

Using Helium Leak Detection CCI Testing to Inform Container Closure System Design

A Prefilled Syringe Case Study

*Container Closure Integrity: Regulations, Test
Methods, Application*

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Outline

- Overview of Helium Leak Detection (HeLD)
- Method development for syringes
 - Fixture design
 - Helium charging
- Applications of Helium Leak Detection
 - Determination of inherent package integrity
 - Evaluation of syringe system and sub-system design
 - Assessment of container closure robustness

Introduction – Helium Leak Detection

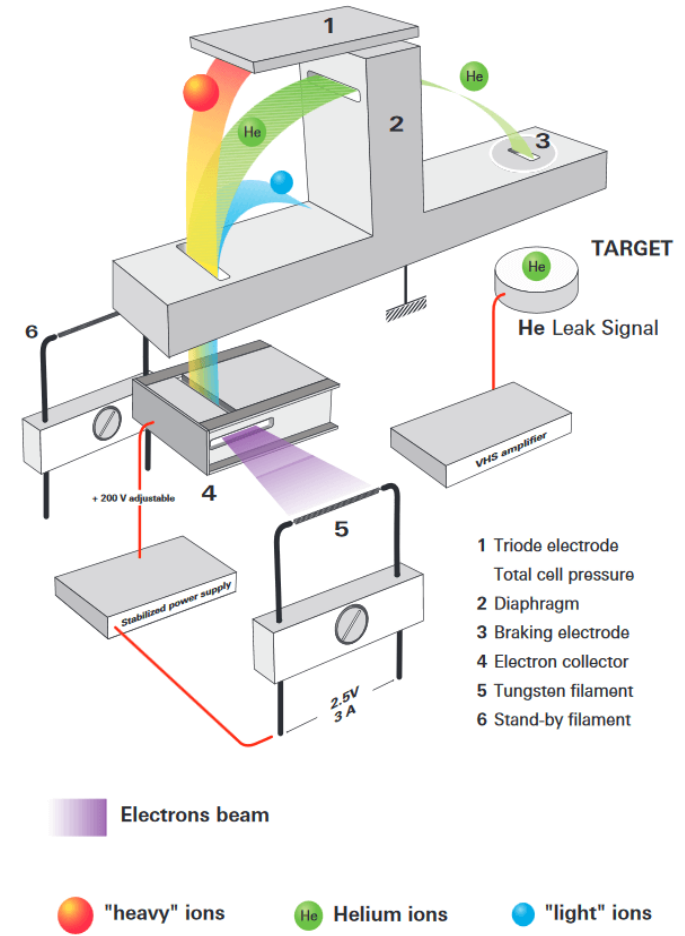
- **Selectivity**

- Low atmospheric interference: Helium in the atmosphere (~5 ppm)
- Do need to minimize lab ambient helium and permeation

- **Flows through cracks ~2.7x faster than air**

- **Sensitivity & Quantitative**

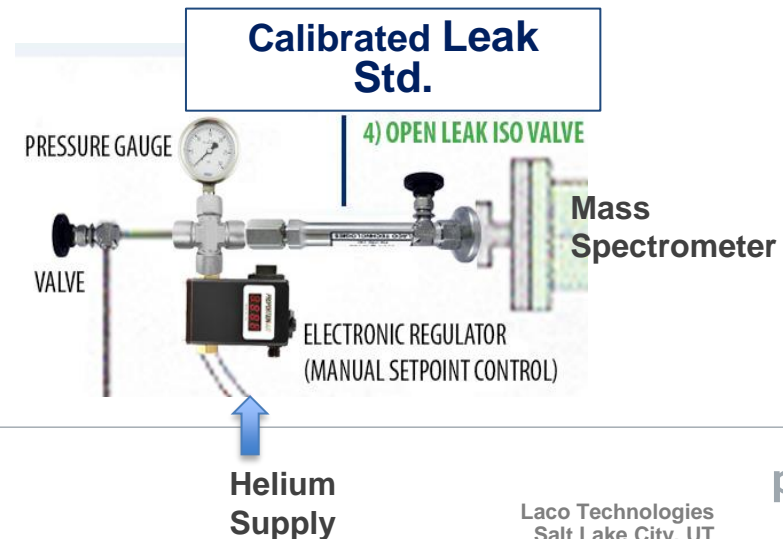
- Mass spectrometer as detector



Leak Detection Associates, Blackwood, NJ

Instrument Capability

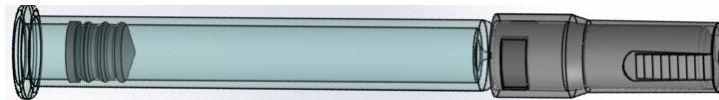
- **Calibration**
 - Internal calibration standards
 - Quantitation Range: 1×10^{-11} to 1×10^{-3} atm-cc/sec
- **System suitability**
 - NIST-traceable standard leaks
 - Verified range: 4×10^{-10} to 6×10^{-4} atm-cc/sec
- **Results reported as helium leak rate**
 - Converted to a nominal leak orifice size using USP <1207> method, where appropriate



Purpose

- **Quantitatively determine inherent package integrity**
 - The leakage rate (or the equivalent leak size) of a well-assembled package using no-defect components. Inherent package integrity is a measure of the leak tightness of a container–closure system, given anticipated variables of material composition, dimension, processing, assembly; package storage, distribution and use. (USP<1207>)
- **Demonstrate conformance to Maximum Allowable Leakage Limit (MALL)**
 - To preserve sterility and product formulation content
 - MALL $\leq 6 \times 10^{-6}$ mbar·L/s (atm-cc/sec) (USP<1207>)
- **Inform packaging system design and process development**
 - Assess critical seal elements, sub-systems, and system design
 - Evaluate sealing robustness (e.g. impact of potential defects on package integrity)

Prefilled Syringe System

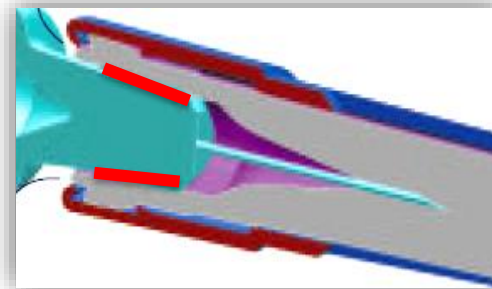


Drug Product Compartment

- Plunger-barrel seal
- Needle shield seal
 - Needle tip seal
 - Glued needle stem

