PDA Training Course

Container Closure Integrity
Regulations, Theory, Test Methods, Application

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Outline

Container Closure Integrity
Regulations, Theory, Test Methods, Application

Part 1. Introduction

Part 2. Test methods

Part 3. Test method selection and application

Part 4. Test method development and validation

Part 5. Wrap-up

Outline

Container Closure Integrity
Regulations, Theory, Test Methods, Application

Part 1. Introduction

A. Definitions
B. Maximum allowable leakage limit as a function of product-package
C. Maximum allowable leakage limit and microbial/liquid ingress

Outline

Container Closure Integrity
Regulations, Theory, Test Methods, Application

Part 2. Test methods

A. Introduction
B. Deterministic leak test methods
C. Probabilistic leak test methods
D. Seal quality test methods

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Part 3. Test method selection and application

A. Product life cycle and CCI testing
B. Test method selection criteria
C. Test application examples

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Part 4. Test method development and validation

A. Positive and negative controls, masters, blanks
B. Instrument/equipment qualification
C. Method development
D. Method validation

Outline

Container Closure Integrity
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Part 5. Wrap-up

A. Current regulations: US, EU
B. Future direction
   1. USP <1207> proposed revision
   2. PDA TR 27 revision

Definitions

Product

- ***Pharmaceutical formulation***
  - Alternatively: API, bulk, intermediates
- ***Packaged headspace***
  - **Air** or **nonreactive gases**
  - At specified **water vapor** content
  - At ambient or sub-ambient **pressures**

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Definitions

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

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Definitions

Closure by mechanical fitment

- ***Examples***
  - **Stopper/vial**
  - **Syringe**
    - Barrel/plunger(piston)
    - Needle shield/needle tip
    - Needle shield/barrel ??????????
  - **Screw-cap/bottle**
    - **NOTE:** Bottle/cap threads offer no barrier to liquid or microbial ingress

Definitions

Closure by mechanical fitment

- **Tiny gap(s) permitting gas leakage exists**
- **Extent of leakage a function of**
  - **Surface morphology**
  - **Surface viscoelasticity**
    - E.g., Coated vs. uncoated elastomeric closures
  - **Forces holding components together**
    - E.g., Residual seal force of stopper/vial

Definitions

Closure by physicochemical bonding

- ***Examples***
  - **Syringe**
    - Needle base/barrel adhesive bond
  - **Heat-sealed film/tray**
  - **Ultrasonically welded IV bag seal**
  - **Glass/plastic ampoules**

Definitions

Closure by physicochemical bonding

- **Gas permeation exists thru bonding material and/or components**

  Exception: glass ampoules

- **Leakage (if present) a function of**
  - **Bond completeness**

    E.g., Frangible vs. non-frangible heat seal

Definitions

Closure systems not covered

1. **Vent filtration closure systems**

- **Filters used to filter out/limit microbial ingress, allowing air/sterilant-gas exchange**

  E.g., Porous barrier film on drug kit tray

2. **Multidose-product microbial blockage closure systems**

- **Product egress allowed while ingress of microbes/debris limited by filters, plugs, valves, etc.**

  E.g., Multidose ophthalmic solutions/ointments

Definitions

Although parenteral packages must keep products STERILE,

Package integrity *is not* defined as

- **Absence of microbial or liquid ingress**
- **Product sterility**

Definitions

Package integrity

The absence of gaps/breaches in packages that COULD risk product quality by allowing contaminant ingress and/or product loss

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Definitions

Leakage

A measure of the rate of gas flow (mass or volume units) which passes through a leak path under defined conditions of temperature and pressure

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Definitions

Leakage Units

Mass flow conversion units

Standard temperature (273K), pressure (760 torr)

Pascal Cubic Meter Per Second	Standard Cubic Centimeter Per Second	Mole Liter Per Second	Millibar Liter Per second	Torr Liter Per Second
$Pa \cdot m^3 \cdot s^{-1}$	Std $cm^3 \cdot s^{-1}$ (Alternatively, sccs)	$mol \cdot s^{-1}$	$mb \cdot L \cdot s^{-1}$	$torr \cdot L \cdot s^{-1}$
1	9.87 ($\simeq$ 10)	4.40×10^{-4}	1.00×10^{1}	7.50

