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

PDA Parenteral Drug Association

PDA TRAINING

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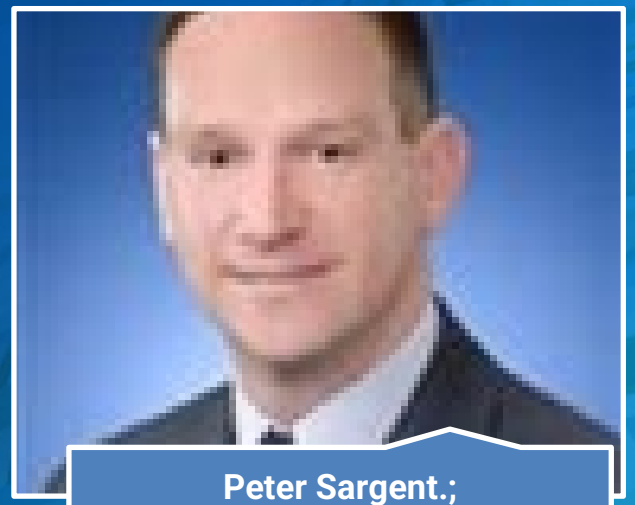
Meet the Instructors -



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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?

COURSE OUTLINE

Fundamentals

Hands-On

Special Topics

COURSE OUTLINE : Fundamentals

Container Closure Integrity: Regulations, Test Methods, Applications

Part 1
Regulations

Part 2
Test Methods

Part 3
Test method development & validation

Part 4
Test method selection & application

Regulatory Landscape

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.

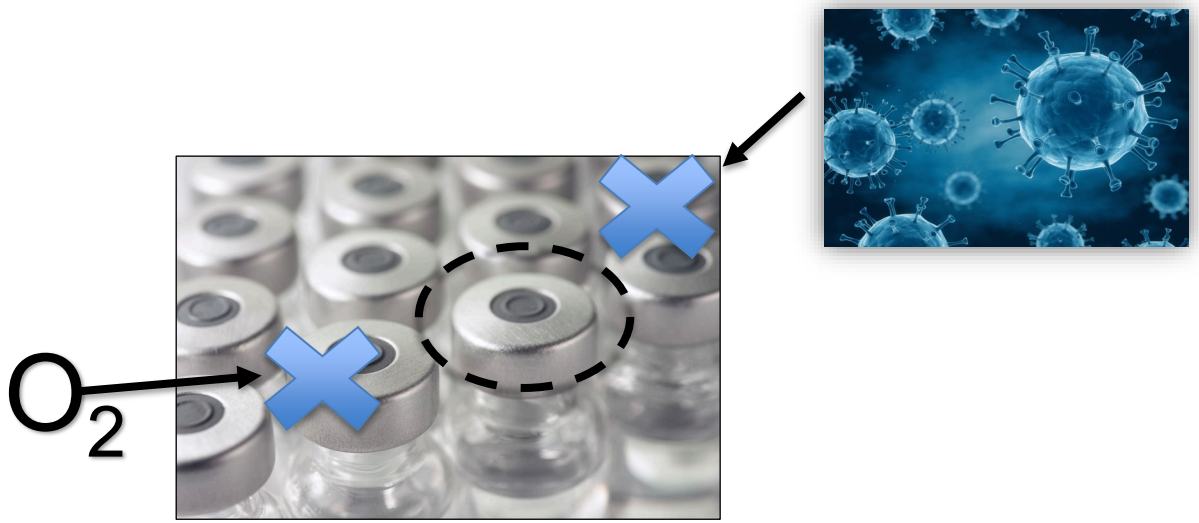
Mfg. Batch CCI Eval.

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
- Stability CCI Eval.
- Mfg. Batch CCI Eval.
- Process Val. CCI Eval.
- Prod. Dev. CCI Eval.

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

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

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*.

Industry Consensus

Stability CCI Eval.

Mfg. Batch CCI Evaluation

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.

Industry Consensus

Stability CCI Eval.

Mfg. Batch CCI Evaluation

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/TC76: 11040-Series - Prefilled Syringes - Published

ISO 11040-1:2015
Prefilled syringes — Part 1: Glass cylinders for dental local anaesthetic cartridges

ISO 11040-2:2011
Prefilled syringes — Part 2: Plunger stoppers for dental local anaesthetic cartridges

ISO 11040-3:2012
Prefilled syringes — Part 3: Seals for dental local anaesthetic cartridges

2024

ISO 11040-4:2015
Prefilled syringes — Part 4: Glass barrels for injectables and sterilized subassembled syringes ready for filling

ISO 11040-4:2015/Amd 1:2020
Prefilled syringes — Part 4: Glass barrels for injectables and sterilized subassembled syringes ready for filling — Amendment 1

ISO 11040-5:2012
Prefilled syringes — Part 5: Plunger stoppers for injectables

ISO 11040-6:2019
Prefilled syringes — Part 6: Plastic barrels for injectables and sterilized subassembled syringes ready for filling

2024

ISO 11040-7:2015
Prefilled syringes — Part 7: Packaging systems for sterilized subassembled syringes ready for filling

ISO 11040-8:2016
Prefilled syringes — Part 8: Requirements and test methods for finished prefilled syringes

ISO 11040-4 (Pre-filled Syringe System)

7.4 Container closure integrity

The container closure system sealing surfaces shall ensure integrity throughout filling, terminal sterilizations (if applicable, e.g. moist heat by autoclaving), further manufacturing steps, storage and transportation (considering different external air pressures) to ensure content sterility and to prevent leakage.

