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

PDA Parenteral Drug Association

PDA TRAINING

INTRODUCTION

1. 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)

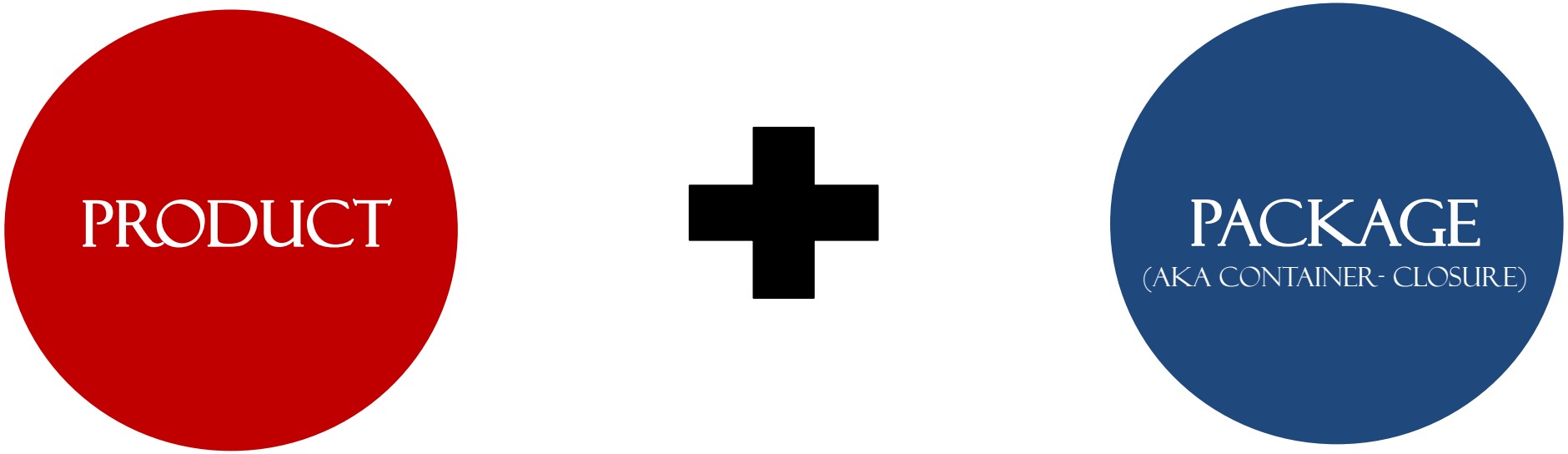
Out of Scope of USP <1207> - Methodologies Apply

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

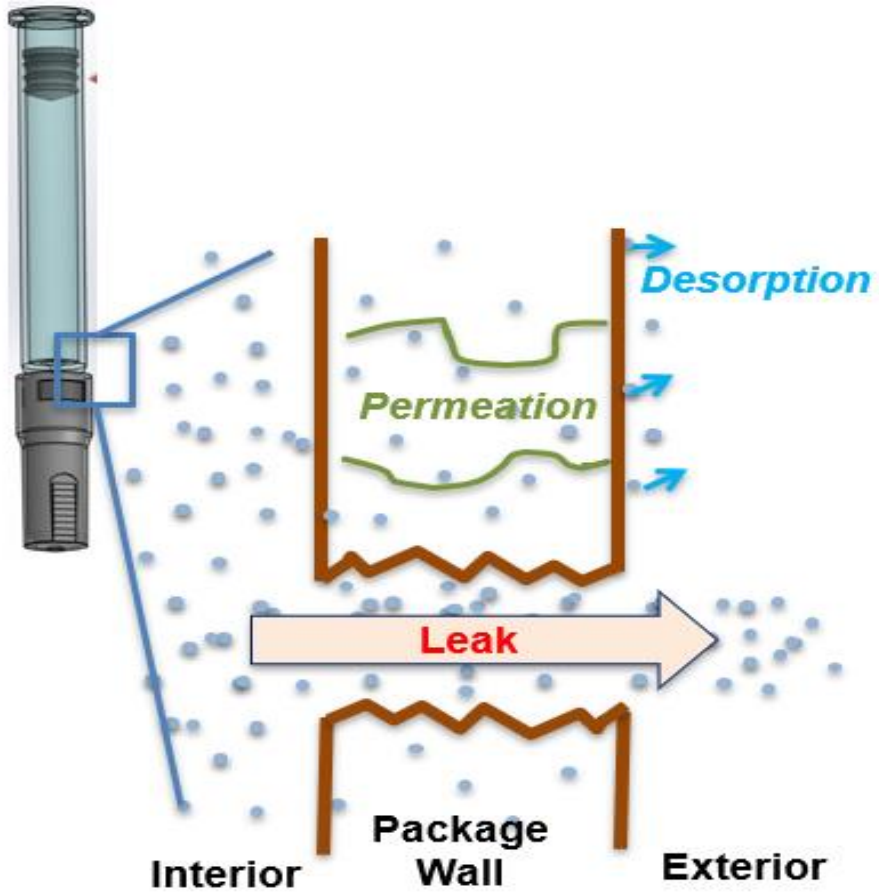
The primary package with critical secondary components
(the container-closure system) **AND**
the packaged contents (the product)

