Container Closure Integrity Testing and Finishing

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Container Closure Requirements

EU GMP Annex 1

Original Language

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.

118. The container closure system for aseptically filled vials is not fully integral until the aluminium cap has been crimped into place on the stoppered vial. Crimping of the cap should therefore be performed as soon as possible after stopper insertion.

121. Vials with missing or displaced stoppers should be rejected prior to capping. Where human intervention is required at the capping station, appropriate technology should be used to prevent direct contact with the vials and to minimise microbial contamination.

123. Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.

124. Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eye-sight checks, with spectacles if worn, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. Results should be recorded.

100% testing for fused containers.

Definition of integral vial.

Capping process.

Containers under vacuum.

Visual Inspection

Sections 8.21-8.25 Container Closure Integrity (CCI)

- Changes in the last several draft revisions.
- Significant implications for SVP and LVP bags.
- Appropriately validated physical integrity test methods.
- Scientifically justified sampling plans.
- Product life cycle approach

Container Integrity – sealing / closing process

8.21 Final containers should be closed by appropriately validated methods.

- Validated methods
- Scientifically justified QRM strategy
- Physical measurement of integrity
- Scientifically justified sampling plans

Container Integrity Testing – Fusion Sealed

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**.

- Validated methods
- Scientifically justified QRM strategy
- Physical measurement of integrity
- Scientifically justified sampling plans

Container Integrity Testing - General

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**.

- Validated methods
- Scientifically justified QRM strategy
- Physical measurement of integrity
- Scientifically justified sampling plans

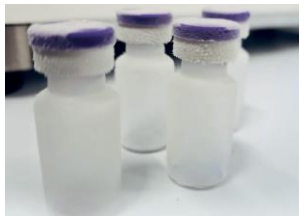
Container Integrity – Vacuum Retention

8.24 Containers sealed under vacuum should be tested for maintenance of vacuum after an appropriate pre-determined period prior to certification/release and during shelf life.

- Validated methods
- Scientifically justified QRM strategy
- Physical measurement of integrity
- Scientifically valid sampling plans

Container Integrity – Transportation & Shipping

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).



- Validated methods
- Scientifically justified QRM strategy
- Physical measurement of integrity
- Scientifically justified sampling plans

Remarks: 8.22 – 8.23 CCI Testing

- Validated methods for CCIT
- Based on knowledge and experience of the container and closure systems: product life cycle approach with implied requirements on development
- Scientifically justified sampling plan.
- Visual inspection alone is not considered as an acceptable integrity test method.

Validated methods

Scientifically justified QRM strategy

Physical measurement of integrity

Scientifically justified sampling plans

Remarks: 100% Inspection of Flexible Parenterals

Challenging:

- Line speed and surface moisture
- Product physiochemistry
- Flexible geometries
- IV Overwrap
- Physics of current technologies

Remarks: Improving Assurance & Data Generation

USP <1207> Deterministic: the leakage event is based on phenomena that follow a ***predictable*** chain of events, and leakage is ***measured*** using ***physicochemical technologies*** that are readily ***controlled*** and ***monitored***, yielding objective ***quantitative data***.

Deterministic methods

- Electrical Conductivity and Capacitance (HVLD)
- Laser-Based Gas Headspace Analysis
- Mass Extraction
- Pressure Decay
- Tracer Gas Detection, Vacuum Mode
- Vacuum Decay

Other validated methods exist and require knowledge and justification of the application, and a scientifically justified approach to the method and sampling.

Supporting Resources

ISO 11607

- Menu of ASTM methods for container validation.
- Not inclusive of all recognized methods.
- Includes method focused on sterile barrier (F02) and transportation (D10).

USP <1207>

- Prescriptive guidance document for container closure integrity.
- Detailed summary of available deterministic test methods.

