Packaging Process Validation
&
Container Closure Integrity Testing Strategy and Method Development

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Lilly
Answers That Matter.

Contents

Introduction

- Process validation demonstrates that the intended manufacturing process is capable of consistently producing product in compliance with predefined specifications and quality attributes.
- Conformation of the process validated state must be performed periodically (e.g., every five year three batches, annual single batch verification, etc).
- Must be completed for a new product and any significant changes from packaging component or process
- Packaging processes are parts of manufacturing processes
- Manufacturing process validation includes packaging process validation
- Develop a validation plan – pre-validation requirements and criteria for all testing and operational procedures
- Validation must meet the defined acceptance criteria

Manufacturing process (example)

For sterile bioproducts

- ⇨ Filtration of excipient solution
- ⇨ Drug substance thawing
- ⇨ Product mixing and filling
- ⇨ Plunger insertion (for syringes and cartridges)
- ⇨ Stopper and aluminum crimp seal (for vials)
- ⇨ Labeling
- ⇨ Packing
- ⇨ etc,

⇦ Will be focused as "Packaging Process Validation"

Packaging Process Validation

Must be completed for a new product and any significant changes from packaging component or process

Pre-requirements

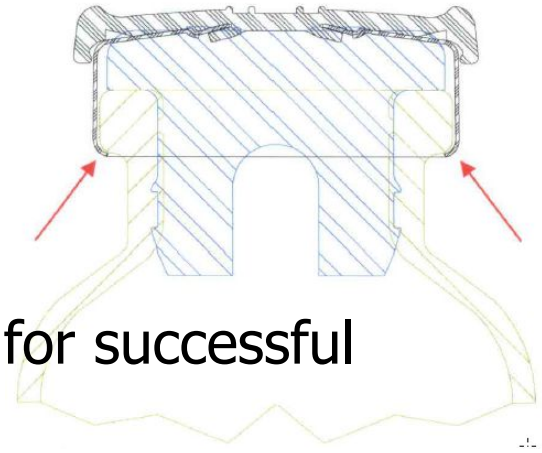
- Proven acceptance range
  - stopper/aluminum sealing pressure (vial)
  - plunger position (syringe, cartridge)
  - etc.
- Equipment qualification
- Container-closure components and system qualification
- CCI testing method qualification

Packaging Process Validation – proven acceptance range

Proven acceptance range for vial sealing process (example)

- Design a study to define a range of capping pressure and line speed to provide acceptable crimp seal
- Need to consider variation of critical dimensions on stopper, vial and aluminum seal – tolerance stack-up analysis
- The acceptable crimp seal can be determined by visual or by CCI physical testing
- Demonstrate the upper and lower limits of capping pressure and line speed can provide acceptable seal and can be controlled consistently

Packaging Process Validation – tolerance stack-up analysis



Two analysis tools

"worst case" stack-up analysis

- ❑ extreme least compatible component dimensions for successful sealing
- ❑ a lower likelihood, so conservative approach

Statistical analysis

- ❑ probability of failure among the container closure components
- ❑ tolerance and standard deviation should be known for all critical dimensions

Packaging Process Validation – CCI testing method qualification

- ❑ method should be developed and qualified for its intended use
- ❑ development and qualification should demonstrate the method is robust and capable
- ❑ qualified method is used to decide that the seal is acceptable
- ❑ testing strategy should be developed
  a. at line vs. lab testing
  b. sample size and sampling frequency

CCI testing strategy development

- Regulatory expectations:

"Show the microbiological integrity of sterile product packaging until the time of use of its contents."

"…. product sterility testing is not normally considered sufficient. The sensitivity of the experimental method used for container-closure integrity testing should be specified and provided."

- Limitations of sterility testing: sample size, only microorganisms present at the time of the test, only microorganisms in the specified culture media, contamination interference, destructive testing & can't reexamine

- Develop cost-effective, reliable, and reproducible CCI physical testing methods, and testing strategy.

CCI testing strategy (example)

Each column conducts a CCI related testing such as tolerance stack-up analysis, CCI physical testing, visual inspection, etc.

