A case study for seal quality and container closure integrity testing across the life cycle of sterile products

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Presentation overview

Topics

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   i. Review of revised contents
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   iii. Defining CCIT and seal quality requirements
2. Renovating the internal standard
   i. Building a strategy
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4. Summary

Review of revised contents

A major change to initiate a gap assessment

USP <1207> - Package Integrity Evaluation – Sterile Products

Content examples

Former USP <1207>	Revised USP <1207>
2 pages	**~40 pages** comprising 4 chapters
Product life cycle approach	Product life cycle approach with **in-depth review** of the subject
Physical CCIT to be correlated to microbial CCIT in development	**Correlate test sensitivity to product risk**, i.e. microbial contamination, gas ingress, or multi-use
Preference to use physical methods with sensitivity comparable to or greater than microbial methods	**Deterministic methods are preferred** over probabilistic leak test technologies when establishing inherent integrity, sample quantity is limited, or risk of leak of concern is too great
Seal quality tests may be valuable	**Seal quality tests complement evaluation** of package integrity
Dual function container closure systems are considered	Supports **rationales for the method sensitivity across the product life cycle**
	Reviews **test method selection, instrument qualification, method development, and method validation**
	References **peer-reviewed scientific publications** on CCIT and seal quality test methods

Product quality risks

Posed by leaks of concern

Leaks of Concern	Product Quality Risks Posed by Leaks
Capable of allowing entry of microorganisms	Failure of **product sterility**
Capable of allowing escape of the product dosage form or allowing entry of external liquid or solid matter	Failure of **relevant** product physicochemical **quality attributes**
Capable of allowing change in gas headspace content	Failure of **relevant** product physicochemical **quality attributes** and/or **hindrance of product** access by the end-user

The container closure integrity must ensure absence of all package leaks that risk product quality.

CCIT and seal quality testing

Defining the requirements

Inherent package integrity – the leakage rate of a well-assembled CCS using defect-free components. Should be measured using a method to qualify the CCS against the potential risk, e.g. microbial ingress.

→ Acceptance criteria depend on product requirements (science and risk-based)

Maximum allowable leak limit – greatest leakage rate tolerable for a given product

→ Acceptance criteria depend on product requirements (science and risk-based)

Seal quality tests - used to characterize and monitor the quality and consistency of a package seal or closure system parameter, which can influence the ability to maintain integrity. Are not leak tests.

→ Acceptance criteria depends on the critical quality attribute, e.g. force, dimension, etc.

Building a strategy

Step by step

- Describe the issue
  - Educate about the revised USP <1207>
  - Discuss with stakeholders to increase awareness
  - Engage all necessary functions
  - Create a global network to do a full gap assessment
- Assess the status quo
  - Report on the current ways of working
  - Identify the risks to mitigate
  - Align on best practices

Identifying internal requirements

Goals to achieve success

- Collaborate across the global network
  - Re-invigorate and standardize the end-to-end approach
  - Develop a deeper knowledge of the CCS across the product lifecycle
  - Harmonize a strategy across divisions, departments, and line units
- Meet HA expectations
  - Revised USP <1207> shows a move towards using deterministic methods
  - Understand the drivers from probabilistic to deterministic CCIT
- Optimize the way of working
  - Apply the right method at the right time with the right amount of samples (the right efficiency)
  - Define methods that remain current and for what purpose
  - Define methods that require development

Creating the plan

Based on gap assessments and best practices

- Define the strategy
  - Determine the scope, e.g. life cycle approach, products in development vs. currently marketed, global and local needs
  - Develop a position paper for the strategy
  - Collect broad feedback for more points of view
  - Seek sponsorship from senior management, e.g. Quality Plan
  - Create sub-teams to define tasks & timelines
  - Secure global and local resources

Life cycle approach

Quality assurance of sterile products

Development

- Planning
- Requirement setting
  - ✓ Maximum allowable leak limit
- Qualify closure system
  - ✓ Inherent package integrity
  - ✓ Seal quality
- Technical studies
- Tech transfer docs

Validated processes

- Closuring
- Packaging
- Shelf life
- Shipping

Quality Controls

- Supplier mgmt
  - ✓ Specs
  - ✓ Quality agreement
  - ✓ Audits
- Incoming goods inspection
- IPCs
- Cameras
- Seal quality
- CCIT
- Change control
- Monitoring

Stability programs

- Standard approach across life cycle phase
- Strategic on CCS format

Seal quality attributes

On specific formats

CCS formats for sterile products (examples)

Vials, pre-filled syringes, cartridges, bottles, bags, tubes, ampoules, etc.

