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衛生福利部食品藥物管理署委辦計畫

「提升國內無菌與新興生醫藥品品質管理之研究」

無菌產品製造 GMP 作業論壇(二)

日　期　：(北區)民國 111 年 8 月 22 日

(南區)民國 111 年 8 月 17 日

主辦單位：衛生福利部食品藥物管理署

承辦單位：TPDA 社團法人中華無菌製劑協會

講　師　資　料

陳逸修　協理/松瑞製藥股份有限公司品質管理部

時　間　表

時 間	內　　容	講　師
13:00-13:30	報　　到	
13:30-13:40	➢ 長官致詞	TFDA 監管組代表
13:40-14:50	➢ Challenges with CCIT Methodologies and Package Design	松瑞製藥 陳逸修 協理
14:50-15:10	休　　息	
15:10-16:20	➢ Additional Considerations of Package Integrity Profiling and Innovative CCIT	松瑞製藥 陳逸修 協理
16:20-17:00	交 流 討 論 及 課 後 測 驗	TFDA 長官 及講師群

目　　錄

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TR. NO.86
INDUSTRY CHALLENGES AND CURRENT TECHNOLOGIES FOR PHARMACEUTICAL PACKAGE INTEGRITY TESTING

SPEAKER : AYERS CHEN

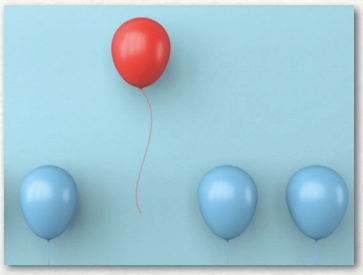
AGENDA

- Introduction
- Challenges with Methodologies
- Challenges with Package Design
- Innovative Methods for Existing Technologies
- Additional Considerations for Package Integrity Profiling
- Conclusion

INTRODUCTION

Package Integrity test

- The measure of the ability of the package to prevent product loss or maintain product sterility and the ability to maintain the internal environment (eg., loss of vacuum seal)
- From package development and continuous throughout the life of the product.
- Maximum Allowable Leak Limit(MALL): The greatest gap or leak rate that does not put product quality at risk.



CHALLENGES WITH METHODOLOGIES

➢Deterministic leak test method:

- Leakage event is based on phenomena that follow a predictable chain of events, and leakage is measured using physicochemical technologies that are readily controlled and monitored, yielding objective quantitative data.
- Ex. tracer gas, pressure/vacuum decay, laser-based gas headspace analysis, high voltage leak detection

➢Probabilistic leak test method:

- Leakage event relies on a series of sequential and/or simultaneous events each associated with uncertainties, yielding random outcomes described by probability distributions.
- Ex. bubble emission, tracer liquid, microbial challenging (Immersion test)

CHALLENGES WITH METHODOLOGIES

➢Probabilistic leak test method:

bubble emission

tracer liquid

Microbial challenging (Immersion test)

B. diminuta as the challenge organism is based on its very small size

CHALLENGES WITH METHODOLOGIES

➢Probabilistic leak test method:

Test method	EP 3.2.9 USP<381>	Modified EP/USP	ISO 8362-5	Modified ISO
Dye solution	1 g/L (0.1% w/v) Methylene Blue Aqueous Solution	1 g/L (0.1% w/v) Methylene Blue Aqueous Solution	0.1% w/v Methylene Blue Aqueous Solution	0.1% w/v Methylene Blue Aqueous Solution
Vacuum	-27 kPa	-37 kPa	-25 kPa	-37 kPa
Time Vacuum	10 mins	10 mins	30 mins	30 mins
Time atmosphere pressure	30 mins	30 mins	30 mins	30 mins

CHALLENGES WITH METHODOLOGIES

➢Deterministic leak test method

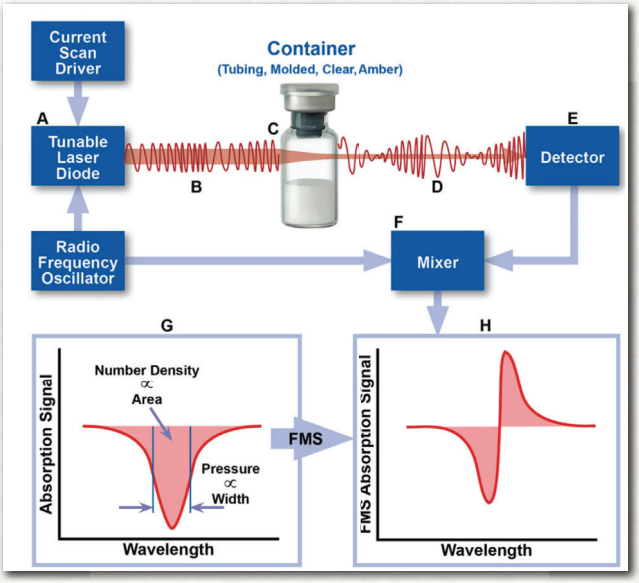
Mass extraction

ATC Inc. Advanced Test Concepts

Exhaust the system after passing the test

Remove the lid and place it back on the test chamber

laser-based gas headspace analysis

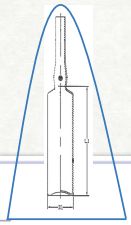


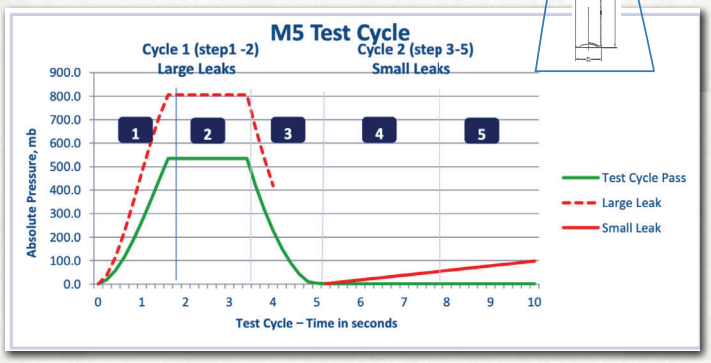
Pharmaceutical Technology, Pharmaceutical Technology-09-01-2020, Volume 2020 Supplement, Issue 4 Pages: s32–37