A suitable container closure integrity test method (e.g. physical, microbiological) shall be qualified and validated to assess the finished prefilled syringe.

In Scope: glass barrels and sterilized sub assembled syringes ready for filling are intended for single use
Out of Scope: components such as plunger, stopper, plunger rod

ISO 11608-3 (Autoinjector & Pen Injector)

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.

Standard for needle injection system this applies when qualifying the device
Depending on lifecycle, might not have a device ready to qualify against this standard

Functionality Tests for Elastomeric Components

<381> Elastomeric Components in Injectable Pharmaceutical Product Packaging/Delivery Systems

- 1. INTRODUCTION
- 2. SCOPE
- 3. TEST SAMPLES
- 4. PROCEDURES
  - 4.1 Biological Reactivity
  - 4.2 Physicochemical Tests
  - **4.3 Functionality Tests**

<382> Elastomeric Components Functionality Suitability in Parenteral Products Packaging/Delivery Systems

- 1. INTRODUCTION
- 2. SCOPE
- 3. GENERAL TEST REQUIREMENTS
- 4. PACKAGING/DELIVERY SYSTEM INTEGRITY TESTS
- 5. NEEDLE AND SPIKE ACCESS FUNCTIONAL SUITABILITY TESTS
- 6. PLUNGER FUNCTIONAL SUITABILITY TESTS
- 7. TIP CAP AND NEEDLE SHIELD FUNCTIONAL SUITABILITY TESTS

(New) <382> published in the USP-NF 2020
Official Dec. 1, 2025

USP 382

- Moving away from testing elastomeric components individually by the supplier, as under *USP <381> Elastomeric Components in Injectable Pharmaceutical Production Packaging/Delivery Systems*, to a holistic evaluation of these components when assembled into drug product packaging and delivery systems.
- Testing performed with product filled systems or systems filled with suitable proxy, so suppliers cannot perform these test without knowledge of the drug product/proxy, so testing shifts back to drug manufacturer
- New chapter incorporates container closure integrity testing and an update to the functionality tests for elastomers
- Similar language to USP 1207 around verifying inherent leak integrity
  - Specifies to use 30 units for verification of inherent package integrity
- Adds multi-puncture requirement – requires inherent leak testing to in-use MALL
  - # punctures and meets in-use MALL vs # punctures and blue dye test
  - Must consider worst-case use

CHP (China Pharmacopeia)

- Draft Guidance Issued 2024 ; open for comments
- Similar to USP <1207>
  - Includes vacuum decay, laser headspace, high voltage leak detection, vacuum helium detector, sniffing helium detection, color water method and ultrasound

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 27 (TR 27) -1998

Pharmaceutical Package Integrity

PDA TR86 – Revised 2021

Industry Challenges and Current Technologies for Pharmaceutical Package Integrity Testing

JP Packaging Integrity Evaluation of Sterile Products

JP Leak Tests for Packaging of Sterile Products

PDA TR86 Revision (Published May 2021)

European Journal of Pharmaceutics and Biopharmaceutics 194 (2024) 20–35

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Industry perspective on a holistic container closure integrity approach to parenteral combination products☆