Needle Stem Compartment

- Needle shield/syringe head



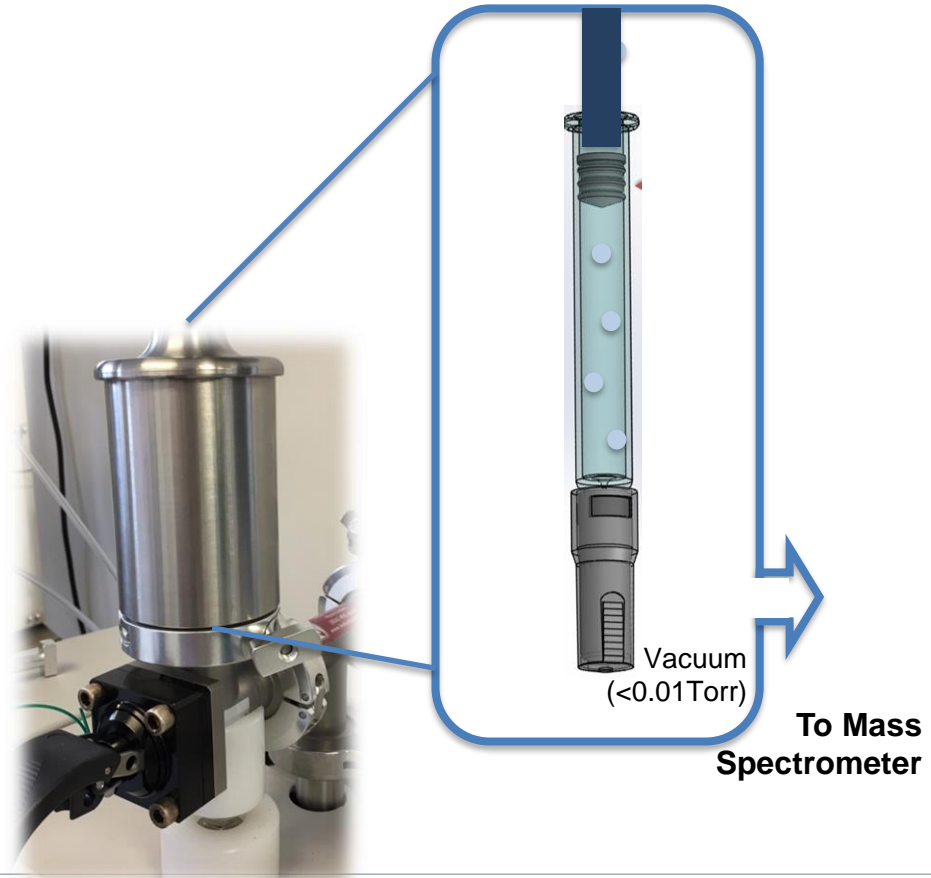
Preliminary Testing

1. **Filling:** syringes charged with helium and plungered in a glove box



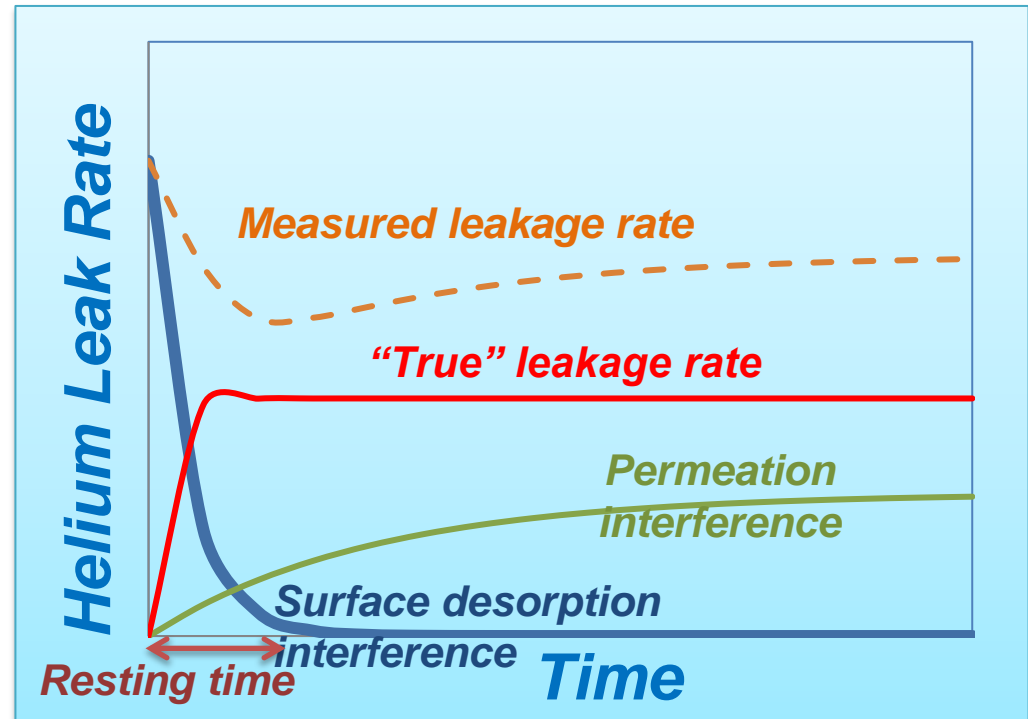
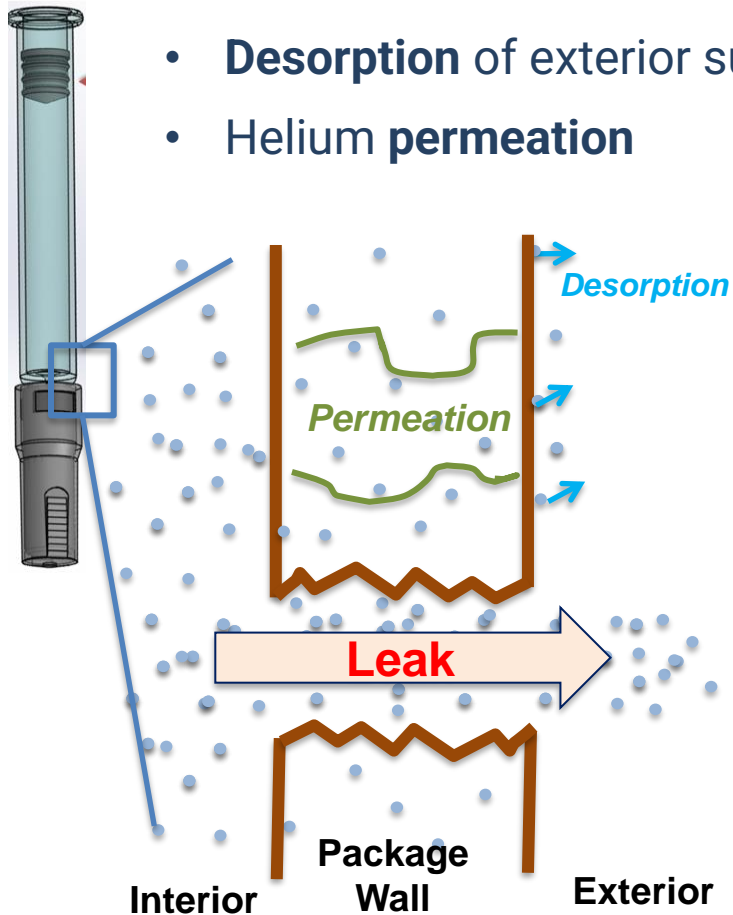
2. **Testing:** filled syringe is placed in a sample chamber for testing