CHALLENGES WITH METHODOLOGIES

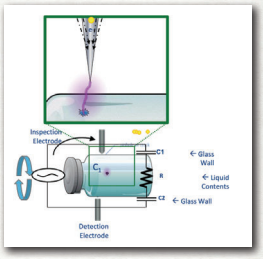
➢Deterministic leak test method

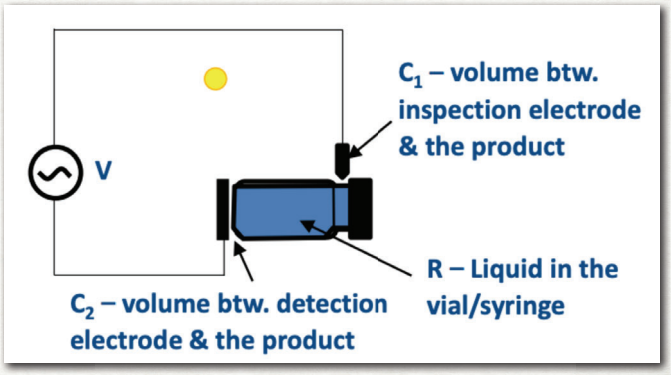
pressure/vacuum decay





High voltage leak detection





Product package quality requirements and the maximum allowable leakage limit

Most package types display very low but definite gaseous leakage flow through the gap that exists even between well-fitted closures.

packages be absolutely leak-free → NOT PRACTICAL

Mmaximum Allowable Leakage Limit(MALL)

- Science and risk -based decision
  - Package construction and assembly
  - Package contents
  - Exposure environments during shelf life. (Pressure/ temperature.)

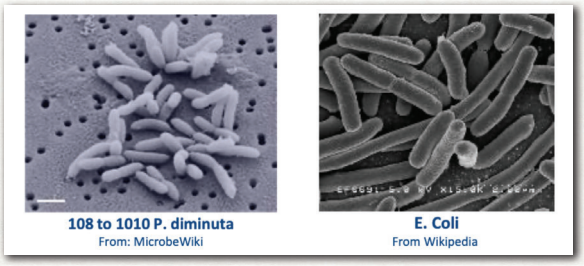
Category 1
Sterility and Product Formulation Content must be Preserved; Gas Headspace Content Preservation is not Required.
X Microorganism
O Gas → No risk to product quality
X Foreign substance

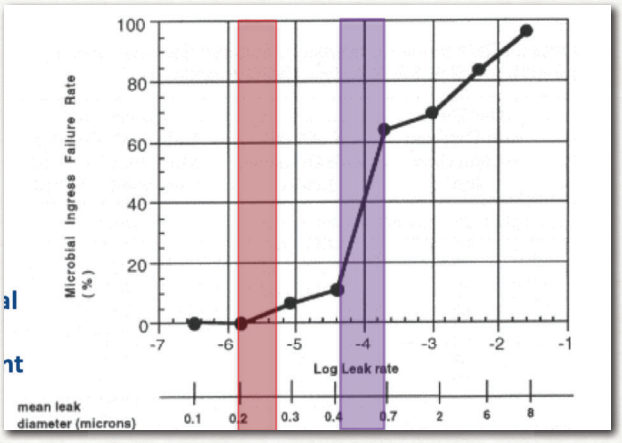
Category 2
Sterility, Product Formulation Content and Gas Headspace Content Preservation must be Preserved.
X Microorganism
X Gas/Pressure(aid end-user product access)
X Foreign substance

Sub-Category - multiple-dose (In-use MALL)
Sterility must be preserved; Product access is Required.

USP <1207>

Product package quality requirements and the maximum allowable leakage limit





PDA J Pharm Sci & Technol, Vol. 51, No. 5, 1997

CHALLENGES WITH METHODOLOGIES

The inherent characteristics of the methods and other unknown factors can increase variability

- Formulations that impact flow through a leak or that create blockage within the leak
- Methods that impact formulations, e.g., a method that applies an energy level or introduces a new chemical compound that impacts the original formulation in any way
- Unintended impacts of method on a container closure system (CCS) potentially introducing a defect to or masking a defect in an otherwise unadulterated sample, e.g., pressure changing the shape of the container and potentially the nature of the defect.

CHALLENGES WITH METHODOLOGIES

Positive control (leak artifacts)

- Design and development of the container
- Development of a test method.
- Determination of the level of sensitivity to various types of leaks
- Determination of detection limits
- Validation of a test method
- Validation or system suitability of the level of sensitivity to various types of leaks
- Testing of containers for their stability properties
- Development of container manufacturing process (quality control) parameters

Different purposes and during different stages of test methods and product development

CHALLENGES WITH METHODOLOGIES

Calibrated leaks	systematically built into the CCIT system hardware to simulate a leak.		
Naturally occurring leaks	the geometry and leak size of naturally occurring leaks are unknown	difficulty of using the normal container production processes to generate consis- tent, naturally occurring leaks	qualification of a CCIT method.
Simulated defects	hole-type defects with channels) usually have leak paths with known geometry that can be generated using a controlled process		

CHALLENGES WITH METHODOLOGIES

- Considerations of Selecting Positive Controls

Product package profile

Method type

Lifecycle

→ Different size/type of positive control → CCI method development and Validation → System suitability for sample analysis

*Deterministic method : X, periodical calibrated
*Probabilistic method: O

CHALLENGES WITH METHODOLOGIES

- Considerations of Selecting Positive Controls

Theoretical defects

- Naturally occurring - wide variability, not used for validation
- Gross Leak
- Daily function test
- MALL
- LOD

*There is a limit to these types of defects; therefore, the method cannot be fully characterized to understand its capability or the true MALL of a CCS.

Engineered defects for positive controls can have the added advantage of being a micron-sized defect, but other factors should also be considered:

- Percentage of the micron-sized defects that can be consistently and reliably detected using a chosen CCIT method *(NOTE: All positive controls with leaks at or above the claimed limit of detection (LoD) of the test method must be detected with high confidence (e.g., 95%).*
- Size and geometry of leaks that occur in real life and the ability of the test method to accurately detect those defects.
- Leak size needed for microbial contamination to occur and pose a risk to product sterility or qual- ity over the entire lifecycle of the product.