Development Phase				
			Clinical Trial Manufacturing	
c/c design verification	c/c system qualification	primary stability	process control	product stability

Conduct tech transfer

Commercial Manufacturing Phase				
		routine process control for sealing		
incoming containers and closures QC	process validation for sealing	100% in-line	or periodic batch check	product stability

CCI testing method development

Key considerations

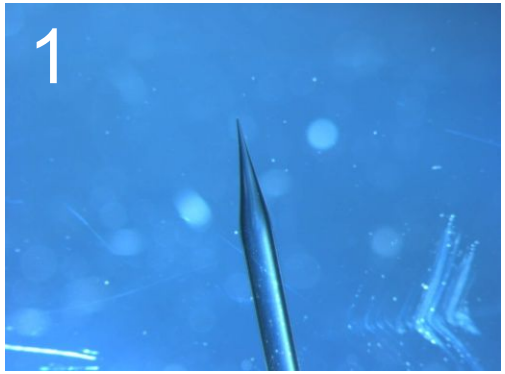
- Defect simulation – how to demonstrate the method capability?
- Correlation with microbial ingress – is a physical CCI testing better than or equivalent to the microbial ingress?
- Method capability (or sensitivity) – what size of defects should be acceptable?

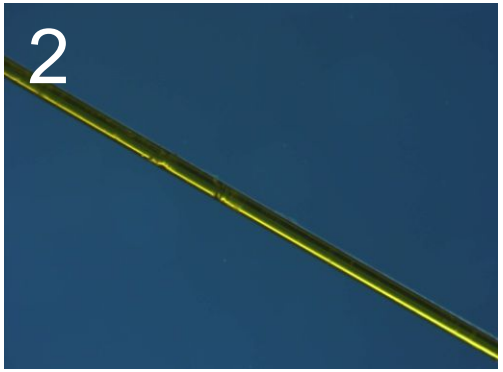
Available CCI Testing Methods

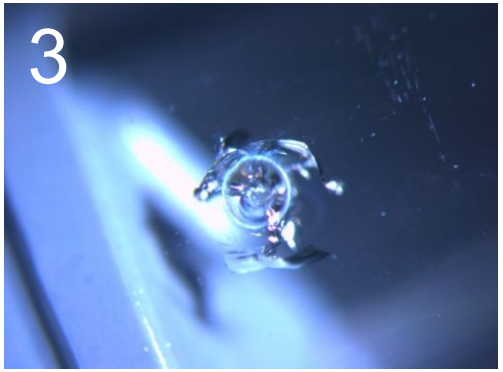
Microbial Challenge	Challenge media filled samples with microorganisms; should be distinguished from media fill study/sterile process validation.
Dye Ingress	Submerge samples in a dye solution, apply vacuum, release vacuum to ambient, and observe dye ingress into samples
Bubble	Submerge samples in water, apply vacuum, and observe bubbles from samples
Vacuum Decay	Apply vacuum in a testing chamber, maintain a consistent vacuum level, observe vacuum level change.
Pressure Decay	Apply pressure in a testing chamber or directly to samples, maintain a consistent pressure, observe pressure change.
Mass Extraction	Apply vacuum in a testing chamber, maintain a consistent vacuum level, measure the mass flow.
Helium	Measure helium mass change
Oxygen	Monitor oxygen concentration change
Moisture	Monitor total weight, moisture content, water activity, or RH change
FTL	Force to leak, apply a load and observe exerted force from the plunger compression seal
RSF	Residual seal force, apply a load and observe exerted force from the aluminum crimp seal
Visual	Any technology relying on human eye or camera vision system
Imaging	Any imaging technology such as ultrasonic energy
HVLD	High voltage leak detection. Apply high voltage, a discharge current will flow through the hole

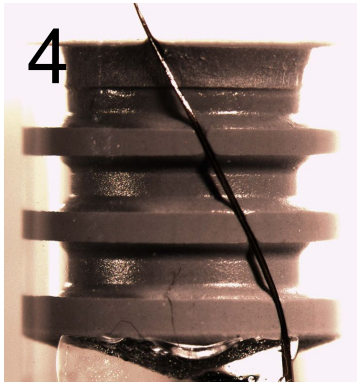
Defect simulation

1. Glass micropipette: tapered, diameter can be measured & estimated length of defect is ~0.5 mm
2. Micro tube: glass tube coated by a polymer, consistent diameter in the entire length
3. Laser drilled cracks – nominal size determined by leak rate
4. Wire in rubber contact seal – nominal size determined by leak rate