- A plunger rod is used to retain plunger during testing



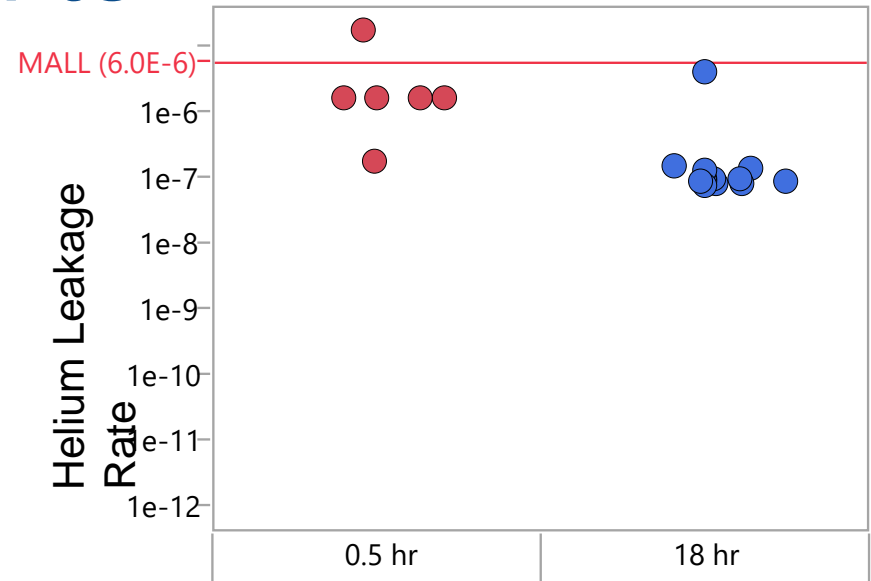
Potential Interferences

- Desorption of exterior surface-adsorbed helium
- Helium permeation



Preliminary Results

- ✓ **Estimated overall leakage rate**
 - Results can be artificially high due to surface desorption and permeation
- ✓ **Demonstrated conformance to MALL**



Improvement Needs

- Reduce helium background noise to measure “true” leakage rate
 - Exterior surface desorption
 - Permeation
- Need to evaluate sealing capability of critical seal elements and sub-systems

Method Improvement Strategy

- ❑ “Fast and Clean” helium charging
 - **Fast:** allow testing to start prior to significant permeation
 - **Clean:** eliminate helium contact with interfering sample surfaces

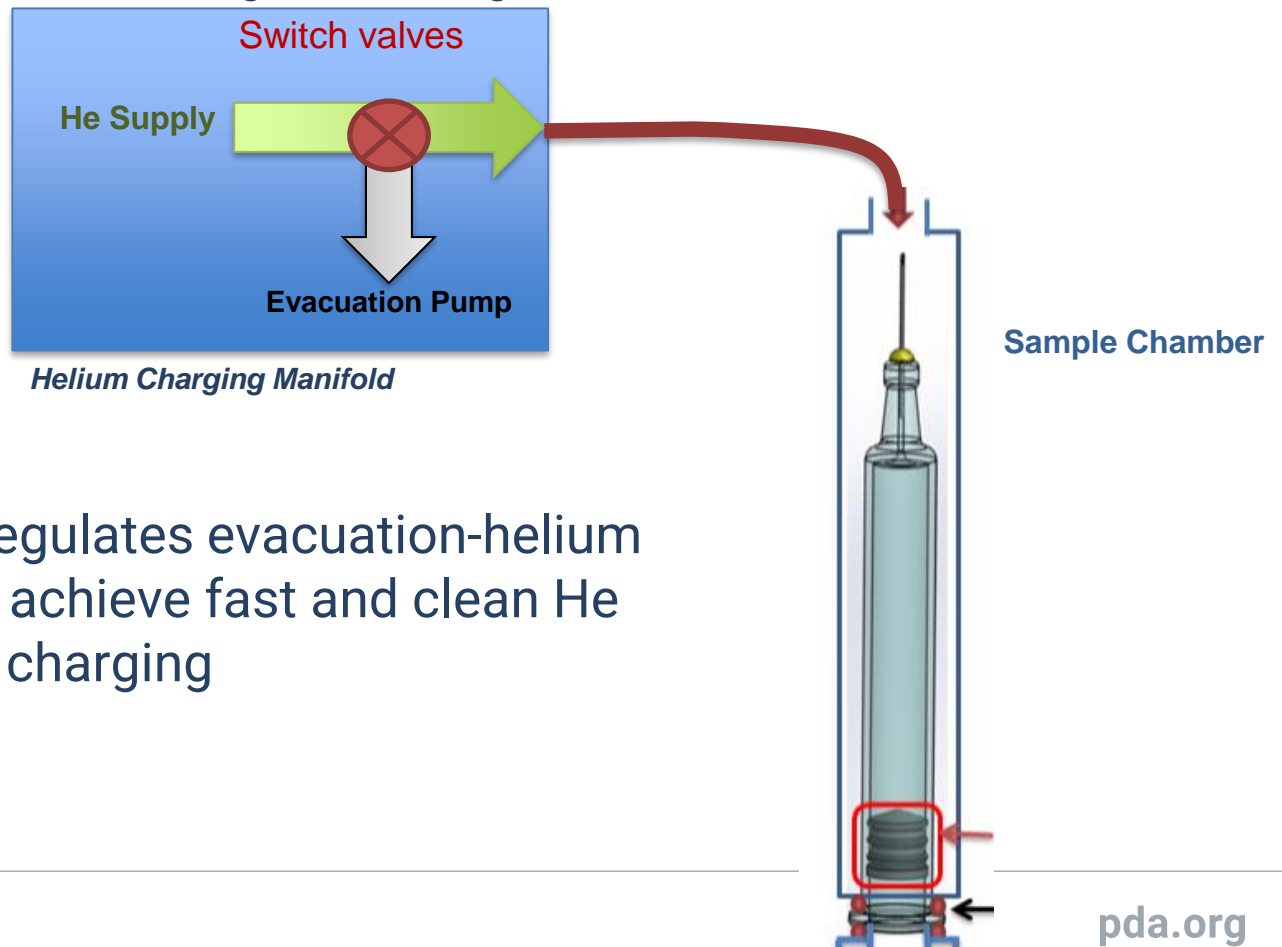
- ❑ “Divide and Conquer” critical seal elements
 - Isolate critical seal elements for independent assessment



Key Enabler: Sample Fixture Design

Fast & Clean Charging of Helium

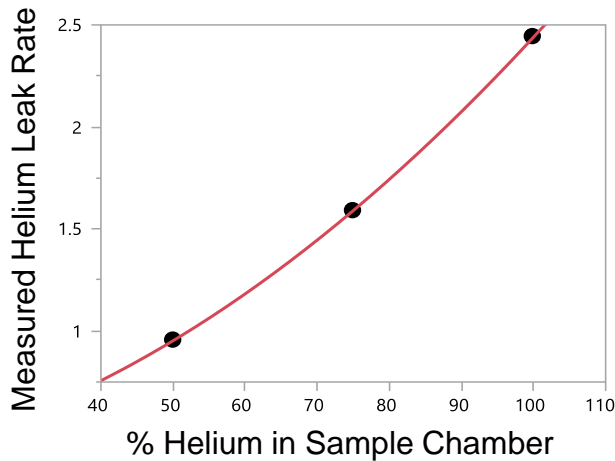
Goal: to achieve consistent 100% helium charging in the sample chamber to allow accurate quantitative leakage rate testing



Manifold design regulates evacuation-helium backfill cycles to achieve fast and clean He charging

