



# Container Closure Integrity: Regulations, Test Methods, Application

## Test Method Selection and Application

### Instructors

*Lei LI, Ph. D.; Eli Lilly and Company; [lileix@lilly.com](mailto:lileix@lilly.com)*

*Jennifer Roark; Eurofins Medical Device Testing; [jenniferroark@eurofinsus.com](mailto:jenniferroark@eurofinsus.com)*

*With significant contribution from Dr. Dana M. Guazzo PhD, RxPax, LLC, [dguazzo@rxpax.com](mailto:dguazzo@rxpax.com)*

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## Test method selection and application

- Test method selection criteria
- Test application examples
- Case study – Group Exercise & Discussions

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	---

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## Single-dose liquid packaged in a stoppered vial. Low O<sub>2</sub> headspace

Stage	Closure system	Critical leakage	Leak tests, Other
Pre-capping	<ul style="list-style-type: none"> <li>• Closure inserted, not capped</li> <li>• Seal at plug/vial-neck</li> </ul>	Nitrogen content loss	<ul style="list-style-type: none"> <li>• R&amp;D/stability/manufacturing               <ul style="list-style-type: none"> <li>• Laser-based H.A., vision system</li> </ul> </li> </ul>
Post capping	<ul style="list-style-type: none"> <li>• Closure capped</li> <li>• Seal at closure/vial-flange</li> </ul>	Nitrogen content loss thru expiry	<ul style="list-style-type: none"> <li>• R&amp;D/Manufacturing               <ul style="list-style-type: none"> <li>• Laser-based H.A. as a function of RSF</li> </ul> </li> <li>• Stability               <ul style="list-style-type: none"> <li>• Laser-based H.A.</li> </ul> </li> </ul>
Upon use	<ul style="list-style-type: none"> <li>• Puncture site</li> </ul>	Product loss	<ul style="list-style-type: none"> <li>• R&amp;D/stability               <ul style="list-style-type: none"> <li>• Dose delivery</li> </ul> </li> </ul>

**Summary:** 2 package seals, 2 critical leakage scenarios, 1 leak test

## Multi-dose liquid product in a stoppered vial. Air headspace

Stage	Closure system	Critical leakage	Leak tests, Other
Pre-capping	<ul style="list-style-type: none"> <li>Closure inserted, not capped</li> <li>Seal at <b>plug/vial-neck</b></li> </ul>	<b>Airborne microbial ingress</b>	<ul style="list-style-type: none"> <li><b>Manuf:</b> Media fill, vision system</li> </ul>
Post capping	<ul style="list-style-type: none"> <li>Closure capped</li> <li>Seal at <b>closure/vial-flange</b></li> </ul>	<b>Liquid product loss and microbial ingress thru expiry</b>	<ul style="list-style-type: none"> <li><b>R&amp;D:</b> <b>Tracer gas (vacuum mode)</b> as a function of RSF</li> <li><b>Stability:</b> <b>HVLD</b></li> <li><b>Manuf:</b> <b>HVLD</b>, RSF</li> </ul>
Upon use	<ul style="list-style-type: none"> <li><b>Puncture sites</b></li> </ul>	<b>Product loss</b>	<ul style="list-style-type: none"> <li><b>R&amp;D/stability:</b> <b>HVLD</b>, dose delivery</li> </ul>

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**Summary:** 3 package seals, 3 critical leakage scenarios, **2 leak tests**

## Lyo product in a stoppered vial; cryo-storage. Vacuum headspace

Stage	Closure system	Critical leakage	Leak tests, Other
Pre-lyo	<ul style="list-style-type: none"> <li>• Closure in 'lyo' position</li> <li>• Seal at plug-lug/vial-neck</li> </ul>	Closure kept in open-leak-path position; vial upright	<ul style="list-style-type: none"> <li>• Manuf: Media fill, vision system</li> </ul>
Post-lyo Pre-capping	<ul style="list-style-type: none"> <li>• Closure inserted, not capped</li> <li>• Seal at plug/vial-neck</li> </ul>	Vacuum headspace loss	<ul style="list-style-type: none"> <li>• R&amp;D/Manuf: Laser-based H.A.</li> </ul>
Post capping	<ul style="list-style-type: none"> <li>• Closure capped</li> <li>• Seal at closure/vial-flange</li> </ul>	Vacuum headspace loss thru expiry <ul style="list-style-type: none"> <li>• At RT</li> <li>• At cryo-temps</li> </ul>	<ul style="list-style-type: none"> <li>• R&amp;D: Laser-based H.A. as a function of RSF and Temp</li> <li>• Stability: Laser-based H.A.</li> <li>• Manuf: Laser-based H.A., RSF</li> </ul>
Upon use	<ul style="list-style-type: none"> <li>• Puncture site</li> </ul>	Product loss	<ul style="list-style-type: none"> <li>• R&amp;D/stability: dose delivery</li> </ul>