CHALLENGES WITH METHODOLOGIES

- Types of Simulated Positive Controls

Common materials used to create simulated defects include:

	Size	Adventage	Disavantage
Glass micropipette	0.1~10 um	Consistent defect, Clear fluid path	Fragile, Difficult to ensure a complete seal between micropipette
Wire/Needle/ Microfilament	10um	Easy and inexpensive approach	Very different from real-world defects
Laser-drilled	2 um	Most resembles natural defects	Higher cost Hole size needs to be calibrated to a leak rate Actual hole size on container may differ from nominal hole size or the hole diameter confirmation by microscopic measurement

CHALLENGES WITH METHODOLOGIES

- Types of Simulated Positive Controls

	Size	Advantage	Disavantage
Glass micropipette	0.1~10 um	Consistent defect, Clear fluid path	Fragile, Difficult to ensure a complete seal between micropipette

WPI can quickly supply your need for consistently sized, pre-pulled, glass, calibrated micropipettes. Tip diameters (ID) range from 0.1 to 10 µm. Silanized Tips (Luer Shank) are available. Silanization waterproofs the glass to retard when inserting into cells. This will not let the outside fluid run down the glass pipettes and get inside so easily. These glass needles are fabricated from Schott Duran borosilicate glass.

- **Every glass pipette individually tested and inspected**
- Schott Duran borosilicate glass pipettes
- 0.5 µm and smaller ID micropipettes include internal glass fiber for easy filling
- Tip inner diameter tolerance ±20%
- Short taper yields high strength
- Nominal length ≈ 50 mm
- OD:ID = 1.33:1
- Vacuum packed
- Glass Outside Diameter: 1.0 mm thin wall
- MicroTips with an ID smaller than 1 µm have a filament
- 10 Micropipettes per package

https://www.wpiinc.com/blog/post/microtips-perfect-for-ccit

CHALLENGES WITH METHODOLOGIES

- Types of Simulated Positive Controls

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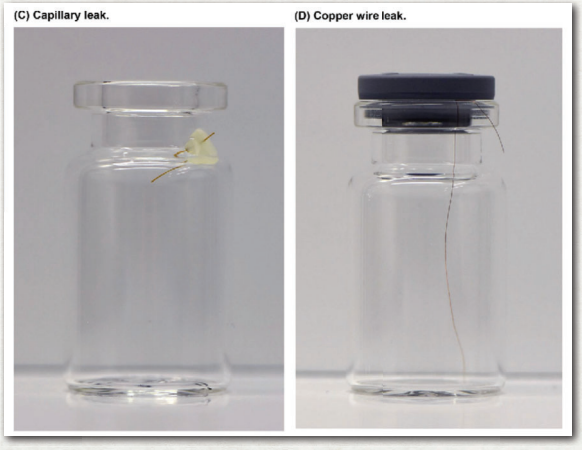
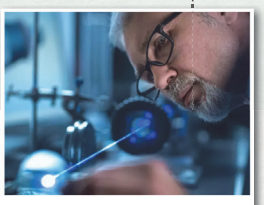


Published in PDA Journal of Pharmaceutical Science and Technology 2019
Comparing Physical Container Closure Integrity Test Methods and Artificial Leak Methodologies

CHALLENGES WITH METHODOLOGIES

- Types of Simulated Positive Controls

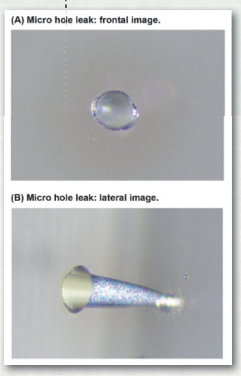
	Size	Adventage	Disavantage
Laser-drilled	2 um	Most resembles natural defects	Higher cost Hole size needs to be calibrated to a leak rate Actual hole size on container may differ from nominal hole size or the hole diameter confirmation by microscopic measurement



Laser Micromachining

From micro holes with diameters down to a few microns and sub-micron tolerances to laser scribes a few 10s microns wide, laser processing and micromachining provides a highly versatile manufacturing solution.

https://optek.humaneticsgroup.com



CHALLENGES WITH METHODOLOGIES

Blockage of Leak Paths

- Formulations that impact flow through a leak or that create blockage within the leak

Highly concentrated protein solution

Surrogate solution With the same viscosity

Crystallization Upon drying

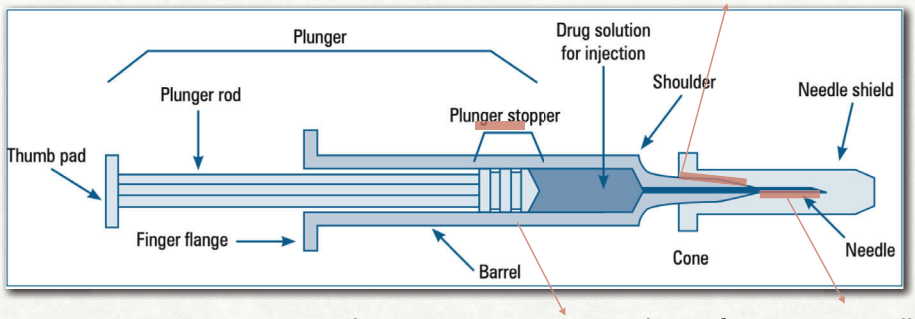
Manufacturers can develop different ways of CCI test to resolve the clogging challenge

CHALLENGES WITH PACKAGE DESIGN

- Profiled syringes
- Single-use systems — Flexible bulk containers
- IV Bags — Flexible Finished Pharmaceutical Containers
- Cryogenic Conditions

CHALLENGES WITH PACKAGE DESIGN -PREFILLED SYRINGE

Barrel — Needle shield interface



Plunger stopper — Barrel interface

Needle — Needle shield interface

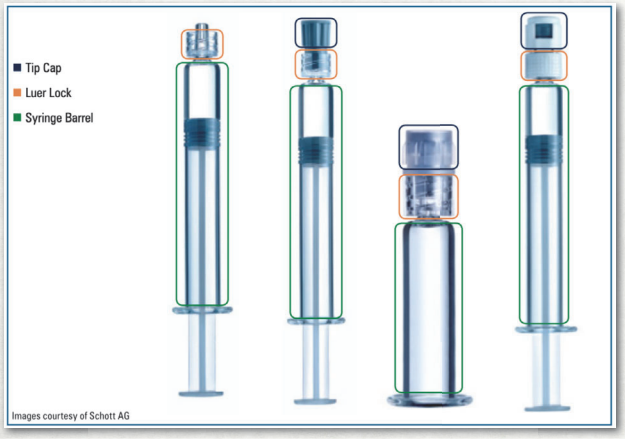
Proper interface fit between the closure system and syringe barrel is an essential requirement to ensure CCI.

