



Container Closure Integrity: Regulations, Test Methods, Application – Introduction

INTRODUCTION

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Terms, Definitions, and Concepts

2

Maximum Allowable Leak Limit (MALL)

3

Inherent package integrity

4

Package integrity profile

SCOPE

In-Scope of USP <1207> - Focus of the Course



Sterile pharmaceutical product packaging (SVP, LVP)

Examples:

- Vials or bottles closed with elastomeric closures or screw-thread caps
- Form-fill-seal plastic or glass ampules
- Syringes or cartridges
- Flexible bags or pouches
- Packages for some drug/device combination products (e.g., autoinjectors)

Out of Scope of USP <1207> - Methodologies Apply

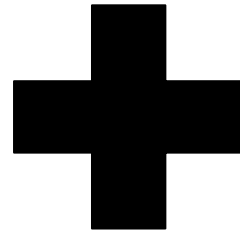


Packaging systems involved in prep, storage, manufacture

Examples:

- API, intermediate/final bulk
- Sterile diagnostic products or medical devices
- Some packages for sterile drug/device combo products
- Primary packages with porous barrier materials designed to allow air or gas sterilant passage

DEFINITIONS



Pharmaceutical formulation

- Principles apply to containers for API, bulk, intermediates

Packaged headspace

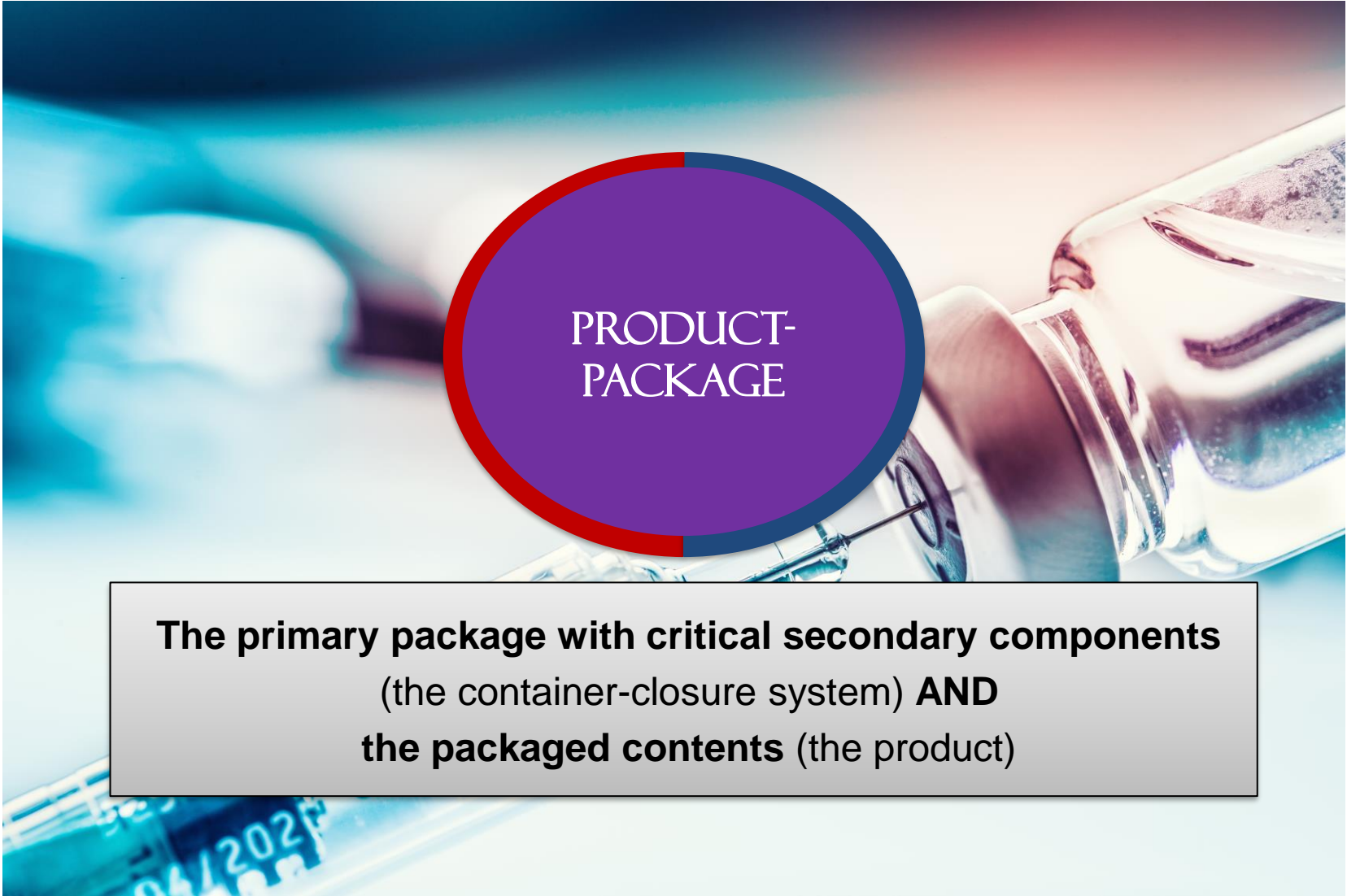
- Air or nonreactive gases
- At specified water vapor content
- At ambient or sub-ambient pressures

