

Holistic CCI Approach

*2020 PDA European Two-Day Training:
Container Closure Integrity Testing
for the Advanced Users*

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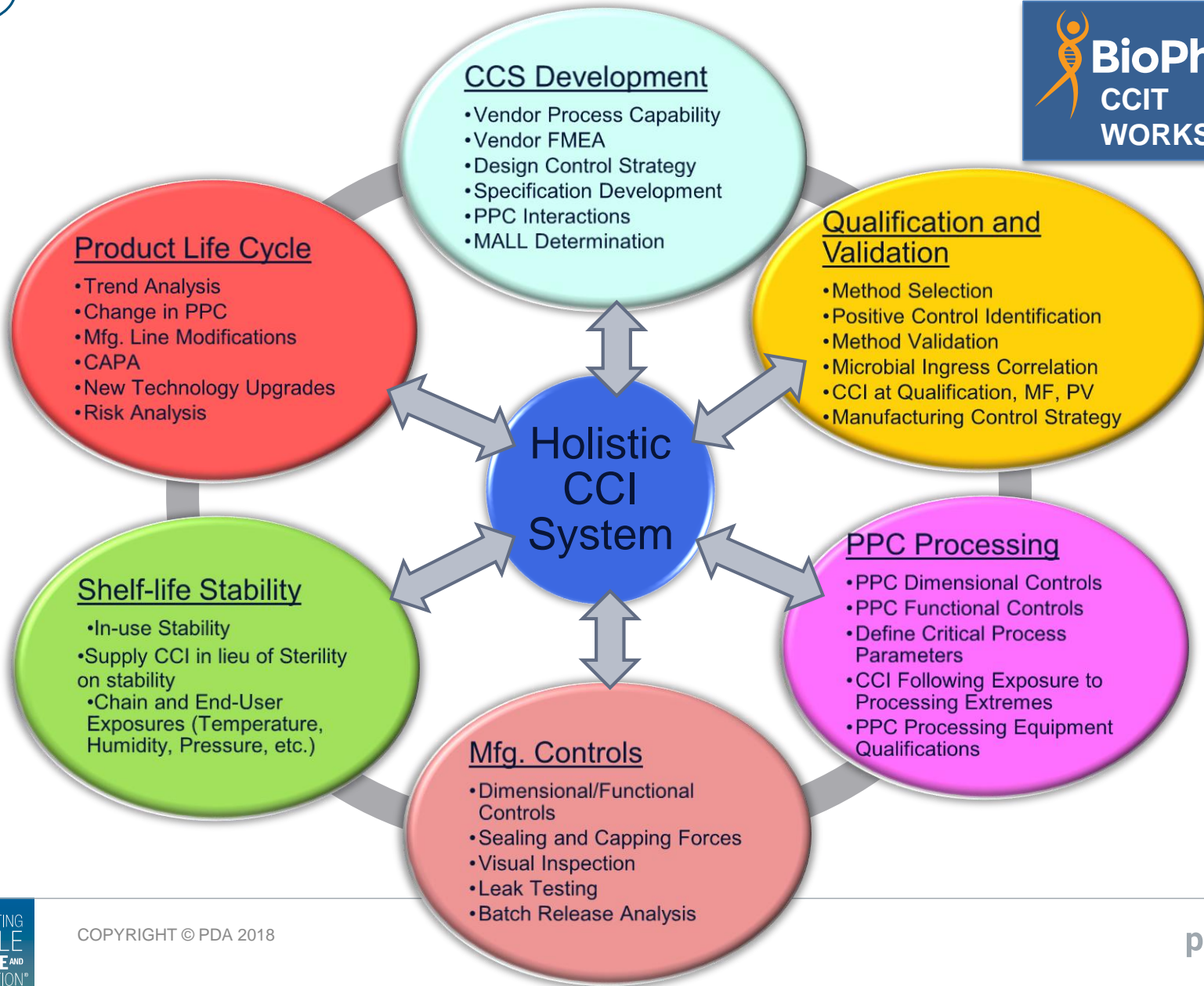
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Disclosure of potential conflicts of interest

David Riesop is an employee of AbbVie Deutschland and may own AbbVie stock.

The presentation reflects the view of the author and not necessarily by any means the view of AbbVie Deutschland.



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

It requires suitability of the selected container closure system be sufficient 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.

CCS Development

21 CFR

- “Container closure system shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product” (§211.94(b)).
- “..., 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.” (§600.11(h))

Eudralex
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- “Samples of other containers should be checked for integrity according to appropriate procedures”. “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” (Annex 1).
- “There should be a system to assure the integrity and closure of containers after filling where the final products or intermediates represent a special risk and procedures to deal with any leaks or spillages” (Annex 2).
- “Any leakage test should be performed in a way which avoids microbial contamination or residual moisture” (Annex 10).

USP 1207 – General Overview

USP <1207> Package Integrity Evaluation – Sterile Products

- [...] Thus, sterile product-package integrity is the ability of a sterile product CCS to keep product contents in, while keeping detrimental environmental contaminants out.
- Product quality risks posed by leaks of concern

USP <1207.1> Package integrity testing in the product life cycle – test method selection and validation

- Package development, package processing and assembly validation
- Product manufacturing
- Commercial product shelf-life stability assessment




USP <1207.2> Package integrity leak test technologies

- Deterministic and Probabilistic test method: Description, Application, Test Equipment, Test Parameters
- [...] Test technologies vary in terms of their potential detection limits, reliability, and applications; therefore, none are universally appropriate for leak testing of all product-packages.

