Container Closure Integrity: Regulations, Test Methods, Application

Test Method Selection and Application

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Outline

Test method selection and applications

- Understanding Product Requirements
- Container closure integrity control strategy development
    - Risk based approach
- Product lifecycle and CCI testing
- Test method selection considerations

- Case study – Group Exercise & Discussions

What is ”integrity”?

“. . . degree of package protection demanded by the product to ensure that all relevant product physicochemical and microbiological quality attributes are met through product expiry and use.”[1]

“. . . degree of package protection demanded by the product . . .” [1]

“. . . demanded by the product . . .” [1]

IT DEPENDS

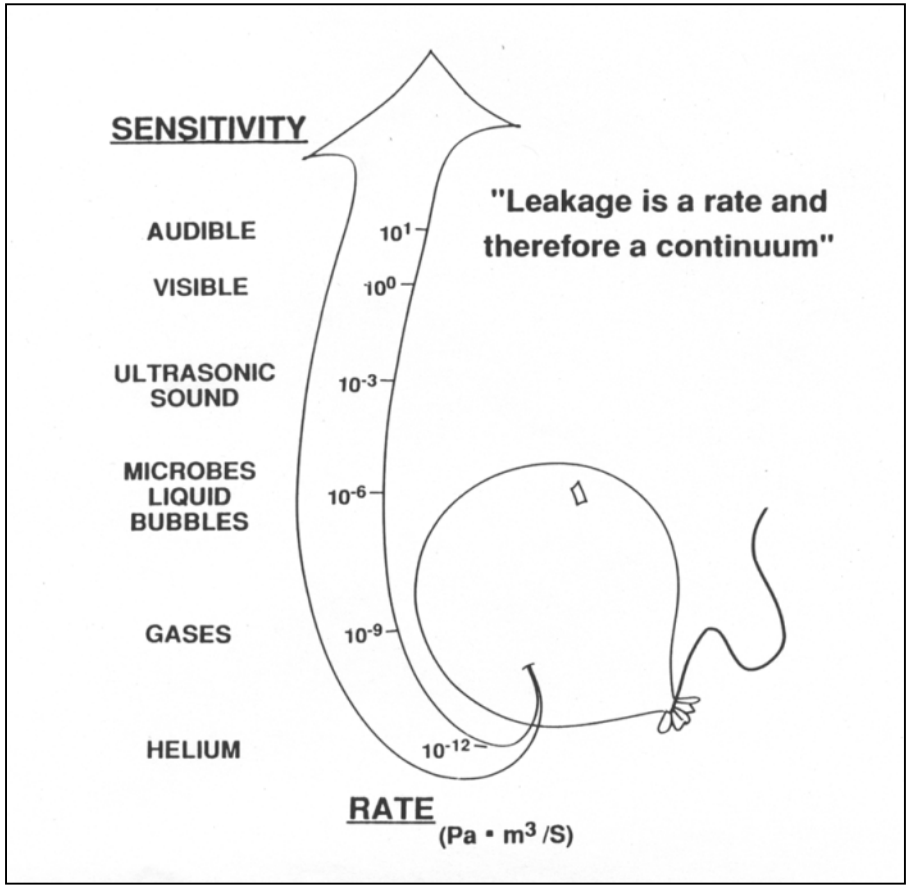
[1]Quotes taken from USP 41 NF 36, Chapter <1207>

Understanding Product Requirements

Attribute of Concern	Leak of Concern	Product Quality Risks
Must maintain dosage form	Capable of allowing escape of product dosage form, or entry of external of liquids/solids	Failure of relevant physicochemical quality attributes
Must maintain sterility	Capable of allowing entry of microorganisms	Failure of product sterility
Must maintain critical headspace	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

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**

MALL: Product-Package Specific

The MALL is based on product quality requirements

1. **Prevention of microbial ingress** to ensure product sterility
2. **Prevention of product formulation loss** and **product formulation contamination by external solids/liquids** to ensure conformance to relevant physicochemical product quality attributes.
3. **Prevention of headspace content change** to ensure conformance to relevant physicochemical product quality attributes, and to assure product access.

Establishing the MALL is a science-based

and often a risk-based decision

What is ”CCIT”?

If the applied definition of CCI can vary with product, what about the applied test?

Testing can vary with product, but is also impacted by the package and unique study goals.

[1]Quotes taken from USP 41 NF 36, Chapter <1207>

Testing for the MALL?

