Container Closure Integrity: Regulations, Test Methods, Application

Introduction

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Venice Italy, March 21-22, 2019

Introduction

- Terms, definitions, and Concepts
- Maximum Allowable Leak Limit (MALL)
- Inherent package integrity
- 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

Product:

- ***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

Package (aka Container-closure):

- ***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:

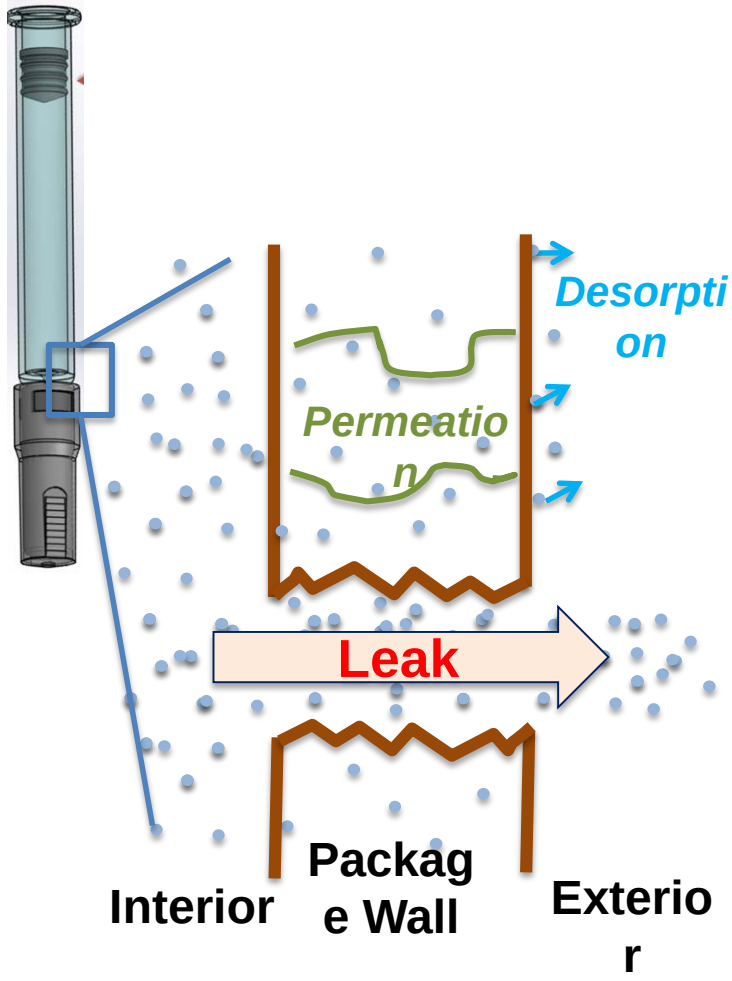
1. The unintentional entry or escape of matter (solid, liquid or gas) through a breach in a package wall or through a gap between package components.
2. The leaking matter itself.

Definitions

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 and MALL

Sterile product package integrity

***or* "container closure integrity" (CCI)**

Definition: The ability of a package to…

Keep good stuff in, and

Keep bad stuff out

"A package with integrity"

<u>Does not mean</u>

the package has passed or is able to pass a

Microbial ingress test, or product sterility test

Package Integrity and MALL

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 and MALL

CONSIDER

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

?

D. Guazzo, RxPax, LLC

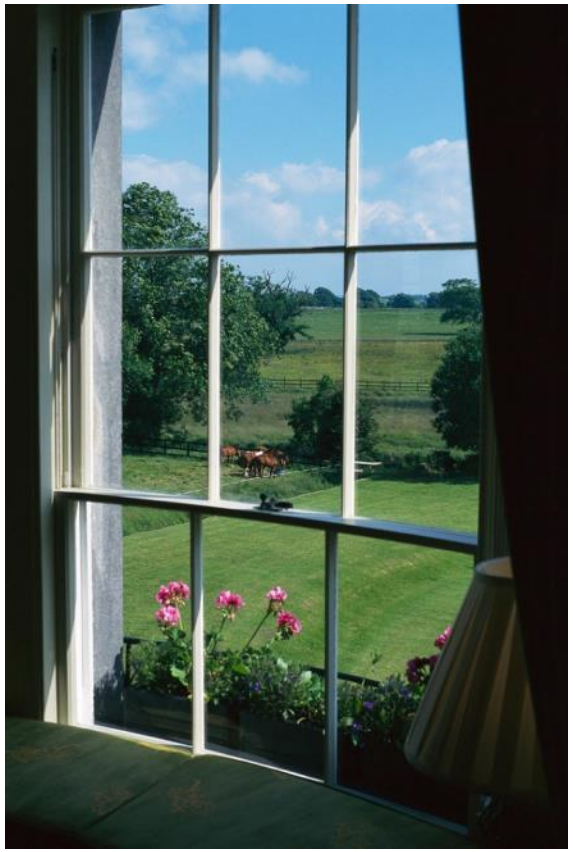
Package Integrity and MALL

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

<u>Testing goals may vary during the product life cycle</u>

Package Integrity and 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 and 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?