Optimize Helium Charging Parameters

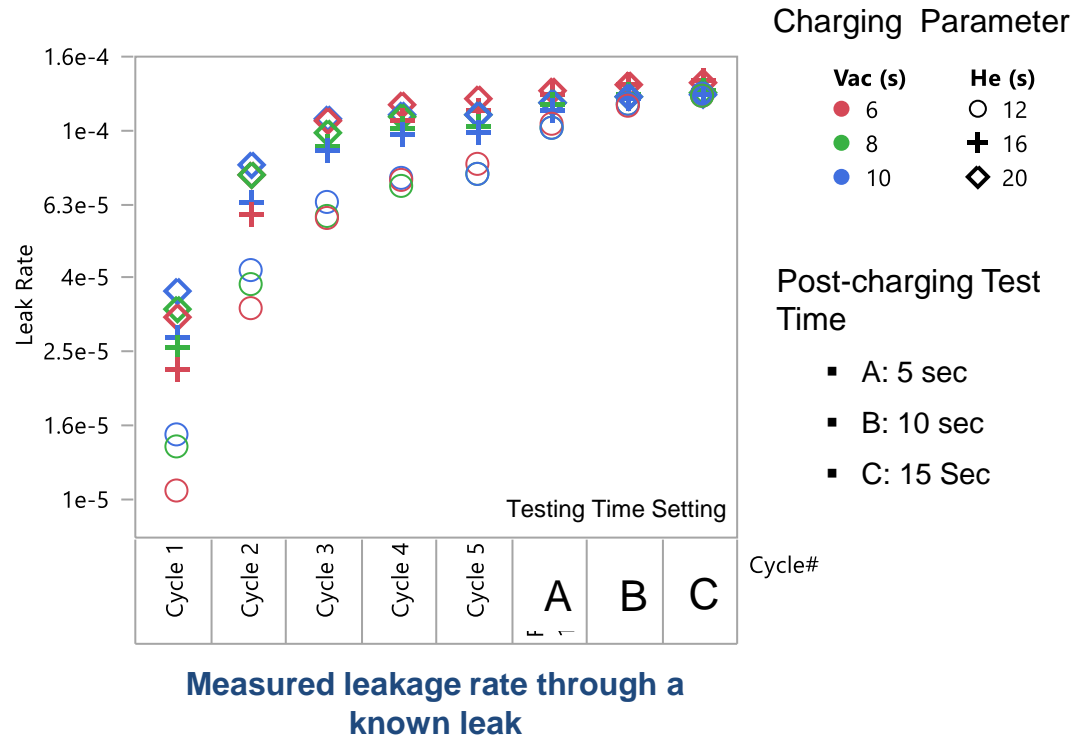
Leakage Rates dependence on He% in Sample Chamber



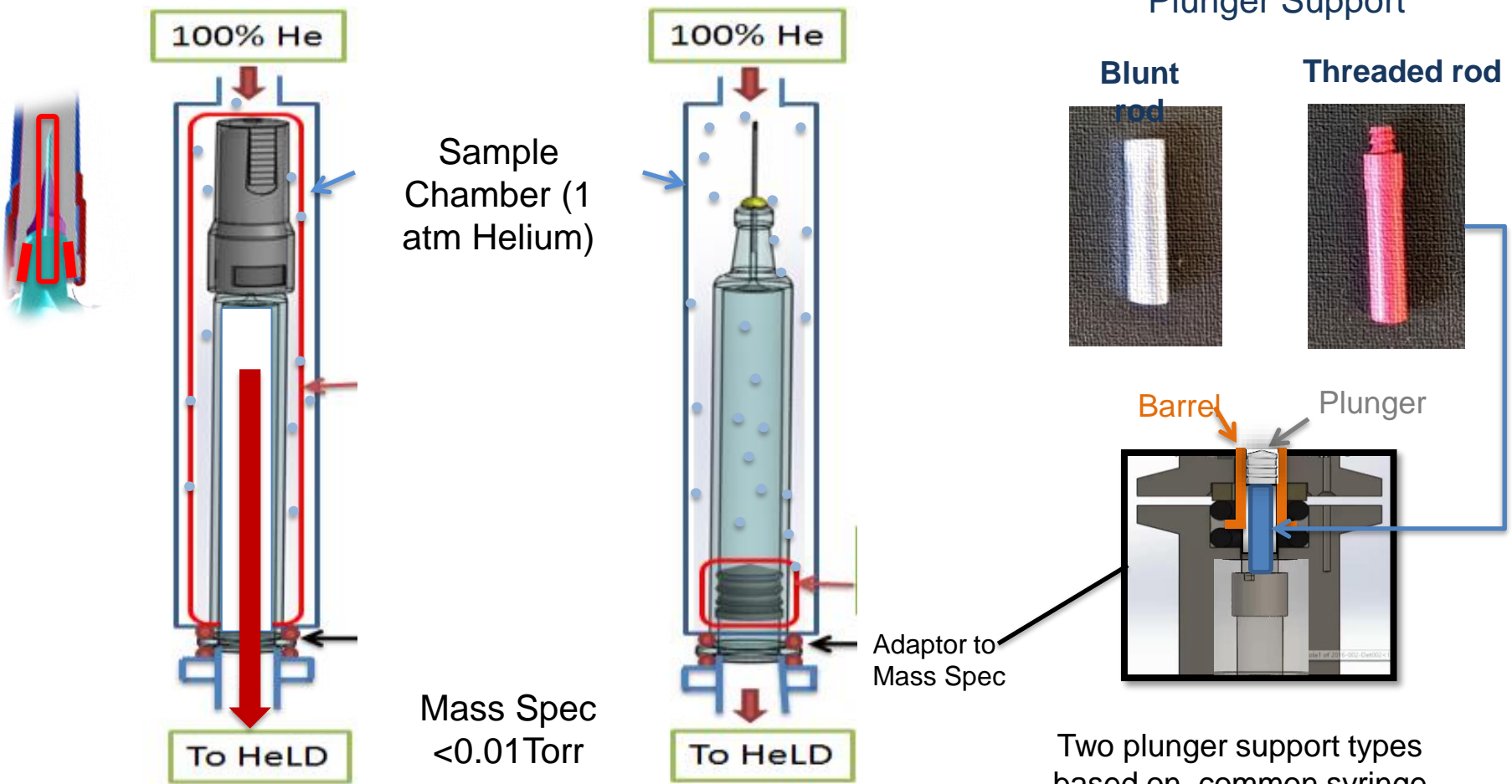
Key Parameters

- Charging cycle
 - Evacuation time (sec)
 - He back-fill time (sec)
- Number of Cycles
- Post-charging testing time (sec)

