Case Study: Systemic Evaluation of Vial Container Closure System Suitability at Frozen Conditions

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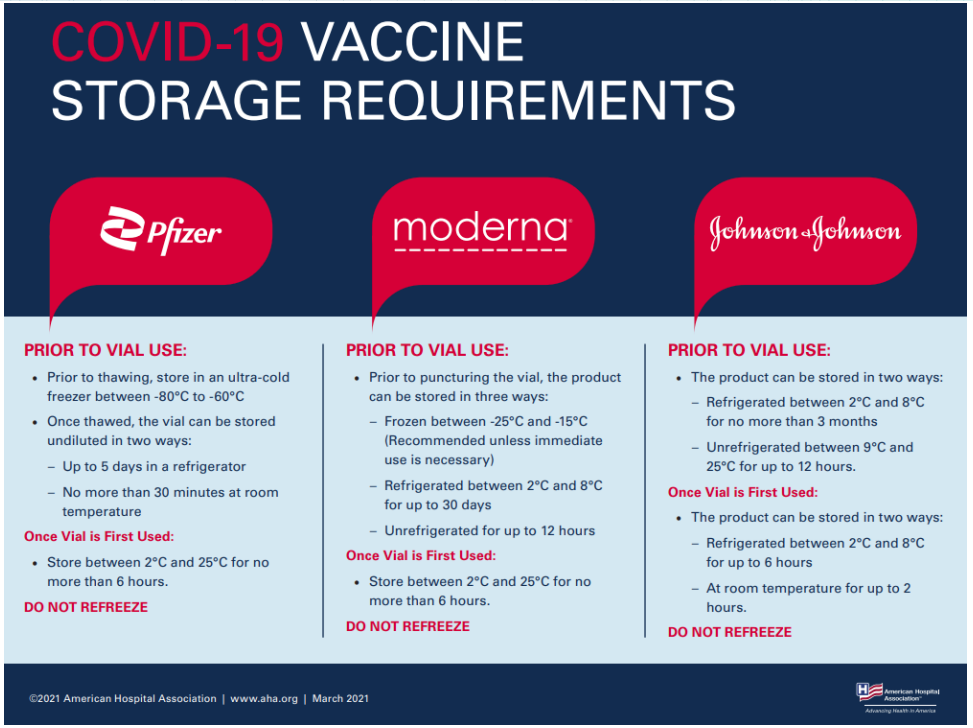
- With Significant Contribution from Peter Sargent, Eli Lilly and Company

Agenda

- Background
- Risk Assessment
  - Suitability Hazards
- Phase based strategy
  - Screening Assessment
  - Development
  - Scale Up
- Takeaways

Background



Evolving needs for deep frozen storage

- Cell/gene therapies
- Vaccines

Opportunies for extended expiry

- Increased protein stability for biologics
- Establish shelf-life with limited stability knowledge

Risk Assessment: Suitability Hazards

Protection Risk

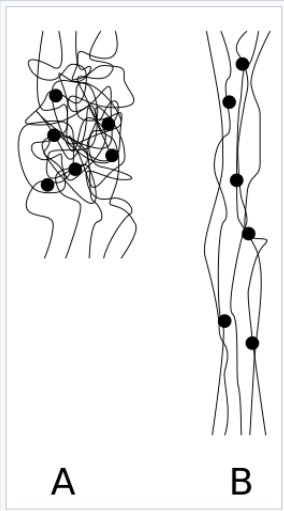
- Loss of elastomer elasticity below Tg
- Increased risk for breakage due to liquid expansion
- Difference of CLTE (coefficient of linear thermal expansion)

Performance Risk

- Mechanical/thermal stresses of shipping
- Thermal stresses of processing streams
- In-use performance after thaw

Safety & Compatibility

- Frozen conditions favorable for DP stability and E/L



(A) is an unstressed polymer; (B) is the same polymer under stress. When the stress is removed, it will return to the A configuration. (The dots represent cross-links)