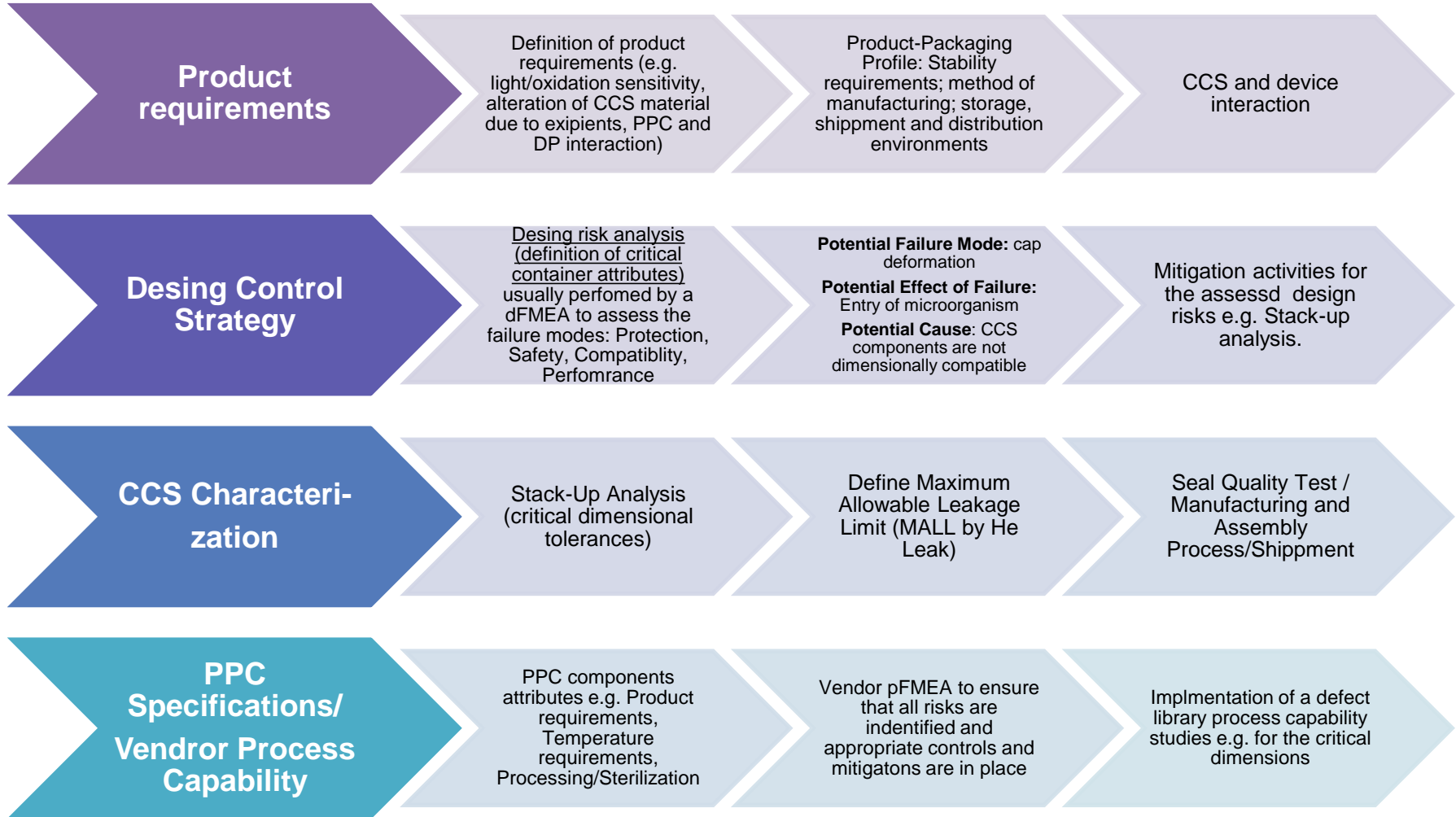
USP <1207.3> Package seal quality test technologies

- Summary of test methods for characterizing and monitoring package seal quality
- [...] These methods are not leak tests but provide additional data regarding package seal characteristics that may affect package integrity and leakage.
- [...] Seal quality tests ensure that seal attributes, package materials, package components, and/or the assembly process are consistently kept within established limits, thus further supporting package integrity.

New Requirements for CCIT according to USP 1207

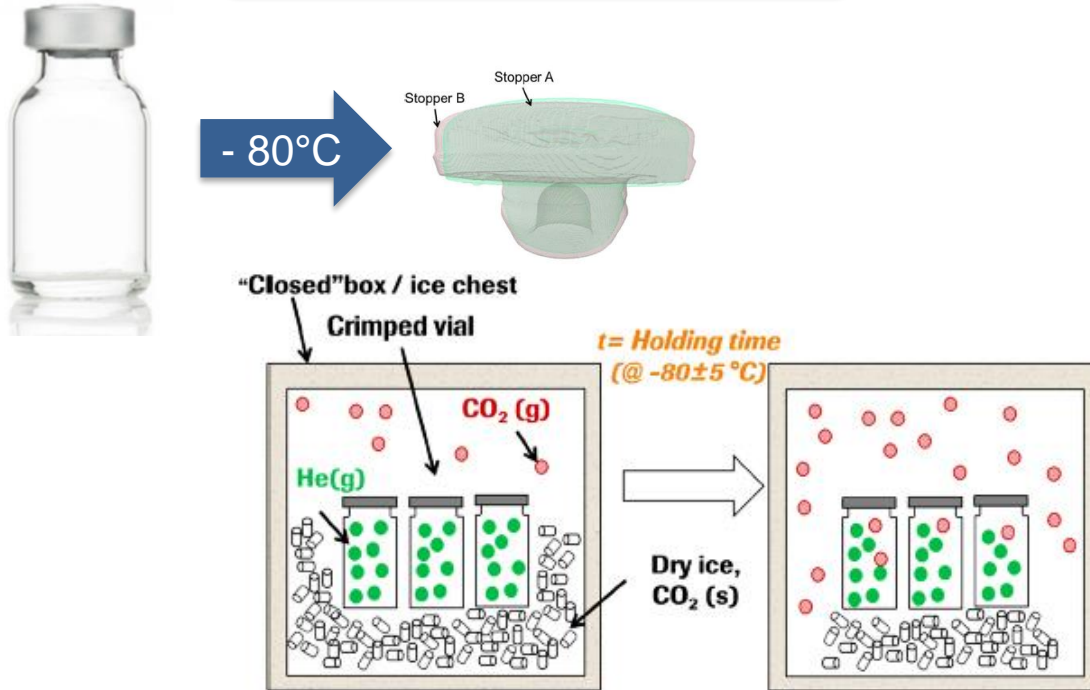
Leaks of Concern	Product Quality Risk Posed by Leaks
 <p>Capable of allowing entry of microorganism</p>	<p>Failure of product sterility quality attribute</p>
 <p>Capable of allowing escape of the product dosage form or allowing entry of external liquid or solid matter</p>	<p>Failure of relevant product physicochemical quality attributes</p>
 <p>Capable of allowing change in gas headspace content. For example, loss of headspace inert gases (e.g. nitrogen), loss of headspace vacuum, and/or entry of gases (e.g. oxygen, water vapor, air).</p>	<p>Failure of relevant product physicochemical quality attributes</p>