- The needle embedded into the elastomer is the most critical portion of the needle shield–needle interface, as it forms the closure between the drug product and the environment. The drug manufacturer should then verify that additional fill-finish steps and shipping conditions do not adversely affect the needle-shield positioning or introduce needle-shield piercing.

CHALLENGES WITH PACKAGE DESIGN -PREFILLED SYRINGE

Three common types of prefilled syringe designs, regardless of materials of construction, are:

- Staked needle (barrel–closure and the needle shield–needle interfaces)
- Luer lock
- Luer slip (or luer cone)



For sufficient CCI, the luer lock adapter, tip cap, and/or screwed rigid closure must be adequately positioned.

During manufacturing, precautions should be taken to avoid potential silicone contamination of the luer lock adapter, which may impact the sealing integrity of the system. This may require additional line clearances to ensure residual silicone does not agglomerate on luer lock adapters.

CHALLENGES WITH PACKAGE DESIGN -PREFILLED SYRINGE

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- Staked needle (barrel–closure and the needle shield–needle interfaces)
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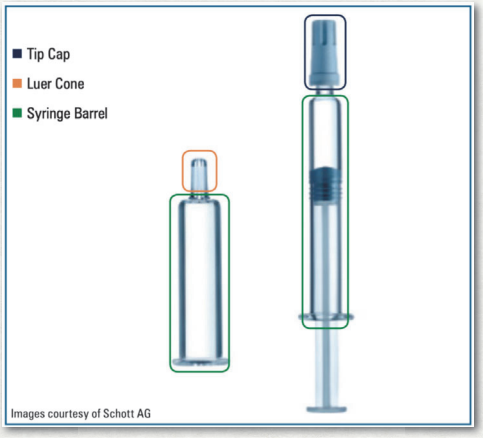
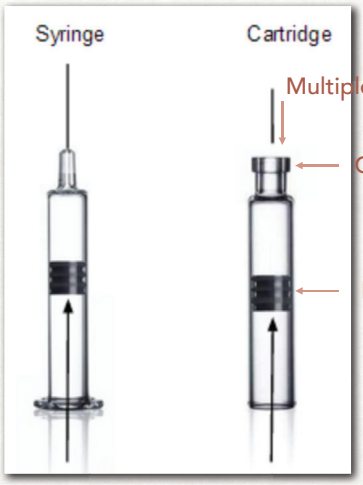


Cone-glazing or cone-coating is used on syringes to provide surface roughness that enhances the fit of the tip cap with the syringe cone.

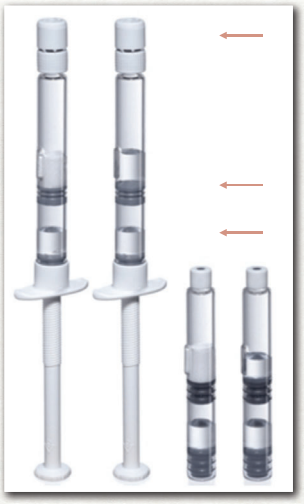
The presence of silicone at the tip cap of a syringe may impact sealing integrity

CHALLENGES WITH PACKAGE DESIGN -PREFILLED SYRINGE

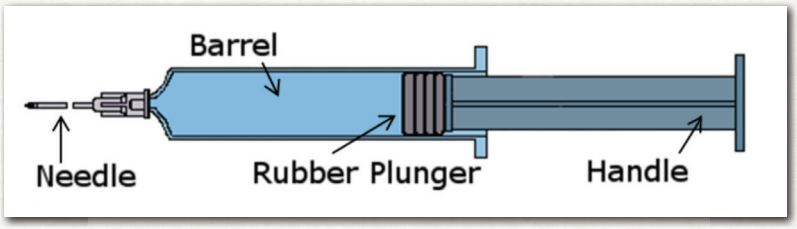
Cartridge



Dual-chambered cartridge



CHALLENGES WITH PACKAGE DESIGN -PREFILLED SYRINGE



Primary seal rib

Stabilize the seal and provide the secondary CCI assurance

CHALLENGES WITH PACKAGE DESIGN -PREFILLED SYRINGE

Polymer materials : a unique set of risks for forming and maintaining seal integrity throughout the product lifecycle

- Physicochemical changes - heat, oxygen, irradiation, mechanical stresses, or various combinations of such stress conditions throughout manufacturing, sterilization, and storage.
- These risks are related not only to the syringe barrel design, but to its molding and sterilization processes, downstream handling, packaging, and distribution processes
- The supplier of plastic syringe components is responsible for establishing and validating design requirements as well as critical process parameters (CPPs) for ensuring CCI
- Polymer resin manufacturing, syringe molding, sterilization, packaging, and distribution processes to ensure the quality of components related to CCI.

CHALLENGES WITH PACKAGE DESIGN -PREFILLED SYRINGE

The Mechanism of Filling and stoppering a prefilled syringe may impact CCI

A. When using mechanical means of placing the plunger stopper, the stopper may be compressed into a tube, the tube inserted into the syringe, and a metal rod used to push the stopper out of the tube where it expands to form a compression fit inside the syringe barrel. The compression and pushing may create wrinkles on the plunger which should be evaluated for any impact to CCI.

B. Vacuum stoppering is another means of stoppering the syringe; it involves creating a vacuum in the syringe, thus pulling the plunger into the syringe. Vacuum methods are less likely to create wrinkles, but an incorrect vacuum setting may cause the filled liquid in the syringe to boil, creating other concerns.

CHALLENGES WITH PACKAGE DESIGN -PREFILLED SYRINGE

	Dye ingress test	HVLD	Laser-based headspace oxygen analysis	Vacuum decay/ massextraction
Point to consideration	Sufficient fill volume for the spectrophotometric testing(Cuvette height)	Sufficient fill volume to cover any defect - location - formulation	Minimum headspace volume	• Stopper movement should be minimized • No residue moisture (terminal sterilization)

Semi-finished syringe.

