Container Closure Integrity: Regulations, Test Methods, Application

Introduction

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Rome Italy, March 1-2, 2018

Introduction

- Terms and definitions
- 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:

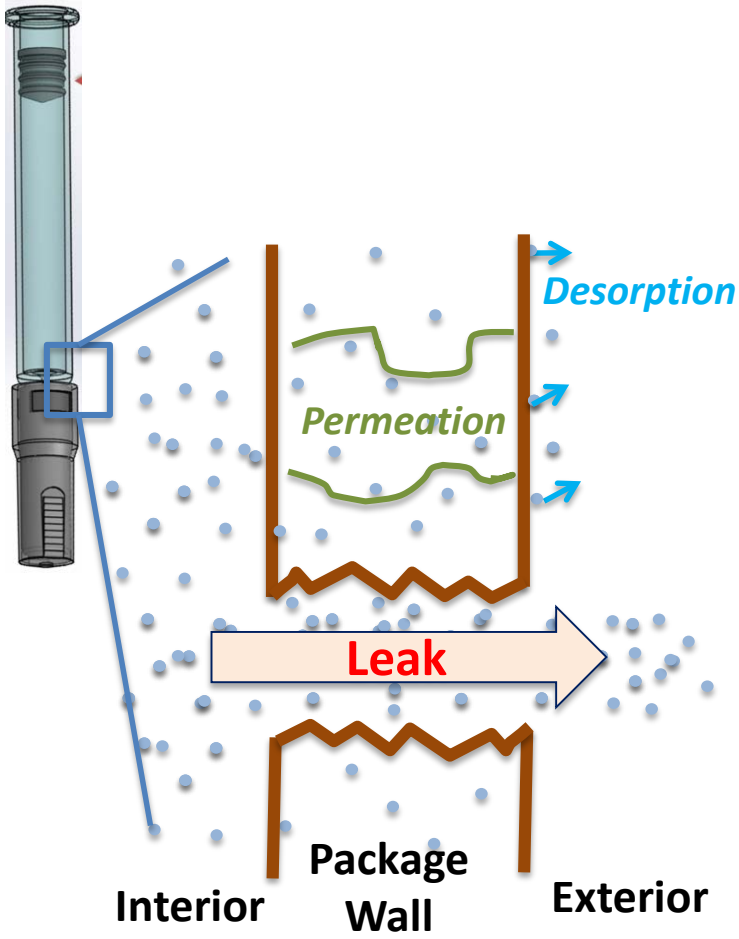
1. The unintentional entry or escape of matter (solid, liquid or gas) through a breach in a package wall or through a gap between package components.
2. The leaking matter itself.

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

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 :

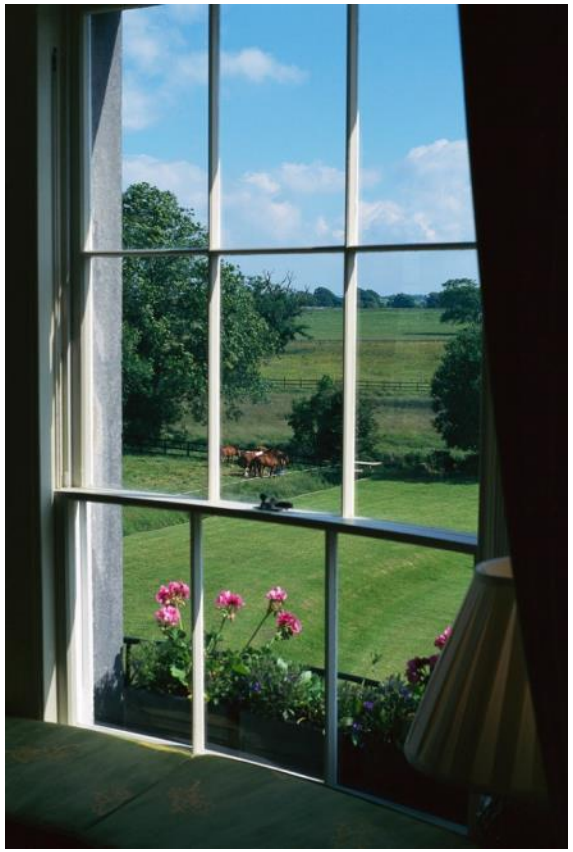
IS NOT passing microbial ingress or product sterility tests

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>



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?