Test Method Options

Probabilistic	Deterministic
• Bubble Emission	• Laser-Based Headspace Analysis (HSA)
• Microbial Challenge	• Mass Extraction
• Tracer Gas (Helium) in Sniffer Mode	• Pressure Decay
• Tracer Liquid (Dye)	• Vacuum Decay
	• High Voltage Leak Detection (HVLD)
	• Tracer Gas (Helium) in Vacuum Mode

What do all methods have in common?

No one method or technology is applicable to all product-package systems or use cases.

Laser-Based Headspace Analysis

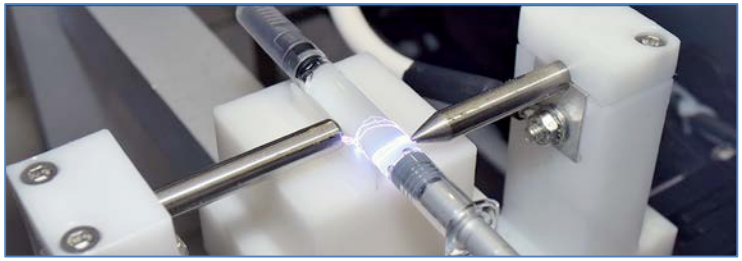
- Analyzes package headspace content
  - Oxygen, CO2, Water Vapor, Pressure can be quantitatively measured
- Leakage detection dependent on gas exchange
- Applications
  - Translucent packaging
    - Glass or plastic, colorless or amber
- Advantages
  - Can be very sensitive – gas diffusion
  - Can evaluate leakage in the absence of a current defect (ultracold)
- Limitations
  - Time dependency
  - Requires pressure and / or concentration gradient
  - Package must have headspace

Lighthouse Instruments FMS-Oxygen

Photo Credit: www.lighthouseinstruments.com/wp-content/uploads/2017/07/Lighthouse-Instruments-Oxygen-Headspace-Analyzer-showing-on-screen-data-for-reporting.png

High Voltage Leak Detection (HVLD)

- Package exposed to low amp current
  - Leak path results in a spike in current passing through the package
  - Drop in resistivity is quantitatively measured
- Applications
  - Nonporous, liquid filled packages
    - PFS, Vial, Cartridge, Tubes, etc.
- Advantages
  - Product clogging less of a concern
- Limitations
  - Product must be conductive & non-flammable
  - Probes need access to liquid holding cavity



PFS Undergoing HVLD Test
PTI eScan-625

Photo Credit: www.whitehouselabs.com/wp-content/uploads/2016/10/HVLD_banner.png

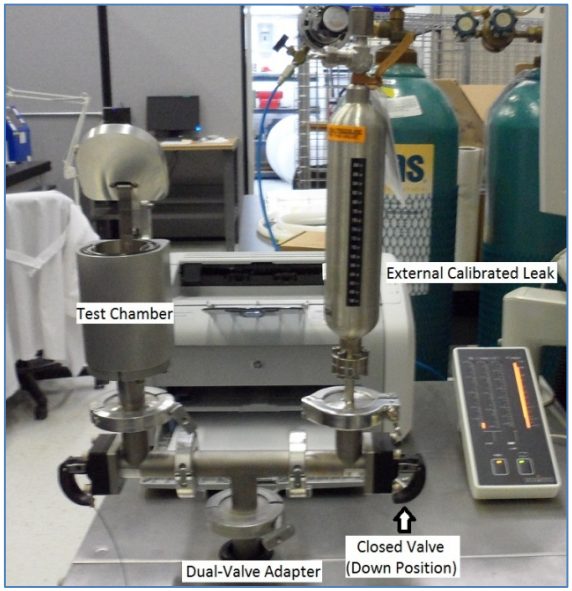
Pressure-Based Technologies

- Direct or indirect but quantitative measurement of flow through a defect
  - Method-induced pressure differential
- Includes vacuum decay, pressure decay, and mass extraction
- Applications
  - Nonporous rigid or flexible packages containing gas or solid product
    - Lyo, granulated product, med device in package, etc.
- Advantages
  - Flexible application
- Limitations
  - Liquid-based product may clog defects
  - Outgassing may mask smaller defects in large or flexible package systems

Sample and Test Chamber
PTI VeriPac 455-M5

Tracer Gas (Vacuum Mode)