CCS Development



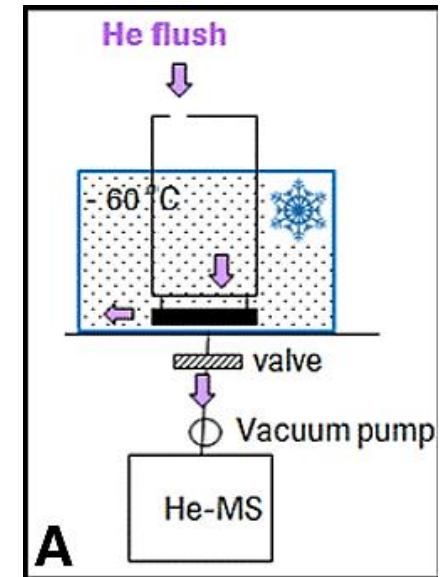
CCS Characterization – Impact of frozen storage

CO₂ Headspace Analysis



Nieto et al. ; Evaluation of container closure system integrity for frozen storage drug products; PDA J Pharm Sci and Tech 2016, 70, 120-133

He Leak Analysis at low temperature



Nieto et al. ; Evaluation of container closure system integrity for frozen storage drug products; PDA J Pharm Sci and Tech 2016, 70, 120-133

CCS Development/ Qualification and Validation

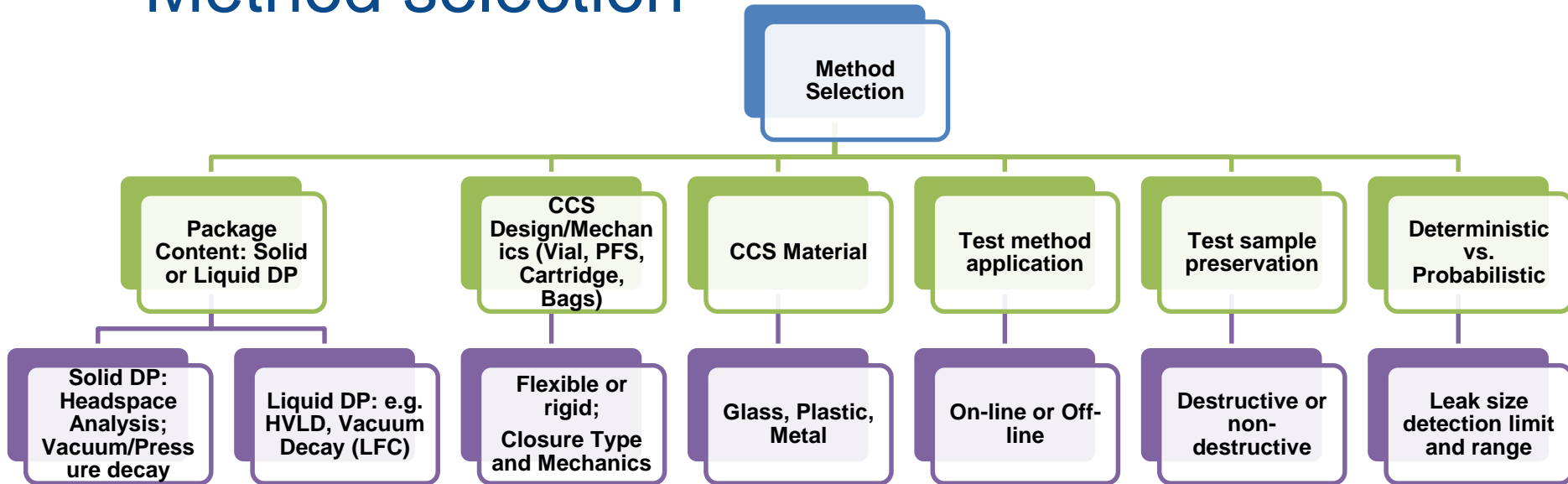
ICH Q8 (R2) (2009)

- 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 [...]

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.
- CCI should be demonstrated on product units that have been exposed to the maximum sterilization cycle(s) [...]
- For initial validation of microbiological integrity of CCS, product sterility testing is not normally considered sufficient. CCIT methods and results should be summarized to demonstrate the integrity of the microbiological barrier.
- The ability of the CCS to maintain the integrity of its microbial barrier, and, hence, the sterility of the DP throughout its shelf life, should be demonstrated [...]
- The sensitivity of the experimental method used for CCIT should be specified and provided.

Qualification and Validation – Method selection



USP 1207:

- No single package leak test or package seal quality test method is applicable to all product-packaging system
- Often more than one test method is employed during a given product's life cycle

USP 1207 – Deterministic CCI techniques (not all tabulated)

CCI Technique	Measurement Outcome and Data Analysis	Effect of Method on Package	Requirements: DP / CCS	Limit of Detection
Oxygen Headspace Analysis (HSA)	<ul style="list-style-type: none"> ▪ Quantitative measure of gas headspace content by laser-based gas analysis ▪ Leakage rate is determined by compiling readings as a function of time 	Nondestructive	<ul style="list-style-type: none"> ▪ Gas volume, path length and content must be compatible with instruments detection capability ▪ Allows transmission of near-IR light 	$< 1.4 \times 10^{-6} \text{ std} \cdot \text{cm}^3/\text{s}$ < 0.1 μm
Vacuum Decay (VD)	<ul style="list-style-type: none"> ▪ Quantitative measure of pressure rise within an evacuated test chamber ▪ Leakage rate is determined by comparing VD results to leak rate of PC 	Nondestructive	<ul style="list-style-type: none"> ▪ Gas or liquid must be present at leak site and product must not clog leak path ▪ Rigid, or flexible with package restraint mechanism 	$< 1.4 \times 10^{-4} - 3.6 \times 10^{-3} \text{ std} \cdot \text{cm}^3/\text{s}$ < 1.0 – 5.0 μm
High Voltage Leak Detection (HVLDT)	<ul style="list-style-type: none"> ▪ Quantitative measurement of electrical current ▪ Drop in elec. Resisivity, increase in voltage reading 	Nondestructive	<ul style="list-style-type: none"> ▪ Liquid, must be more electrically conductivity than package and must be present at leak site ▪ Less electrically conductive than liquid DP 	$< 1.4 \times 10^{-4} - 3.6 \times 10^{-3} \text{ std} \cdot \text{cm}^3/\text{s}$ < 1.0 – 5.0 μm
He-Leak	<ul style="list-style-type: none"> ▪ Quantitative measure by spectroscopic analysis of tracer gas ▪ Leakage rate is determined by NIST ref. standards 	Destructive	<ul style="list-style-type: none"> ▪ Tracer gas must be added to package ▪ Able to tolerate high vacuum test conditions and limited tracer gas permeability 	$< 1.4 \times 10^{-6} \text{ std} \cdot \text{cm}^3/\text{s}$ < 0.1 μm

