Connecting People, Science and Regulation

Proposed Revisions to USP <1207> STERILE PRODUCT - PACKAGE INTEGRITY EVALUATION

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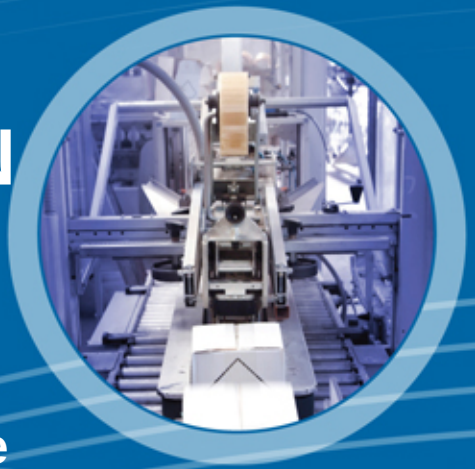

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PDA Europe
Parenterals Conference
5 Nov 2014

Presentation Outline

- Introduction
- Revision Rationale
- Revision Content
- Revision Timeline

USP <1207> Proposed Revision (PR)

The USP <1207> proposed revision (PR) can be found in:

USP-NF Pharmacopeial Forum Sep/Oct 2014

- **Stimuli article**
- **<1207>**
- **<1207.1> Package Integrity and test method selection**
- **<1207.2> Package integrity leak test technologies**
- **<1207.3> Package seal quality test methods**

The initial text was prepared by an Expert Panel, Commissioned by the USP Packaging, Storage and Distribution Expert Committee and the USP Microbiology Expert Committee

USP <1207> PR Expert Panel

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USP <1207> Revision Rationale

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

- **RESEARCH AND EXPERIENCE**
  - 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.

continued

USP <1207> Revision Rationale

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

continued

USP <1207> Revision Rationale

➢ 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

USP <1207> PR Stimuli Article

- **Provides historical context** to package integrity concerns and testing approaches

- **Summarizes key research findings**, including
  - **Traditional, probabilistic test methods**
    dye/microbial ingress, bubble emission
  - **With comparisons to less traditional, deterministic test methods**
    pressure/vacuum decay, tracer gas detection

- **Provides reader with greater perspective and insight** when reading <1207>

USP PR <1207>

Introduction - Scope

- Sterile pharmaceutical dosage form packages
- Primary container closure systems
- Packages of nonporous, rigid or flexible, materials
- OTHER applications include, but are not limited to
  - Porous flexible packages
  - Critical secondary packages
  - Sterile API, Intermediates, final bulk volume packages
  - Drug/device combination packages
- OUTSIDE the scope, but chapter concepts still apply
  - Sterile medical device packages (nonporous only)
  - Sterile diagnostic product packages

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Definitions

- ***"Package integrity"*** = ***"container closure integrity"*** **(CCI)**

  "… the absence of package leakage greater than the product package ***maximum allowable leakage limit."***

- ***"Integral package"***
  - Prevents microbial ingress (ensures sterility)
  - Maintains product CQA within P-C label claim specs
    - Limits loss of product contents
    - Prevents entry by debris or detrimental gases

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Definitions

- ***"Leak Tests (CCIT)"***
  - Leak tests detect the presence of (and in some cases the size or location of) package defect(s)
  - Such defects are capable of permitting
    - Loss of product contents
    - Loss of critical headspaces gases
    - Entry of non-viable particulates, liquids, reactive gases, microorganisms
- ***"Seal Quality Tests (SQT)"***
  - SQT characterize and monitor seal quality and consistency
- **Permeation** tests are NOT included in <1207>

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Chapter concepts

Regarding current published standard tests (e.g., ISO/ASTM)

- Reader is directed *to "existing methods and technologies supported by **peer-reviewed publications** and **internationally recognized standards**, based on sound scientific package testing principles."*
- The USP *"encourages the development and implementation of novel, innovative test methods."*
- Any chosen CCIT or SQT (even standard methods) require optimization and validation.