Backstop

Once all the desired components are added, the syringe is referred to as a finished syringe.

CHALLENGES WITH PACKAGE DESIGN -FLEXIBLE BULK CONTAINERS

CHALLENGES WITH PACKAGE DESIGN -FLEXIBLE BULK CONTAINERS

- Flexible bulk containers:
  The application of single-use flexible technologies, commonly referred to as bioprocess containers, bioprocess bags, or single-use system(SUS) for the manufacturing process of bulk drug substance and bulk drug product.


Image courtesy of Sartorius

Micro:
The bulk container system is crucial if product can not be terminally sterilized

Physical and chemical:
Barrier properties v.s. Gas permeation

<u>Establish MALL during the intended use condition</u>

CHALLENGES WITH PACKAGE DESIGN -FLEXIBLE BULK CONTAINERS

Microbial challenge testing

Immersion : for the storage component

Testing by aerosol : Under normal use conditions of flexible bulk containers

Due to the flexible nature of these container systems, the variation of atmospheric pressure associated with elevation changes in air transport is not expected to increase the risk of integrity loss,

- Higher occurrences for defects related to transportation processes, due to **vibration** or **shocks**, and to **transient pressure increases** above the normal static pressure

Feature	Helium Technology	Pressure Drop Technology
Sensitivity	≥ 2 µm	≥ 10 µm
Environmental Effects	Low	Medium (Temperature)
Volume Impact	Low to Medium	Medium to High
Material Impact	Medium to High	Low to Medium
Handling	Complex	Simple
Test Time	Low to Medium	Medium to High
Maintenance	Complex	Simple
Investment Cost	High	Low

- Size of leaks that occur in real life.
- Maximum leak size that poses no risk to microbial ingress (MALL).
- Minimum leak size that can be rapidly and reliably detected by the inspection system (LoD).
- Selection and creation of model defects for qualification of the test method.

CHALLENGES WITH PACKAGE DESIGN -FLEXIBLE BULK CONTAINERS

No single test method can sufficiently assess all criteria throughout a product's entire life- cycle

- Size of leaks that occur in real life.
- Maximum leak size that poses no risk to microbial ingress (MALL).
- Minimum leak size that can be rapidly and reliably detected by the inspection system (LoD).
- Selection and creation of model defects for qualification of the test method.

CHALLENGES WITH PACKAGE DESIGN -IV BAG

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IV bag

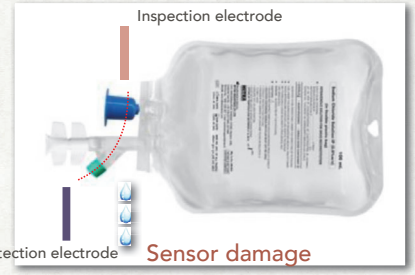
A pharmaceutical product container made of flexible material, closed at the bottom and along the sides by sealing; the top of the container may be closed by fusion to IV tubing or a medication port, depending on the intended us.

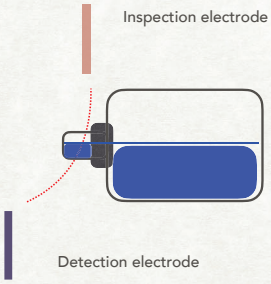
CHALLENGES WITH PACKAGE DESIGN -IV BAG

High voltage

- Any leak from the container can pose a challenge if the product leaks and contaminates the test system (equipment and/or test chamber)

High risk location?
Formulation - conductivity





- The location of the defect can have a significant impact : defect contact with air or liquid -vibration
- The residual moisture has to be removed after moist sterilization

Arc forming:
EHS
Package damage and stability?

CHALLENGES WITH PACKAGE DESIGN -IV BAG

Pressure change/Mass extraction

- Dry and crystallization: potentially clogging micron-size defects
- The escape of residual volatile gases and vapors from the outside surface of IV bags when they are exposed to vacuum conditions may affect leak test results by giving false positives during testing - equilibration time

CHALLENGES WITH PACKAGE DESIGN -CRYOGENIC CONDITIONS

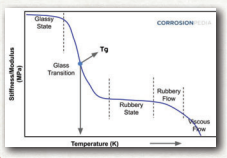
CHALLENGES WITH PACKAGE DESIGN -CRYOGENIC CONDITIONS

Many sterile products are stored at cold (2 °C to 8 °C), freezing (-20 °C), and ultra-cold (-80 °C to -196 °C) temperatures to limit formulation degradation and extend product shelf life. Several considerations should be addressed regarding cryogenic storage and package integrity:

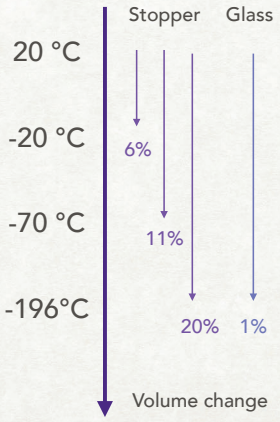
- Risks to package after fill and freeze.
- Risks to large-scale bags after fill and freeze
- Loss of integrity in frozen state due to material differences at low temperatures that are restored at high temperatures.
- Risk to package integrity in frozen state during transport and handling.
-

CHALLENGES WITH PACKAGE DESIGN -CRYOGENIC CONDITIONS

Observations of overpressure have been reported in a significant number of vials after storage at -80 °C



Markedly different thermal expansion coefficients



Non sterile/reactive gas

25°C

P V = n R T

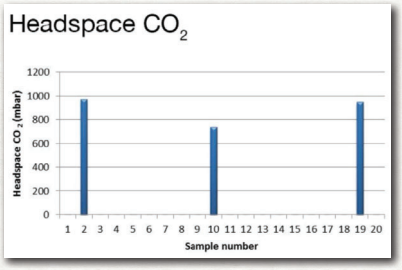
-80°C

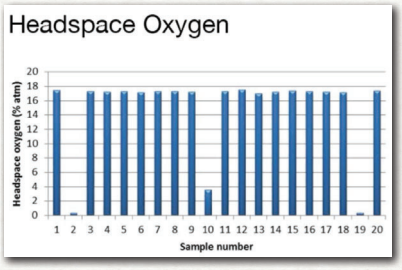
1 atm→ 0.66 atm

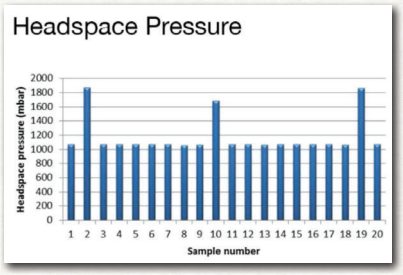
For product packages that will be stored at cryogenic temperatures, CCI should be assessed as part of the package development phase