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

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

Package Integrity & 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 & 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?

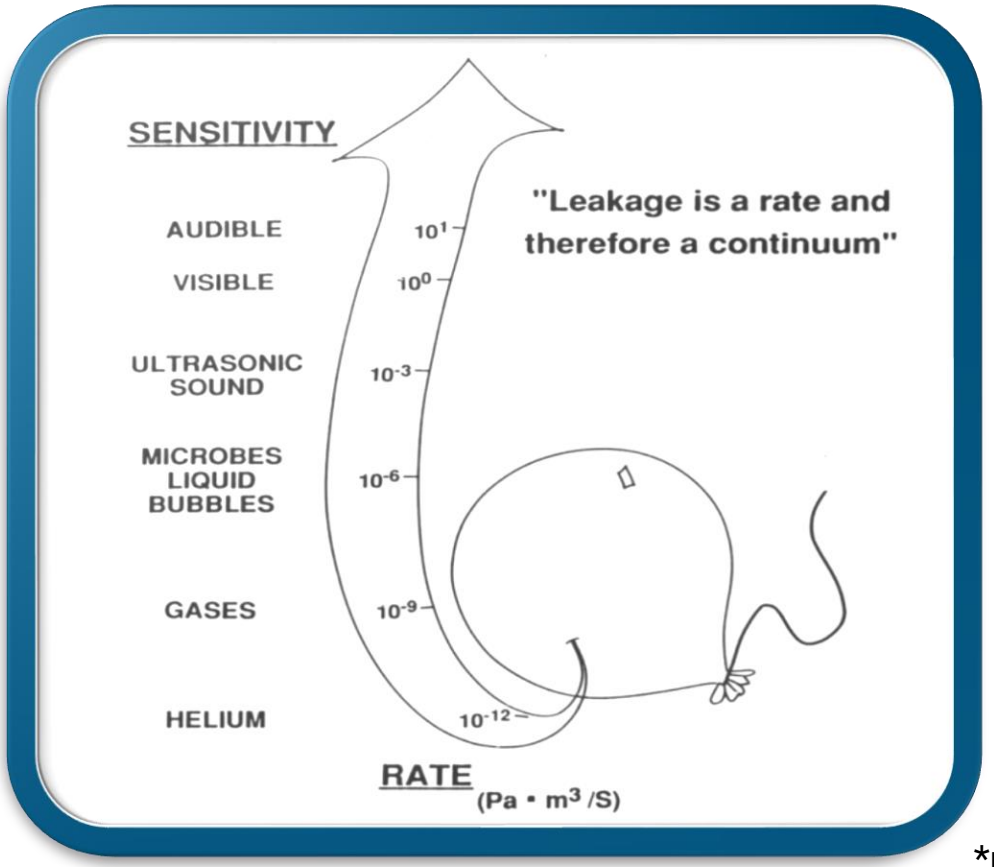
Maximum Allowable Leakage Limit (MALL)