Product life cycle testing

3 Phases

1. Product package development and validation
2. Routine manufacturing
3. Marketed product stability

USP <1207.1>
Package integrity and test method selection

Phase 1. Product package development and validation

Factors that influence test method selection

- Product package profile
  - End use
  - Stability requirements
  - Method of manufacture
  - Anticipated storage, shipment, distribution environment
- Package mat'ls, sources, dimensional tolerances
- Package processing steps and max. limits
- Package filling, assembly, terminal sterilization
- Package robustness for storage, shipping, distribution

Phase 2. Routine manufacturing testing

Important concepts

- **Procedures & controls can minimize, not eliminate, CCI failure risk**

  "The goal…is to prevent, or identify and remove those failures of greatest concern, precluding shipment of non-integral CC that risk product contamination or loss."

- **CCI to be verified post major changes** in package design, materials, or manufacturing

- **Nondestructive tests preferred** in some cases

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Package integrity and test method selection

Phase 3. Marketed product stability testing

Important concepts

- CCIT (not sterility tests) recommended to ensure integrity over long-term storage
  - CCIT cannot replace initial sterility test
- CCIT needed to verify absence of package damage or deformation that could result in loss of product or sterility
- Indirect testing for CCIT may be acceptable

  e.g., headspace content verification

Closure Seal Type and Mechanics

Cites role of each in package integrity assurance

- **Physically mated** closure systems
  - Vial stopper, Syringe plunger
- **Physicochemically bonded** closure systems
  - Glass or plastic ampoules
- **Vent filtration** closure systems
  - Porous lidding on a tray
- **Multi-dose product microbial blockage** closure systems
  - Ophthalmic product packages with product blockage mechanics

10 Leak test selection criteria

1. Package contents

Gaseous ***or*** Vacuum ***or*** No headspace

Liquid ***or*** Dry product

Proteinaceous ***or*** Small molecules

Electrically conductive ***or*** Nonconductive

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Package integrity and test method selection

10 Leak test selection criteria

2. **Package design and materials of construction**

Flexible ***or*** Rigid

Nonporous ***or*** Porous

Electrically conductive ***or*** Nonconductive

Contiguous containers ***or*** Multiple seal types and locations

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Package integrity and test method selection

10 Leak test selection criteria

3. Product package maximum allowable leakage

- ***"Most package types demonstrate at least miniscule gaseous leakage plus permeation*** *even when optimally designed and assembled. …with the exception of [well-sealed] glass ampoules…"*

- ***"…the maximum allowable leakage into and out of intact packages should be so minimal that there is no impact*** *on product safety, and no consequential impact on the product's physicochemical stability."*

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Package integrity and test method selection

10 Leak test selection criteria

3. Product package maximum allowable leakage

Categories

1. **Liquid leakage** must be blocked
   - preserving product contents and product sterility

2. **Headspace gas or pressure** must be preserved
   - ensuring product stability and sterility

3. **Microbial ingress** must be prevented, while still permitting gas/liquid flow
   - ensuring product sterility (e.g, Tyvek® barrier material)

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Package integrity and test method selection

10 Leak test selection criteria

4. Deterministic vs. Probabilistic methods

- **Deterministic**
  - Leakage is based on predictable fluid flow mechanics (gas/liquids)
  - Leak detection relies on P-C technologies
  - NON-probabilistic
  - Validatable
  - **Preferred <u>if</u>** desired outcome permits
- ***Examples***: Tracer gas, Vacuum decay, Electrical conductivity

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Package integrity and test method selection

10 Leak test selection criteria

4. Deterministic vs. Probabilistic methods cont'd

- **Probabilistic**
  - Leakage is based on unpredictable, random events
  - Leak detection often relies on human interpretation
  - Error prone
  - **NOT preferred <u>unless</u>** desired outcome demands
- Examples: Microbial ingress, Tracer liquid (dye), Bubble