USP 1207 – Definition of package integrity

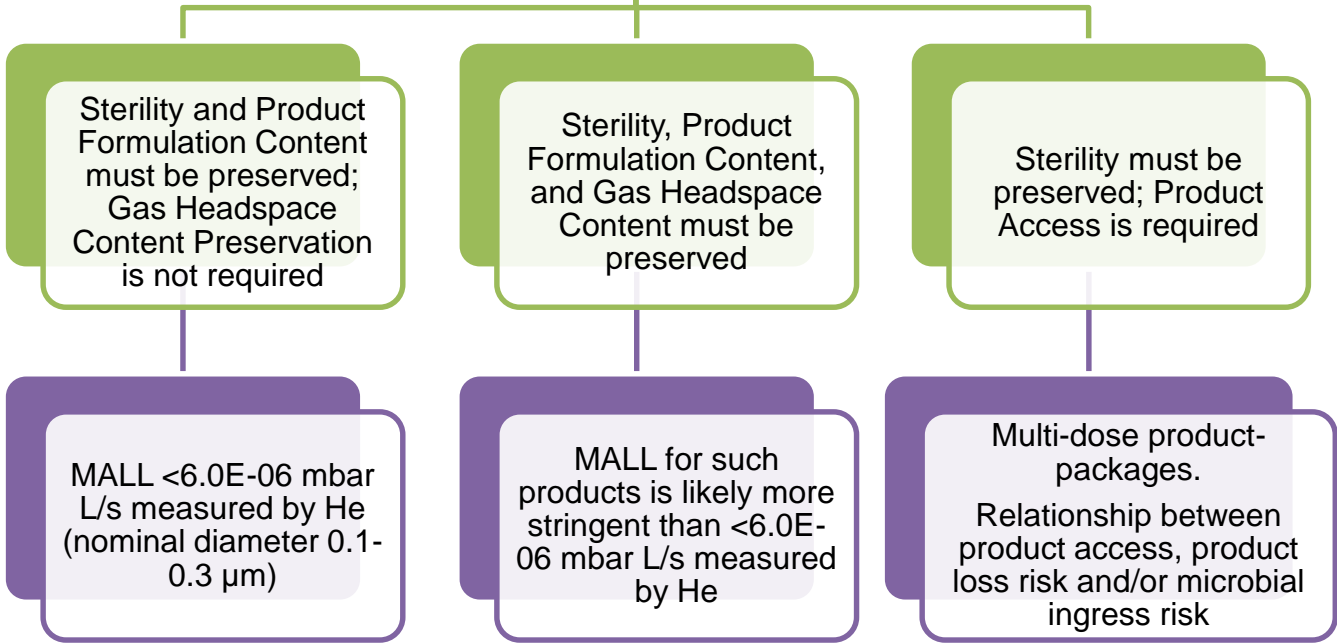
Inherent Package Integrity

- Inherent package integrity is the leakage rate (or leak size) of a well-assembled CCS using no-defect package components
- Inherent package integrity is a measure of the leak tightness of a CCS, given anticipated variables of material composition, dimension, processing, assembly, package storage, distribution and use

Maximum Allowable Leakage Limit (MALL)

- The MALL is the greatest rate (or leak size) tolerable for a given product-package that poses no risk to product safety and no or inconsequential impact on product quality
- The MALL for a sterile pharmaceutical dosage form package will ensure the content's sterility, preserve product contents, and prevent entry by detrimental gases or other substances, thus ensuring that the product meets relevant physicochemical and microbiological specifications through expiry and use
- For multiple-dose product-packages, the in-use MALL is defined as the degree of protection demanded of the closure to limit microbial ingress and product formulation leakage between and during dosage access

Maximum Allowable Leakage Limit



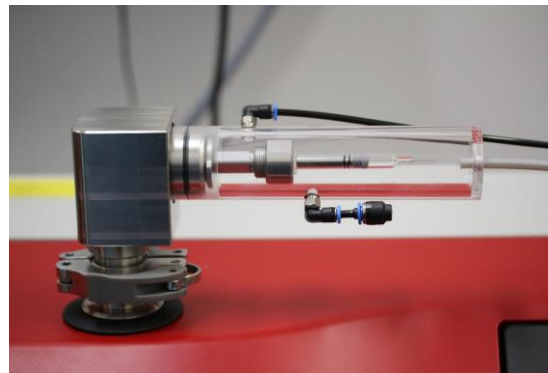
Example of Helium Leak Test Equipment: Janssen Method „Outside – In“ / „Flange Mode“

- ❑ Containers need to be cut and emptied (if filled with liquid)
- ❑ Containers are connected to the Helium mass spectrometer via custom made flange adaptors that are gas tight
- ❑ Helium is applied through the container
 - ❑ Continuously or
 - ❑ From a pre-filled chamber

Adaptors for certified He-Leak standards



Adaptors for pre-filled syringe
(plunger rubber stopper is tested)



Helium Mass Spectrometer



*Interlaboratory Study of Container Closure Integrity
He-Leak Test Method including Comparison of Different
Types of Artificial Leaks (PDA 2019)*

Example of Helium Leak Test Equipment: Sanofi Method „Inside – Out“ / „Chamber Mode“

- ❑ Containers need to be filled with Helium under Helium atmosphere in a glove box
- ❑ Containers are placed in a custom- made vacuum chamber connected to the Helium mass spectrometer
 - 2 vacuum chambers of different sizes available
- ❑ Container specific measurement conditions are applied – depending on size and container materials

Helium glove box



Closed test chamber “large”

Helium Mass Spectrometer



Cartridge device to prevent stopper movement



Opened test chamber “small”