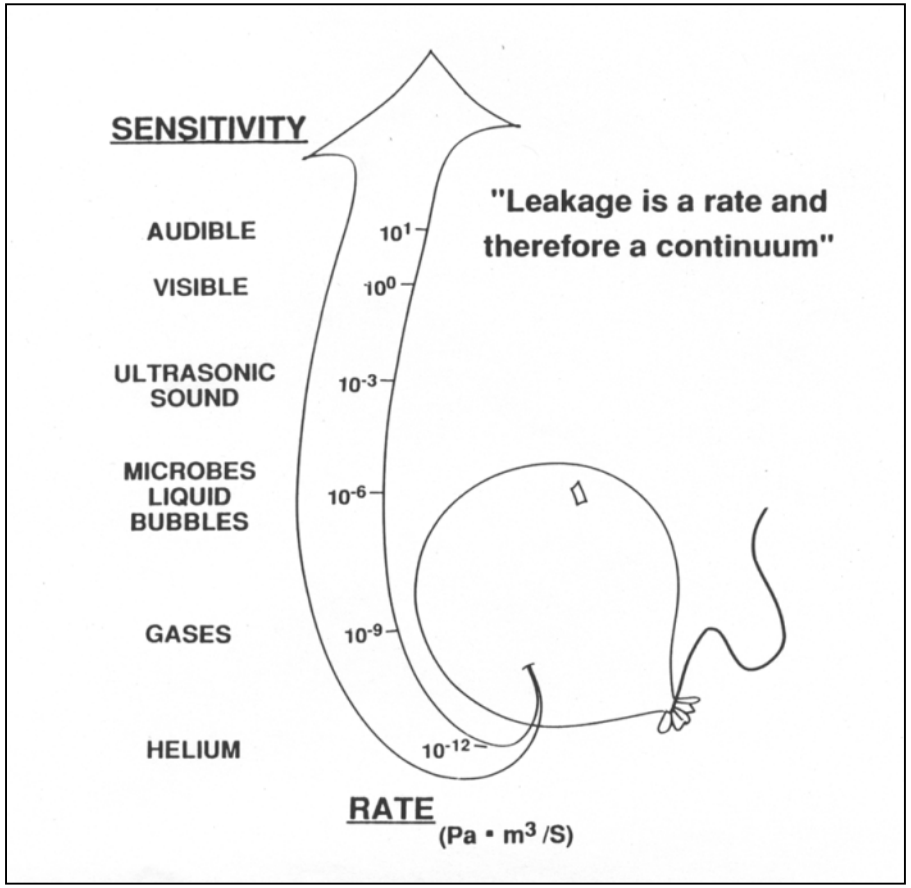
Maximum Allowable Leakage Limit (MALL)

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?

1.Prevention of **microbial ingress**

2.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 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

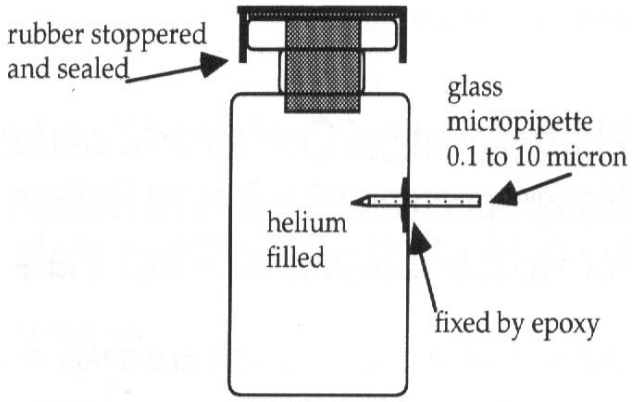


Figure 1—Schematic description of the modified pharmaceutical vials used as test units for the evaluation of mass spectrometry-based helium leak rate measurements.