CHALLENGES WITH PACKAGE DESIGN -CRYOGENIC CONDITIONS

After one week of storage at dry ice temperatures (-80°C), the vials were analyzed using non-destructive laserbased headspace gas analysis







CCI failure while the product was stored at -80 °C. —> stability and sterility risk?

Pharmaceutical technology-October 2020
Effects of Deep Cold Storage at -80°C on the Container Closure Integrity of Sterile Product Vials

INNOVATIVE METHODS FOR EXISTING TECHNOLOGIES

INNOVATIVE METHODS FOR EXISTING TECHNOLOGIES

CCIT

- Helium testing
- Optical emission spectroscopy

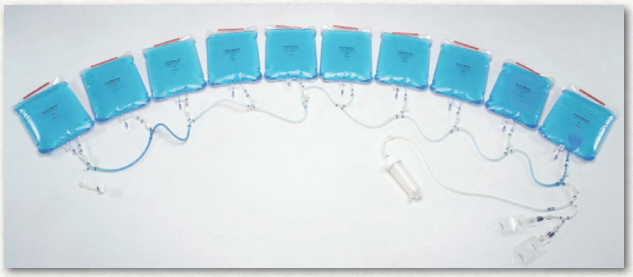
Seal integrity methods

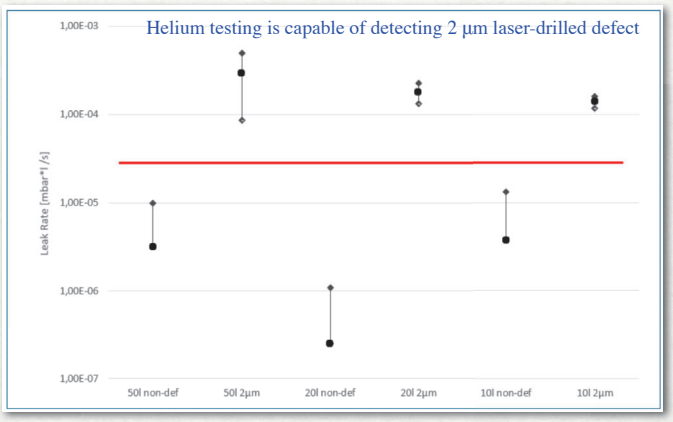
- Ultrasonic detection
- X-ray detection

INNOVATIVE METHODS FOR EXISTING TECHNOLOGIES

Helium Testing

A well-known, deterministic, nondestructive test method that has been used for many years in several industries to test rigid/flexible containers





Test units with reasonable gas barrier properties. If the test unit is highly permeable to helium, then sensitivity drops significantly

INNOVATIVE METHODS FOR EXISTING TECHNOLOGIES

Optical Emission Spectroscopy

The emission spectrum of a chemical element or compound (atom or molecule) is the spectrum of frequencies of electromagnetic radiation emitted due to the atom or molecule making a transition from high energy state to a lower energy state.

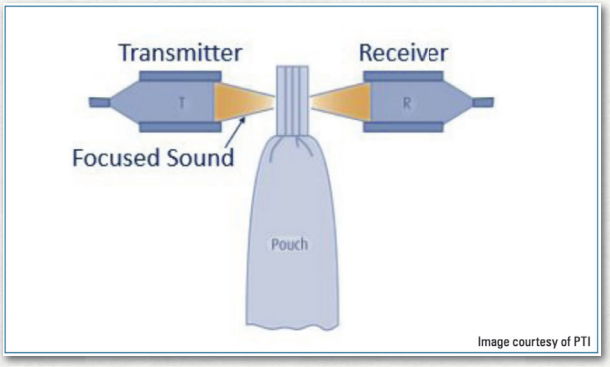
- total leak rate for a specific gas from a sample under vacuum
- Deterministic, nondestructive, easy to use, easy to set up, and highly sensitive

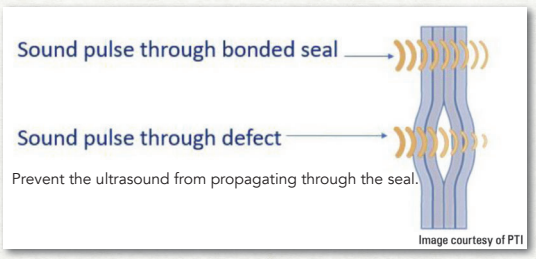
INNOVATIVE METHODS FOR EXISTING TECHNOLOGIES

Airborne Ultrasound

Ultrasonic waves are high-frequency **sound waves** that exhibit behaviors characteristic of sound waves. When a boundary exists between two media with varying acoustic impedances, the ultrasonic waves are partially reflected and partially transmitted through one medium into the other.