Leakage Rates vs. Charging Parameters Study



Testing Fixture Design

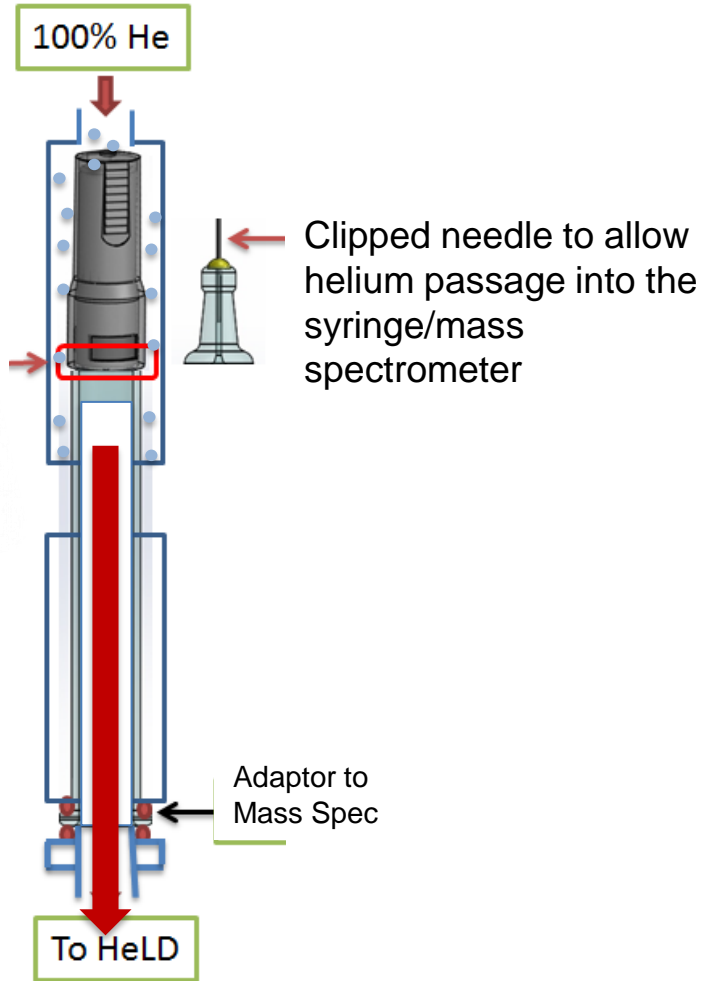
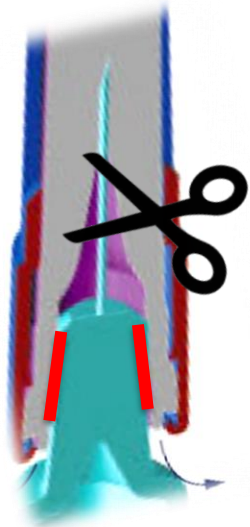


Needle Shield – Barrel Seal

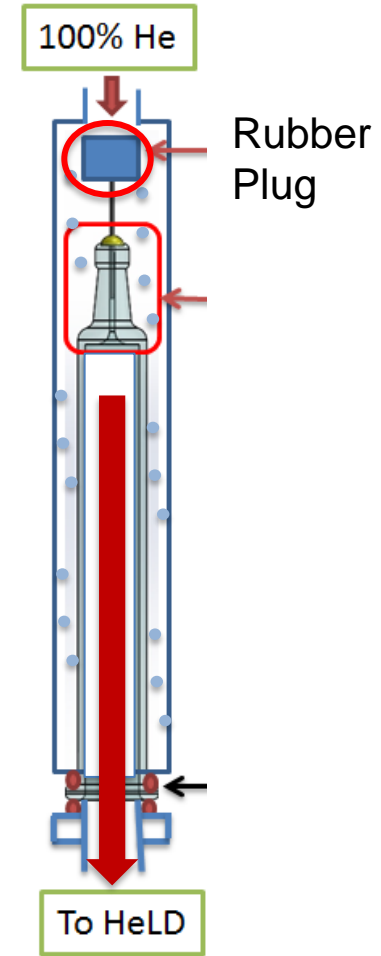
Plunger-Barrel Seal

Two plunger support types based on common syringe injection device designs

Testing Fixture Design



Needle Shield – Barrel head Seal

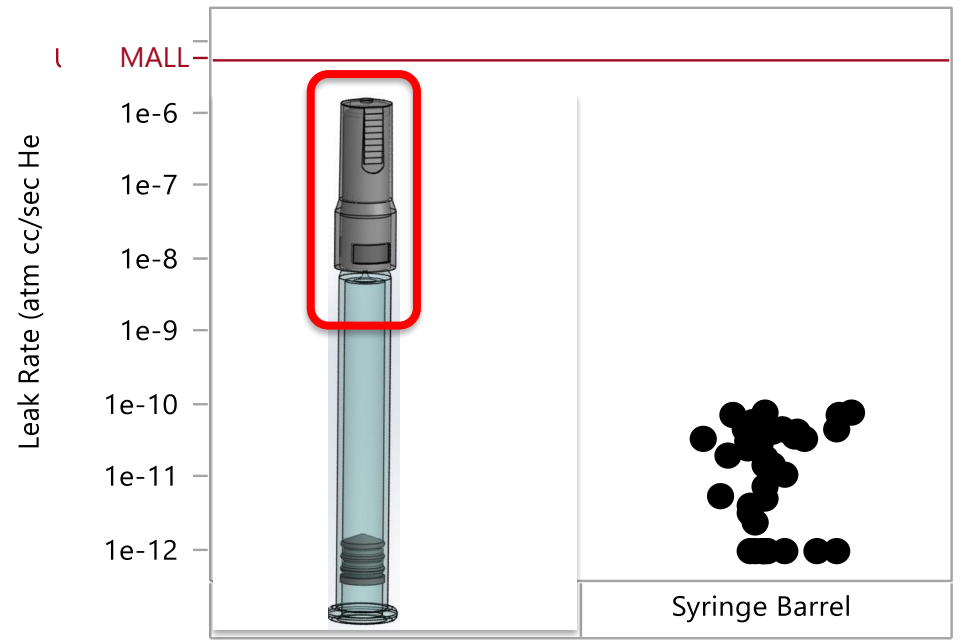


Needle Stem Seals

Evaluation of Needle Shield – Barrel Seal

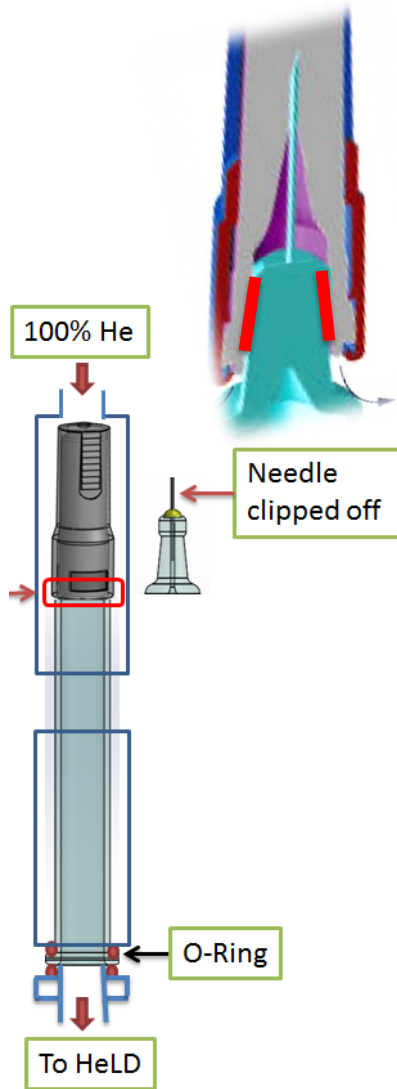
A combination of 3 seal elements

- Needle shield – Syringe head
 - Needle tip – Needle shield
 - Glued staked needle
- Critical to product sterility and formulation content protection