Jackson CN, Sherlock CN, Moore PO, Nondestructive Testing Handbook, 3rd ed. Vol 1 Leak Testing, American Society for Nondestructive Testing, Inc. 1998

Definitions

Leak

A gap or breach in the container capable of permitting the passage of liquid or gas

Syn. “Leak path”

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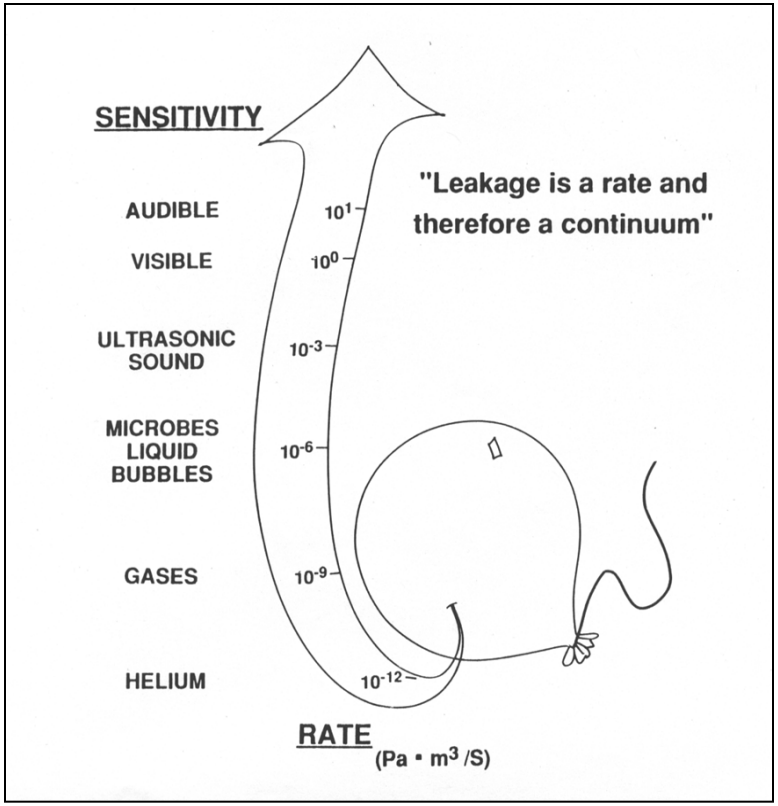
Definitions

All closure systems* allow gas mass flow



Smallest leaks **only** allow

gas flow

Larger leaks **may also** allow

liquid flow

Largest leaks **may also** allow

microbial ingress

*chemically bonded seals may allow permeation only

Definitions

Inherent package integrity

- ***The leakage rate of a <u>no-defect, well-assembled</u> package***
  - **<u>Leakage occurs</u>** between mechanically fitted components
  - **<u>Leakage may occur</u>** between physicochemically bonded components

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- **<u>Leakage > inherent integrity leak rate</u>** caused by
  - Poor assembly
  - Component defects

Definitions

Maximum allowable leakage limit (MALL)

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

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

*Microbiological or physicochemical quality

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Definitions

Integral package

A package of no-defect, well-assembled components that conforms to the product's MALL criterion

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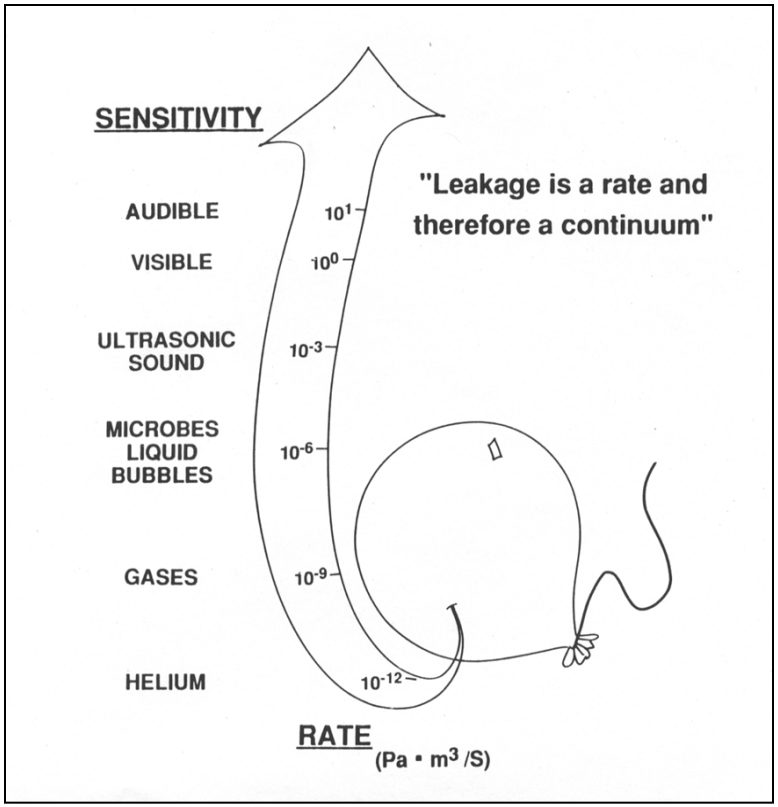
A package considered integral for one product may not be integral for others!