He Leak Analysis – „Outside-In“ vs „Inside-Out

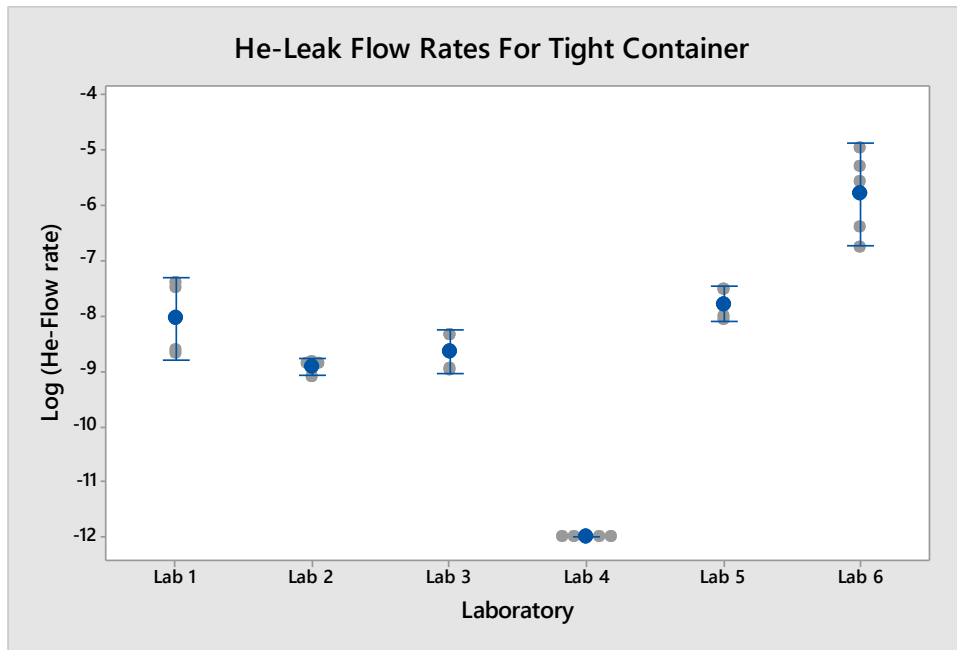
Advantages of “Outside – In” / Flange Mode Method

- Method can be used to test product filled containers (when emptied prior to analysis)
- Different sealing areas can be probed separately (e.g., needle shield vs. plunger stopper of a syringe)
- Applicable for release, stability testing and In-Process-Control (IPC)
- Method-setup can be used to support process optimization of filling lines – e.g. crimping optimization

Advantages of “Inside – Out” / Chamber Mode Method

- Results provide CCI information on the entire container closure system
- Method can be used for the following applications:
 - Characterization of new Container Closure Systems (CCS)
 - Comparative studies of different CCS options
 - Verification of leak sizes in positive controls (e.g. laser-drilled leaks)
- Method-setup not applicable for release, stability testing and In-Process-Control (IPC)

Interlaboratory Study of Container Closure Integrity He-leak Test Method including Comparison of Different Types of Artificial Leaks (PDA 2019)



- ❑ Laboratory 4 showed extremely low He-Leak rates (due to baseline correction, subtraction of He-baseline level from each value)
- ❑ Baseline on average (5 Labs, no baseline correction applied) = 7.9E-07 mbar L/s
- ❑ Very high variability within labs up to 114%
- ❑ Range: 7.9E-10 to 1.1E-05 mbar L/s

Method Validation

General requirements

- USP <1207.1> Package integrity testing in the product life cycle – test method selection and validation
- ICH Q2 Validation of Analytical Procedures
- USP <1058> Analytical Instrument Qualification
- USP <1225> Validation of Compendial Procedures

Test Instrument Qualification





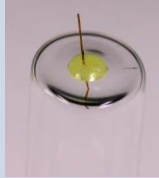

- Operational Qualification (Functionality):
 - Calibration tools e.g. temperature controllers
 - Instrument calibration certificates
- Performance Qualification:
 - Instrument Fixtures
 - Master Sample: A no-leak model of the CCS
 - Leakage reference standards: NIST He gas leak standards, size calibrated micro orifice

Method development/validation

- Development activity: Optimization of leak test method parameters
- Definition of PC: Which kind of artificial leak, Nominal hole size
- Validation activity:
 - Accuracy,
 - Precision,
 - Specificity,
 - Detection Limit, Quantitation limit
 - Linearity
 - Range,
 - Robustness

Positive Control

- ❑ USP 1207 mentioned different kind of positive controls
- ❑ Reason for positive controls:
 - To verify leaks at specific package location can be detected
 - To evaluate the impact of DP and possible other interfering factor (e.g. clogging effect)
 - To determine the leak limit of detection

	Glass vial	Steel capillary	Glass syringe	Glass capillary	Fused Silica capillary	Wire in syringe needle shield
						
Nominal size of leak	5 µm laser drilled	5 µm laser drilled	5 µm laser drilled	2 µm Glass capillary tip	5 µm ID capillary	60µm wire
Average He-Flow Rate	3.2E ⁻⁰³	3.1E ⁻⁰³	3.6E ⁻⁰⁴	3.9E ⁻⁰³	6.1E ⁻⁰⁶	2.0E ⁻⁰²

Interlaboratory Study of Container Closure Integrity
 He-leak Test Method including Comparison of Different Types of Artificial Leaks (PDA 2019)

Microbial Ingress Risk Comparison (USP 1207)

Comparison is not needed

If the validated CCI method has a proven **LOD < MALL** (>6.0 E-06 mbar L/s \approx 0.2 \pm 0.1 μ m)

If the validated CCI method is not used to verify the absence of all leaks of concern, e.g. a rapid online test **25-150 μ m**

Comparison is needed (direct or indirect)

If the validated CCI method has a proven **LOD > MALL** e.g 3 μ m hole size diameter

If the MALL is either lacking or **not well defined**

ICH Q9 – Guideline on Quality Risk Management

Scope

- Description of principles and examples of tools for quality risk management
- Can be applied to: development, manufacturing, distribution, lifecycle of drug product

Principles of Quality Risk Management

- The evaluation of the risk should be based on scientific knowledge and ultimately link to the protection of the patients
- The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risks

Quality risk management process

- Systematic process for the assessment, control, communication and review of risks to the quality of the DP across the product lifecycle
- Common quality risk management components:
 - Initiate Quality Risk Management Process
 - Risk Assessment (Identification, Analysis, Evaluation)
 - Risk Control (Reduction, Acceptance)
 - Result of the Quality Risk Management
 - Risk Review (Events)

Process Risk Assessment

pFMEA should be conducted for every process operation: Procurement of materials, In-coming control, Fill and Finish, Device assembly, Shipping, Storage