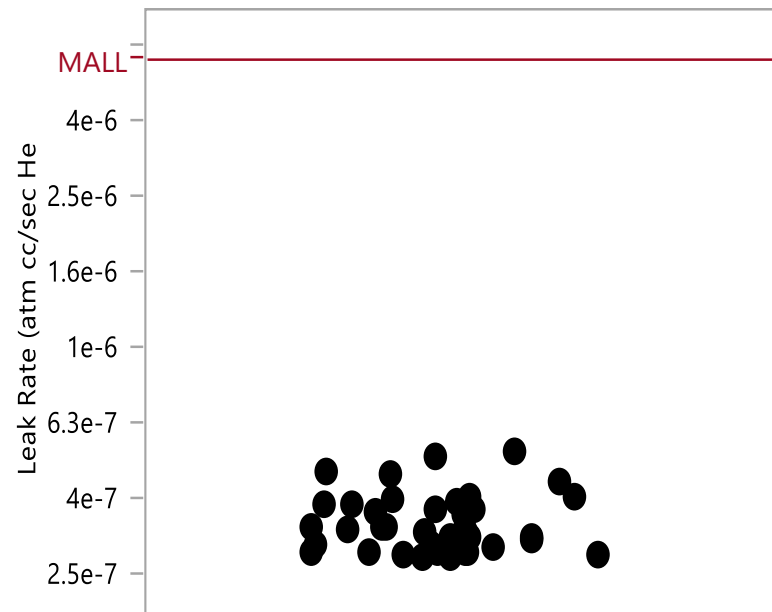


Leakage Rate $\leq 8 \times 10^{-11}$ atm-cc/sec

- Confirm to MALL for preserving sterility and product formulation content



- **Physically mated (compression) seal**
 - Critical to needle stem sterility protection

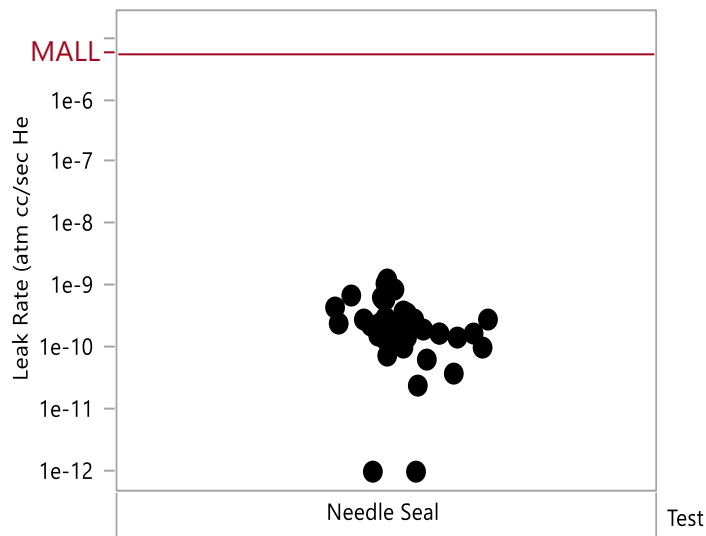
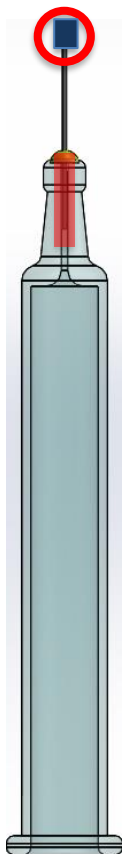


Leakage Rate $\leq 6 \times 10^{-7}$ atm-cc/sec

- Confirm to MALL for preserving sterility

Evaluation of Needle Stem Seals

- Glued (physicochemically bonded) at the base
- Physically mated (compression) seal at the tip
 - Not definitive sterility barriers
 - Poor seals may result to product loss or injection issues



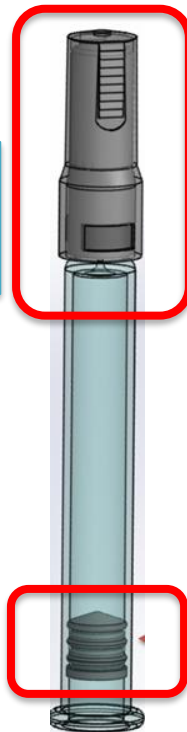
Leakage Rate $\leq 2 \times 10^{-9}$ atm-cc/sec

- Confirm to MALL for preserving sterility and product formulation content

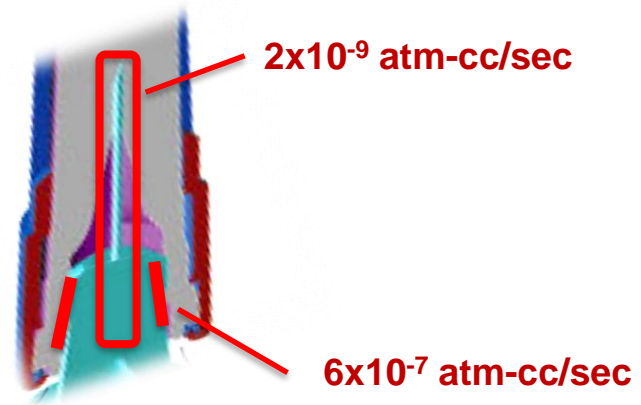
- DP compartment (Plunger & Needle Shield) $\leq 5 \times 10^{-10}$ atm-cc/sec
- Needle stem compartment $\leq 6 \times 10^{-7}$ atm-cc/sec
- All individual critical seals conform to MALL

8×10^{-11} atm-cc/sec

“Layered” seal design in needle shield significantly lowers overall leakage rate
– Added protection to drug product