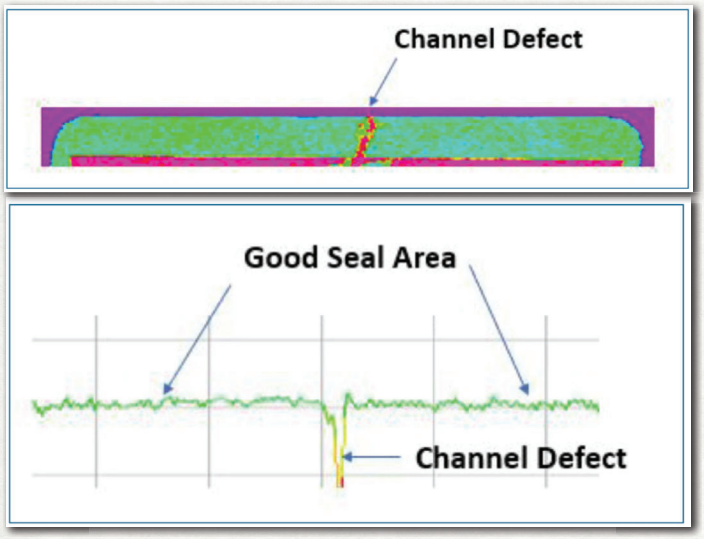
- Acostic signature of bond materials or material characteristics based on thickness, density, and material uniformity
- Point focused measurement





INNOVATIVE METHODS FOR EXISTING TECHNOLOGIES

Airborne Ultrasound



Challenge

- Liquids can propagate an ultrasonic signal effectively from one material to another, which means the sound would transfer through a defect if liquid were present in the defect. The presence of liquids in the seal can produce test results similar to that of a good seal.
- Seal geometry can also affect seal inspection
  - The edge of a seal
    - ultrasonic signal is impacted by sound reflecting within the seal
    - sound passing around a seal edge to reach the receiver

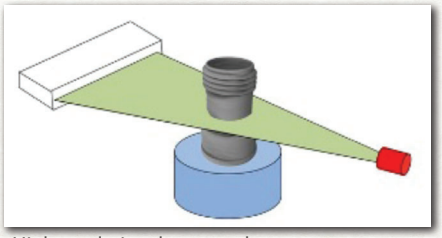
INNOVATIVE METHODS FOR EXISTING TECHNOLOGIES

X-ray detection

X-ray detection may not be considered a leak test, as it neither quantitatively nor qualitatively evaluates leak rates or leakage; however, X-ray technologies support CCI evaluations in a variety of ways.

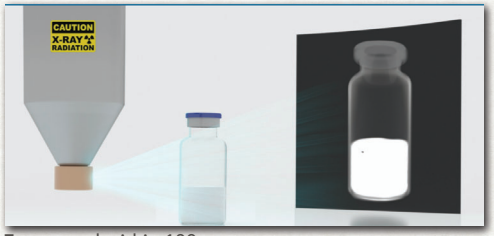
- Evaluate physical attributes of the test system that may not be visible to the naked eye or even to some visual inspection systems
- A supplemental means of characterizing a package system

Line scan Imaging



High resolution, low speed

Area scan Imaging

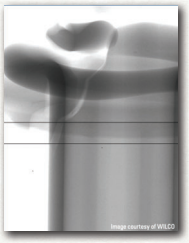


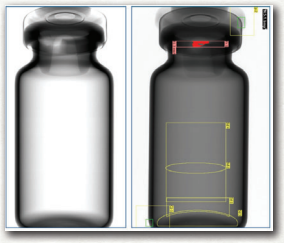
Fast speed within 100 ms

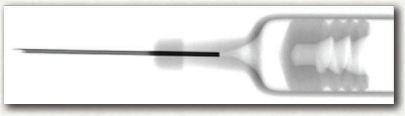
INNOVATIVE METHODS FOR EXISTING TECHNOLOGIES

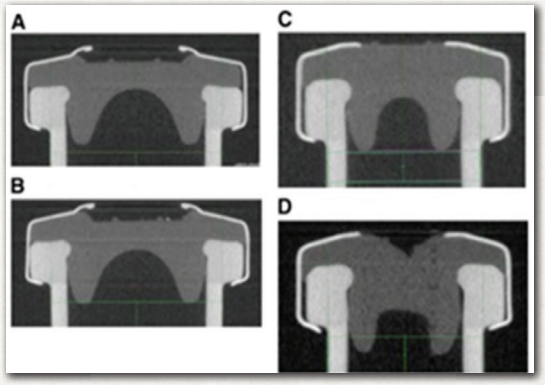
X-ray detection

X-ray technology can detect cracks in glass containers like syringes, vials, and cartridges if the spatial resolution of the separation of the glass edges is adequate.









ADDITIONAL CONSIDERATIONS FOR PACKAGE INTEGRITY PROFILING

ADDITIONAL CONSIDERATIONS FOR PACKAGE INTEGRITY PROFILING

- Transportation and Distribution
  - Physical stressors
  - Pressure
  - Testing approach
- 100% online Testing
- Building a Quality by Design Approach into the Container Closure Integrity Testing Program
- Bulk Container lifecycle Approach

ADDITIONAL CONSIDERATIONS FOR PACKAGE INTEGRITY PROFILING

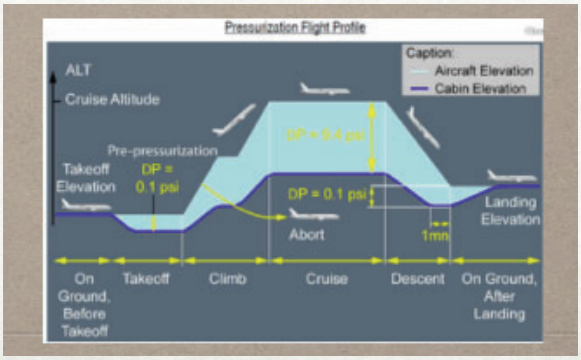
- Transportation and Distribution
  - Physical stressors

    Vibration, shock, and compression — Gross leak
    This type of gross defect is easily detected and generally prevents final use of the product.

    The formation of cracks, checks, chips, and other small defects, however, may result in leakage that negatively impacts product quality but is not readily detectable by the end user

    Secondary and tertiary packaging should be considered - ASTM and ISTA (International Safe Transit Association)

  - Pressure



The ability of a sealed flexible container to resist creep or burst during air shipment is an example of risk that should be characterized.