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

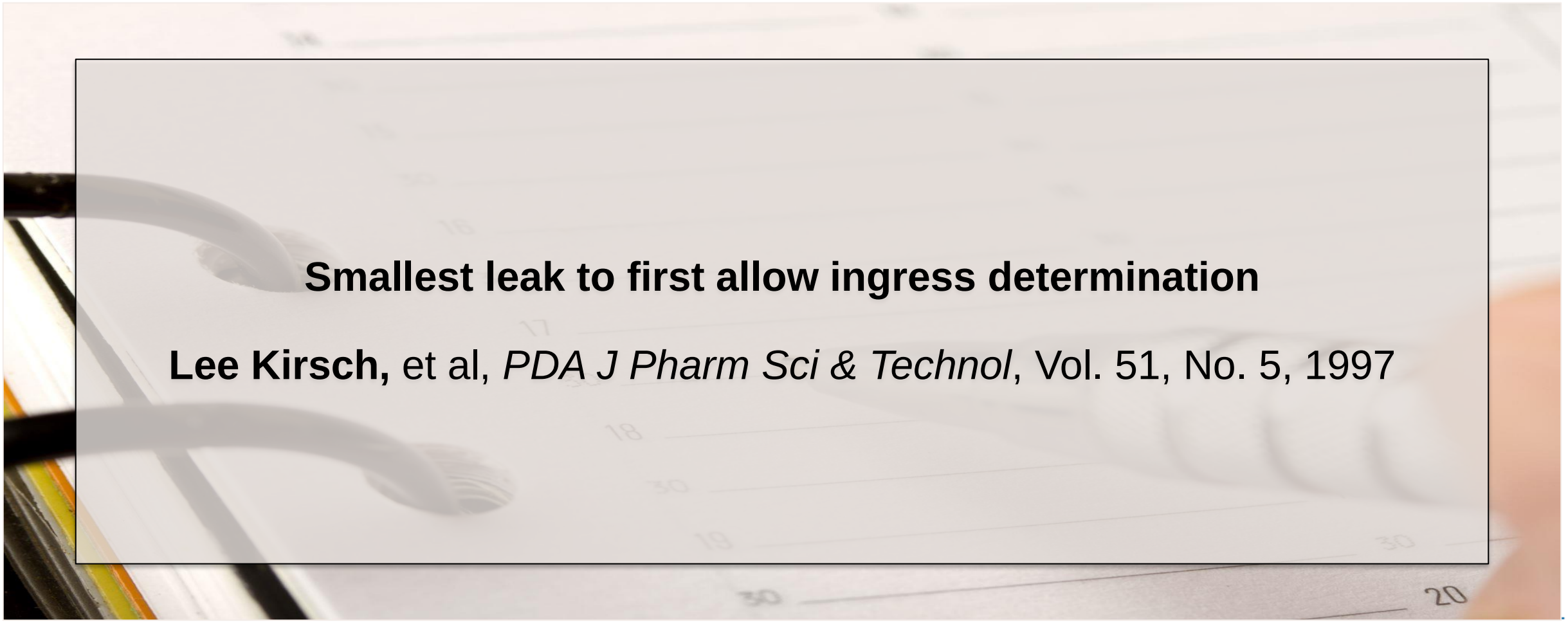
*physico-chemically bonded seals may only allow permeation

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



Smallest leak to first allow ingress determination

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

Package Integrity & MALL

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 60ºC 2hr, then 25ºC 1hr
  - 24 hr. immersion, ambient pressure