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A B S T R A C T

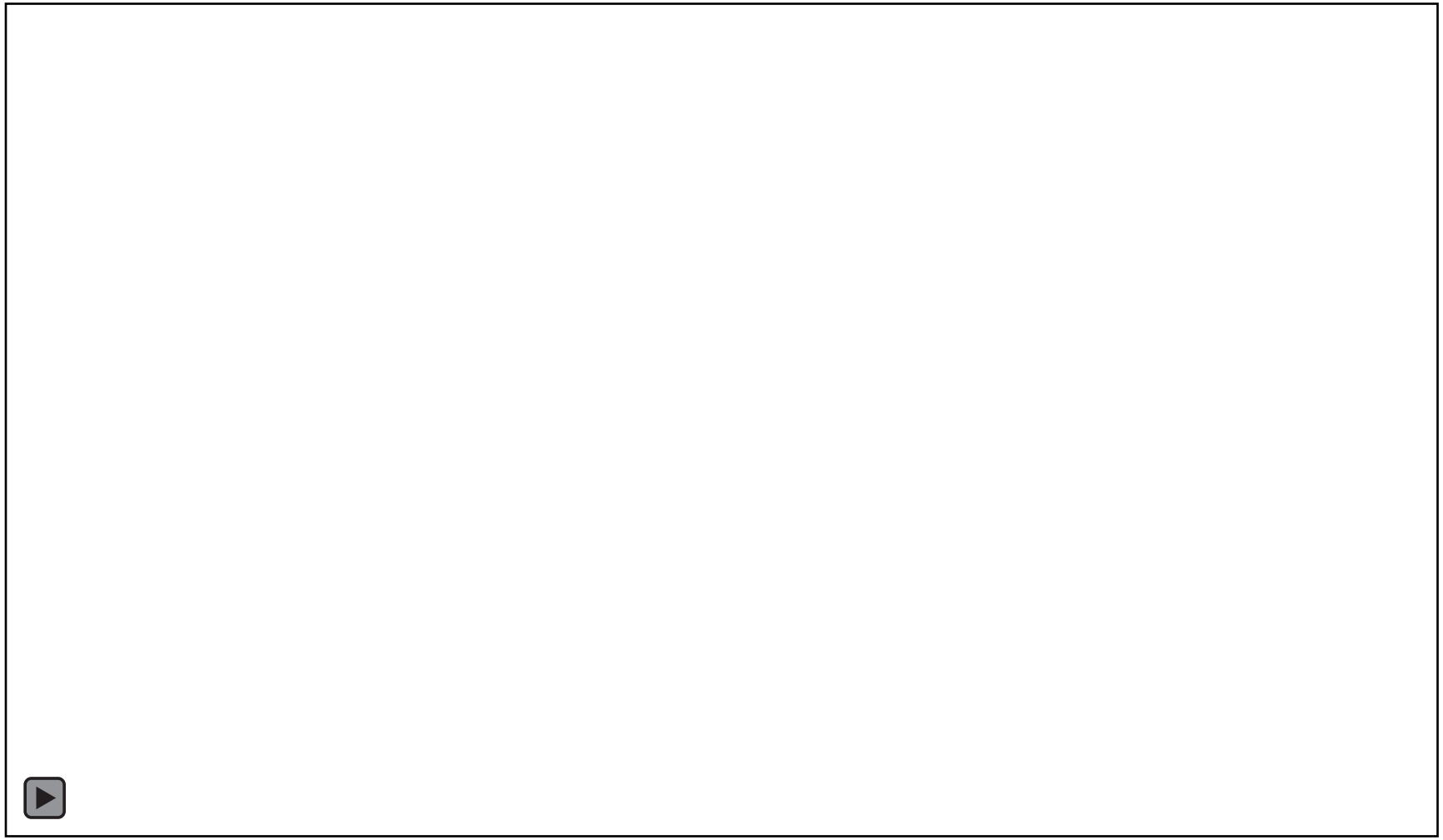
Biologics are being developed more and more as parenteral combination products with drug delivery devices. The maintenance of sterility is imperative for such medical devices throughout their life cycle. Therefore, the container closure integrity (CCI) should, preferably, be built into the overall process, and not just demonstrated during the final testing of the combination product. The integrity is an important Critical Quality Attribute (CQA) and in the scope of specific considerations and studies during the combination product life cycle i.e., design robustness, assembly processes, storage (to end of shelf life), and shipping prior to patient use.

The goal of this paper is to summarize an industry holistic approach to ensure CCI, for a combination product, and to build a scientifically based justification that Quality (in terms of CCI) is built into the overall process. Current analytical approaches used for characterization or Good Manufacturing Practice (GMP) CCI testing during combination product development will be described. However, the use of quality by design (QbD) during product development can reduce or eliminate routine batch level or stability testing of the combination product.

BioPhorum Holistic Approach to CCI

- Published January 2024
- It provides an industry perspective on ensuring CCI throughout the product lifecycle and includes discussions on development, validation, routine manufacturing, shipping and stability, and the ongoing monitoring of holistic CCI strategy.

Contents



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

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.

USP 382

Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems

- Verifying inherent leak integrity
- Generic to use of container/closure system
- Adds multi-puncture requirement – requires inherent leak testing
  - # punctures and meets in-use MALL vs # punctures and blue dye test

Inherent integrity: The leakage rate (or leak size) of a well-assembled packaging/delivery system with no system defect; it is a measure of packaging/delivery system leak tightness.

See *Package Integrity Evaluation—Sterile Products* ⟨1207⟩, as well as its subchapters, for further guidance on the concepts of inherent integrity and maximum allowable leakage limit, and for guidance on the proper selection, development, validation, and use of appropriate leak test methods.

Procedure:

Select 30 samples per test. Test each sample for integrity according to the leak test method of choice. No one specific integrity test method is applicable to all packaging/delivery systems. For systems with multiple closures (e.g., syringes with a plunger and a needle shield), separate and perhaps different types of leak tests may be required to effectively evaluate the system's inherent integrity, given all the various closure seal types. The leak test(s) chosen are to be capable of verifying that the system's inherent integrity meets the maximum allowable leakage limit for the intended product packaging/delivery system.

When reporting test results, include a full description of the integrity test method, including critical attributes and settings, test acceptance criteria (with justification for such criteria), test sample quantity, and the test sample quantity that passed/failed as per acceptance criteria.

Acceptance criteria:

The packaging/delivery system is acceptable if the inherent integrity results for all test samples conform to the maximum allowable leakage limit demanded of the product to ensure that there is no risk to product microbiological quality and no impact, or inconsequential impact, on product physicochemical quality attributes.