Validation activities should include each parameter that will become part of the manufacturing control strategy (line speed, heat-sealing temperature, screw-cap application torque, vial capping, sterilization process, labeling, packaging processes)

Evaluation can occur through a combination of development activities, representative small-scale activities, engineering/technical runs or routine clinical manufacture

Process Control Strategy (PCS) established prior to qualification activities for the product manufacturing process

Impact of Critical Process Parameters (CPP) regarding CCI should be evaluated including likely process extremes

Critical Process Parameters (CPPs) for product package integrity need to be controlled, measured and monitored in a direct or indirect manner to ensure consistent product quality

Manufacturing Control Strategy

Procurement of materials/ Incoming Material Control

- ❑ CCS component specification and requirements identified during development activities
- ❑ Assessment of the supplier's manufacturing process of primary packaging components (PPC)
- ❑ Incoming component quality control
- ❑ Appropriate procedures for establishing corrective and preventive action when vendor falls short of quality expectation



Fill and Finish

- ❑ Component sterilization (e.g. multiple sterilization cycles)
- ❑ Capping controls (depends on CCS):
 - Capping force (pre-compression force, residual seal force (RSF))
 - Capping plate height
 - Rotational speed of the turntables
- ❑ Plunger Placement:
 - Camera or laser-based inspection system for plunger presence and position
 - Inspection for sealing integrity e.g. DP solution between sealing rib and barrel



Labeling/Device Assembly/Secondary and Tertiary Packaging Process

- ❑ Device assembly control:
 - Risk assessment during design verification phase of device development
 - CCIT for critical assembly process steps or assessment by CCIT before and after assembly
 - X-Ray scan
- ❑ Camera, laser or vision control to ensure proper orientation of primary container in device and proper assembly of the device



Shipping/Commercial Product Stability

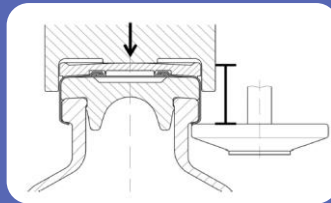
- ❑ Simulated or real-world shipping study to assess the potential impact on container closure integrity:
 - mechanical stress e.g. vibration
 - Temperature variation
 - pressure gradients of the container closure integrity
- ❑ CCIT should be a part of the stability protocol for sterile products

Characterization of the crimping process

Closure Type and Mechanism

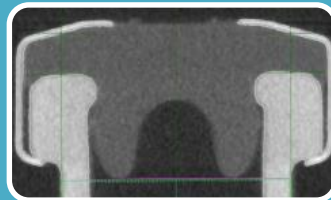


- **Physical Mated Closure:**
 - Two surfaces that often are dissimilar in material composition
 - Not bonded together → tiny gap exists even between well-closed components
- **Physicochemically Bonded Closures:**
 - Similar surfaces are mated of a heat or ultrasonic welding process
 - Dissimilar surfaces using an intermediate bonding material
- **Multiple-Dose Package Closure:**
 - Product access while limited microbial ingress and product leakage between doses



Vial Capping Process

- Capping plate height
- Compression Force
- Rotational speed of the turntables



Analysis of the Crimping Process

- Residual Seal Force (RSF) analysis
- Computed Tomography analysis (μ CT) of capped vials
- Analysis of He Leakage rates

- PPC Dimensional Controls
- PPC Functional Controls
- Define Critical Process Parameters
- CCI Following Exposure to Processing Extremes
- PPC Processing Equipment Qualifications

USP 1207 – Vendor selection

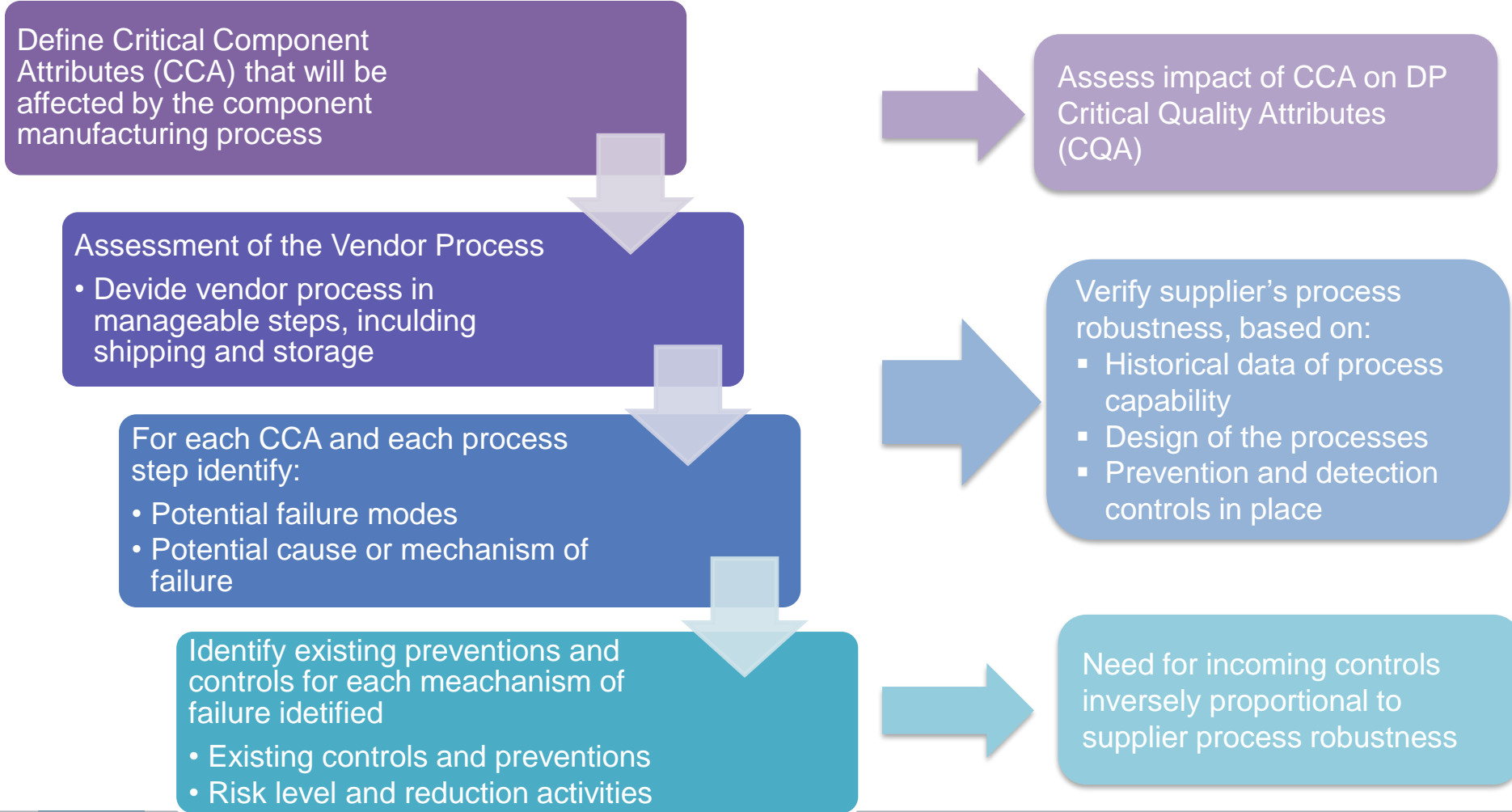
Acceptable results of the initial vendor or supplier evaluation

