# Container Closure Integrity: Regulations, Test Methods, Application – Regulatory Requirements

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PDA Parenteral Drug Association

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# Welcome

- Introduction
  - Your name and company
  - Your position and how it relates to CCI
  - Goals and expectations for the short course
- Group Discussion (VoC)
  - What are the needs and pain you experienced?
  - How can this course help you?

# FDA Guidelines

**Food and Drug Cosmetic Act**

- 1962 Amendments added cGMP provision, Section 501 (a) (3)

  "A drug … shall be deemed to be adulterated if… its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health"

**The 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.

# Container Closure Integrity

US FDA (1999). Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics

- It requires suitability of the selected container closure system be sufficiently established in the four key aspects: protection, safety, compatibility, and performance.
- Container closure integrity is considered an essential part of suitability, especially in the aspect of protection against microbial contamination, reactive gases (e.g., oxygen), and moisture.
- A container closure system that permits penetration of microorganisms is unsuitable for a sterile product.

# Product Development CCI Evaluation

- ICH Q8(R2) (2009) Pharmaceutical Development
  - The choice of materials for primary packaging should be justified. The discussion should describe studies performed to demonstrate the integrity of the container and closure. A possible interaction between product and container or label should be considered.

- US FDA (1994). Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products
  - Study designs should simulate the stresses of the sterilization process, handling, and storage of the drug and their effects on the container-closure system.
  - Container-closure integrity should be demonstrated on product units that have been exposed to the maximum sterilization cycle(s). If a product is exposed to more than one process, then exposure to the maximum cycle of all processes should be incorporated into the study design. The studies must be described and included in the submission to gain regulatory approval.

# Process Validation CCI Evaluation

US FDA (1994). Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products

For initial validation of microbiological integrity of container-closure systems, product sterility testing is not normally considered sufficient. Container closure integrity testing methods and results should be summarized to demonstrate the integrity of the microbiological barrier.

The ability of the container-closure system to maintain the integrity of its microbial barrier, and, hence, the sterility of a drug product throughout its shelf life, should be demonstrated.

As previously stated, sterility testing at the initial time point is not considered sufficient to demonstrate the microbial integrity of a container-closure system. Documentation of the sensitivity of the container-closure integrity test should be provided.

The sensitivity of the experimental method used for container-closure integrity testing should be specified and provided.

# Manufacturing Batch CCI Evaluation

**EU Guideline to Good Manufacturing Practice (2008)**. Medicinal Products for Human and Veterinary Use, Annex 1. Manufacturer of Sterile Medicinal Products.

**Current wording:**

117. Containers should be closed by appropriately validated methods. 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*.

**Proposed wording (second targeted consultation extended):**

8.21 Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g., Blow-fill-seal (BFS), Form-Fill-Seal (FFS), Small and Large Volume Parenteral (SVP & LVP) bags, glass or plastic ampoules, should be subject to *100% integrity testing*. Samples of other containers closed by other methods should be taken and checked for integrity using validated methods. The frequency of testing should be based on the knowledge and experience of the container and closure systems being used. A *statistically valid* sampling plan should be utilized. The sample size should be based on information such as supplier approval, packaging component specifications and process knowledge. It should be noted that visual inspection alone is not considered as an acceptable integrity test method.

8.23 The container closure integrity validation should take into consideration any transportation or shipping requirements that may negatively impact the integrity of the container (e.g. by decompression or temperature extremes).

# Manufacturing Batch CCI Evaluation

**Annex 1 Updated August 2022**

8.21 Final containers should be closed by appropriately validated methods.

8.22 Where final containers are closed by fusion, e.g. Blow-Fill-Seal (BFS), Form-Fill-Seal (FFS), Small and Large Volume Parenteral (SVP & LVP) bags, glass or plastic ampoules, the critical parameters and variables that affect seal integrity should be evaluated, determined, effectively controlled and monitored during operations. Glass ampoules, BFS units and small volume containers (≤100 ml) closed by fusion should be subject to 100% integrity testing using validated methods. For large volume containers (>100 ml) closed by fusion, reduced sampling may be acceptable where scientifically justified and based on data demonstrating the consistency of the existing process, and a high level of process control. It should be noted that visual inspection is not considered as an acceptable integrity test method.

8.23 Samples of products using systems other than fusion should be taken and checked for integrity using validated methods. The frequency of testing should be based on the knowledge and experience of the container and closure systems being used. A scientifically justified sampling plan should be used. The sample size should be based on information such as supplier management, packaging component specifications and process knowledge.

8.25 The container closure integrity validation should take into consideration any transportation or shipping requirements that may negatively impact the integrity of the container (e.g. by decompression or extreme temperatures).