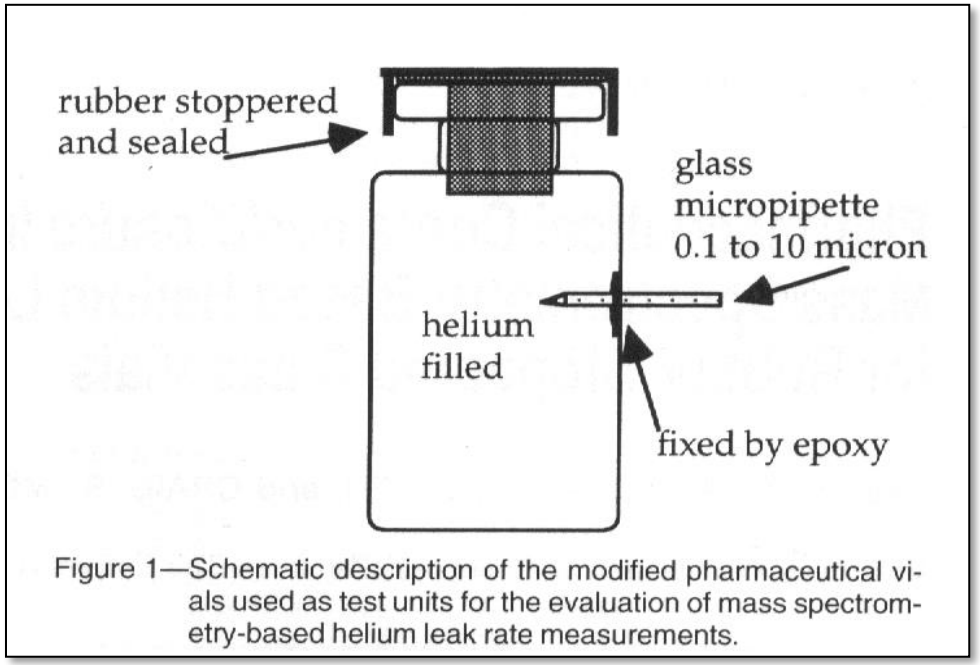


Figure 1—Schematic description of the modified pharmaceutical vials used as test units for the evaluation of mass spectrometry-based helium leak rate measurements.

Package Integrity & MALL

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

- Microbial ingress risk dropped dramatically at Log -3.8 secs

  (< ~1μm)

- Low risk of ingress (< 0.10) at helium leak rate of 6 x 10^{-6} mbarL/s

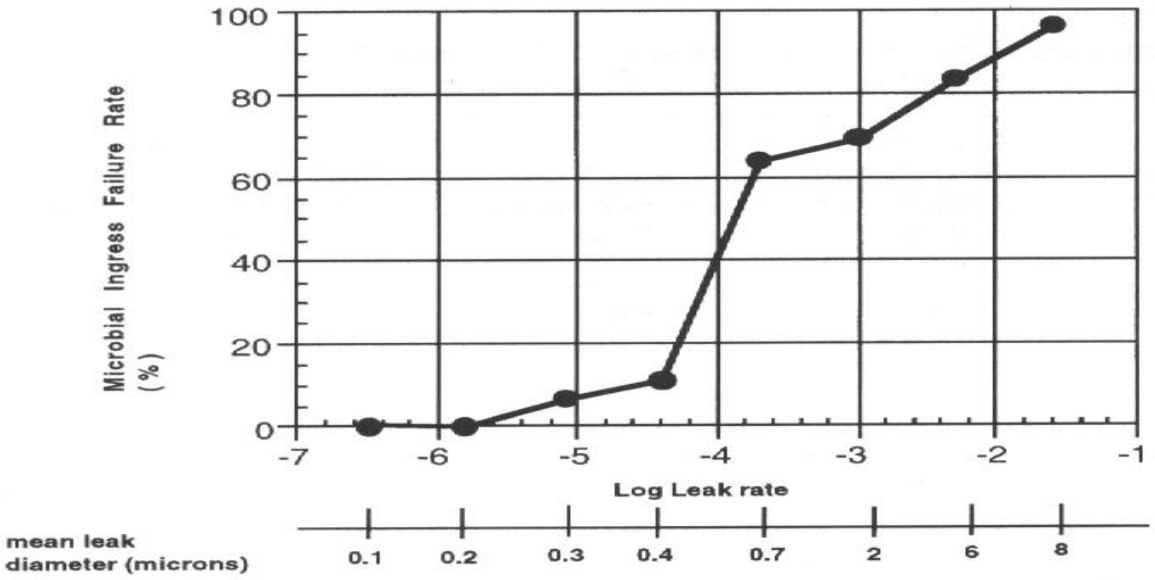


Figure 2—The correlation of microbial failure rate (%) and the mean logarithm of the absolute leak rate and nominal leak diameter for modified SVPs. The absolute leak rate (standard cubic centimeters per second) was determined by mass spectrometry-based helium leak rate detection. Microbial failure was 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.