Primary package components

- In direct product contact (or may be)

Secondary package components critical for ensuring package assembly

- E.g., Aluminum crimp seal on vial/stopper



**PRODUCT-
PACKAGE**

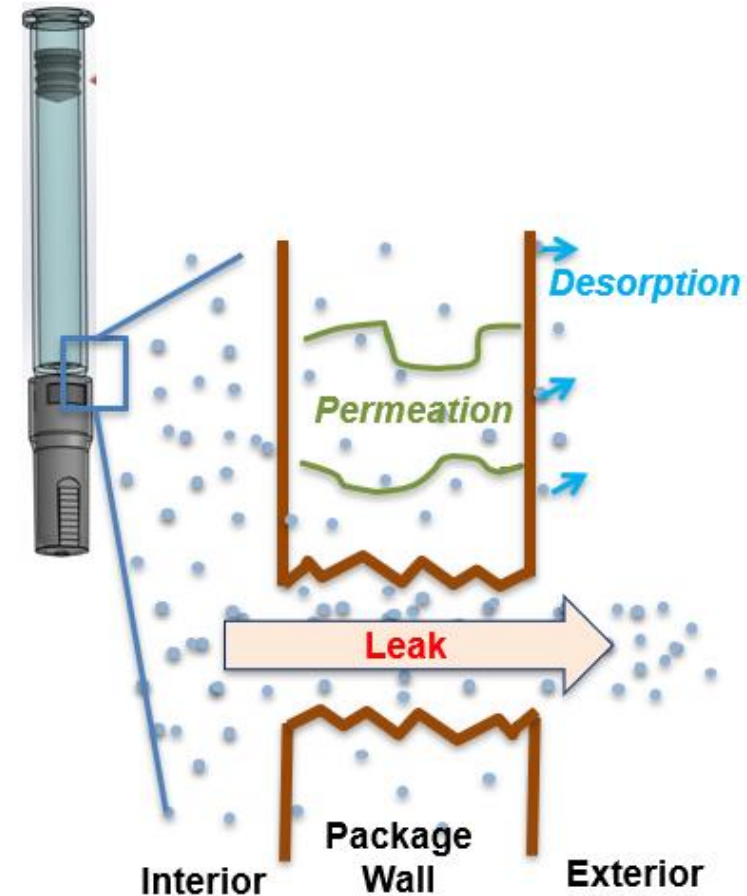
**The primary package with critical secondary components
(the container-closure system) AND
the packaged contents (the product)**

DEFINITIONS

- ❑ **Leak:** A **gap** or **breach** in the container capable of permitting the passage of liquid or gas. Otherwise known as “leak path.”

- ❑ **Leakage:**
 - The unintentional entry or escape of matter (solid, liquid or gas) through a breach in a package wall or through a gap between package components.
 - The leaking matter itself.

- ❑ **Permeation:**
 - The passage of fluid (e.g., gas) into, through, and out of a nonporous package wall.
 - Permeation (NOT leakage) occurs when only a small fraction of molecules is able to move through a barrier by way of any one hole.





