Container Closure Integrity: Regulations, Test Methods, Application - Test Method Selection and Application

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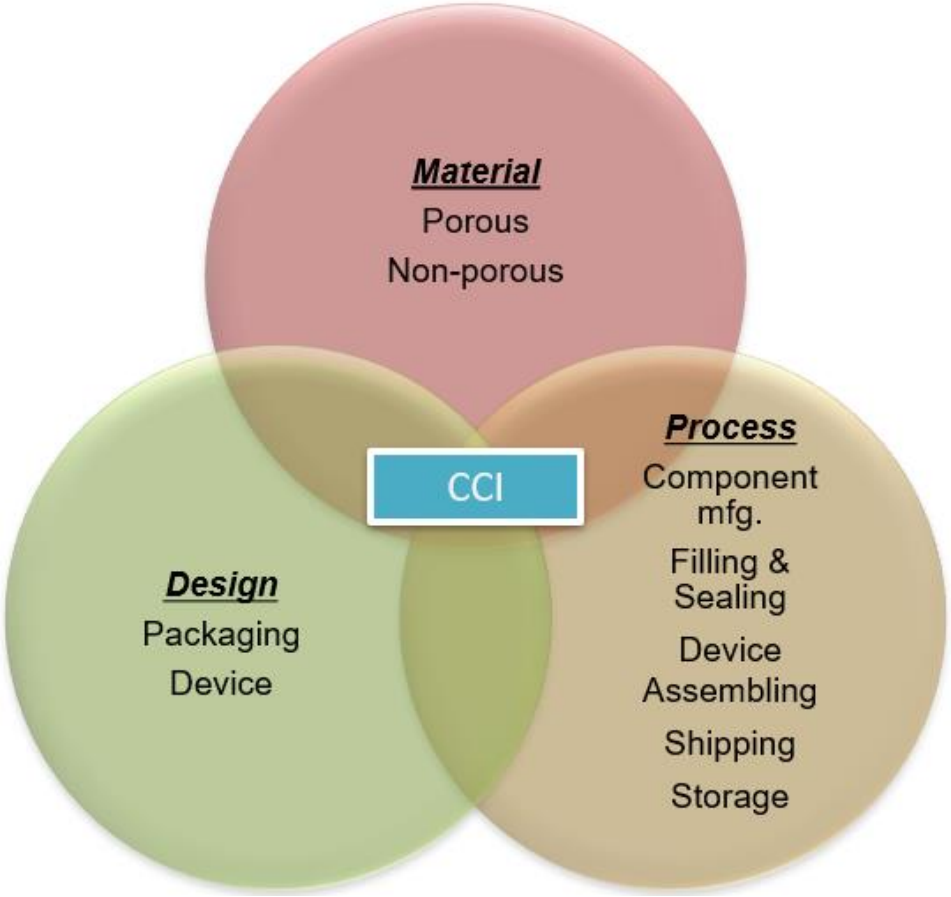
Outline

Test method selection and applications

- Container closure integrity control strategy development
  - Risk based approach
- Product lifecycle and CCI testing
- Test method selection considerations
- Case study – Group Exercise & Discussions

CCI Control - Key Considerations



Material and Design

Physically Mated Closures

- Closure made by close physical contact of surfaces
- Surfaces are often dissimilar in material composition
  - *Examples:*
    - Stopper/vial
    - Syringe
      - Barrel/plunger (piston)
      - Needle shield/needle tip
      - Needle shield/syringe luer
    - Screw-cap/bottle

NOTE: Bottle/cap threads *do not offer an optimal barrier* to gas or liquid leakage, or to microbial ingress in the event of liquid in cap threads.

- Tiny gap(s) permitting gas leakage exist
- Extent of closure (leakage prevention) is a function of
  - Surface morphology
    - Surface viscoelasticity
      - *E.g.*, Coated vs. uncoated elastomeric closures
    - Forces holding components together
      - *E.g.*, Residual seal force of stopper/vial

Material and Design

Physico-chemically Bonded Closures

- Closure made by material P-C bonding/fusion
- Material composition may be similar or dissimilar
- An intermediate layer may provide bonding
  - *Examples*
    - Syringe
      - Needle base/barrel adhesive bond
    - Heat-sealed film/tray
    - Ultrasonically welded IV bag seal
    - Glass/plastic ampoules

- Gas permeation exists thru bonding material and/or components
  - *Exception*: glass ampoules

- Leakage (if present) is a function of bond completeness
  - *E.g.*, Frangible vs. non-frangible heat seal

Material and Design

Multi-dose Package Closures

Designed to permit product access while limiting microbial ingress and product leakage between doses.