Package Integrity and MALL

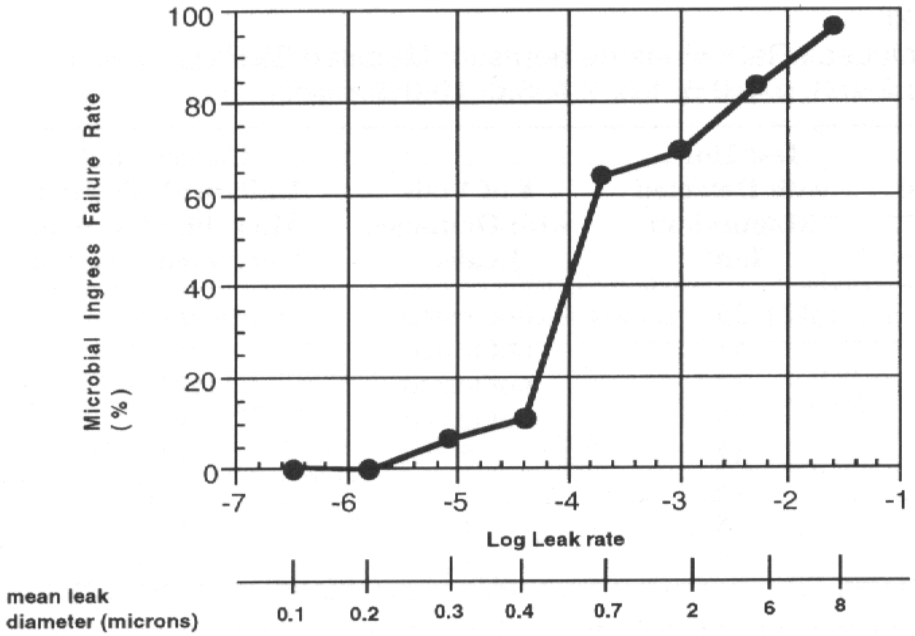


Figure 2—The correlation of microbial failure rate (%) and the mean logarithm of the absolute leak rate and nominal leak diameter for modified SVPs. The absolute leak rate (standard cubic centimeters per second) was determined by mass spectrometry-based helium leak rate detection. Microbial failure was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

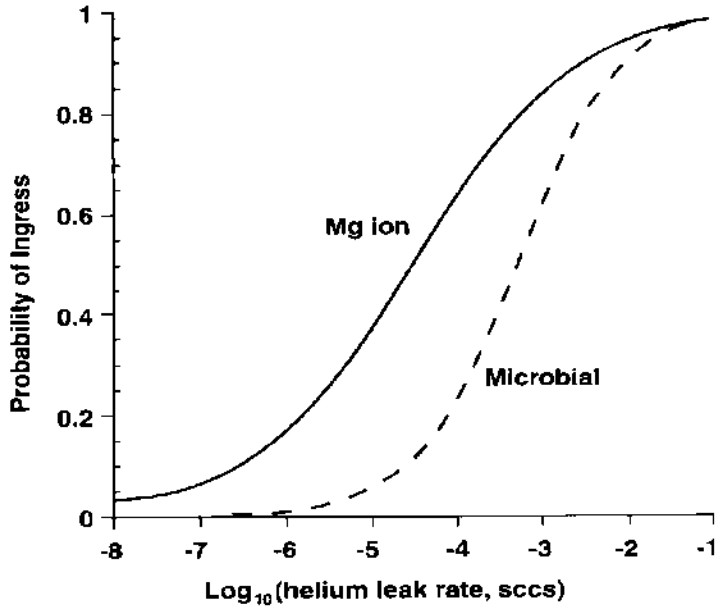
Low risk of ingress (< 0.10) at helium leak rate of

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

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

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

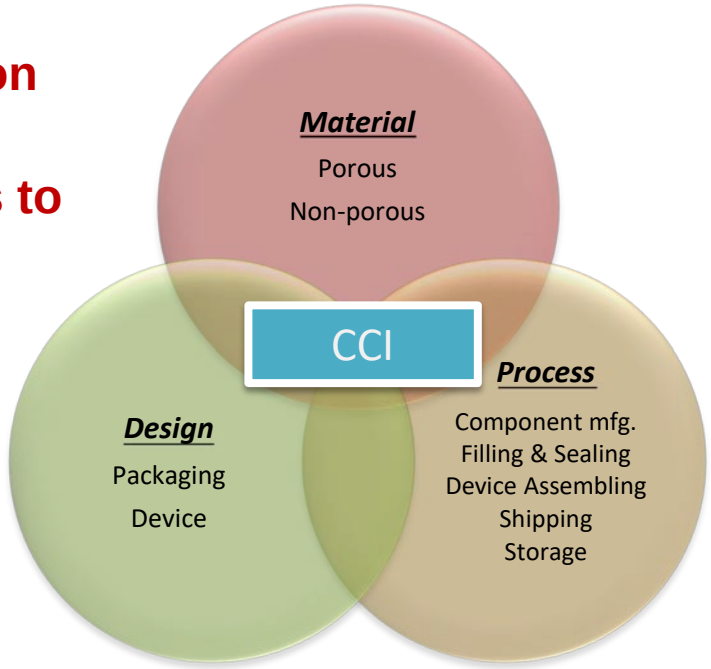
The leakage rate (or the equivalent leak size) of a well-assembled package using no-defect components.