Package Integrity & MALL

Sterile product package integrity or “container closure integrity” (CCI)

The ability of a package to...

Keep good stuff in, and

Keep bad stuff out

“A package with integrity”

Does not mean

the package has passed or is able to pass a

Microbial ingress test, or product sterility test

Microbial Ingress is a **PROBABILISTIC EVENT**

Difficult to control, predict, measure

FACTORS	
Leak Path	Size/shape/length/material/blockage
Ingress test parameters	Time/pressure/temp
Microorganism	Type/size
Liquid tracer	Chemistry/concentration
Carrier fluid	Viscosity/surface tension/solvent
Visual detection	Human variables/inspection conditions
Instrumental detection	Instrument/test parameters

Package Integrity & MALL

CONSIDER

IF windows keep out birds, THEN why not detect defective windows by checking homes for birds?



D. Guazzo, RxPax, LLC

Package Integrity & MALL

Package Integrity

- **IS NOT** passing microbial ingress or product sterility tests
- **IS** the absence of a gap/defect that risks product quality
- **IS** the conformance of the package to the maximum allowable leakage limit (i.e., critical leak)
 - Product quality requirements define MALL

Testing goals may vary during the product life cycle

Package Integrity & MALL

INSTEAD of Checking for Bats.....

- **Design and make** windows that close well based on meaningful, reliable tests
- **Test** for absence of defects that could permit birds
- **Monitor** to ensure control over materials, processes



Package Integrity & MALL

“**A package with integrity**” means that *Gaps/breaches that **COULD** risk product quality are absent*; i.e., The package meets the **MAXIMUM ALLOWABLE LEAKAGE LIMIT (MALL)**.

What's the difference?

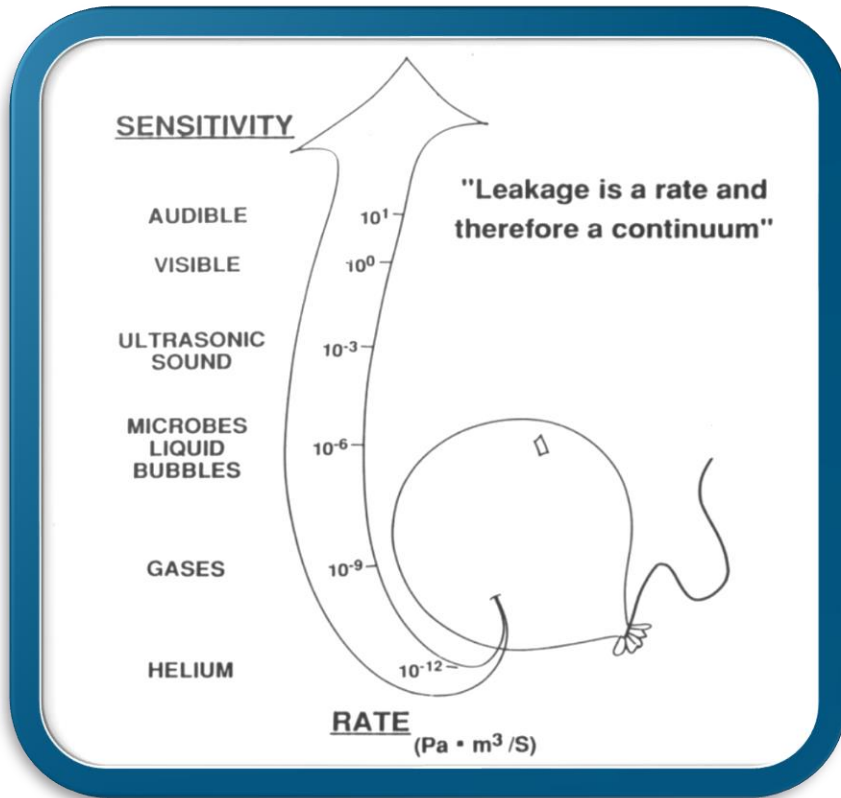
Maximum Allowable Leakage Limit (MALL)

is that smallest gap or leak rate that puts product quality at risk

(sometimes called the 'critical leak')

