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

PDA
Parenteral Drug Association

CONNECTING PEOPLE SCIENCE AND REGULATION®

Meet the Instructors -

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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)

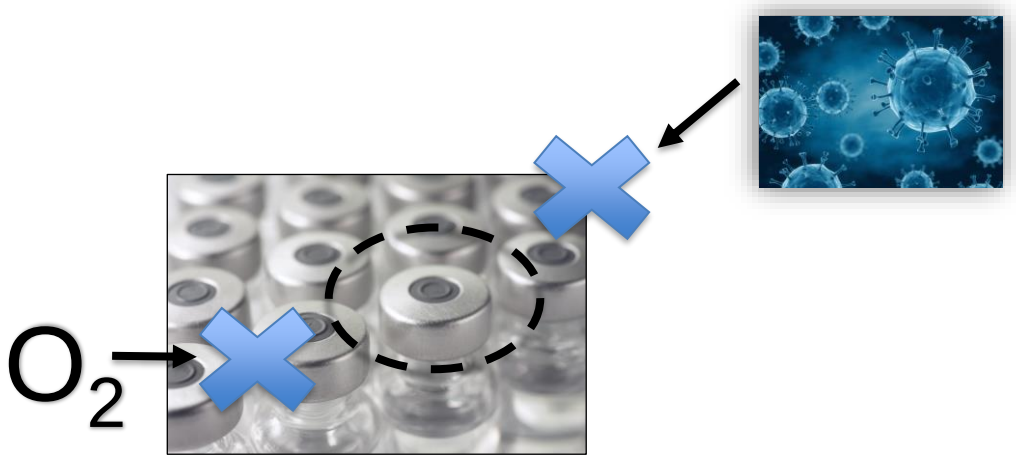
  Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.

Container Closure Integrity

Industry Consensus
Stability CCI Eval.
Mfg. Batch CCI Eval.
Process Val. CCI Eval.
Prod. Dev. CCI Eval.

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

- 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.



Container Closure Integrity

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

- A container closure system that permits penetration of microorganisms is unsuitable for a sterile product.
- 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

Industry Consensus

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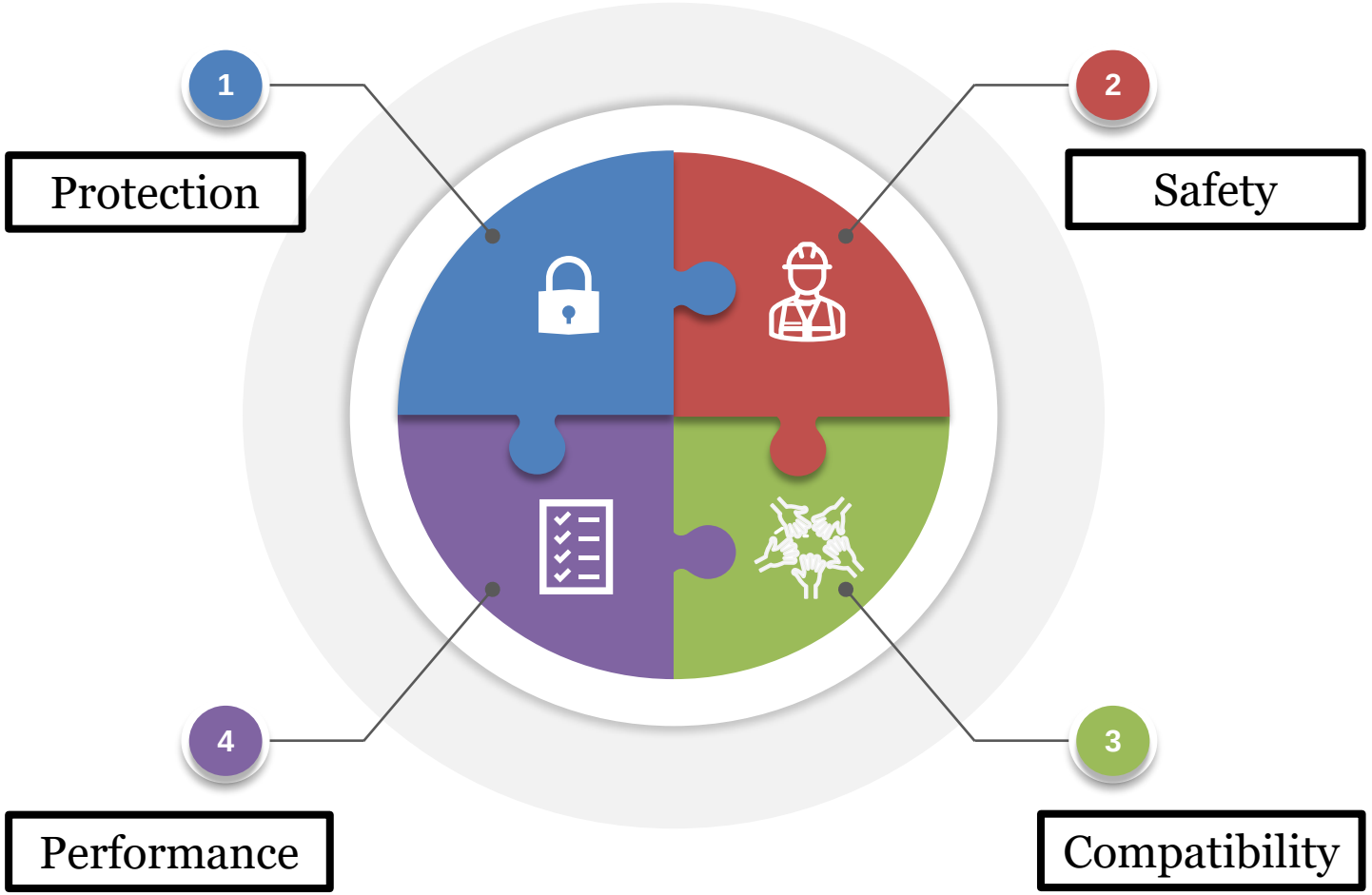

Product Development CCI Evaluation

- Industry Consensus
- Stability CCI Eval.
- Mfg. Batch CCI Eval.
- Process Val. CCI Eval.