Examples

- **Parenteral product closures punctured for product access**
  - Elastomeric closures on vials, cartridges
- **Ophthalmic dosage form packages**
  - Specialized closure mechanisms with plugs, filters, pinch points or other

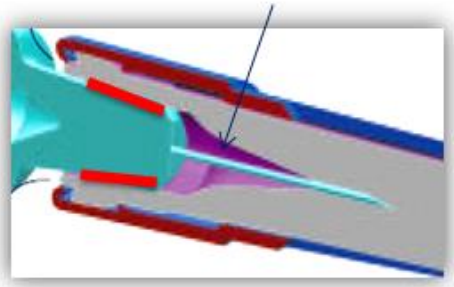
Example - Prefilled Syringe

Drug Product Compartment

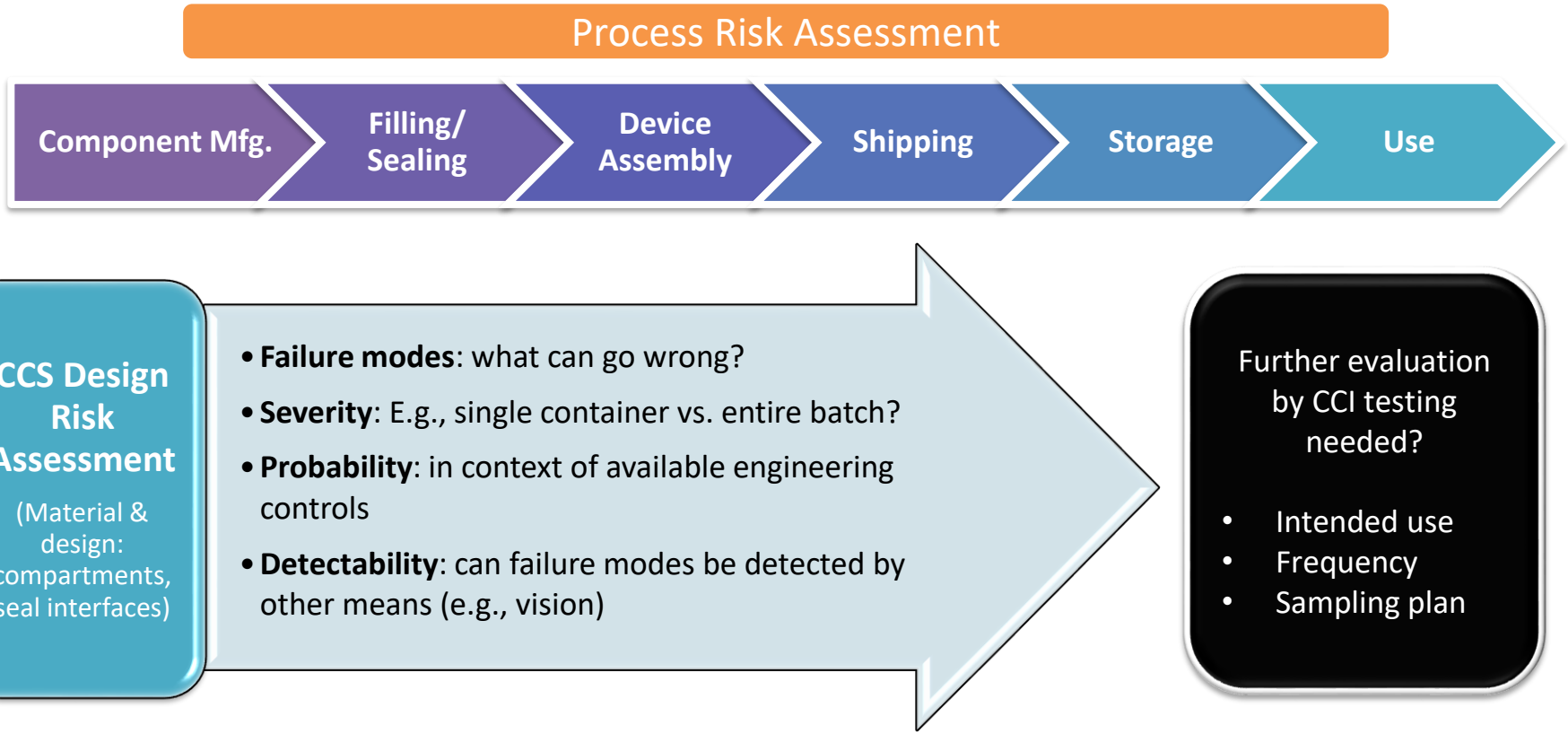
- Plunger-barrel seal
- Needle shield seal
  - Needle tip seal
  - Glued needle stem
  - Needle shield/syringe head