Package Integrity & MALL

All physically mated closure systems* leak to some degree



Smallest leaks only allow gas flow

Larger leaks may also allow liquid flow

Largest leaks may also allow microbial ingress

*physico-chemically bonded seals may only allow permeation

Sterile product package integrity (CCI)

Category	Leaks of concern	Product quality risks
1	Capable of allowing entry of microorganisms	Failure of product sterility
2	Capable of allowing escape of product dosage form, or entry of external of liquids/solids	Failure of relevant physicochemical quality attributes
3	Capable of allowing change in gas headspace content. E.g., escape of nitrogen, loss of vacuum, entry of oxygen, water vapor, or air	Failure of relevant physicochemical quality attributes, and/or hindrance of product access by end-user

What is the maximum allowable leakage limit (MALL) for categories 1 and 2?

- Prevention of **microbial ingress**
- Prevention of **product loss** (liquid or solid) or **external contamination** by liquid or solid matter

Package Integrity & MALL

Smallest leak to first allow ingress determination

**Lee Kirsch, et al, *PDA J Pharm Sci & Technol*, Vol. 51,
No. 5, 1997**

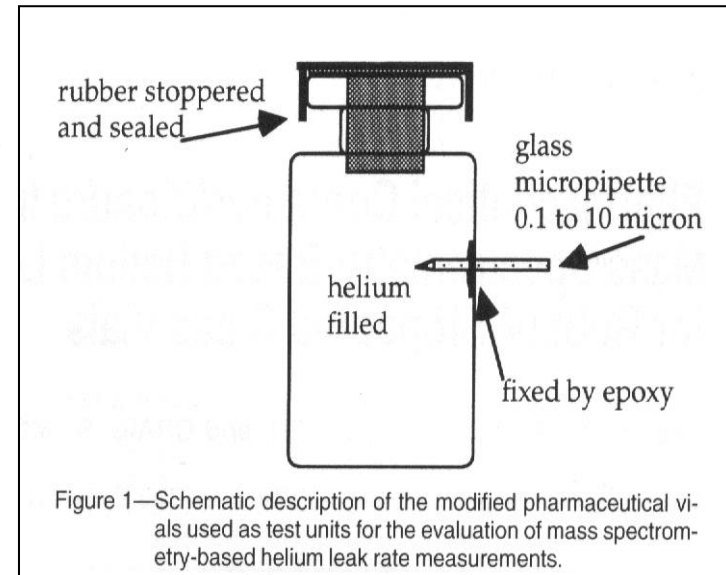
Comparison of orifice helium leak rate vs microbial and liquid tracer ingress

❑ Glass micro-pipettes through wall of stoppered glass vial

- Sized via helium mass spec
- 0.1 to 10µm diameter

❑ Microbial challenge by immersion + liquid tracer element

- 10^8 to 10^{10} *P. diminuta* and *E. coli* cfu/mL
- Tween 80 additive
- Mg ion tracer for liquid path verification
 - ✓ Detection by atomic absorption