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

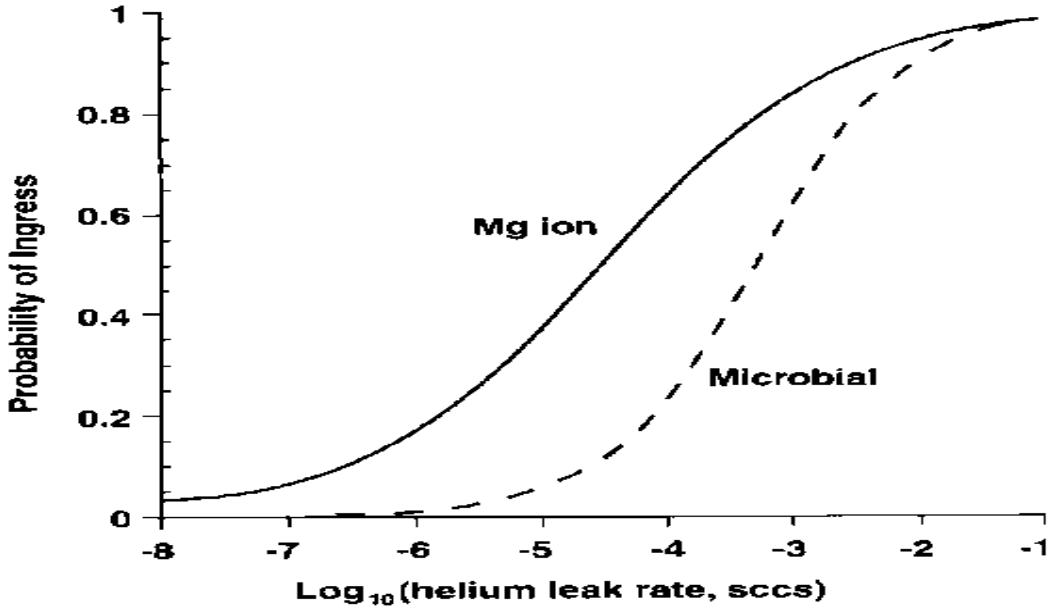
Package Integrity & MALL

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 ≠ microbial ingress

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

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).



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	*P. diminuta* *E. coli*	Glass micro-pipette through vial wall	Airlock elimination step + 24 hrs ambient	0.3 μm orifice
Burrell JPDA 2000	Liquid	*E. Coli*	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	*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. Appl. Packag. Res. 2006*	Aerosol	*P. Fragi*	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 $< 6\ E^{-6}$ 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 & 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., 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 & 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.

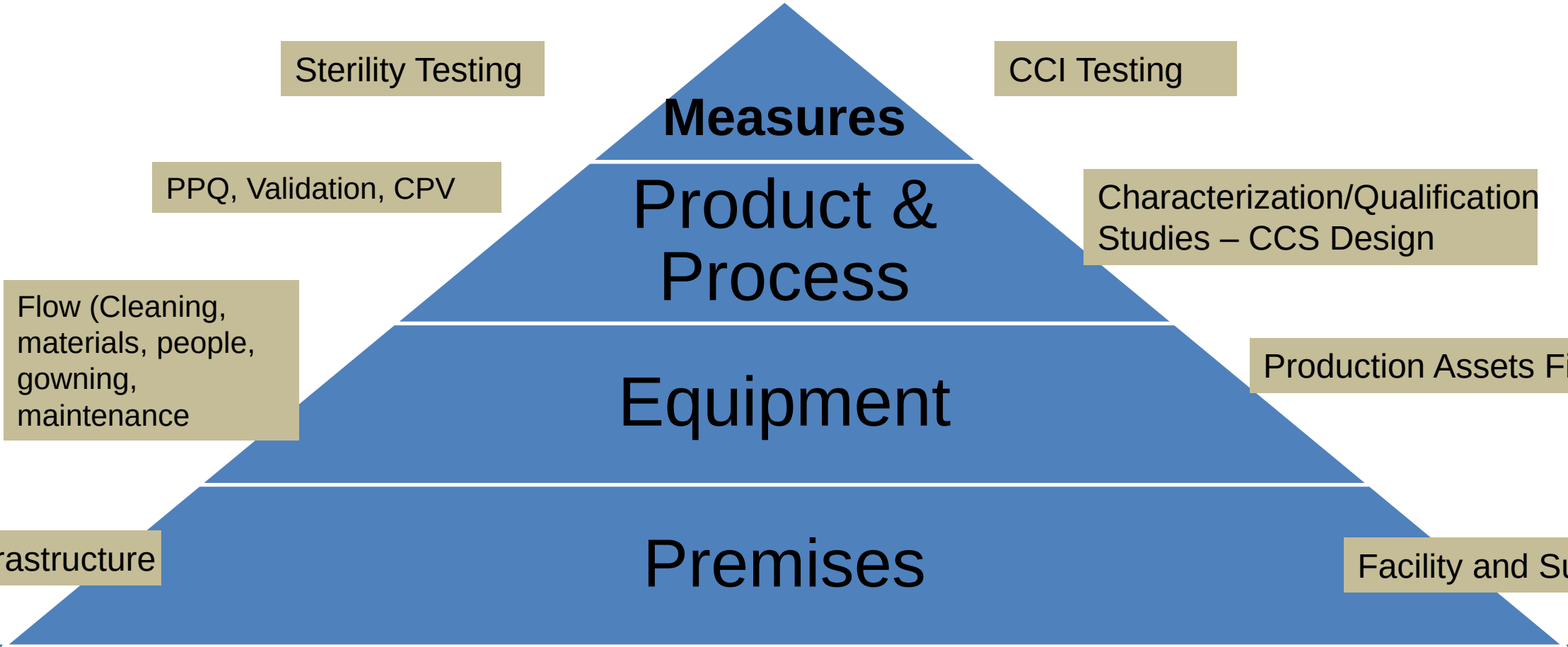
Determined during product-package **R&D and validation.**