4×10^{-10} atm-cc/sec



2×10^{-9} atm-cc/sec

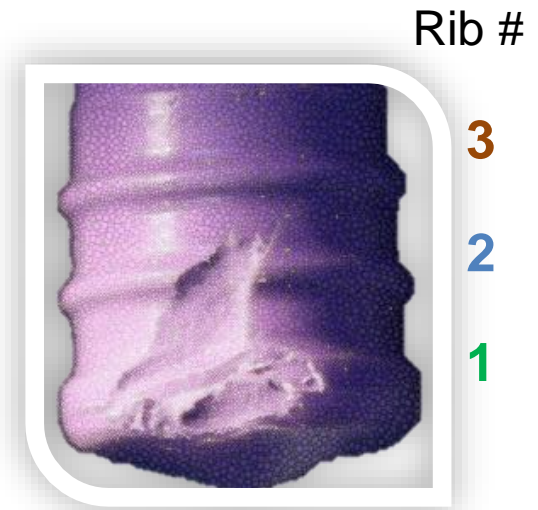
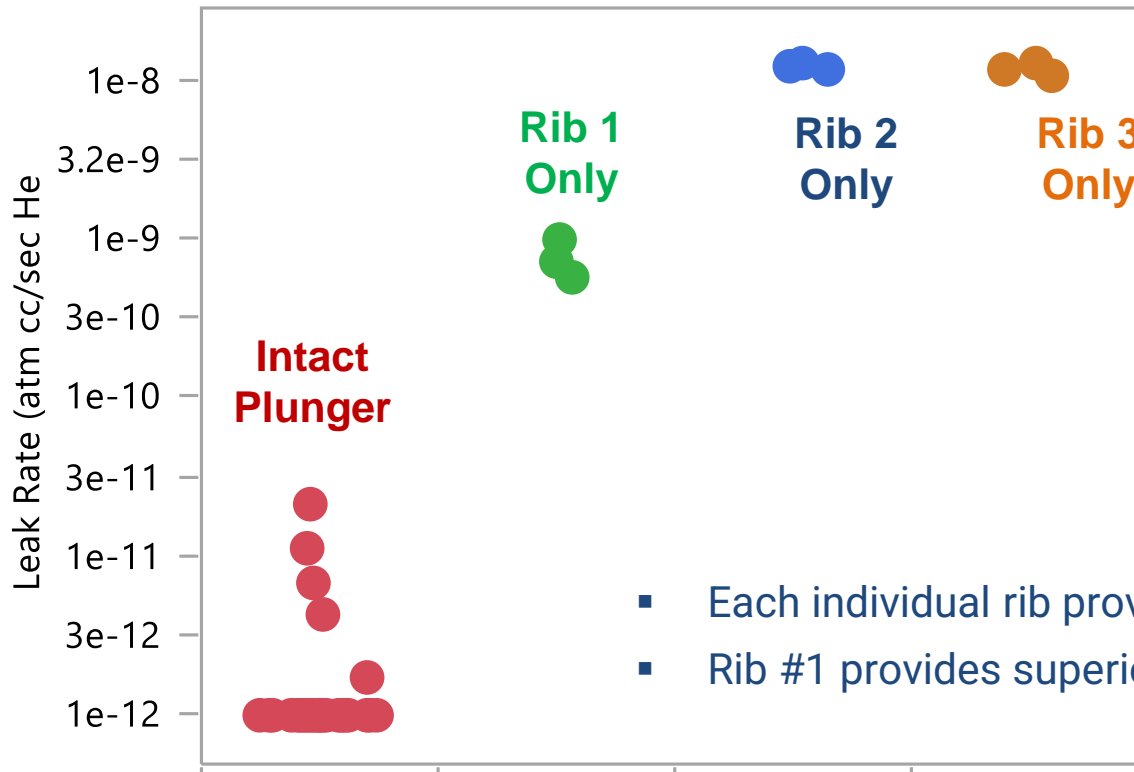
6×10^{-7} atm-cc/sec

The needle shield – barrel head seal is the weakest among all seals

Package Integrity was verified for preserving sterility and formulation content

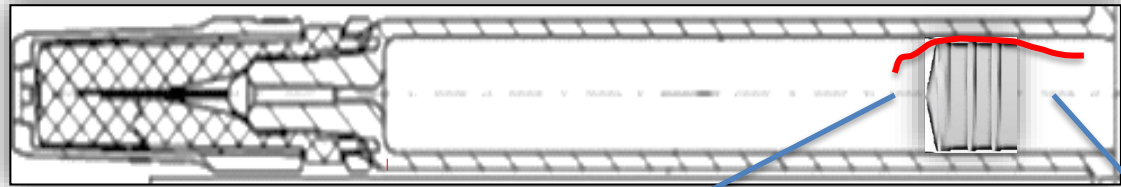
Design Robustness: Plunger Ribs

- Each plunger rib assessed individually for sealing capability
 - Assessed by compromising 2 of the 3 ribs, leaving 1 intact rib
 - Evaluate impact of potential plunger molding defects

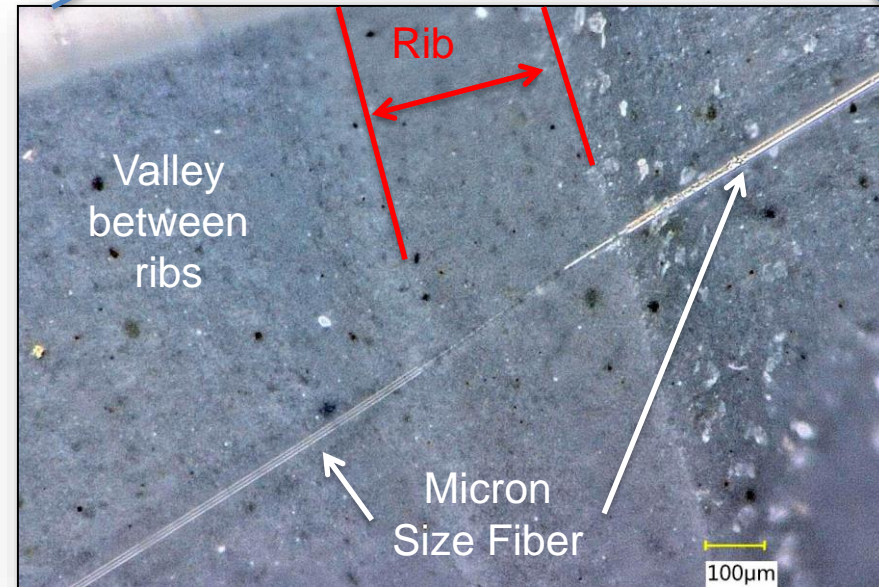


- Each individual rib provides adequate seal
- Rib #1 provides superior sealing performance

Design Robustness: Fiber Interference

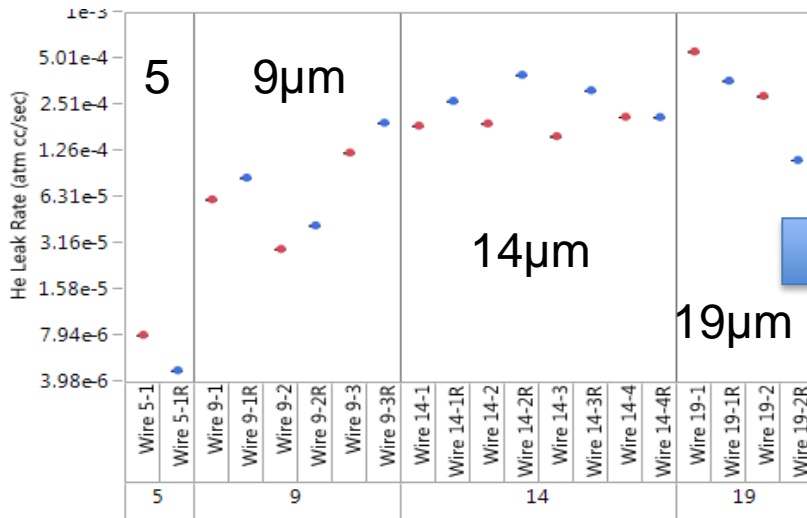


- Fiber Interference between plunger rib and barrel
- Industry needs a practical means to fabricate and characterize sub-micron size defects
- Assess impact of interfering fibers of various sizes