PDA TR 86

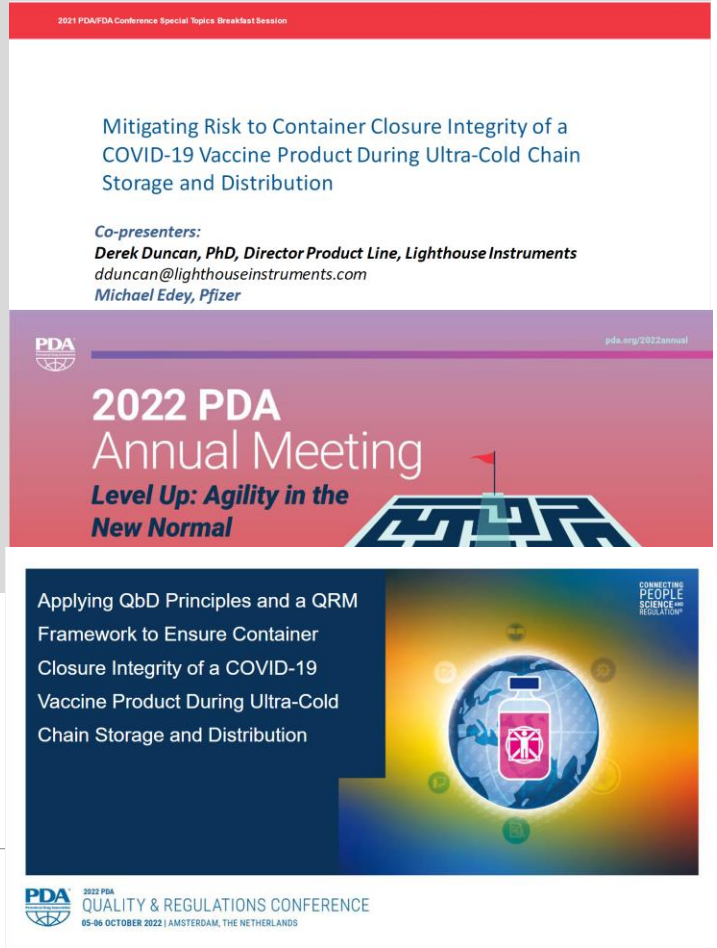
- Review best practices for CCI.
- Provides insights and guidance on methods outlined in USP <1207>.

Guiding Questions

- What CCI test methods do you use today?
- Are the deployed test methods appropriate for generating the required container performance data?
- Are QRM / QbD principles applied in a product life cycle approach?
- What is your current sampling plan? Is it commensurate with the product/application risk?
- What tools do you use for sample size and frequency justification?
- Can you place CCIT strategy into a holistic framework? (container closure integrity assurance - CCIA)

Example Industry Case Study: Pfizer COVID-19 Vaccine

EU GMP Annex 1



Evolving Regulatory Landscape – Published Annex 1

Volume 4 EU Published Annex 1 now states

- Under Pharmaceutical Quality System (PQS), use of risk management also its use in a contamination control strategy (CCS) and lists container integrity in this section.

- 'Risk management is applied in the development and maintenance of the CCS, to identify, assess, reduce/eliminate (where applicable) and control contamination risks. Risk management should be documented and should include the rationale for decisions taken in relation to risk reduction and acceptance of residual risk.'

Evolving Regulatory Landscape – Published Annex 1

- ….'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.'

Emphasis with this approach is the importance of packaging and process data collection during development and validation phases with QRM

- '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).'

Development of a Robust Package of a mRNA vaccine

- Selection of readily available primary packaging components – Vial/ Stopper/Flip off Aluminum Seal.
- QbD used to produce a test plan that takes a science-based holistic approach
- Use of risk assessment to document existing process and material controls lowering reliance on stability program
- Use of empty containers to ensure no product interference ie; leak path blockage
- Use of seal quality as part of a control plan for the risk of temporary leaks, rather that CCI

Quality by Design (QbD) Application in CCI

- Application of QbD principles to the development phase.
- Use a risk assessment using ICHQ9 principles in this case a pFMEA to assess risk to package integrity across the lifecycle of the product
- Developed a test plan based on the assessment of;
  - ✓ Target product profile that identifies the CQAs ie; frozen product
  - ✓ Critical material attributes - CMAs ie; Tg of stoppers
  - ✓ Process design and understanding identifies the CPPs ie; need for freezing below stopper Tg
  - ✓ Control strategy with consideration for specifications including vial and stopper CpK – Execution By Pfizer Team in later section on Data Analytics
  - ✓ Control strategy controls during each step of the manufacturing process ie: Use of a seal quality measure – Residual Seal Force (RSF)

Ensuring CCI of a mRNA vaccine

A science-based holistic approach was defined

1. Develop headspace CCIT method for use in development studies
2. Execute CCI studies to test and choose primary packaging components (vial/stopper combination)
3. Generate science-based statistical RSF vs. CCI data
4. Characterize sealing performance of the production lines (RSF testing)
5. Determine acceptable limits for crimping settings per line.
6. Qualify production line CCI with lower and upper crimping limits
7. Use validated CCIT method for shipping validation, worst case fit testing, batch testing, end of shelf-life testing as appropriate

Key Takeaways: Ensuring CCI of a mRNA vaccine

- It is known that deep cold storage poses risks to the CCI of stoppered vials
- QbD principles applied with a risk assessment – which follows published Annex 1
- It was therefore necessary to perform robust development studies to do the following:
  - ✓ Choose appropriate primary packaging components
  - ✓ Determine the critical attributes affecting CCI at ultra cold temperatures (Freezing Rate, End Point Temperature and Compression Force)
  - ✓ Qualify the vial sealing process (Capper Qualification)
  - ✓ Validate CCI for deep cold storage and cold chain transportation
- Holistic science-based approach was defined using statistical sample enabling data-driven decisions on packaging components and capping & crimping settings
  - ✓ Lab studies performed CCI and RSF testing on tens of thousands of vials
  - ✓ RSF implemented in production as on going in-process monitoring tool

Thank You