Container Closure Integrity

Container Closure Integrity Control versus Integrity Testing during Routine Manufacturing
White Paper: Container Closure Integrity Control versus Integrity Testing during Routine Manufacturing

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1. Introduction

Container closure integrity (CCI) is the ability of a container closure system to maintain the sterility and product quality of sterile injectable pharmaceutical, biological, and vaccine products throughout their shelf life.

It is a regulatory requirement that the design of a container closure system be qualified. There are multiple methods available to qualify the effectiveness of a selected container closure system as detailed in industry guidance and literature. Selection of an appropriate method is based on the container closure system to be qualified and its contents. The normal variation within the manufacturing process should be testing during routine manufacturing should be considered. The scope of this paper includes drug product manufacturing of sterile injectable products, including vials, syringes, bags for intravenous application, and inhalation products, but not products compounded in pharmacies.

2. Establishing Process Control: A Holistic Approach

Demonstration of CCI is required throughout the lifecycle of a sterile pharmaceutical product, assuring integrity of the closure system through to its expiration date.
Current Requirements:

CCI demonstration is required throughout the lifecycle

Initial CCI qualification/validation requirements are well defined

Fused packages require 100% integrity testing

For other container types, in-process integrity testing is not a regulatory requirement
In-Process Controls

Advancing Technology

100% Integrity Testing
An Integrated Holistic System

Communication

Package Engineering

Commercial Manufacturing

Manufacturing Science and Technology

Quality and Regulatory Departments
An Integrated Holistic System

Holistic CCI

- CCI Test Method
- CCI for Commercial Stability
- Change Control Process
- Primary Package (Design)
- Product Manufacturing Process
- Manufacturing Process
An Integrated Holistic System
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No Single Test Method:
- Package configuration
- Product Type
- Leak Quality Risk
- Use

Industry practices are variable with regards to test method selections, validation approaches and the use of positive and negative controls.

<table>
<thead>
<tr>
<th>Leaks of Concern</th>
<th>Product Quality Risks Posed by Leaks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capable of allowing entry of microorganisms</td>
<td>Failure of product sterility quality attribute</td>
</tr>
<tr>
<td>Capable of allowing escape of the product dosage form or allowing entry of</td>
<td>Failure of relevant product physicochemical quality attributes</td>
</tr>
<tr>
<td>external liquid or solid matter</td>
<td></td>
</tr>
<tr>
<td>Capable of allowing change in gas headspace content. For example, loss of</td>
<td>Failure of relevant product physicochemical quality attributes and/or hindrance of product access by</td>
</tr>
<tr>
<td>headspace inert gases (e.g., nitrogen), loss of headspace vacuum, and/or entry</td>
<td>the end-user</td>
</tr>
<tr>
<td>of gases (e.g., oxygen, water vapor, air).</td>
<td></td>
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</tbody>
</table>
Microbial Ingress

• Referee method? (widely used for decades)
  – Outside of the container is challenged with a microorganism at a prescribed concentration (broth culture or aerosolized), typically while cycling a vacuum/pressure
  – Visual turbidity is the end point analysis

Advantages
• Widely used for decades
• Well known with regulators
• Easily included in a media fill

Disadvantages
• Less sensitive, non-quantitative
• Detection is probabilistic for small-size defects (< 20 μm)
• Requires growth media
• Off-line
• Not suitable for stability testing
• Not suitable for assessing non-microbial leaks, e.g. O₂, H₂O, etc
Dye Leak/Ingress

• Common physical test method (also widely used)
  – A vacuum is cycled in a chamber containing the test container and a tracer liquid (dye), e.g. methylene blue, at a prescribed concentration
  – Visual presence of dye is the typical end point, spectrophotometers may also be used to detect the presence of dye

Advantages
• Widely used for decades
• Industry & Regulatory familiarity
• Std test methods available from ASTM & ISO
• Simple

Disadvantages
• Less sensitive, non-quantitative
• Detection is probabilistic for small-size defects (< 20 μm)
• Destructive
• Off-line
• Not suitable for opaque, non-transparent containers
Vacuum/Pressure Decay; Mass Extraction