- Test samples flooded with tracer gas and placed into evacuation chamber
  - Mass spectrometer quantitatively measures tracer gas leakage rate
- Applications
  - Empty nonporous rigid or flexible packages
  - Best used as a design / development tool
    - Evaluation of inherent integrity
- Advantages
  - Extremely sensitive (helium, ~1 atm differential)
  - Flexible in application
- Limitations
  - Preferable to perform without product
  - Permeation through materials may impact detection



SIMS 1282+ Helium Leak Test System

Test Method Options

Deterministic Method	Advantages	Limitations
Laser-Based Headspace Analysis (HSA)	Sensitive – Gas Diffusion Detect transient leaks	Requires headspace, gradient, risk of product clogging / interference
Mass Extraction	Flexible in application	Liquid product may clog defect pathways (reduce/no flow), noise from outgassing
Pressure Decay		
Vacuum Decay		
High Voltage Leak Detection (HVLD)	Product clogging less of a concern	Product conductivity Direct access required
Tracer Gas (Helium) in Vacuum Mode	Sensitive – Helium, ~1 atm Flexible application	Helium permeation Empty CCS preferred

What do all methods have in common?

No one method or technology is applicable to all product-package systems or use cases.

Test Method Selection Criteria

Leak test selection factors	Options
1. Product-package quality requirement (considering the MALL)	Sterility, product formulation preservation Additional need for gas headspace preservation Multi-dose product preservation at time of use
2. Package materials of construction	Metal, glass, plastic, composite, opacity
3. Package design, mechanics	Flexible/rigid Closure mechanism
4. Package contents	Liquid, solid, gas, vacuum
5. Test method outcome requirement	Leak presence, size ,location Gas leakage rate determination Liquid leakage risk Microbial ingress risk
6. Leak size detection limit and range	<<0.01 microns to several mm
7. Test sample preservation	Destructive or nondestructive
8. Test method application	High speed or Slower speed Product life cycle phase On-line or Off-line

Factors Affecting Method Selection

In summary, CCI Method Selection will be impacted by:

1. Product
    - Sets requirements, introduces limitations
2. Package
    - Defines critical seals to be evaluated, introduces limitations
3. Study Goal / User Requirements
    - Defines required outcome

Common Method Selection Pitfall:

Searching for the ”silver bullet”

“I want to test my final product-package to the MALL. Which method can do that?”

Consider Combination Products:

Limitation	Impact(s)
Liquid dose	Product clogging
Liquid-holding cavity in device body	Limits application of HVLD
	Introduces “noise” to pressure-based analyses

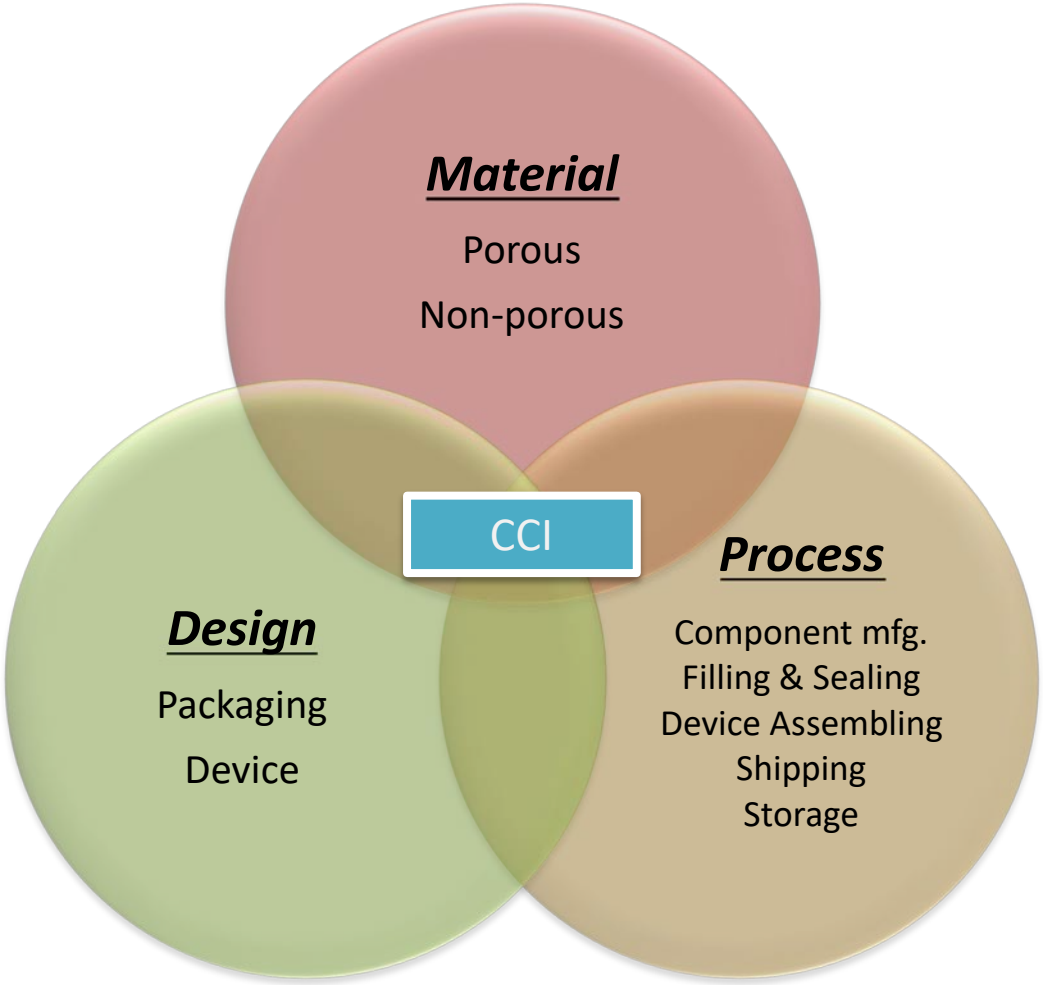
Most methods developed for assembled injection systems containing product are validated to 20µm **or larger.**