Needle Stem Compartment

- Needle shield/syringe head



Design & Process Risk Assessments



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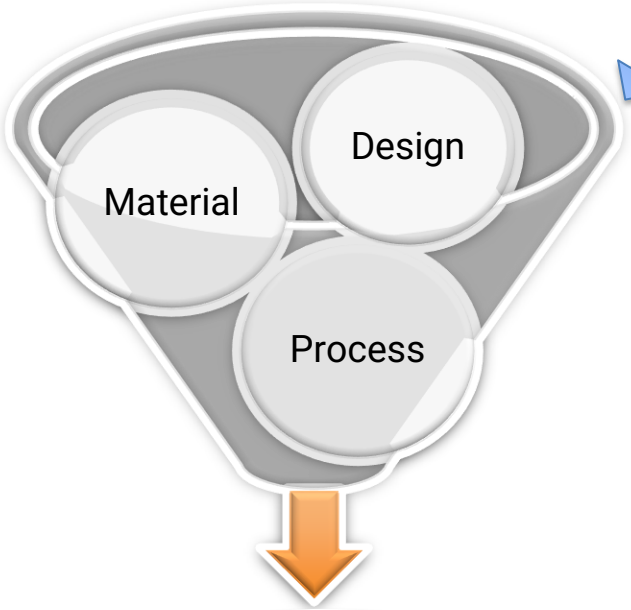
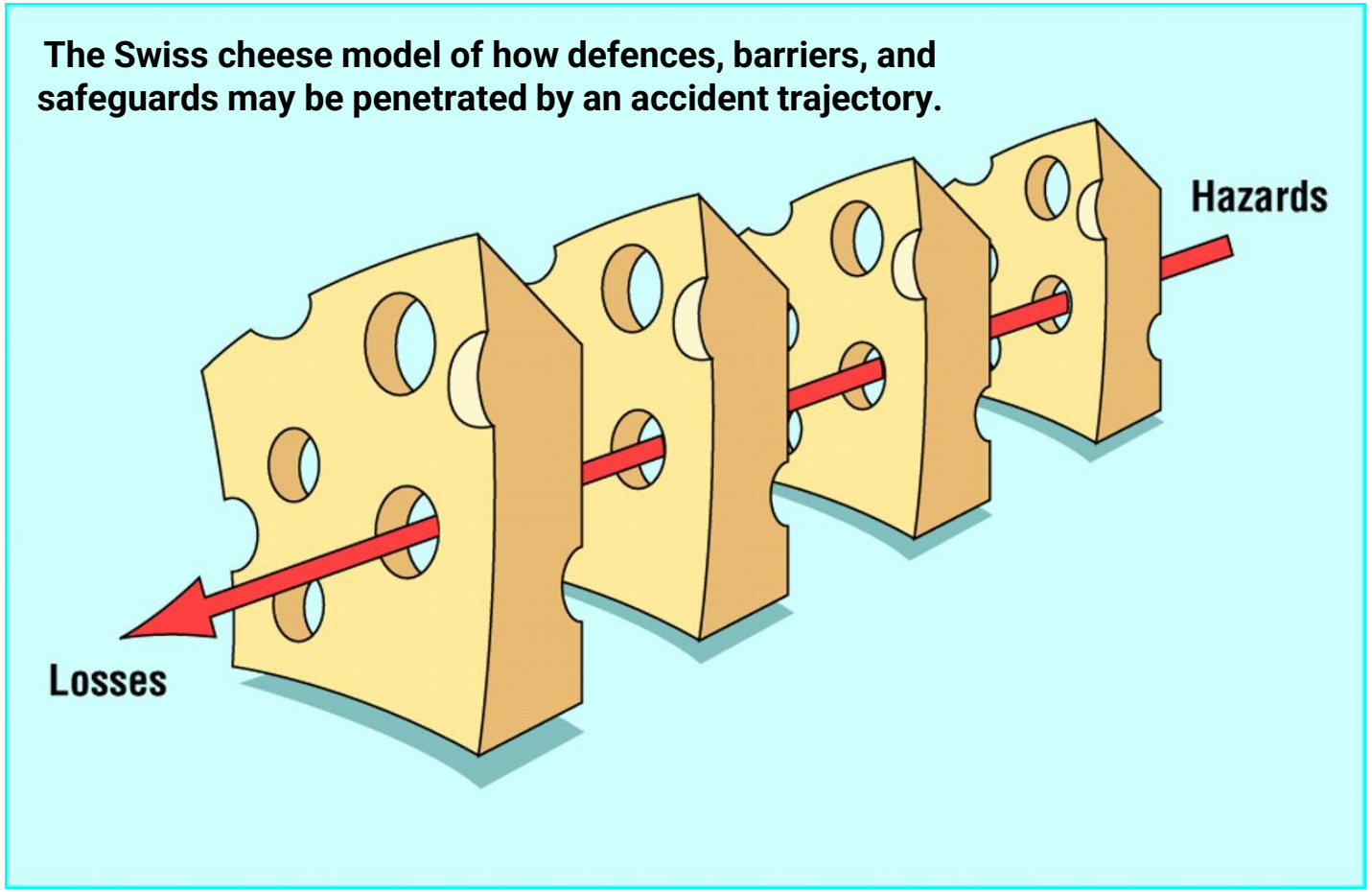