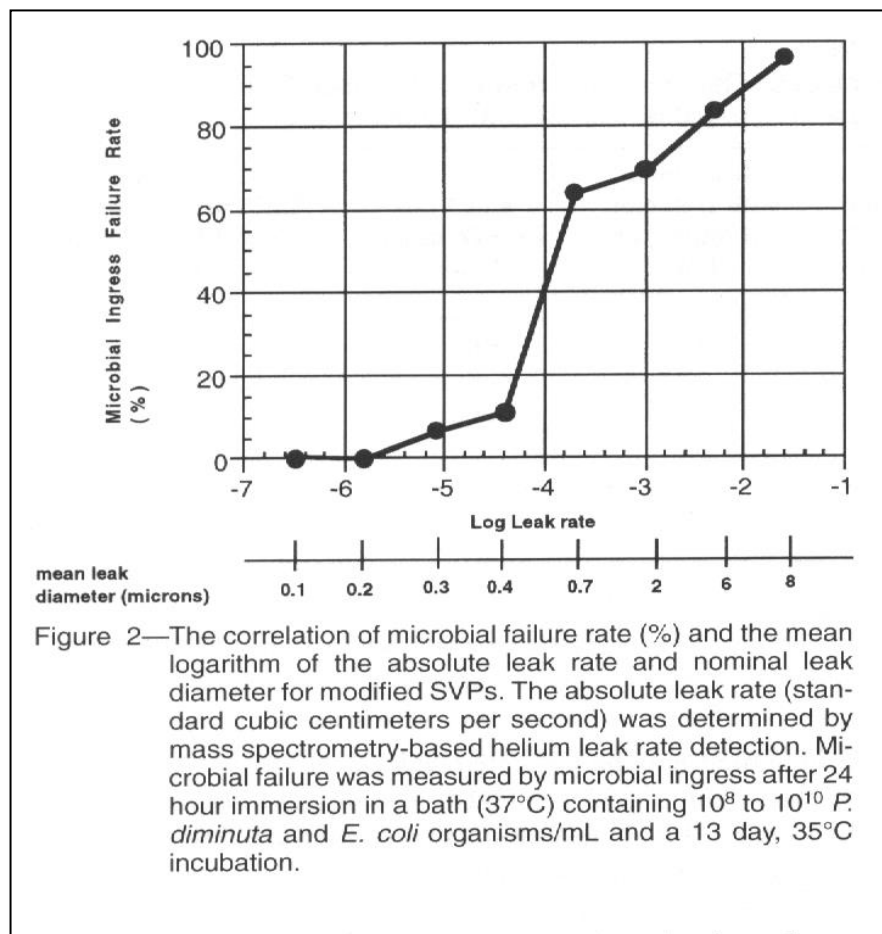
❑ Challenge conditions

- Airlock elimination procedure
 - ✓ Water bath immersion 60°C 2hr, then 25°C 1hr
- 24 hr. immersion, ambient pressure

Package Integrity & MALL

Comparison of orifice helium leak rate vs microbial and liquid tracer ingress

- ❑ Microbial ingress risk dropped dramatically at Log -3.8 sccs (< ~1µm)
- ❑ Low risk of ingress (< 0.10) at helium leak rate of 6×10^{-6} mbarL/s



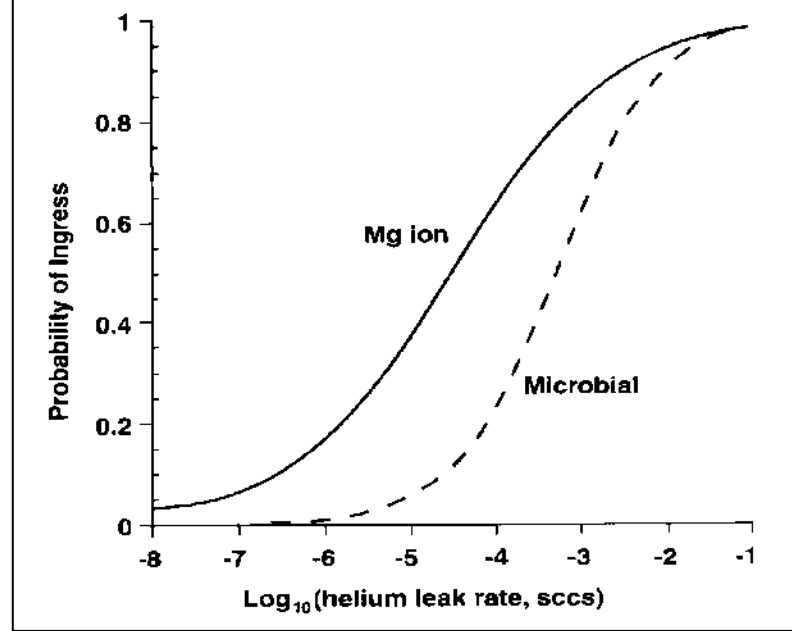
Kirsch, et al, *PDA J Pharm Sci & Technol* 51, 5, 1997 p. 195 – 202

Comparison of orifice helium leak rate vs microbial and liquid tracer ingress

- ❑ Microbial ingress requires liquid flow
 - Increased liquid flow equals increased microbial ingress risk

- ❑ Liquid flow \neq microbial ingress

Figure 1: Logistical regression models describing the probability of microbial or liquid tracer (Mg ion) as a function of the logarithm of the helium leak rates. Curves were generated using Equation 1 and parameters estimated with the logistical regression platform in the software JMP (10).