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



Physically Mated Closures

Closure made by close physical contact of surfaces

Surfaces are often dissimilar in material composition

Examples:

- **Stopper/vial**
- **Syringe**
  - Barrel/plunger (piston)
  - Needle shield/needle tip
  - Needle shield/syringe luer
- **Screw-cap/bottle**
  - ***NOTE*: Bottle/cap threads *do not offer an optimal barrier* to gas or liquid leakage, or to microbial ingress in the event of liquid in cap threads.**

Tiny gap(s) permitting gas leakage exist

Extent of closure (leakage prevention) is 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

Physicochemically Bonded Closures

Closure made by material P-C bonding/fusion
Material composition may be similar or dissimilar
An intermediate layer may provide bonding

Examples

Syringe

Needle base/barrel adhesive bond

Heat-sealed film/tray

Ultrasonically welded IV bag seal

Glass/plastic ampoules

Gas permeation exists thru bonding material and/or components

Exception: glass ampoules

Leakage (if present) is a function of bond completeness

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

Multi-dose Package Closures

Designed to permit product access while limiting microbial ingress and product leakage between doses

Examples

Parenteral product closures punctured for product access

Elastomeric closures on vials, cartridges

Ophthalmic dosage form packages

Specialized closure mechanisms with plugs, filters, pinch points or other

Processes

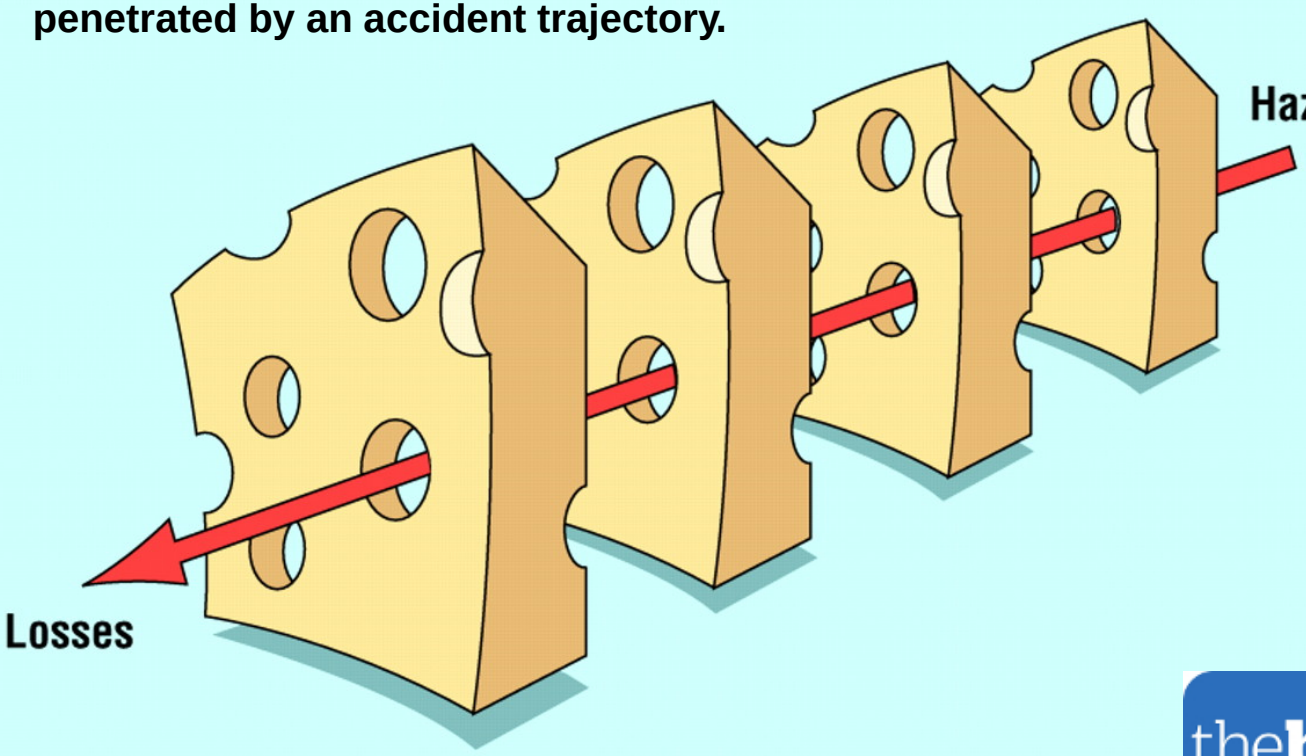
Final Product = (Design * Process) + Patient