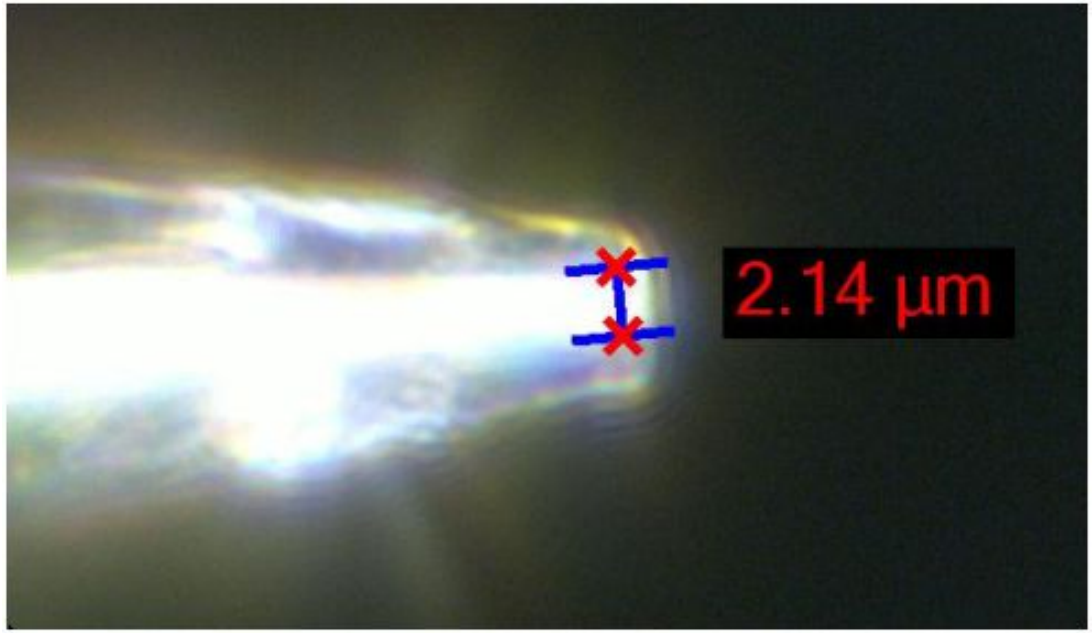






Defect – glass micropipette

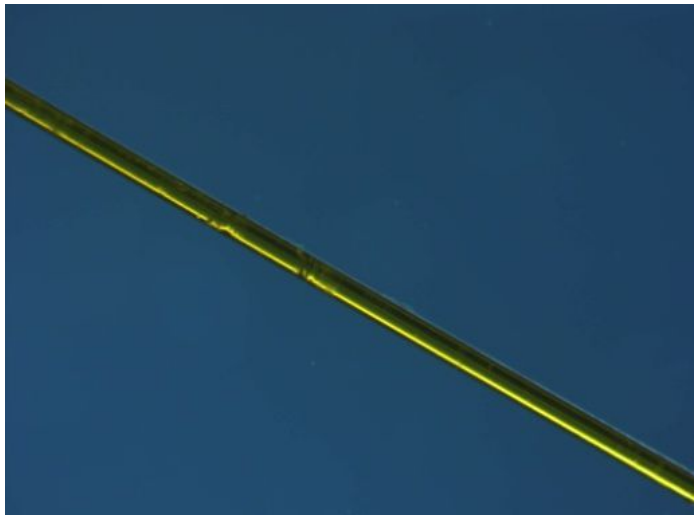
- Morphology can be defined
- Use as a reference sample to determine a leak rate from a known size of defect
- Fragile and difficult to install
- Difficult to verify intact or broken



Example for 2 µm glass micropipette

Defect – micro tube

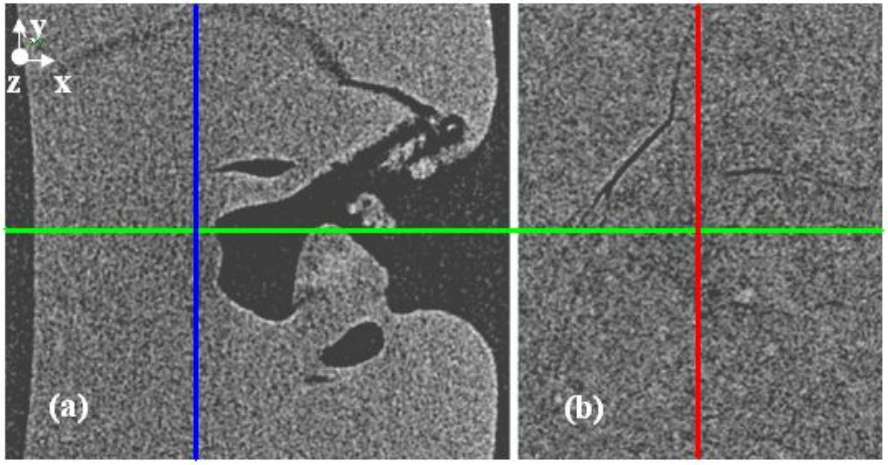
- Various size available from 2 μm
- Consistent internal diameter – confirmed by x-ray μCT
- Easy to handle and install
- Length of a defect is significantly long comparing to other defects