Kirsch, *PDA J Pharm Sci & Technol*, 54, 4, 2000
p. 305 – 314

Package Integrity & MALL

MALL as a function of leak path morphology and test conditions

Study Author	Challenge medium	Challenge microbe	Challenge path	Challenge conditions	Microbial ingress first observed
Kirsch JPDA '97-'99	Liquid	<i>P. diminuta</i> <i>E. coli</i>	Glass micro-pipette through vial wall	Airlock elimination step + 24 hrs ambient	0.3 µm orifice
Burrell JPDA 2000	Liquid	<i>E. Coli</i>	Poly-coated glass micro-tube through stopper	ISO closure reseal: 30 min 22" Hg + 30 min ambient	10 µm ID tube
Morrical JPDA 2007	Liquid	<i>Serratia marcescens</i>	Metal plate micro-hole in stopper	-0.4 bar 1 hr. +0.4 bar 1 hr.	4 µm orifice
Morrical JPDA 2007	Liquid	<i>Serratia marcescens</i>	Copper wire between stopper/vial	-0.4 bar 1 hr. +0.4 bar 1 hr.	20 µm OD wire
Keller <i>J. Appl. Packag. Res. 2006</i>	Aerosol	<i>P. Fragi</i>	Nickel micro-tube in 3mL vial	Varied: -20 kPa to +20 kPa 4 to 37°C	5 µm ID tube

Package Integrity & MALL

Kirsch reported smallest leak (nominal hole size) that first demonstrated:

- **Microbial ingress: 0.2 - 0.3 μm**
- **Aqueous liquid passage: 0.1 μm^***

***Absolute cut-off was not defined as smaller leaks were not evaluated**

- **Liquid presence** in the leak path was **required**, but **did not guarantee** microbial ingress
- **Airborne microbial ingress** only possible with larger leaks

MALL size of “Real leaks” is undefined

- Real leak paths are not holes, tubes, pipettes
- Natural defects are long, complex, irregular channels
- Defects consist of actual package materials
- Air pockets, debris, product may block leak flow or microbial ingress

Choosing the critical leak size (rate) that will ensure product sterility and prevent product formulation loss is a *SCIENCE AND RISK BASED DECISION*

Package Integrity & MALL

In general, for **nonporous rigid packages** such as

- Parenteral vials, bottles
- Syringes, cartridges
- Form fill seal glass/plastic ampoules
- Drug/Device package systems (e.g., autoinjectors)

**Helium leakages rate of $< 6 \text{ E}^{-6} \text{ mbarL/s}$
(leakage through an orifice of about 0.1 to 0.3 μm)
have a low risk of microbial ingress or liquid product loss**

Adopting this MALL for such product-packages may eliminate the need for microbial ingress or liquid challenge studies as a function of leak size.

Package Integrity & MALL

Ingress or product loss risk is not as well defined

For other package systems such as **Flexible polymeric packages**

For leak types/morphologies more **complex** or **lengthy**

For products more likely to leak such as **cosolvent systems**

The MALL is UNIQUE for each product-package
A SCIENCE AND RISK BASED DECISION

Determine the risk of microbial ingress or liquid passage as a function of defect size/type

Package Integrity & MALL

What is the maximum allowable leakage limit (MALL) for Category 3?

Prevention of **change in gas headspace content** that risks product quality, and/or risks ease of product access. *E.g.*, N₂ escape; vacuum loss; entry of O₂, H₂O vapor, or air.

The MALL is UNIQUE for each product-package

A SCIENCE BASED DECISION

Consider

- ✓ Headspace quality requirements: Initial and at expiry
- ✓ Package headspace volume
- ✓ Package permeation
- ✓ Product-package storage, distribution environment

Package Integrity & MALL

What is the “in-use” maximum allowable leakage limit (MALL) for multiple dose product packages?