Processes


Secondary packaging
Device
Shipping & Distribution
Packaging/ Sealing
Practitioner, Care-taker
Drug Formulation / Filling
Patient
Packaging Integrity
Packaging Component

Design & Process Risk Assessments

The Swiss cheese model of how defences, barriers, and safeguards may be penetrated by an accident trajectory.



James Reason BMJ 2000;320:768-770

Design & Process Risk Assessments

Process Risk Assessment

CCS Design Risk Assessment

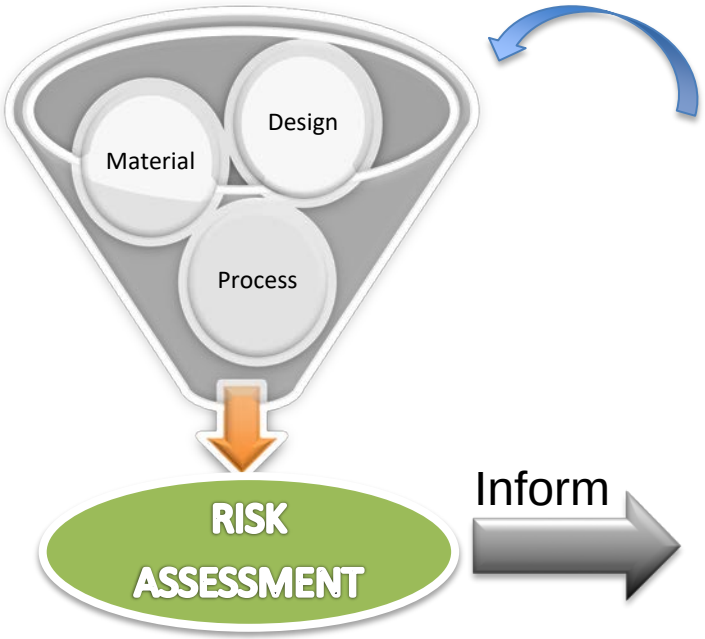
(Material & design: compartments, seal interfaces)

- **Failure modes**: what can go wrong?
- **Severity**: e.g. single container vs. entire batch?
- **Probability**: in context of available engineering controls
- **Detectability**: can failure modes be detected by other means (e.g., vision)

Further evaluation by CCI testing needed?

- Intended use
- Frequency
- Sampling plan

Package Integrity Profile Development



Package Integrity Profile & Testing Strategy

Risks/Failure Mode	CCI Testing
…	…
Elastomer degradation upon DP contact compromises CCI	CCI Testing incorporated into stability studies
…	…

Continuous Refinement throughout Development Phases

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

Product life cycle phases

1. **Package development and validation**
   a. Package development
   b. Package processing and assembly validation
2. **Product manufacturing**
3. **Commercial product stability**

1a. Package Development

Product-package profile is prepared (e.g., user requirements spec), considering

- Product end use
- Stability requirements
- Method of manufacture
- Anticipated storage, distribution environments

Package is identified, considering

- Design and critical dimensions, stack heights
- Materials of construction
- Component/material suppliers

Package process parameters are identified, considering

- Component cleaning, sterilization, other processes
- Package assembly (or formation)
- Package processing parameters

1a. Package Development

Define Max. allowable leak limit (product-package specific)

Inherent integrity is checked throughout early phase package development

CCI testing should check for integrity deviations at **key parameter EXTREMES**

- **Leak test methods** chosen should be capable of testing **as close as possible to the Max. allowable leak limit**
- **Seal quality tests** should be incorporated as appropriate