Is this sufficient?

Comprehensive control strategies reduce risk.

Photo credit: https://en.m.wikipedia.org/wiki/File:Epipen_design.jpg

CCI Control - Key Considerations



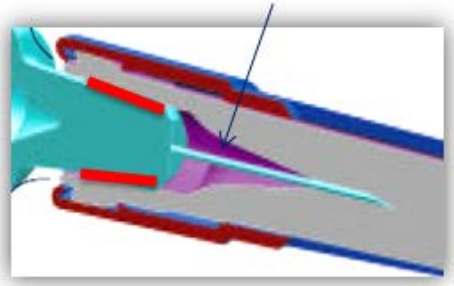
Example - Prefilled Syringe

Drug Product Compartment

- Plunger-barrel seal
- Needle shield seal
  - Needle tip seal
  - Glued needle stem
  - Needle shield/syringe head

Needle Stem Compartment

- Needle shield/syringe head



Design & Process Risk Assessments

Process Risk Assessment

CCS Design Risk Assessment

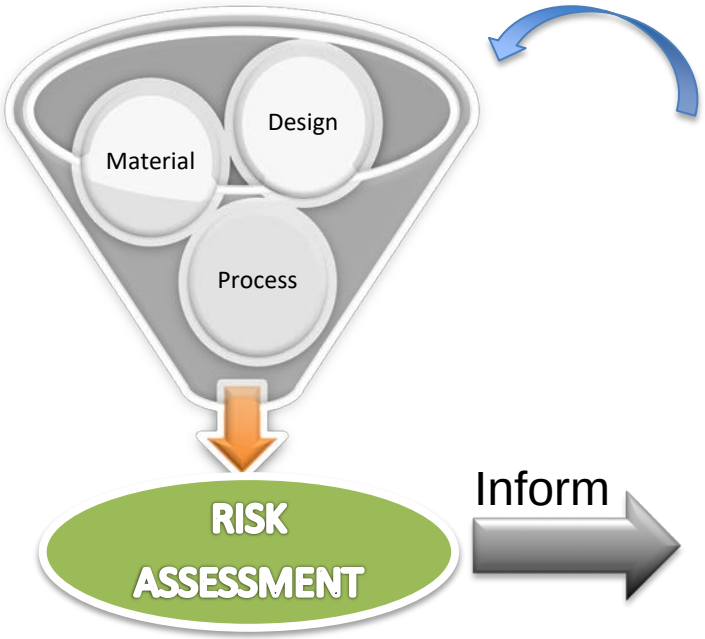
(Material & design: compartments, seal interfaces)

- **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

Design & Process Risk Assessments



Container Closure Integrity Control Strategy development

Risks/Failure Mode	Control or CCI Testing
Molding defects from plunger suppliers - causing CCI	Plunger 100% vision inspection; incoming material sampling
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

Framework for assessing different aspects of CCI at different timepoints – no "silver bullet".