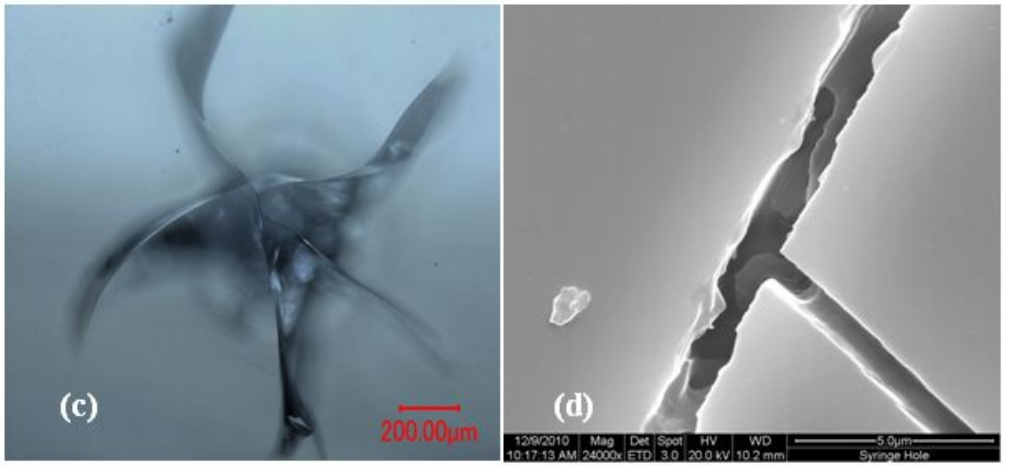


Defect – laser drilled cracks

- There is a series of cracks.
- Morphology cannot be defined, so the nominal size is determined by a leak rate.
- easy to handle but expensive

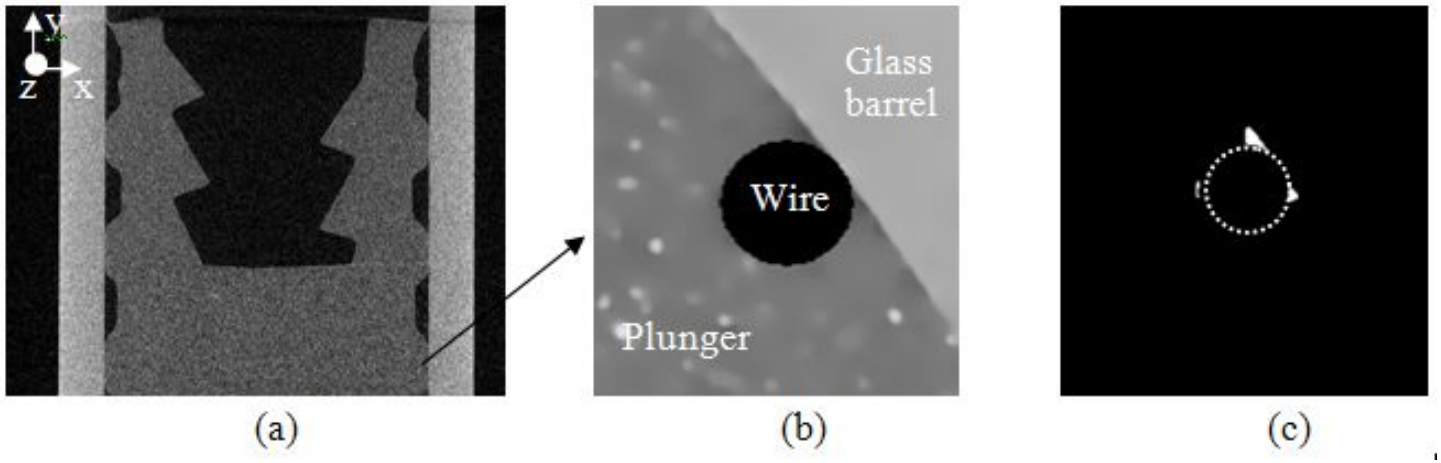
(~$50/sample)





Defect – wire in rubber contact seal

- Known size of wire is placed in the rubber contact seal
- Channels can be created depending on rubber deformation
- Variation is relatively large (e.g., 5-10 μm nominal size instead of saying ~5 μm)
- Easy to install and handle



Leak rate comparison

- Samples: empty c/c system + directly installed defect

- 5 μm glass micropipette = ~5 μm (nominal) laser drilled cracks = ~20 μm and 40 mm length microtube (calculated) = ~50-75 μm wire in a plunger contact seal

Q. Similar CCI testing results with product solution filled samples? No!!

For examples,

- For laser drilled cracks, a product solution can easily flow out to the surface of container and can be dried quickly. It blocks channels.