# Manufacturing Batch CCI Evaluation

**US FDA (2004).** Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice

> For drug products produced by aseptic processing, US FDA cGMP guidance requires any damaged or defective units should be detected, and removed, during inspection of the final sealed product.

# Routine Stability CCI Evaluation

- US State Food and Drug Administration (2008). Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products
  - US FDA promotes container and closure system integrity (CCI) testing as a component of the stability protocol for sterile products.
  - The guidance recommended CCI testing on stability in lieu of traditional end-of-shelf-life sterility testing for better sterility assurance, especially continued sterility of a drug product.
  - This does not eliminate the need to test sterility at release
  - The guidance requires stability CCI testing methods be appropriately validated.
- ICH Q5C Guidance for the industry “Quality of Biotechnological products: Stability testing of Biotechnological / Biological products”
  - Sterility testing or alternatives (e.g. container closure integrity testing) should be performed at a minimum initially and at the end of the proposed shelf-life.

# ISO standard? 1168

- ISO standard?

# Industry Consensus Guidance & Best Practices

**<1207>** Package integrity evaluation – Sterile products

**<1207.1>** Package Integrity in the product life cycle - Test method selection and validation

**<1207.2>** Package integrity leak test technologies

**<1207.3>** Package seal quality test technologies

(Official date: August 2016)

**PDA Technical Report 86 (TR 86):** Pharmaceutical Package Integrity

**JP** Packaging Integrity Evaluation of Sterile Products
**JP** Leak Tests for Packaging of Sterile Products

# PDA TR86 Revision (Published May 2021)

1.0 INTRODUCTION
2.0 Glossary
3.0 Challenges with Methodologies
- 3.1 Positive Controls
- 3.2 Blockage of Leak Paths

4.0 Challenges with Package Design
- 4.1 Prefilled Syringes
- 4.2 Single-Use Systems – Flexible Bulk Containers
- 4.3 IV Bags – Flexible Finished Pharmaceutical Packaging Systems
- 4.4 Cryogenic Conditions

5.0 Innovative Methods for Existing Technologies
- 5.1 Helium Testing
- 5.2 Optical Emission Spectroscopy
- 5.3 Airborne Ultrasounds
- 5.2 X-Ray Detection

6.0 Additional Considerations for Package Integrity Profiling
- 6.1 Transportation and Distribution
- 6.2 100% Online Testing
- 6.3 Building a Quality by Design Approach into the Container Closure Integrity Testing Program
- 6.4 Bulk Container Lifecycle Approach
- 6.5 Educational Simulation about Limits of Detection and Method Selection

7.0 Conclusion
8.0 References
9.0 Additional Reading

# Course Outline

- Container Closure Integrity: Regulations, Test Methods, Applications
  - Part 1. Introduction
  - Part 2. Test methods
  - Part 3. Test method development and validation
  - Part 4. Test method selection and application

# Instructors' Perspective: What We Can Deliver

- **A scientific foundation** for understanding and applying various CCIT technologies
  - Working principles, advantages and disadvantages
  - Technical considerations for method selection
  - Application case studies
- **A risk-based approach to** applying CCIT throughout product life cycle
  - CCI data package during development, validation, routine manufacturing
  - Key considerations for developing testing requirements, study design, method selection, and sampling plan
- Method development and validation **best practices**
- **Focus: Enable you to make sound technical decisions to support business needs**

# Instructors' Perspective: What We Can NOT Deliver

- "What hole size do I need to detect?"
- A one-size-fits-all or ideal CCIT technology that is capable of covering all CCI testing needs
- A decision tree or cheat sheet for method selection, sampling plan

# Conclusions: FDA CCIT Expectations

- During the development and validation phases:
  - Selection of CCS suitable for the product
  - Selection of a CCIT method:
    - CCIT suitable for the type of CCS and product.
    - CCIT conducted on the proposed commercial drug product CCS
    - CCIT limit of detection able to detect “leaks of concern” (those that may impact product quality and safety).
    - Validation of the CCIT, including selection of breached positive controls.
    - Demonstration of CCI after worst-case manufacturing conditions:
      - Worst-case capping/crimping
      - Worst-case sterilization cycles

# Conclusions: FDA CCIT Expectations (cont.)

- During the development and validation phases (cont.):
  - Demonstration of CCI after secondary assembly (pre-filled syringe into autoinjectors (PFS), assembly of plunger rod, finger flange, safety device, etc.).
  - Demonstration of CCI after handling and shipping of PFS/autoinjectors devices.
    - Demonstration that plunger movement of prefilled syringes due to pressure changes during air transportation do not impact the sterile boundary of the syringe.
- During Shelf-life:
  - Inclusion of CCIT in the stability plan to ensure that a sterile product remains sterile during its shelf-life.