ICH harmonisation for better health

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.

Product Development CCI Evaluation

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

U.S. FOOD & DRUG ADMINISTRATION

Industry Consensus

Stability CCI Eval.

Mfg. Batch CCI Eval.

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.

Process Validation CCI Evaluation

U.S. FOOD & DRUG ADMINISTRATION

Industry Consensus

Stability CCI Eval.

Mfg. Batch CCI Eval.

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

- 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.

Mfg. Batch CCI Evaluation

Industry Consensus

Stability CCI Eval.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EU Guideline to Good Manufacturing Practice (2009)

Medicinal Products for Human and Veterinary Use, Annex 1. Manufacturer of Sterile Medicinal Products.

Previous 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*.

Mfg. Batch CCI Evaluation

Industry Consensus

Stability CCI Eval.

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Mfg. Batch CCI Evaluation

Industry Consensus

Stability CCI Eval.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EU Guideline to Good Manufacturing Practice (2022)

Medicinal Products for Human and Veterinary Use, Annex 1. Manufacturer of Sterile Medicinal Products.

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 or 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 system 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.

Mfg. Batch CCI Evaluation

Industry Consensus

Stability CCI Eval.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EU Guideline to Good Manufacturing Practice (2022)

Medicinal Products for Human and Veterinary Use, Annex 1. Manufacturer of Sterile Medicinal Products.

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 temperature extremes).

Mfg. Batch CCI Evaluation

Industry Consensus

Stability CCI Eval.

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

Industry Consensus

US State Food and Drug Administration (2008)

ICH Q5C Guidance for the industry

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.
- The guidance requires stability CCI testing methods be appropriately validated.

Routine Stability CCI Evaluation

Industry Consensus

US State Food and Drug Administration (2008)

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 11608-3

4.2.1 Container Closure Integrity (CCI)

Container closure integrity shall be ensured until the expiration date of the first intentional user interaction that breaks CCI.

If the NIS is manufacture- assembled with a primary container closure to form a single integral unit, the manufacturing processes, including assembly, shall be shown to not adversely impact container closure integrity, in accordance with applicable pharmacopeia.

Industry Consensus Guidance & Best Practices

Official Date - 2016

<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

PDA Technical Report TR 86

Pharmaceutical Package Integrity

JP Packaging Integrity Evaluation of Sterile Products

JP Leak Tests for Packaging of Sterile Products

The suitability of a container closure system should be established in which key aspects?

- ❑ Protection
- ❑ Dimensions
- ❑ Safety
- ❑ Compatibility
- ❑ Performance

Which USP guidance talks about Package Integrity Evaluation – Sterile Products?

- ❑ USP 1207
- ❑ USP 659
- ❑ USP 671
- ❑ USP 661

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

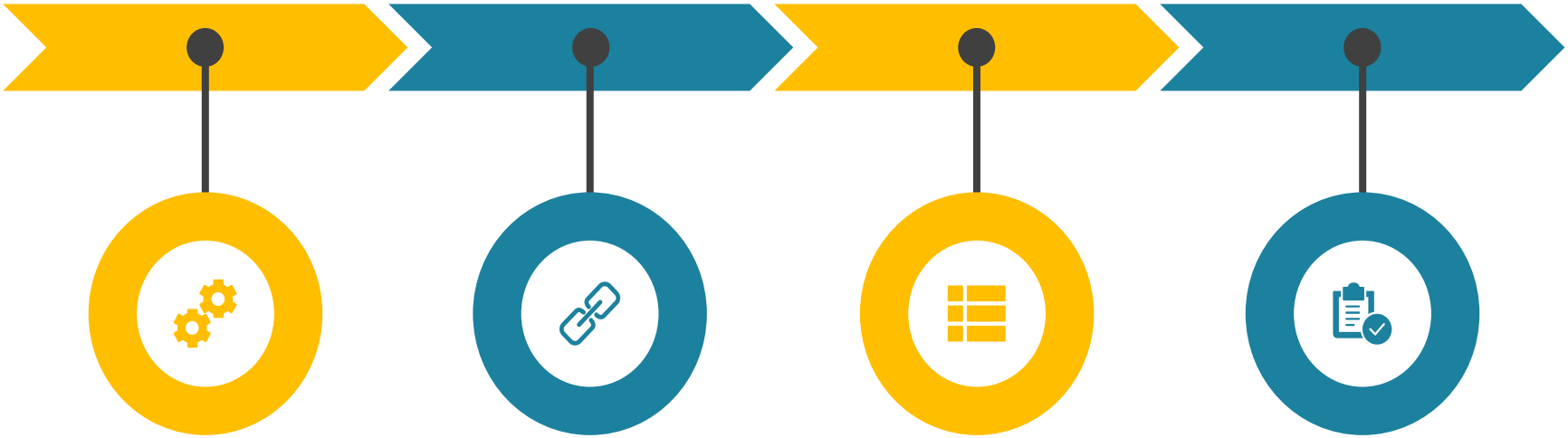
5.0 Innovative Methods for Existing Technologies
- 5.1 Helium Testing
- 5.2 Optical Emission Spectroscopy
- 5.3 Airborne Ultrasounds
- 5.2 X-Ray Detection

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 & validation

Part 4
Test method selection & 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**
- **<u>Focus:</u> 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.