



Container Closure Integrity: Regulations, Test Methods, Application

Test Method Selection and Application

Instructors

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Test method selection and application

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



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	---

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Single-dose liquid packaged in a stoppered vial. Low O₂ headspace

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

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

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

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

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

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"> • R&D: Vacuum decay (empty) • Stab/Manuf: HVLD, X-ray
All	Needle shield seal at needle base	Airborne microbial ingress	<ul style="list-style-type: none"> • R&D/Stab.: <ul style="list-style-type: none"> • Vacuum decay • Shield removal force • Manuf: Vision system

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

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



- **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