- For glass micropipette, a product solution remains in the tip and not dried quickly.

Correlation with microbial ingress

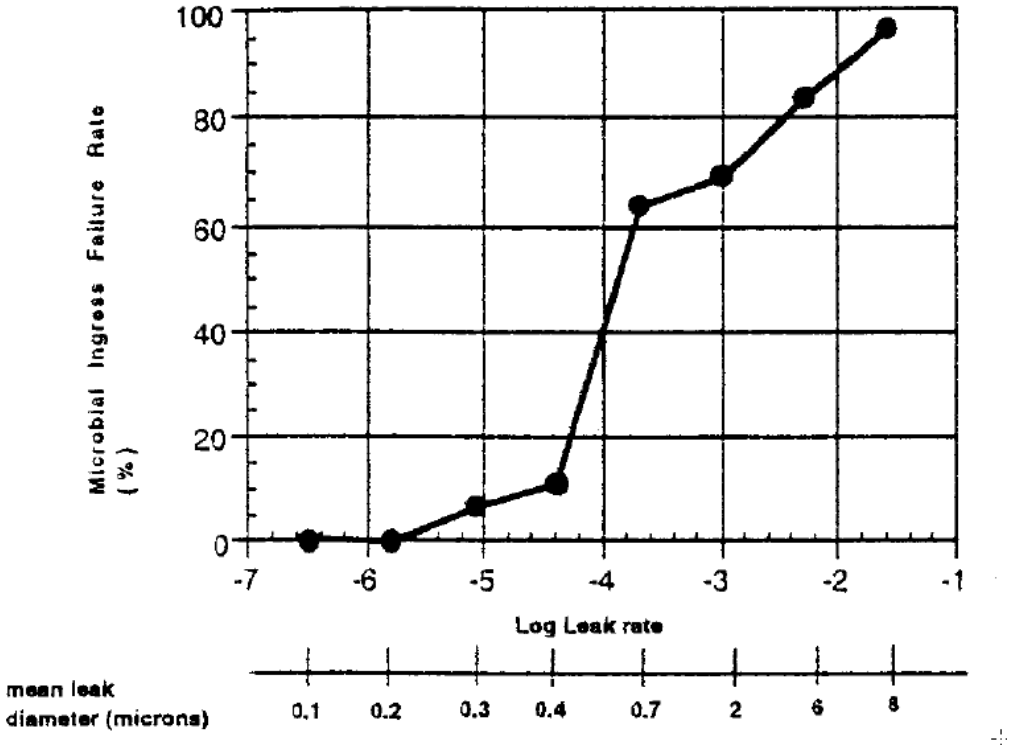


Fig. The correlation of microbial failure rate (%) and the mean logarithm of the absolute leak rate and nominal leak diameter

Kirsch, L.E., Nguyen, L., Moeckly, C.S. and Gerth, R., "Pharmaceutical Container/Closure Integrity II: The Relationship Between Microbial Ingress and Helium Leak Rates in Rubber-Stoppered Glass Vials", *Journal of Parenteral Science & Technology*, **51**, 195-202 (1997)

Micro organisms: *Pseudomonas Diminuta, Escherchia coli*

- Defect type: glass micropipette, # of defect samples ranges from 17 to 60 per size
- Difficult to achieve 100% positive results with glass micropipettes smaller than 8 µm

Method capability (or sensitivity)

- Smallest microorganisms: 0.3 to 0.7 μm (e.g., *Brevundimonas diminuta*, *Escherichia coli*, and *Pseudomonas aeruginosa*)

- Ideally, the CCI method may need to detect the defect size around 0.3 μm.

- No practical testing technology currently available that can achieve this sensitivity reliably within a short testing time and a non-destructive test method as desired.

- Better to show the correlation between detection probability and various size/type of defects.

- Current testing capability from published methods (mass extraction, HVLD, vacuum decay, Lighthouse, etc): 2-5 μm with 100% detection probability for empty and powder filled, and 5-10 μm for liquid filled.

Conclusions

- Packaging, especially sealing process validation, is one of the critical processes in manufacturing process validation.
- Packaging process should be well understood – proven acceptable range, controllable within acceptable range, consistent, etc.
- CCI testing strategy and methods should be developed to demonstrate consistent sealing process validation state.
- There is no single CCI method to cover all types of products. The method must be developed per product and c/c type.