Container Closure Integrity Control Strategy Development

Risks/Failure Mode	Control or CCI Testing
Molding defects from plunger suppliers - causing CCI	Plunger 100% vision inspection; incoming material sampling
Elastomer degradation upon DP contact compromises CCI	CCI Testing incorporated into stability studies
…	…

Continuous Refinement throughout Development Phases

Control Strategy Development



James Reason BMJ 2000;320:768-770

Package Integrity Profile

<u>Ongoing database</u> – Product life-cycle leak and seal quality tests' results

Offers a risk management tool of package integrity assurance

Demonstrates integrity as a function of ongoing, operative variations

- Package component design/material
- Package assembly
- Package and package component processing
- Package storage, distribution, stability

Product Life Cycle and CCI Testing

Product life cycle phases

- Package development and validation
  - Package development
  - Package processing and assembly validation
- Product manufacturing
- Commercial product stability

1a. Package Development

Product-package profile is prepared (e.g., user requirements spec), considering

- Product end use
- Stability requirements
- Method of manufacture
- Anticipated storage, distribution environments

Package is identified, considering

- Design and critical dimensions, stack heights
- Materials of construction
- Component/material suppliers

Package process parameters are identified, considering

- Component cleaning, sterilization, other processes
- Package assembly (or formation)
- Package processing parameters

1a. Package Development

Define Maximum Allowable Leak Limit (product-package specific)

Inherent integrity is checked throughout early phase package development.

CCI testing should check for integrity deviations at **key parameter EXTREMES.**

- **Leak test methods** chosen should be capable of testing **as close as possible to the Max. allowable leak limit**
- **Seal quality tests** should be incorporated as appropriate

A satisfactory package meets the MALL.

1a. Package Development

Outputs: Final user requirement specs

Package component purchasing specs

Equipment user requirement specs

- Component processing equipment
- Package formation/assembly equipment
- Allied materials supply and component feed systems

Equipment purchase and/or contract manufacturing direction

1b. Package Processing & Assembly Validation

CCI testing

Part of larger process validation activity

Scope and sample quantities tested may vary with experience, package complexity, and risk assessments

CCI test methods chosen

- **Smallest leak tests.** Tests able to verify conformance to MALL
- **Larger leak tests.** Tests able to identify leaks caused by package misassembly or other assembly/process related defects

Seal quality testing

Incorporate as appropriate

Consideration given to user requirement specs

Sterilization; package formation/assembly processes

- Extreme condition impact on CCI (E.g., re-sterilization, line speed max/min, assembly procedures)
- Secondary, tertiary packaging impact on CCI

Supports technical transfer to final manufacturing site

Package Development and Validation

FINAL OBJECTIVE

- Package meets user requirement specs (and MALL).
- Quality product-package prepared by packaging processes that reliably and consistently run within specified operating parameters.
- Critical package defects occur at satisfactorily low rate.
- CCI in-process and end-product testing, as well as seal quality testing should complement, not replace package development and validation efforts.