MALL as a function of product-package



All leaks allow **gas flow**

PLUS

Polymeric materials allow **gas permeation**

So for some products, TOTAL gas mass transfer must be considered

MALL as a function of product-package

MALL as a function of product

Package	Product	Leakage risk between components	Permeation risk through components
Vial/stopper	• Air headspace • Aq. liquid dosage form	• Sterility failure • Liquid product loss	• None

	• Vacuum headspace
	• Lyo-powder
		• Sterility failure
		• Product loss
		  • Constituted liquid loss
		  • Oxygen rise
		  • Pressure rise
		  • Moisture rise
			• Oxygen rise
			• Pressure rise
			• Moisture rise

MALL and microbial/liquid ingress

MALL and microbial ingress

As all parenteral packages must prevent microbial ingress, MALL is often thought to mean leakage that first allows microbial (or liquid) ingress

Question: What is this MALL?

MALL and microbial/liquid ingress

Smallest leak to allow ingress determination

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

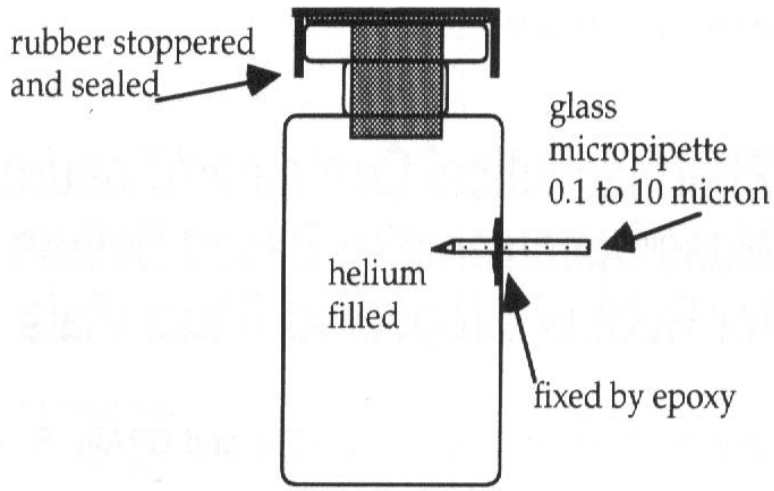


Figure 1—Schematic description of the modified pharmaceutical vials used as test units for the evaluation of mass spectrometry-based helium leak rate measurements.