ADDITIONAL CONSIDERATIONS FOR PACKAGE INTEGRITY PROFILING

100% online testing

A holistic approach to controlling CCI

- CCIT method (in-line, near-line, off-line)
  - In-line testing is defined as 100% testing of all filled and sealed primary packages for CCI during the production process, after the final sealing operation(ampules, blow-fill-seal containers)
  - most process failure modes result in medium to large defects in the pack- age, widening the reject limit for in-line testing is a reasonable and low-risk decision
- Quality of primary package components
- Primary package design
- Manufacturing process qualification
- Product manufacturing process
- Change control process
- Shelf-life assessment

ADDITIONAL CONSIDERATIONS FOR PACKAGE INTEGRITY PROFILING

Building a Quality by Design Approach into the Container Closure Integrity Testing Program

A QbD concept can be built into a CCIT program, including such elements as:

- Quality target product profile that identifies the critical quality attributes (CQAs) of the product-package system
- Package design and understanding, including identification of critical material attributes that can affect package integrity
- Process design and understanding, including identification of CPPs, linking the material attributes and process parameters to the CQAs
- Control strategy that includes specifications for the product-package configuration with respect to CCI as well as controls during each step of the manufacturing process that will help meet those specifications
- Regular quality checks on process capability and continual improvement initiatives

ADDITIONAL CONSIDERATIONS FOR PACKAGE INTEGRITY PROFILING

Building a Quality by Design Approach into the Container Closure Integrity Testing Program

CCI is ongoing and operative variations

- Design and material of the package
- Package assembly
- Processing conditions
- Storage, distribution, and stability conditions

ADDITIONAL CONSIDERATIONS FOR PACKAGE INTEGRITY PROFILING

Building a Quality by Design Approach into the Container Closure Integrity Testing Program

Risk-based CCIT program

- CCI over the entire lifecycle of product

  More than one test may be employed during a given product's lifecycle
- Choice of deterministic versus probabilistic methods
- Choice of off-line versus in-line, on-line or at-line test methods
  - **Off-line methods:** Measurement does not involve samples removed directly from the manufacturing line. Test methods are typically not high speed, are not integrated into the manufacturing line, and are usually implemented in a laboratory setting.
  - **In-line methods:** Measurement where the sample is not removed from the process stream and methods are not destructive to the sample
  - **On-line methods:** Measurement where the sample is diverted from the manufacturing process and may be returned to the process stream; these test methods are not destructive to the sample
  - **At-line methods:** Measurement where the sample is removed, isolated from the process stream, and analyzed.

*At-line and off-line tests are better suited for testing based on a scientifically valid sampling plan, stability study, and development environments

ADDITIONAL CONSIDERATIONS FOR PACKAGE INTEGRITY PROFILING

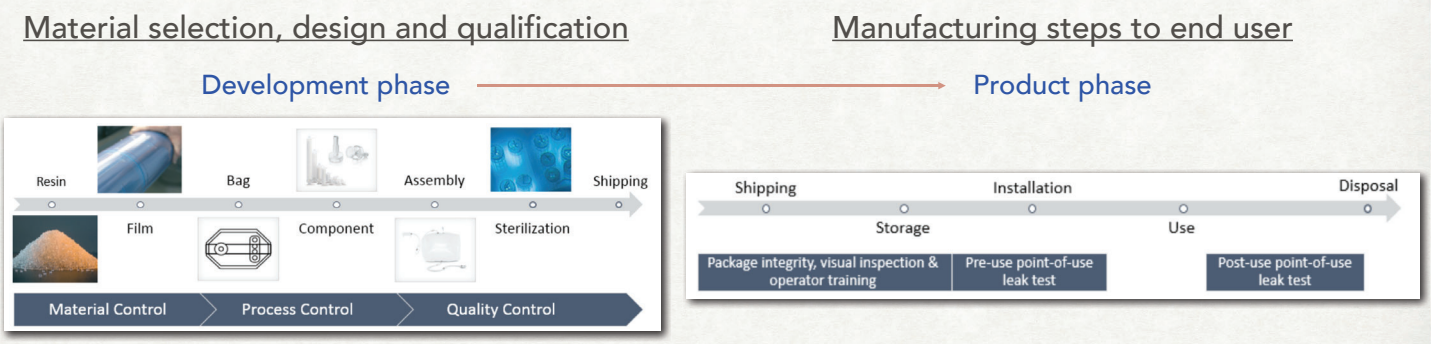
Building a Quality by Design Approach into the Container Closure Integrity Testing Program

Risk-based CCIT program

- Sampling
  Risk assessment in association with appropriate statistical criteria
- Defining the MALL
- Designing a CCIT tool kit
  Encompass different test methods that can be employed to detect defect types critical to product quality and sterility
  - Test method
  - Application
  - Leak detection capability
  - Testing efficiency - testing speed and throughput
- Ensuring continuous improvement

ADDITIONAL CONSIDERATIONS FOR PACKAGE INTEGRITY PROFILING

Bulk Container Lifecycle Approach



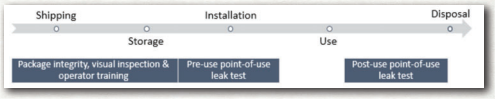
ADDITIONAL CONSIDERATIONS FOR PACKAGE INTEGRITY PROFILING

Bulk Container Lifecycle Approach

Area to Manage Product Quality	Considerations
Risk assessment	Evaluate the quality risk from the supply chain as well as the risks associated with their processes that can affect integrity; develop a control strategy, which may involve use of a physical leak test method
Incoming goods inspection	Identify seal quality and integrity attributes to be evaluated upon receipt
Assembly storage	Ensure that products are stored in a manner that prevents damage
Assembly unpacking and installation	Ensure that assemblies are transported through the plant in a manner that does not induce damage; support the product appropriately (large surface), eliminating use of sharp tools and short-term storage racks with sharp edges
Visual inspection	Check visually for marks, damages, and abnormalities on the SUS
Pre-use leak testing	Verify integrity after transportation and handling directly before use; supplement release testing at supplier
Use	Use the SUS within its specifications
Post-use leak testing	Verify integrity of the SUS after use to support the sterility claim on the final product
Operator training	Ensure that operators understand in which modes assemblies may be damaged by handling and deployment, how to inspect an assembly prior to use, and how to run a leak test
Supplier feedback	Inform supplier of integrity failures so supplier can understand and correct issues

Manufacturing steps to end user

Product phase



CONCLUSION

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No one-size-fits-all approach for packaging integrity testing methods

a risk-based approach and leveraging existing test methods as described in PDA TR. 86 can assist in better understanding and potentially mitigating

THANKS

REFERENCE

- Wilco
- PDA TR86 Industry Challenges and Current Technologies for Pharmaceutical Package Integrity Testing
- USP<1207> PACKAGE INTEGRITY EVALUATION—STERILE PRODUCTS
- OpTek Systems