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

Container Closure Integrity Paradigm

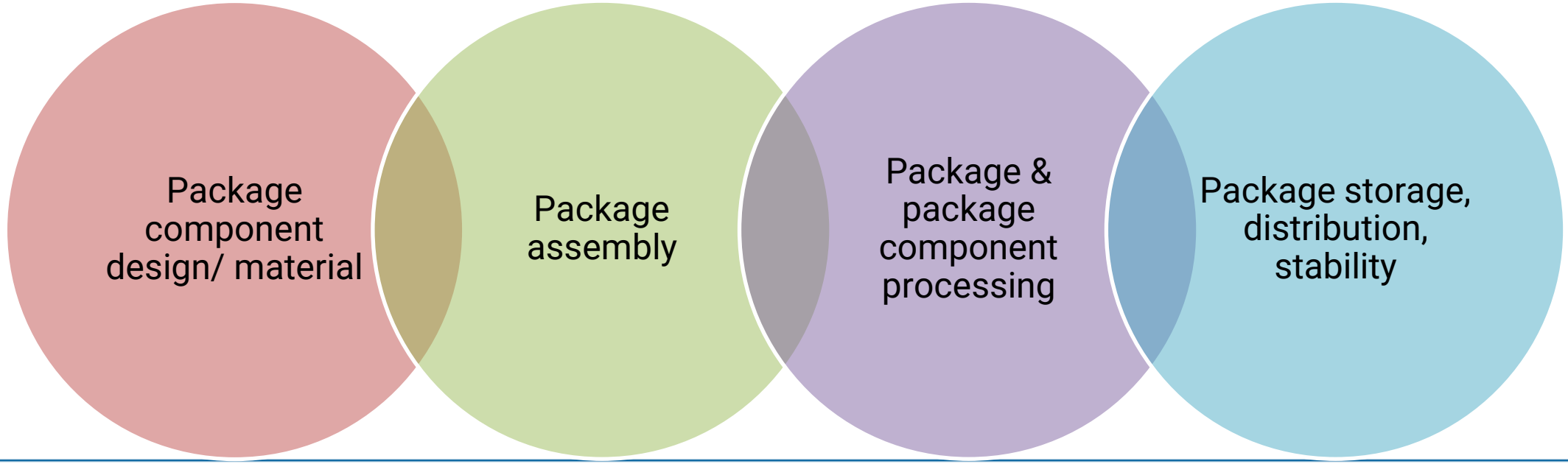
Sterility Assurance Pyramid

CC Integrity Assurance Pyramid



Package Integrity Profile

- ***<u>Ongoing database</u> – 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.