- ❖ An in-use sub-category of categories 1, 2, 3.
E.g., Multiple dose vials or cartridges.
- ❖ Prevention of product loss or microbial ingress between and during dosage access

The MALL is UNIQUE for each product-package

A SCIENCE AND RISK BASED DECISION

Determine

- ✓ Attempts of product access – quantity and mode
- ✓ Risk of microbial ingress and/or product loss

MALL –Product-Package Specific

The MALL is based on product quality requirements

- **Prevention of microbial ingress** to ensure product sterility.
- **Prevention of product formulation loss and product formulation contamination by external solids/liquids** to ensure conformance to relevant physicochemical product quality attributes.
- **Prevention of headspace content change** to ensure conformance to relevant physicochemical product quality attributes, and to assure product access.

Establishing the MALL is a science-based
and often a risk-based decision

Inherent Package Integrity

The leakage rate (or the equivalent leak size) of a well-assembled package using no-defect components.

Best-case leak tightness, given anticipated variables:

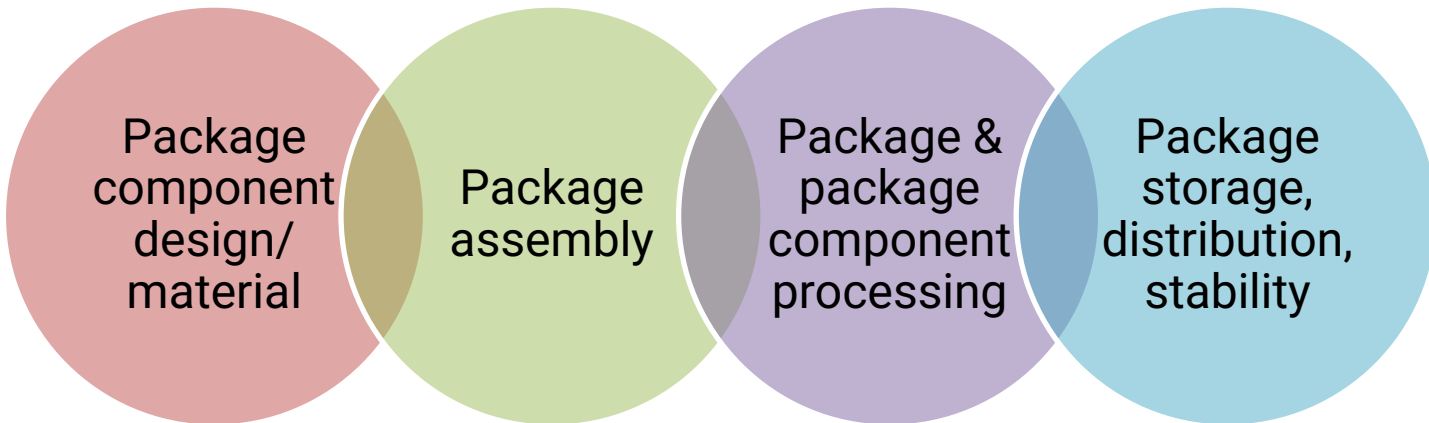
- Material composition, dimension, processing, and assembly.
- Final product storage, distribution and use.

Determined during product-package **R&D and validation**.

Acceptable inherent package integrity conforms to the specific product-package MALL

Package Integrity Profile

- **Ongoing database – 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**



Summary

01



A package with integrity is one with an absence of gaps/breaches in packages that **COULD** risk product quality by allowing solid/liquid contaminant ingress, product formulation loss, and in some cases, headspace change. i.e., Meets the **Maximum Allowable Leakage Limit**.

02



Reporting leak size/rate can be done a variety of ways.

- ✓ **Key is to be clear, noting methodology**
- ✓ **Units of measure should be relevant to the MALL**

Summary



03

Develop/validate **CC system** having inherent **package integrity** that meets the product **MALL specification**.



04

Microbial ingress/liquid tracer tests are probabilistic methods that cannot solely be relied upon for package integrity assurance. - *Tests may miss harmful leak paths*



05

Use ongoing product **package integrity profile data** to monitor for and minimize integrity failure risks.