Kirsch, et al, *PDA J Pharm Sci & Technol* 51, 5, 1997 p. 187 - 194

MALL and microbial/liquid ingress

Smallest leak to allow ingress determination

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

- **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

Part 1. Introduction

MALL and microbial/liquid ingress

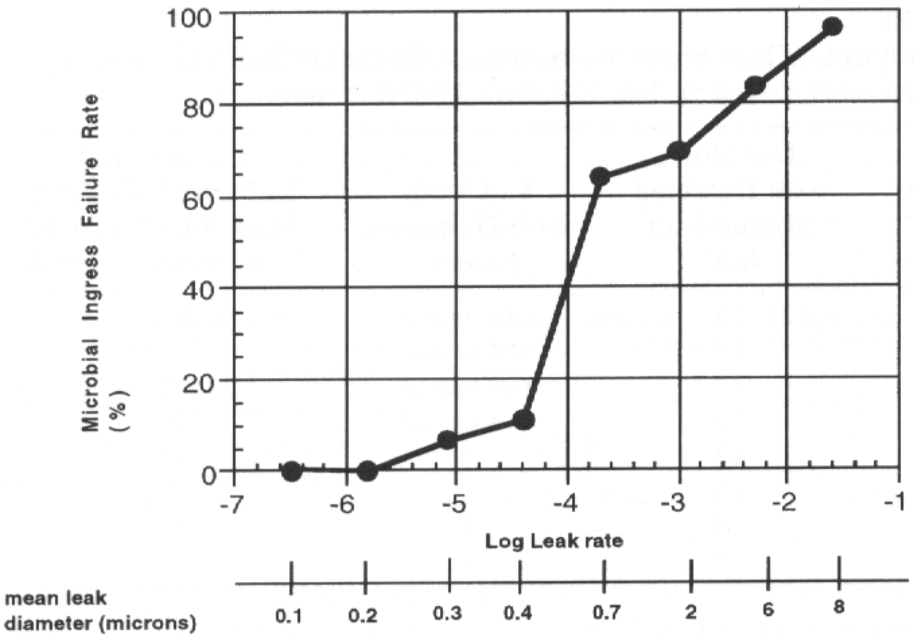


Figure 2—The correlation of microbial failure rate (%) and the mean logarithm of the absolute leak rate and nominal leak diameter for modified SVPs. The absolute leak rate (standard cubic centimeters per second) was determined by mass spectrometry-based helium leak rate detection. Microbial failure was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

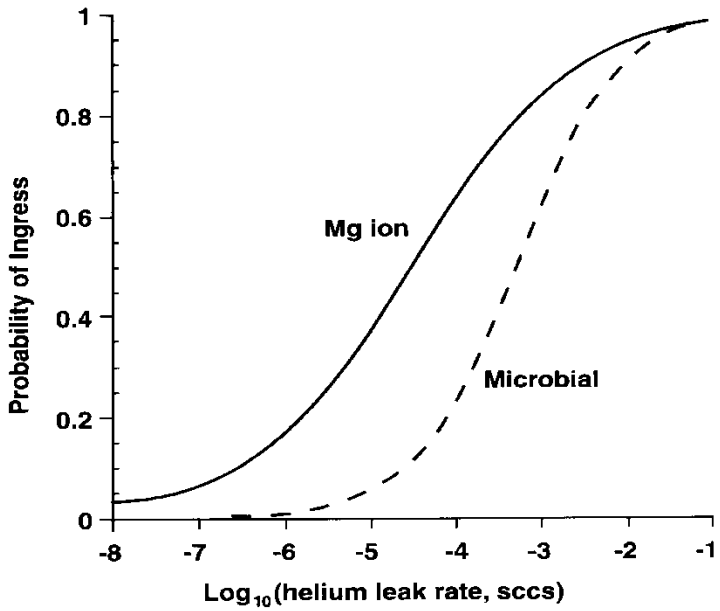
- **Microb. ingress risk dropped dramatically**
  - **Log -3.8 sccs**
  - **< ~1µm**
- **No ingress**
  - **Log -5 to -5.8 sccs**

    (< 1.6E-6 mbarL/s)
  - **~0.3 to 0.2µm**

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

MALL and microbial/liquid 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).