Wikipedia, Elastomer

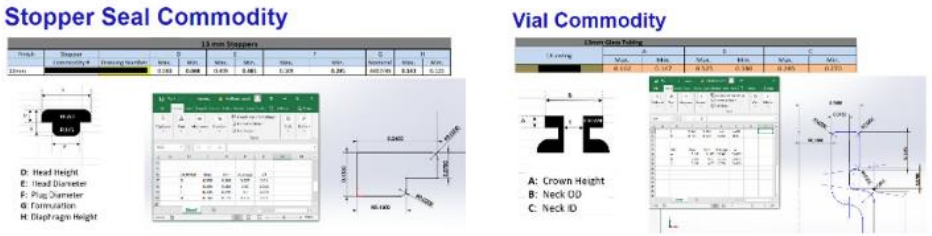
Risk Assessment: Phased Approach

Stage Description	Screen	Confirm	Develop	Scale Up
Activities	• Form/Fit Concerns • Finite Element Analysis	• In-Use conditions •CT X-Ray •Inherent Leak (HeLD)	• Head Space Analysis • Stability • Shipping Hazards	• Process Mapping • Structural Integrity
Phase	**Ph 1/2** **Ph 3/ Primary Stability**			
Focus	**Design and Systemic Risk with Focus on Patient Safety** **Process Suitability and Business Risk**			

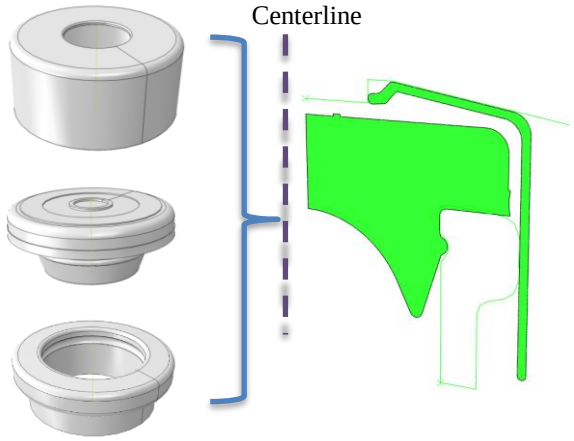
- *Right size the approach*
- *Gate transitions between phases*
- *Expand the system boundaries*