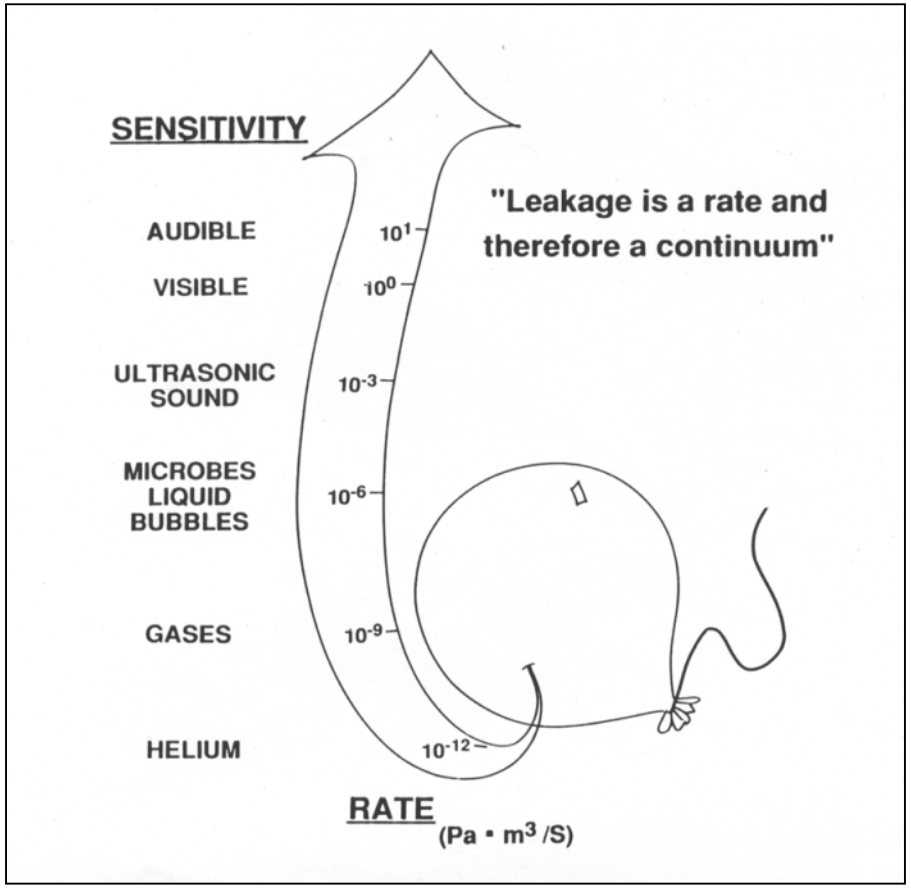
Maximum Allowable Leakage Limit (MALL)

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

(sometimes called the '***critical leak***')

Package Integrity and 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

*physicochemically bonded seals may only allow permeation

Package Integrity and MALL

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.

Package Integrity and MALL

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 and 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 tra**
    - 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 60ºC 2hr, then 25ºC 1hr
    - 24 hr immersion, ambient pressure

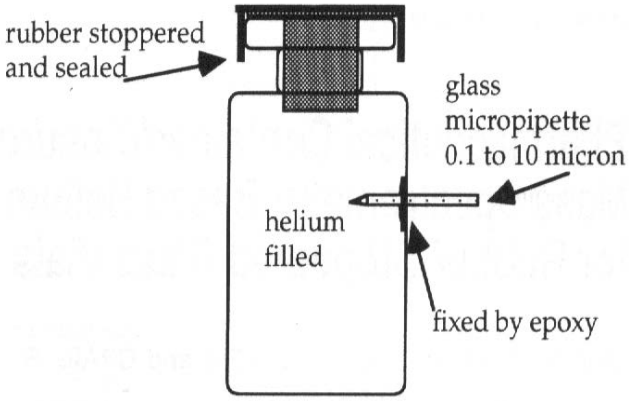


Figure 1—Schematic description of the modified pharmaceutical vials used as test units for the evaluation of mass spectrometry-based helium leak rate measurements.