A satisfactory package meets the MALL

1a. Package Development

Outputs: Final user requirement specs

Package component purchasing specs

Equipment user requirement specs

- Component processing equipment
- Package formation/assembly equipment
- Allied materials supply and component feed systems

Equipment purchase and/or contract manufacturing direction

1b. Package Processing & Assembly Validation

CCI testing

- Part of larger process validation activity
- Scope and sample quantities tested may vary with experience, package complexity, and risk assessments
- CCI test methods chosen
  - **Smallest leak tests.** Tests able to verify conformance to MALL
  - **Larger leak tests.** Tests able to identify leaks caused by package misassembly or other assembly/process related defects

Seal quality testing

- Incorporate as appropriate

Consideration given to user requirement specs

- Sterilization; package formation/assembly processes
  - Extreme condition impact on CCI
    - E.g., re-sterilization, line speed max/min, assembly procedures
  - Secondary, tertiary packaging impact on CCI
- Supports technical transfer to final manufacturing site

1. Package Development and Validation

FINAL OBJECTIVE

Package meets user requirement specs (and MALL)

Quality product-package prepared by packaging processes that reliably and consistently run within specified operating parameters

Critical package defects occur at satisfactorily low rate

CCI in-process and end-product testing, as well as seal quality testing should complement, not replace package development and validation efforts

2. Product Manufacturing

CCI assurance starts with component quality specifications

- Component vendor evaluation
- Incoming component AQL conformance
- Vendor certification and corrective action
- Change control

Manufactured product CCI and SQ tests

- **Selection:** Based on earlier R&D and validation
- **Goal:** Prevent or ID/remove defects of greatest concern
- **CCI Testing:** 100% nondestructive CCI tests, or Sampled product CCI tests
- **Seal Quality Testing:** Not a definitive CCI test, but plays a valuable role by monitoring seal quality and/or sealing process

2. Product Manufacturing

100% nondestructive CCI tests

- Provides greatest quality assurance, but may not be appropriate, necessary, or cost effective
- Increasingly considered as technologies become available
- Recommended or required
  - Glass/plastic ampoules (sealed by fusion)
  - Product with critical headspace (vacuum, inert gas)

Sampled product CCI tests

- More testing options (destructive or nondestructive)
- Some off-line options have greater sensitivity
- Less costly
- No impact on production line speeds, efficiency
- However, unable to provide input for real-time production adjustments

3. Commercial Product Stability

FDA 2008 recommended CCI tests replace sterility test in stability studies to assure package integrity (initial sterility test still required)

Sterility test is a poor measure of integrity

CCIT more sensitive, reliable

Only CCIT able to confirm headspace gas maintenance requirements

Ref. 2008 FDA Guidance: Container and closure system integrity testing in lieu of sterility testing as a component of the stability protocol for sterile products

3. Commercial Product Stability

CCI test method selection

CCIT should verify absence of leaks risking

- Product loss
- Sterility loss
- Gas exchange (if applicable)

Method should confirm conformance to the MALL

Product should not interfere with CCIT

- Proteinaceous ingredients or salts can block gas/liquid flow through leak paths
  - Impacting vacuum decay, mass extraction, tracer gas or liquid

CCI testing considerations

Test sample storage: To mirror marketed product labelled storage conditions

Test quantities per time point: Undefined, chose based on prior R&D and validation data

If nondestructive tests used samples tested for CCI may be used for other tests at same stability time point

Consider CCI testing all samples prior to stability storage, to make sure samples at time zero are integral

CCI test samples should not be retested at later time points, [IF SUCH TESTING REDUCES INFORMATION POSSIBLE]

Package Integrity Profile: Key Studies (Example)

CCS Design Verification	Process Dev Engineering Studies	Process Validation	Stability Studies	Routing Manufacturing
• Verify Package Inherent integrity < MALL • Iterative verifications to evaluate potential interactions	• Evaluate CCI impact of process Parameter EXTREMES	• Verify CCI during: • Filling/Sealing, • 2' Packaging • Device Assembly • Shipping	• Verify and demonstrate continued CCI on Stability throughout product shelf life	Batch Evaluation Stability

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

Case Study: Italian BioTech – Romamab

Risk Assessment → **Testing Strategy** → **Method Selection** → **Method Developt.** → **Method Validn.**