by leak testing experts.

Revision of USP Packaging Integrity Tests

- ***WHY?***

  The world of packaging and leak testing has rapidly evolved, and greater guidance is needed

- **TECHNOLOGICAL ADVANCES**
  - Product-packages are more complex.
  - Better leak testing instrumentation is now commonly available.
  - New methods are being developed.

Revision of USP Packaging Integrity Tests

- ***WHY?***

  The world of packaging and leak testing has rapidly evolved, and greater guidance is needed

- **REGULATORY DEMANDS**
  - More testing throughout the product life cycle is expected.
  - Well-validated, adequately sensitive physical leak test methods (without microbial ingress comparison) are permitted and preferred.

***NEW*:** Methods are categorized as either deterministic or probabilistic

Deterministic methods	Probabilistic methods
Reproducible	Not reproducible
Sensitive	Insensitive
Highly instrumental	Little or no instrumentation used
Quantitative test result outcome	Qualitative, interpretive results
Minimal test sample preparation or manipulation	Considerable test sample preparation and/or manipulation
Risk of error - LOW	Risk of error - HIGH

Proposed Changes

***NEW*:** Each method is fully described, along with appropriate testing applications, with references.

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*	---

added post Oct 2012 presentation

***NEW*:** Test selection factors are fully described.

Leak test selection factors	Options
Package contents	Liquid, solid, gas, vacuum
Package materials of construction	Metal, glass, plastic, composite
Package design	Flexible/rigid Closure mechanism
How much leakage can the product tolerate, and still meet specs?	Gas headspace preservation Liquid content preservation Microbial ingress prevention
What does the leak test measure?	Gas leak rate Liquid migration/presence Microbial growth
Sensitivity (leak size detection range)	<0.1 microns to several mm
Test sample preservation	Destructive vs. nondestructive
Test method application	On-line vs. off-line Product life cycle phase

Proposed Changes

NEW: Concepts previously introduced are fully explored.

Current <1207>	NEW USP chapter
Method validation requirement is stated, no guidance offered	Details added: • Instrument qualification requirements • Method validation requirements
Only one type of complex package described (dual chamber)	More fully explores CCI as a function of: • Package designs • Package materials • Product contents
Product life cycle CCI testing is discussed	More fully explores: • Life cycle application • Regulatory demands

MOST IMPORTANT

The relationship between microbial challenge testing and physical testing is explained, and when/how each are used.

NEW USP chapter

- **ELIMINATES the microbial vs. physical method comparison requirement.**
- **Recommends using ONLY physical methods, unless:**
  - no physical method exists
  - method outcome demands microbial approach (examples given).
- **History text*** to explain chapter direction, validating the importance both physical and microbial testing approaches have played.

To be part of PF stimuli article, not <1207>

***NEW*:** Seal quality tests added

NEW USP chapter

"***Seal quality tests***": Test methods useful for characterizing and monitoring package seal quality. Not leak tests, but provide additional data regarding package seal characteristics that may impact package integrity and leakage.

- Test method description, selection, and use included.
  - Closure application and removal torque
  - Package burst test
  - Package seal strength
  - Residual seal force
  - Airborne ultrasound

USP <1207> Proposed Revision

- USP Gen. Chapters Packaging, Storage and Distribution EC
  - **USP <1207> Expert Panel**

Peter Buus	Novo Nordisk
Shu-chen Chen, PhD	Amgen
Ronald Forster, PhD	Amgen
Dana M. Guazzo, PhD	RxPax, LLC and USP Panel leader
Desmond Hunt, PhD	USP Liaison
Lee E. Kirsch, PhD	University of Iowa
Ron Mueller, PhD	West Pharmaceutical Services
Donald Singer, PhD	GlaxoSmithKline Bio
Marla Stevens-Riley, PhD	FDA CDER
David Walker	Merck & Co.

Future direction

PDA Technical Report 27 Revision

- **PDA TR 27 will reference USP <1207> standard**
- **TR 27 goal will seek to be forward thinking**
  - Issues touched on but not fully explored in USP
  - Unique package designs
  - Unique product challenges
  - Challenges in method validation
  - Case studies

Part 5. Wrap-up

Summary

- **Positive and negative controls, masters, blanks**
  - Population set of product-packages controls needed

Part 5. Wrap-up

Summary

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

End of Part 5