2. Product Manufacturing

CCI assurance starts with component quality specifications

- Component vendor evaluation
- Incoming component AQL conformance
- Vendor certification and corrective action
- Change control

Manufactured product CCI and SQ tests

- **Selection:** Based on earlier R&D and validation
- **Goal:** Prevent or ID/remove defects of greatest concern
- **CCI Testing:** 100% nondestructive CCI tests, or Sampled product CCI tests
- **Seal Quality Testing:** Not a definitive CCI test, but plays a valuable role by monitoring seal quality and/or sealing process

2. Product Manufacturing

100% nondestructive CCI tests –

- Provides greatest quality assurance, but may not be appropriate, necessary, or cost effective.
- Increasingly considered as technologies become available.
- Recommended or required
  - Glass/plastic ampoules (sealed by fusion)
  - Product with critical headspace (vacuum, inert gas)

Sampled product CCI tests

- More testing options (destructive or nondestructive)
- Some off-line options have greater sensitivity
- Less costly
- No impact on production line speeds, efficiency
- However, unable to provide input for real-time production adjustments

3. Commercial Product Stability

FDA 2008 recommended CCI tests replace sterility test in stability studies to assure package integrity (initial sterility test still required)

- Sterility test is a poor measure of integrity
- CCIT more sensitive, reliable
- Only CCIT able to confirm headspace gas maintenance requirements

Ref. 2008 FDA Guidance: Container and closure system integrity testing in lieu of sterility testing as a component of the stability protocol for sterile products.

3. Commercial Product Stability

CCI test method selection

- **CCIT should verify absence of leaks risking**
  - Product loss
  - Sterility loss
  - Gas exchange (if applicable)

- **Method should confirm conformance to the MALL**

- **Product should not interfere with CCIT**
  - Proteinaceous ingredients or salts can block gas/liquid flow through leak paths
  - Impacting vacuum decay, mass extraction, tracer gas or liquid

3. Commercial Product Stability

CCI testing considerations

- **Test sample storage:** To mirror marketed product labelled storage conditions
- **Test quantities per time point:** Undefined, chose based on prior R&D and validation data

If nondestructive tests used samples tested for CCI may be used for other tests at same stability time point.

Consider CCI testing all samples prior to stability storage, to make sure samples at time zero are integral.

CCI test samples should not be retested at later time points, [IF SUCH TESTING REDUCES INFORMATION POSSIBLE].

Package Integrity Profile: Key Studies (Example)

CCS Design Verification	Process Dev Engineering Studies	Process Validation	Stability Studies	Routing Manufacturing
• Verify Package Inherent integrity < MALL • Iterative verifications to evaluate potential interactions	• Evaluate CCI impact of process Parameter EXTREMES	• Verify CCI during: • Filling/Sealing, • 2' Packaging • Device Assembly • Shipping	• Verify and demonstrate continued CCI on stability throughout product shelf life	• Batch Evaluation • Stability

Test method selection criteria

Leak test selection factors	Options
1. Package contents	Liquid, solid, gas, vacuum
2. Package materials of construction	Metal, glass, plastic, composite, opacity
3. Package design, mechanics	Flexible/rigid Closure mechanism
4. Product-package quality requirement (considering the MALL)	Sterility, product formulation preservation Additional need for gas headspace preservation Multi-dose product preservation at time of use
5. Test method outcome requirement	Leak presence , size , location Gas leakage rate determination Liquid leakage risk Microbial ingress risk
6. Leak size detection limit and range	<<0.01 microns to several mm
7. Test sample preservation	Destructive or nondestructive
8. Test method application	High speed or Slower speed Product life cycle phase On-line or Off-line

Test method options

Deterministic methods	Probabilistic methods
Electrical conductivity and capacitance test (HVLD)	Microbial challenge
Laser-based headspace analysis	Liquid tracer tests (e.g., dye)
Pressure decay	Bubble tests
Tracer gas (vacuum mode)	Tracer gas (sniffer mode)
Vacuum decay	---
Mass extraction	---

Summary

- **Fully integrate CCI testing** as a key part of product development and life cycle testing
- **Science and risk-based approach**
- Consider the **product and the package**
- Consider **testing goals**, keeping in mind
  - **Life cycle phase**
  - **Leakage of concern (MALL)**
  - **Leak test method detection limit versus MALL**
  - **Risks of missing vs. finding leaks**
- Employ **other 'non-leak' tests, controls and monitors** to ensure seal quality

Case Study

Risk Assessment → Testing Strategy → Method Selection → Method Development → Method Validation