**Summary:** 3 package seals, 4 critical leakage scenarios, **1 leak test**

## Liquid in a stoppered LV vial, terminally sterilized. Air headspace

Stage	Closure system	Critical leakage	Leak tests, Other
Pre-capping	<ul style="list-style-type: none"> <li>• Closure inserted, not capped</li> <li>• Seal at plug/vial-neck</li> </ul>	Closure insertion maintenance; vial upright. Airborne microbial ingress should be limited	<ul style="list-style-type: none"> <li>• Manuf: Vision system</li> </ul>
Post capping	<ul style="list-style-type: none"> <li>• Closure capped</li> <li>• Seal at closure/vial-flange</li> </ul>	Liquid product loss and microbial ingress thru expiry <ul style="list-style-type: none"> <li>• Pre-sterilization</li> <li>• During sterilization</li> <li>• Post sterilization</li> </ul>	<ul style="list-style-type: none"> <li>• R&amp;D:               <ul style="list-style-type: none"> <li>• Tracer gas (vac) (empty) &amp; HVLD (filled) as a function of RSF, pre/post sterilization.</li> <li>• Liquid tracer as a function of RSF during sterilization</li> </ul> </li> <li>• Stability: HVLD</li> <li>• Manuf: HVLD, RSF</li> </ul>
Upon use	<ul style="list-style-type: none"> <li>• Spike insertion site</li> </ul>	<ul style="list-style-type: none"> <li>• Product loss</li> </ul>	<ul style="list-style-type: none"> <li>• R&amp;D/stability: HVLD, dose delivery</li> </ul>

**Summary:** 3 package seals, 5 critical leakage scenarios, 3 leak tests



## Lyo product in a stoppered vial; 2-8°C storage. Air headspace

Stage	Closure system	Critical leakage	Leak tests, Other
Pre-lyo	<ul style="list-style-type: none"> <li>Closure in 'lyo' position</li> <li>Seal at plug-lug/vial-neck</li> </ul>	Closure kept in open-leak-path position; vial upright Airborne microbial ingress	<ul style="list-style-type: none"> <li>Manuf.: Media fill, vision system</li> </ul>
Post-lyo Pre-capping	<ul style="list-style-type: none"> <li>Closure inserted, not capped</li> <li>Seal at plug/vial-neck</li> </ul>	Airborne microbial ingress	<ul style="list-style-type: none"> <li>Manuf: Media fill, vision system</li> </ul>
Post capping	<ul style="list-style-type: none"> <li>Closure capped</li> <li>Seal at closure/vial-flange</li> </ul>	Airborne microbial ingress thru expiry	<ul style="list-style-type: none"> <li>R&amp;D: Tracer gas (vac) &amp; Vac decay as a function of RSF</li> <li>Stability: Vac decay</li> <li>Manuf: Vac decay, RSF</li> </ul>
During use	<ul style="list-style-type: none"> <li>Puncture site</li> </ul>	Product loss	<ul style="list-style-type: none"> <li>R&amp;D/stability: dose delivery</li> </ul>

**Summary:** 3 package seals, 4 critical leakage scenarios, **2 leak tests**

## Liquid in a staked needle syringe. Air headspace

Stage	Closure system	Critical leakage	Leak tests, Other
All	Needle shield seal at needle tip	Product loss and microbial ingress	<ul style="list-style-type: none"> <li>• R&amp;D: Vacuum decay (empty)</li> <li>• Stab/Manuf: HVLD, X-ray</li> </ul>
All	Needle shield seal at needle base	Airborne microbial ingress	<ul style="list-style-type: none"> <li>• R&amp;D/Stab.:               <ul style="list-style-type: none"> <li>• Vacuum decay</li> <li>• Shield removal force</li> </ul> </li> <li>• Manuf: Vision system</li> </ul>

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**Continued...**

## Continued. Liquid in a staked needle syringe. Air headspace

Stage	Closure system	Critical leakage	Leak tests, Other
All	Plunger/barrel seal	<ul style="list-style-type: none"> <li>• Product loss</li> <li>• Product ingress into ribs</li> <li>• Microbial ingress</li> </ul>	<ul style="list-style-type: none"> <li>• R&amp;D:               <ul style="list-style-type: none"> <li>• Tracer gas (vac mode) (empty)</li> <li>• Tracer liquid (for ribs leakage)</li> <li>• HVLD (filled)</li> </ul> </li> <li>• Stability:               <ul style="list-style-type: none"> <li>• HVLD</li> <li>• Vision (for ribs leakage)</li> </ul> </li> <li>• Manuf: HVLD, vision</li> </ul>
Upon use	Plunger/barrel seal	<ul style="list-style-type: none"> <li>• Product loss</li> <li>• Product ingress into ribs</li> </ul>	<ul style="list-style-type: none"> <li>• R&amp;D/stability:               <ul style="list-style-type: none"> <li>• HVLD</li> <li>• Vision (for ribs leakage)</li> <li>• Dose delivery</li> <li>• Breakloose/extrusion forces</li> </ul> </li> </ul>

**Summary:** 3 package seals, 5 critical leakage scenarios, **6 leak tests**



# 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

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