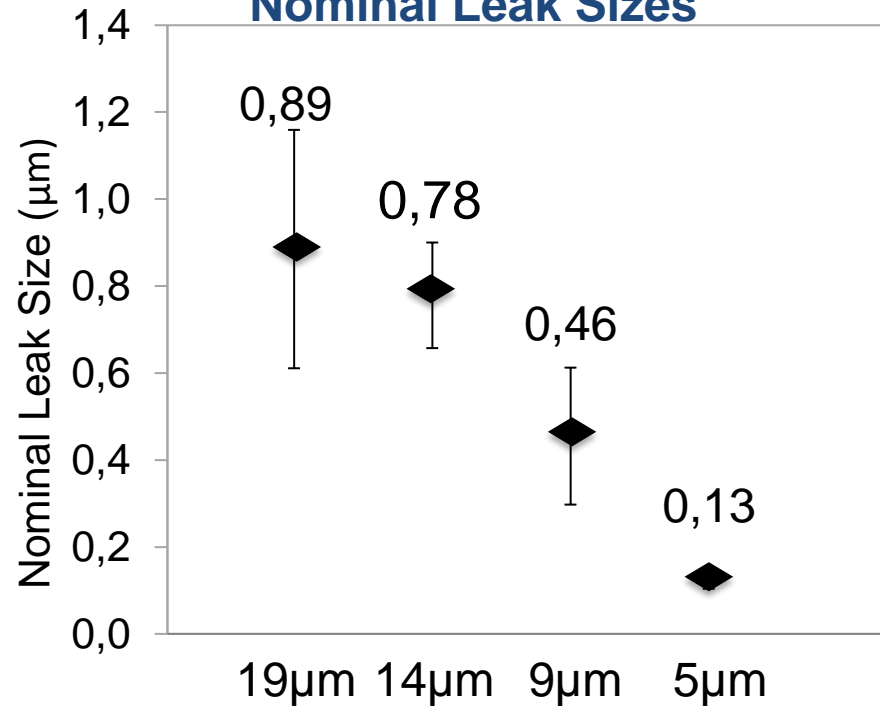


Design Robustness: Fiber Interference

Helium Leakage Rates



Nominal Leak Sizes



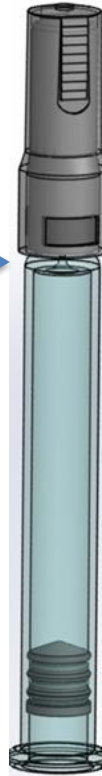
- Presence of interfering fibers could compromise plunger seal integrity
- Interfering fibers provide a practical means for fabricating sub-micron defects
 - Enable development of other CCI testing technologies

Potential Opportunities

Needle Shield Gap Study

- How much needle shield movement until it leaks?
- Use spacer to create controlled gaps

Spacer



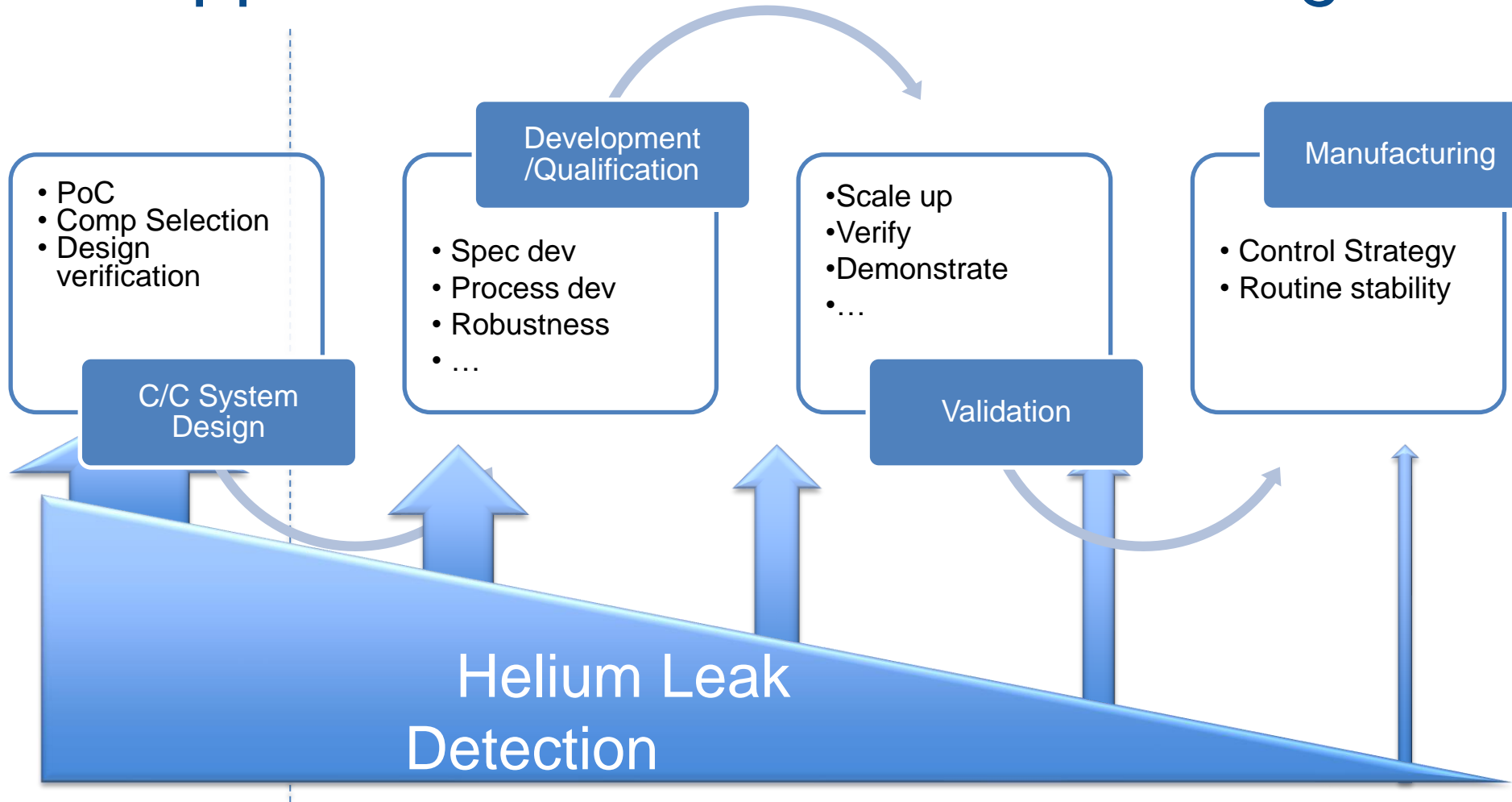
“CCI Capability”

- Multiple Lots
- Cpk of leakage rate?
- Correlation with dimensional Cpk

Component aging study

How does the seal performance change over time?

Application of Helium Leak Testing



Conclusions: Helium Leak Detection

- ❑ HeLD a capable CCI technology: sensitive, precise, and quantitative
 - Enable data-driven decision making: rich information; high throughput
 - Fixture design and helium charging critical for method development

- ❑ Inform container closure design and process development
 - Inform packaging component selection and system design
 - Assess container closure robustness against design, process variability
 - Demonstrate conformance to MALL

- ❑ Enable foundational CCI research
 - Characterize micron and sub-micron leaks

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