Appropriate vendor acceptance quality limits and statistical sampling plan(s), or relevant certification

Incoming component quality verification, including statistical assessment of quality against purchase specifications

Appropriate procedure(s) for establishing corrective and preventive action when a vendor falls short of quality expectations

Supplier control strategy to ensure that CCA are maintained during



US FDA (1994) Guidance for Industry of the submission Documentation for Sterilization Process Validation in Application for Human and Veterinary Drug Products

- For initial validation of microbial integrity of container CCS, product sterility testing is not normally sufficient. CCIT methods and results should be summarized to demonstrate the integrity of the microbiological barrier.
- The ability of the CCS to maintain the integrity of its microbial barrier, and, hence the sterility of a drug product throughout its shelf life should be demonstrated. [...] sterility testing at the initial time point is not considered sufficient to demonstrate the microbial integrity of a CCS.
- [...] Documentation of the sensitivity of the CCIT should be provided.
- [...] The sensitivity of the experimental method used for CCIT should be specified and provided

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

Current wording:

117. Container should be closed by appropriately validated methods. Container closed by fusion, e.g. glass or plastic ampoules should be subjected to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.

Proposed wording:

8.18. Containers should be closed by appropriately validated methods. Container closed by fusion, e.g. From-Fill Seal Small Volume Parenteral (SVP) & Large Volume Parenteral (LVP) bags, glass or plastic ampoules, should be subjected to 100% integrity testing. Samples of other containers should be checked for integrity utilising validated methods and in accordance with QRM, the frequency of testing should be based on the knowledge and experience of the container and closure system being used. A statistically valid sampling plan should be utilized. It should be noted that visual inspection alone is not considered as an acceptable integrity test method.

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

Proposed wording:

8.20 The container closure integrity validation should take into consideration any transportation or shipping requirements

8.23 In the case where capping is conducted as a clean process with grade A air supply protection, vials with missing or displaced stoppers should be rejected prior to capping. Appropriately validated, automated methods for stopper height detection should be in place. Microbial ingress studies (or alternative methods) should be utilized to determine the acceptable stopper height displacement.

Manufacturing Controls

Incoming Control/Component Preparation and Handling

- Control of Critical dimensions
- Washing (shrinking or deformation)
- Sterilization/Depyrogenation (stopper sticking)
- Mechanical stress → reduction of glass to glass contact

Plunger/Stopper insertion and Transportation of CCS

- Insertion mechanism e.g. vacuum parameter
- Stopper placement (stopper height detection system)

Crimping Process

- Compression force
- Capper plate height
- Residual Seal Force testing (RSF)
- 100% Visual Inspection
- IPC testing

Visual inspection

- Visual analysis of CCS specific parameter e.g. crimp cap or glass cracks
- Insufficient sealing and broken closure
- DP solution between plunger and barrel

Device Assembly and Packaging & Labeling

- Appropriate CCIT before and after the assembly process
- 100% visual inspection of primary container orientation in device and proper assembly of the device

CCIT during batch manufacturing

Despite usage of the holistic CCI approach (QbD) it may be required to conduct CCI testing during manufacturing

Specific regulatory requirements may result in CCI testing per each manufactured batch

CCI testing frequency could be realized by a statistically valid sampling plan or by 100% testing utilizing nondestructive leak test methods

Manufacturing testing strategies could depend on **CCS** (100% testing required for CCS closed by fusion), **sensitive headspace** (inert gas), **process risks** based on risk assessment

In contrast of CCI testing performed on each batch manufacturer may implement a rationale for an alternate frequency (e.g. experience with CCS and manufacturing process)

Shelf-life Stability

FDA

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.

ICH

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.

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



Sterility test: Release + Expiration

- For products labeled as sterile, we considered sterility to be a **stability characteristic**.
- The minimum sterility testing generally performed is at the **initial time point (release)** and **final testing interval (i.e. expiry)**



Sterility test is not recommended for shelf life

- Due to **limitation the sterility test** is not recommended as a component of a stability program
- **Alternative methods** may be more reliable in confirming the integrity (e.g. sterility test can only measure microbial ingress, unable to test the gas headspace content)



Implementation

- CCIT could **replace** sterility testing in a stability program
- CCIT **do not** replace sterility testing methods for product sterility testing **prior to release**
- CCIT is **adequately validated** – capable of detecting a **breach** in the container
- CCIT should be conducted **annually and at expiration**

CCIT during product stability

Performance of the CCS over shelf life should be known → development activities according „holistic CCI approach“

Annual stability tests provide a limited data set and cannot replace the QbD and routine monitoring of filling/assembly operations

CCIT is commonly performed for commercial parenteral DP during ICH stability at long-term storage conditions

Common practice for CCIT on stability to adopt a similar sample size to sterility testing, which is justifiable by thoroughly evaluation and validation activities of the aseptic manufacturing process applying an appropriate sample size