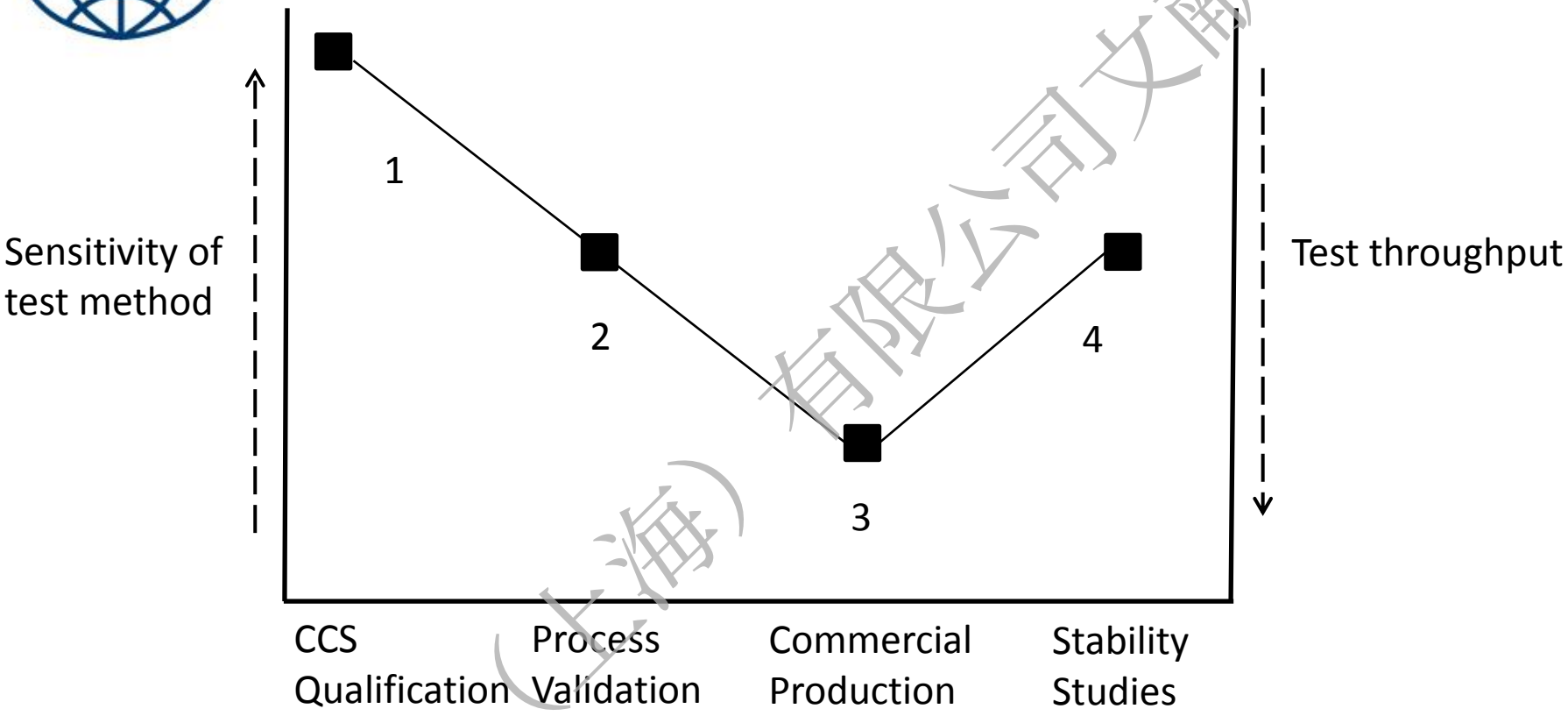
Out of scope:
Blister trays for medical devices (governed via ISO 11607) and others mentioned in revision

Seal quality methods

Closure	Seal Quality Attribute (examples)
Septum or stopper	residual seal force, compression, crimp dimension, headspace gas
Plunger	rib dimension, piston placement, movement during shipping or manufacturing, headspace gas
Needle cap	pull-off force, dimensional fit against needle
Bottle cap	critical feature dimensions, closure application and removal torque
Bag	burst strength, peel force, airborne ultrasound

A test method strategy

Over the product life cycle



<u>Examples of test methods to fulfill requirements</u>

1 – Leak flow method, e.g. tracer gas or headspace monitoring. Correlation of pCCI to mCCIT and seal quality.

2, 4 – HVLD, mass extraction, vacuum decay, blue dye ingress, etc. Relevant seal quality test.

3 – 100% online, e.g. HVLD, vacuum decay or offline CCIT and/or seal quality test.

Summary

- USP <1207> is a major update and a gap assessment is recommended between it and the current way of working
- A case study was presented for the following:
  - Building a strategy for closing gaps and mitigating risks
  - Rationalizing CCIT and seal quality methods as part of the quality assurance with a scientific- and risk-based approach
  - Applying various test methods across the product life cycle for specific CCS formats

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