Package Integrity and MALL

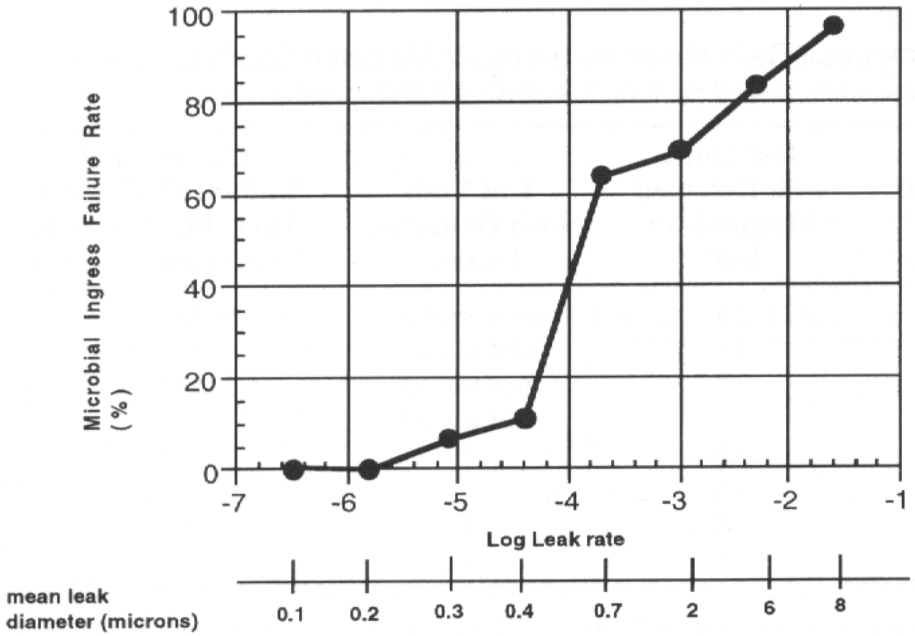


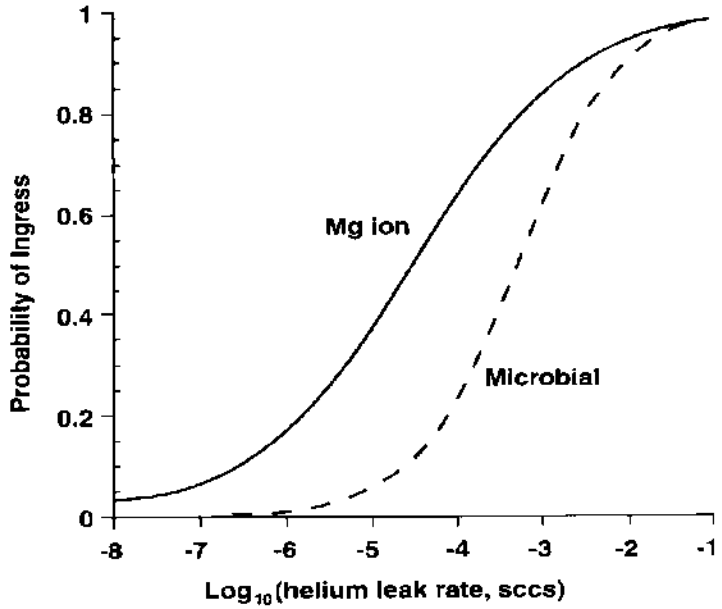
Figure 2—The correlation of microbial failure rate (%) and the mean logarithm of the absolute leak rate and nominal leak diameter for modified SVPs. The absolute leak rate (standard cubic centimeters per second) was determined by mass spectrometry-based helium leak rate detection. Microbial failure was measured by microbial ingress after 24 hour immersion in a bath (37°C) containing 10^8 to 10^{10} *P. diminuta* and *E. coli* organisms/mL and a 13 day, 35°C incubation.

- **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

Package Integrity and MALL

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).



- **Microbial ingress *requires* liquid flow**
  - **Increased liquid flow equals increased microbial ingress risk**
- **Liquid flow ≠ microbial ingress**

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

Package Integrity and 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	*P. diminuta* *E. coli*	Glass micro-pipette thru vial wall	Airlock elimination step + 24 hr ambient	0.3 μm orifice
Burrell JPDA 2000	Liquid	*E. Coli*	Poly-coated glass micro-tube thru stopper	ISO closure reseal: 30 min 22"Hg + 30 min ambient	10 μm ID tube
Morrical JPDA 2007	Liquid	*Serratia marcescens*	Metal plate micro-hole in stopper	-0.4 bar 1 hr +0.4 bar 1 hr	4 μm orifice
Morrical JPDA 2007	Liquid	*Serratia marcescens*	Copper wire between stopper/vial	-0.4 bar 1 hr +0.4 bar 1 hr	20 μm OD wire
Keller *J Applied Pkgg Res 2006*	Aerosol	*P. Fragi*	Nickel micro-tube in 3mL vial	Varied: -20 kPa to +20 kPa 4 to 37ºC	5 μm ID tube

Package Integrity and 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 and 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 E-6 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 and 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 and 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., N_2 escape; vacuum loss; entry of O_2, H_2O 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 and 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

1. **Prevention of microbial ingress** to ensure product sterility
2. **Prevention of product formulation loss** and **product formulation contamination by external solids/liquids** to ensure conformance to relevant physicochemical product quality attributes.
3. **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, 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**
  - Package component design/material
  - Package assembly
  - Package and package component processing
  - Package storage, distribution, stability

Summary

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**

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

Microbial ingress/liquid tracer tests are probabilistic methods that cannot solely be relied upon for package integrity assurance.

Tests may miss harmful leak paths

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

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