- **Microbial ingress *required* liquid flow**

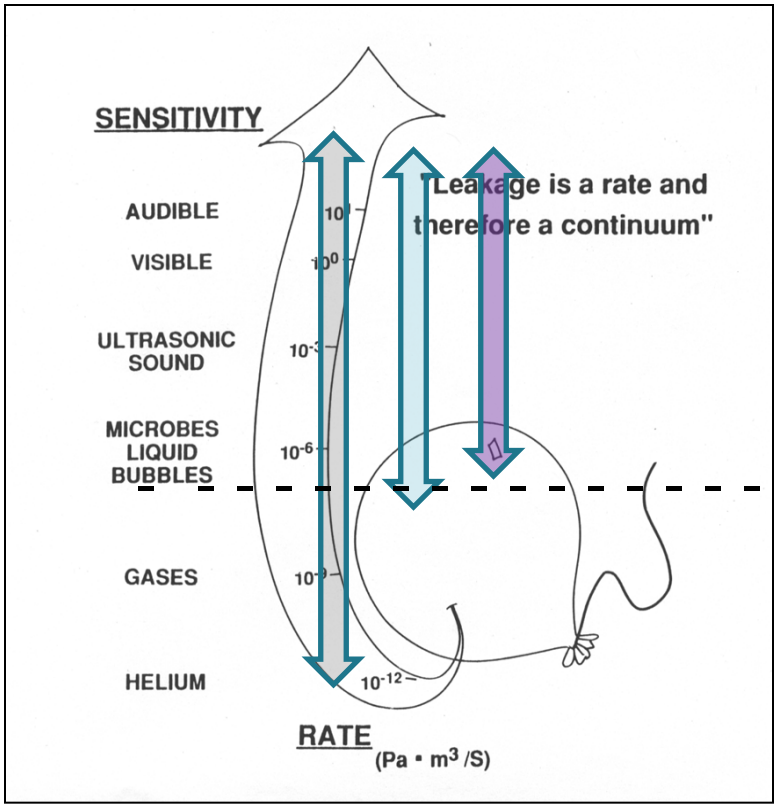
  > Liquid flow =

  > microbial ingress *risk*

- **Liquid flow ≠ microbial ingress**

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

MALL and microbial/liquid ingress



The **Kirsch criterion** equates to the helium leak rate of the smallest orifice found to permit microbial ingress into glass vial positive controls under defined challenge conditions.

"Kirsch criterion" = 1.6 E-6 mbarL/s

Smallest leaks **only** allow **gas flow**

Larger leaks **may also** allow **liquid flow**

Largest leaks **may also** allow **microbial ingress**

NOTE—To convert to mbar·L/s multiply by a factor 10

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

MALL and microbial/liquid ingress

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

MALL and microbial/liquid ingress

- Reported MAL leak that first allows microbial ingress: **0.3µm hole** to **20µm OD wire**

- **Liquid presence** in the leak path is **required**, but **does 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

MALL and microbial/liquid ingress

Sole reliance on ingress tests to confirm Inherent CCI is

NOT RECOMMENDED

Ingress is a PROBABILISTIC EVENT

Difficult to control, predict, measure

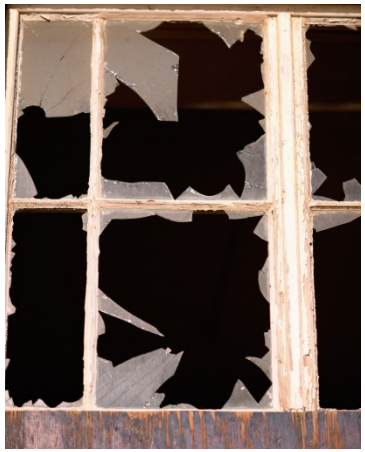
FACTORS

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***

MALL and microbial/liquid ingress

CONSIDER

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



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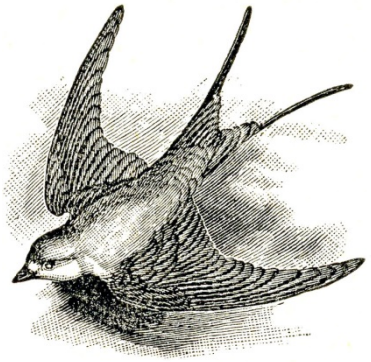

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MALL and microbial/liquid ingress

INSTEAD

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

MALL and microbial/liquid ingress

PARENTERAL PACKAGES

Design and make packages that close well based on meaningful, reliable tests

Test for absence of defects that could permit product contamination, degradation or loss

Monitor to ensure control over materials, processes

Summary

- **Package integrity** is the **absence of gaps/breaches** in packages that COULD risk product quality by allowing contaminant ingress or product loss.
- **The Maximum Allowable Leakage Limit** (the **smallest leak rate that risks product quality**) is the basis for judging CC system integrity.
- **CCI ingress tests** are **probabilistic methods** that cannot solely be relied upon for package integrity assurance.
- **Design and assemble packages** to **minimize risk of integrity failure** using sound scientific methods, backed by appropriate validated and adequately sensitive tests.

End of Part 1