Regulatory expectations for CCIT in relation to shipping

21 CFR Part 211 - Current Good Manufacturing Practice For Finished Pharmaceuticals

- *“(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.”*

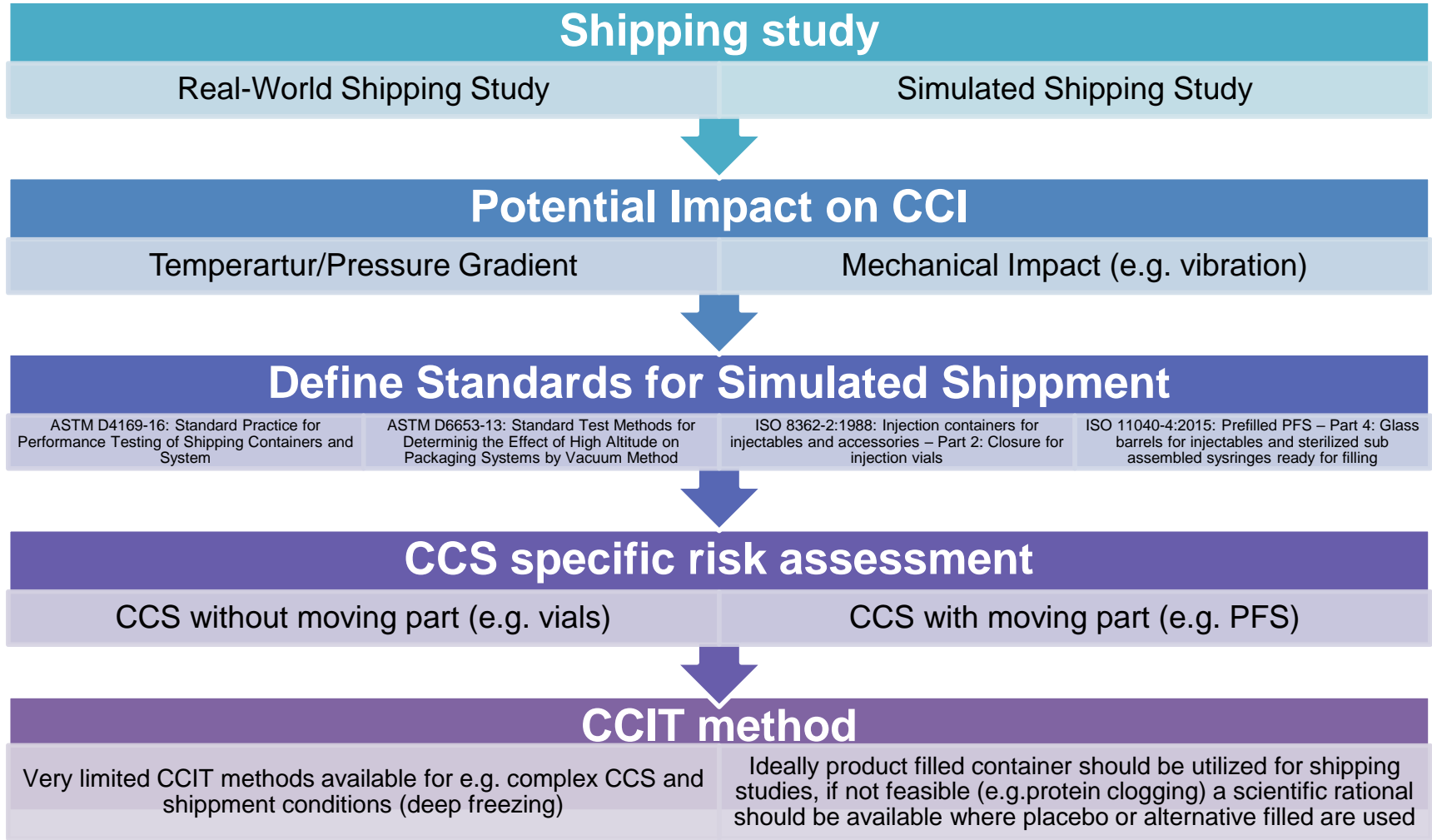
EudraLex Volume 4, Annex 1 – Manufacture of Sterile Medicinal Products (last revision)

- *8.20 “The container closure integrity validation should take into consideration any transportation or shipping requirements”*

Shelf-life Stability

- In-use Stability
- Supply CCI in lieu of Sterility on stability
- Chain and End-User Exposures (Temperature, Humidity, Pressure, etc.)

Impact of shipment on CCI



Product Life Cycle

Change in PPC

- Package integrity re-evaluation for changes in:
 - Design
 - Materials
 - Manufacturing/Processing conditions
- Evaluation of required testing is based on impact assessment

Manufacturing Line Modification

- Re-evaluation of the pFMEA, assessing CPPs regarding CCI
- In case CCI could be impacted the CCP should be studied including process extremes

New Technology Upgrades

- Impact Assessment on e.g. testing procedure, specification limits or the manufacturing process
- Instrument qualification
- Feasibility study, method development and validation activities

Trend Analysis

- Product's package profile is compiled over the course of commercial manufacturing
- Analysis of leak and seal quality test results (database) may be linked to variations in package component design/material and package assembly/processing

Holistic CCI Approach

Holistic CCI Approach includes the following aspects: CCS Development, Qualification and Validation, PPC Processing, Manufacturing Controls, Shelf Life Stability, Product Life Cycle

The holistic CCIT approach is in alignment with the principles of Quality by Design (QbD) explained in ICH Q8(R2) and Quality Risk Management (ICH Q9), which is to shift the focus to invest more in understanding the risk associated with product and process characterization and control instead of testing to quality.

Thank you for your attention



References

- US FDA (1999) Guidance for Industry: Container Closure System for Packaging Human Drugs and Biologics
- 21 CFR Part 211 – Current Good Manufacturing Practice for Finished Pharmaceuticals
- 21 CFR Part 600 – Biological Products: General
- EudraLex Volume 4, Annex 1 - Manufacture of Sterile Medicinal Products
- EudraLex Volume 4, Annex 2 - Manufacture of Biological active substances and Medicinal Products for Human Use
- EudraLex Volume 4, Annex 10 - Manufacture of Pressurised Metered Dose Aerosol Preparations for Inhalation
- FDA Guidance for industry (1999), Container Closure Systems for Packaging Human Drugs and Biologics
- FDA Guidance for industry (2004), Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice
- FDA Guidance for industry (2008), Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products
- EudraLex Volume 4 (2017), Guidelines on GMP specific to Advanced Therapy Medicinal Products
- ICH Q5C Guidance for the industry „Quality of Biotechnological products: Stability testing of Biotechnological/Biological products“
- ICH Q8(R2) – Guideline on Pharmaceutical Development
- ICH Q9 – Guideline on Quality Risk Management
- US FDA (1994) Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products
- USP <1207> Package Integrity Evaluation
- USP <1207.1> Package integrity testing in the product life cycle – test method selection and validation
- USP <1207.2> Package integrity leak test technologies
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