Product Life Cycle and CCI Testing

Product life cycle phases

1. **Package development and validation**
   a. Package development
   b. Package processing and assembly validation
2. **Product manufacturing**
3. **Commercial product storage, distribution, and 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 conformance to the MALL where possible**
- **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

Reconsidering Combination Products

"No one test is appropriate for all packages or for all leak testing applications."[1]

"Package integrity verification plays an important role throughout the product life cycle, starting with product development and continuing through marketed product stability studies."[1]

Consider Combination Products:

Limitation	Impact(s)
Liquid dose	Product clogging
Liquid-holding cavity in device body	Limits application of HVLD
	Introduces "noise" to pressure-based analyses

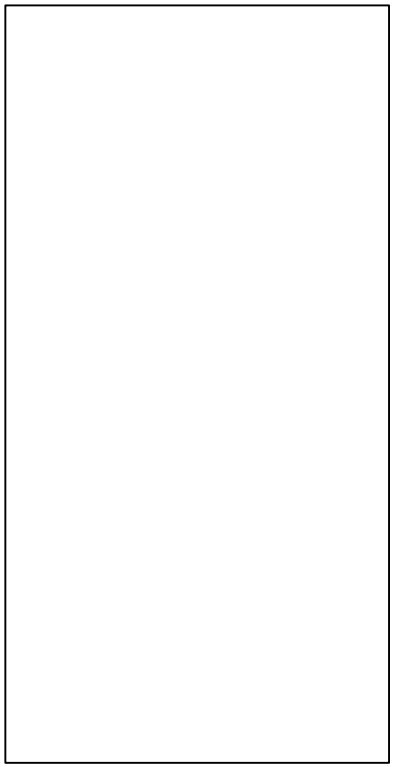
How can we implement technologies at different lifecycle stages that present an overall picture of product-package integrity?

Photo credit: https://en.m.wikipedia.org/wiki/File:Epipen_design.jpg

[1]Quotes taken from USP 1207

Case Example: Step #1

- Stage: Package development
- Goal: Evaluate inherent integrity
- Method: Helium Leak Detection Per ASTM F2391
- Pros:
  - Extremely sensitive technology
  - Leak rates can be correlated to defect size
    - Leak rate of 6.0 E-6 mbar*l/s equivalent to a defect 0.1 - 0.3µm
  - Flexible in application
- Cons:
  - Most suitable for empty packages
    - Unable to capture all process variables



Plunger Under Test

Case Example: Step #2

- Stage: Manufacturing, In-Process
- Goal: Encompass fill finish variables
- Method: High Voltage Leak Detection
- Pros:
  - Assesses liquid-filled packaging
  - Product-clogging not a substantial issue
  - Validated down to 3µm
- Cons:
  - Direct access to the primary package required

PFS Undergoing HVLD Test
PTI eScan-625

Case Example: Step #3

- Stage: Variable, Stability
- Goal: Test final product presentation – in device
- Method: Vacuum Decay Per ASTM F2338
- Pros:
  - Assesses full device
  - Nondestructive
- Cons:
  - Product clogging and material outgassing can make validation difficult or result in an insufficient limit of detection

Sample and Test Chamber
PTI VeriPac 455-M5

Case Example Method Summary

Component Level (Empty)	Product-Filled Syringe	Assembled Device
Helium	High Voltage	Vacuum Decay

All in support of the same final combination product.

Considers CCI from a lifecycle perspective.

Methods tailored to risk and required sensitivity.

Case Example Method Summary

Helium on Components	High Voltage	Vacuum Decay
Component selection	In-process defect detection	Stability test for combo product
Stack up tolerance determination	Stability test for product in PFS	Functional stability test
Inherent integrity evaluation	Evaluate impact of distribution	Determine suitable 2° / 3° packout
Evaluate impact of component sterilization	Assembly process validation	Evaluate impact of final distribution
Evaluate plunger movement impact on sterility		Assembly process validation

Summary

- **Fully integrate CCI testing** as a key part of product development and life cycle testing
- **Science and risk based approach**
- Consider the **product and the package**
- Consider **testing goals**, keeping in mind
  - **Life cycle phase**
  - **Leakage of concern (MALL)**
  - **Leak test method detection limit versus MALL**
  - **Risks of missing vs. finding leaks**
- Employ **other 'non-leak' tests, controls and monitors** to ensure seal quality

Case Study

Risk Assessment → Testing Strategy → Method Selection → Method Develop. → Method Validn.