- Physical integrity test method
  - Samples are pressurized or placed in a vacuum chamber
  - Pressure or vacuum is applied for a period of time
  - Endpoint analysis is a review of any change over time that would indicate a breach in integrity

Advantages
- Sensitive, leaks ≥ 1 μm
- Quantitative
- Can be used on colored, opaque and labeled containers
- Non-destructive

Disadvantages
- Certain products may interfere with defect detection
- May not distinguish between a leak and multiple small leaks
- Off-line system
Helium Leak

- Mass Spectrophotometry based leak rate detection
  - Helium is sealed in the test container then placed in a measurement chamber
  - The rate of He detection can be correlated to the size of the breach

Advantages
- Very sensitive, detects leaks ≥ 0.001 μm
- Quantitative, accurate and reproducible

Disadvantages
- Destructive test
- Limited number of vendors doing the testing
- Certain products may interfere with defect detection
- Expensive
- Off-line
Headspace Analysis

- Laser-based gas headspace analysis
  - Near-IR light is used to detect the presence of O₂, CO₂, H₂O, etc.

Advantages
- Sensitivity varies, capable of detecting leaks ≥ 5 μm
- 100% on-line testing feasible
- Quantitative, non-destructive, non-contact, non-invasive
- No sample prep. required
- Capable of measuring O₂, N₂, CO₂, H₂O & internal pressure

Disadvantages
- Requires:
  - A minimum gas volume and a modified headspace
  - Container that allows transmission of near-IR light
  - Time for gas exchange
- Pressure measurements are temperature dependent
High Voltage Leak Detection (HVLD)

- Electrical Conductivity and Capacitance Testing
- HVLD testing process consists of a set of electrode probes which scan a sealed container

Advantages
- Sensitivity varies, capable of detecting leaks ≥ 5 μm
- 100% on-line testing feasible
- Non-destructive, non-contact, non-invasive test
- No sample prep. required
- Applicable to high-conc. proteinaceous products

Disadvantages
- Requires:
  - conductive liquid fills that are non-combustible
  - Container material must be non-conductive
  - Product must be present at the leak site
- Some products sensitive to the voltage used
An Integrated Holistic System

Holistic CCI

- CCI Test Method
- CCI for Commercial Stability
- Change Control Process
- Component and Product Quality Monitoring
- Design Qualification
- Component Specs
- Package Robustness
- Product Manufacturing Process
- Manufacturing Process
- Method Selection
- Method Validation
- Method Development
- Assembly Qualification
- Equipment Qualifications
- Technical Transfers
- Final Inspections
- Verify Package Integrity
- Component QA

Distribution
- CAPA
- Continuous Improvement
- Innovations
- End-User Environment
An Integrated Holistic System

Component QA

- Vendor inspections
- In-house quality acceptance limits
- Incoming quality verifications
- Visual verification (AQL or 100%)

CCIT during Routine Production

- At-line process control options:
  - In-line component inspections:
  - Seal force
  - 100% non-destructive CCIT

Final CCI Inspections (off-line)

- 100% Visual Inspection
An Integrated Holistic System
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Re-assess

Benchmark

Re-evaluate

Make Changes

Profiling
Should I implement 100% CCIT during routine manufacturing?

**Challenges:**

- The 100% CCI test must be non-destructive
- Retrofitting
- Test method sensitivity ↔ manufacturing line speeds
- Leak detection instrument malfunctions may cause production downtime
- Limited industry guidance documents are available for the validation of the process.
• Can provide real time assurance of seal integrity, thus providing instant feedback

• 100% CCIT can help during the investigation process

• If done well, it’s a good IPC and provides greater assurance of seal integrity
What is Clear:

- Very Little is Clear

- Assurance of container closure integrity is expected to be built into the manufacturing process, as part of a holistic system

- Justification must be provided for your approach (with or without in-line CCIT)
  - Why is your approach an acceptable option for the drug product/container closure system under review?

- Filing historical CCI test methods without further evaluations will invite additional questions, so be prepared...
Is your approach **JUSTIFIABLE** based on the current regulatory requirements and guidelines?

Is your approach **DEFENDABLE** to the regulatory agencies?

Each company is **RESPONSIBLE** for their own individual risk assessments!