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Package integrity and test method selection

10 Leak test selection criteria

5. Method limit of detection (LOD)

- **The smallest leak rate/size reliably detected given the product-package system**
  - Determined experimentally
  - Requires positive controls (with-leak packages) and negative controls (no-leak package)

- **Leak Size Classification Index**

  Tool for categorizing methods by LOD
  - Class 1 (Lowest LOD)
  - Class 6 (highest LOD)

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Package integrity and test method selection

10 Leak test selection criteria

6. Method largest leak detection capability

- **Methods should also find larger leaks** of concern
  - A method with low LOD may not find largest leaks
- Method development efforts should include detection of larger defect sizes and types

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Package integrity and test method selection

10 Leak test selection criteria

7. Method Outcome

Leak location? Leak size?

Gas flow rate? Headspace content?

8. Quantitative vs. Qualitative

- **Quantitative:** measure of leak size, leakage rate
- **Qualitative**: leak presence

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Package integrity and test method selection

10 Leak test selection criteria

9. Nondestructive vs. destructive

- **Nondestructive testing is preferred when**
  - Defect release into commercial or clinical setting is a concern
  - Product-package sample is needed for other tests

10. On-line vs. off-line

- **Considerations**
  - Test speed
  - Product handling
  - Portion of lot to be tested

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Package integrity and test method selection

Leak test instrument Qualification, Method Development and Validation

- **Standard analytical practices to be followed**
- **NOT best-practices** for physico-chemical (PC) methods include
  - Microbial ingress side-by-side comparison
  - Assuming “standard methods” are ready-to-use
    e.g., ASTM tests
  - Reliance on instrument qualification tests alone

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Package integrity and test method selection

Leak test instrument Qualification, Method Development and Validation

- **Best-practice** for PC methods include
  - **Qualify equipment performance**
  - **Develop and validate method**
    - Use negative and positive controls (no-leak, with-leak packages)
    - Randomly ordered testing
    - Multiple operators, days, instruments (if possible)

USP <1207.2>
Package integrity leak test technologies

Leak test technologies included

- Categorized as **deterministic** or **probabilistic**
- **Inclusion based on supportive, relevant DATA** in:
  - Peer-reviewed journal publications
  - P&B studies in international test standards (e.g., ASTM)
- The reader is **NOT restricted** to these methods

USP <1207.2>
Package integrity leak test technologies

Each leak test method is summarized

1. Description
2. Application
3. Test equipment
4. Test parameters
5. Leak size class detection limit
6. Literature references

Technologies categorization review

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

USP <1207.2>

Package integrity leak test technologies

Leak test technologies included

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

USP <1207.3>
Package seal quality test methods

Seal quality test methods included

- Inclusion based on supportive relevant DATA in:
  - Peer-reviewed journal publications
  - P&B studies in international test standards (e.g., ASTM)
- The reader is NOT restricted to these methods

USP <1207.3>
Package seal quality test methods

- **Function of seal quality tests**
  - Properly characterize and monitor seal quality
  - Ensure consistency of package assembly

- **Methods included**

• Airborne ultrasound	ASTM F3004
• Cap application/removal torque	ASTM D2063, D3198, etc.
• Package burst test	ASTM F1140, F2054
• Package seal strength (peel) test	ASTM F88
• Residual seal force	

USP <1207> PR Timeline

- Expert Panel Selection 2010 **COMPLETE**
- Proposed Chapter Prep 2011 **COMPLETE**
- **1ST public review, USP Sep/Oct PF 2014 ONGOING**
- Chapter Revision *(based on public comment)* **2015**
- USP Expert Committees approval **2015**
- USP Official Chapter **2016**

Summary

USP-NF Pharmacopeial Forum Sep/Oct 2014

- **Stimuli article**
- **<1207>**
- **<1207.1> Package Integrity and test method selection**
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USP <1207> Proposed Revision

The USP encourages and welcomes your comments

Thank you!