Screening: Form / Fit + Computed Aided Engineering

Form fit: Component Stack Tolerances



CAE / Modeling: characterize component Materials of Construction as inputs

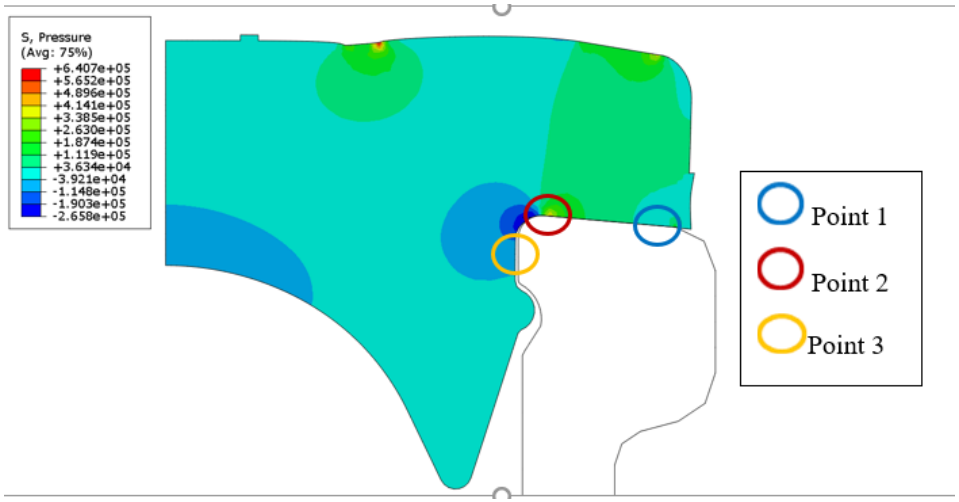


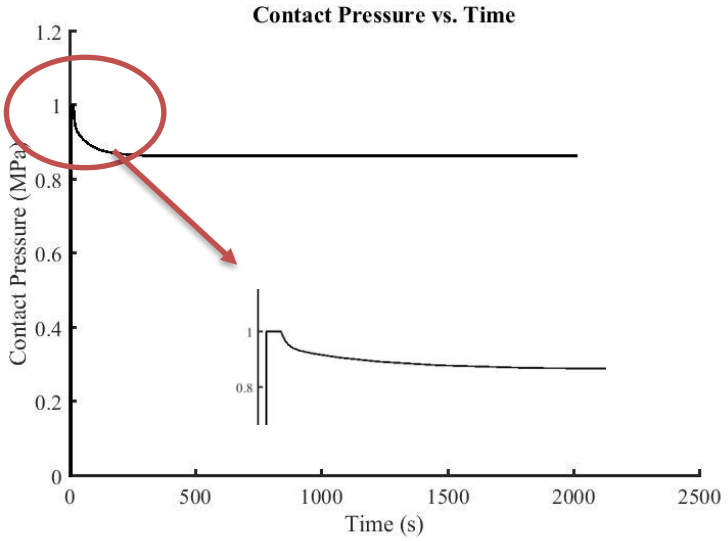
Vials	***Elastomer***	***Seals***
Assumed to be a rigid body	• Viscoelastic characterization > T_g • Elasto-plastic characterization < T_g	• T_g • CTE • Poisson

Screening: CAE

Evaluate contact pressure

- Consider shelf life
- Consider temperature





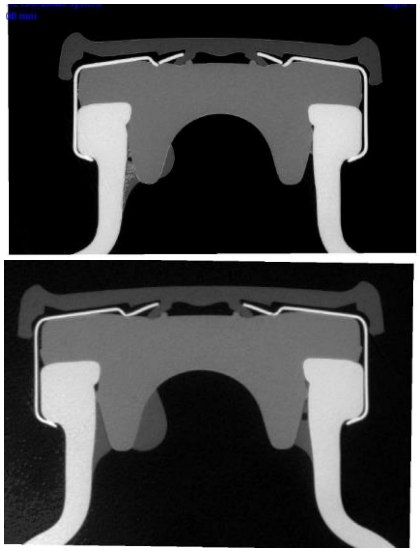
	Contact pressure (MPa)	Contact force (N)
Maximum	1	25.7
Relaxed	0.864	22.2

Development: CT Imaging

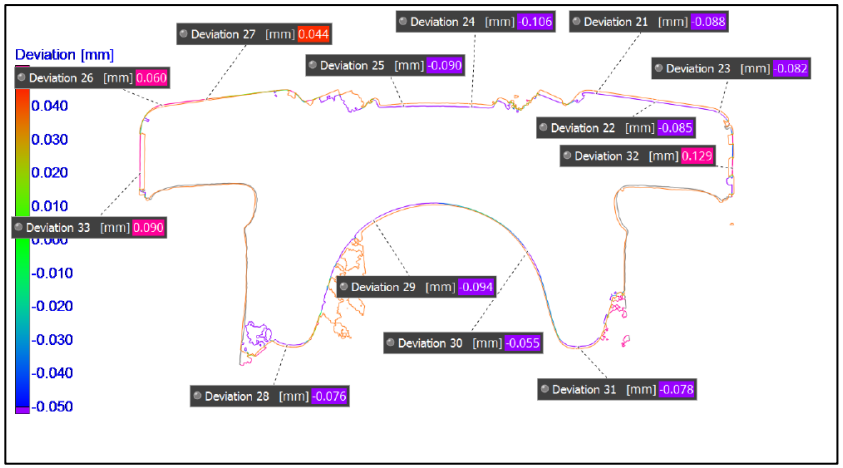
Confirm modeling assumptions via CT x-ray

– Look for variance between normal conditions and frozen

Pre-Freeze



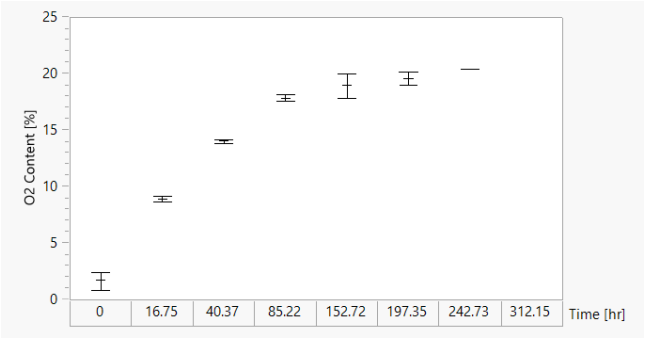
Frozen



Development: CCI

Inherent Leak Rate

- Conduct as guided by USP <1207>
- Conduct at temperature via HELD
- Focused on design risk



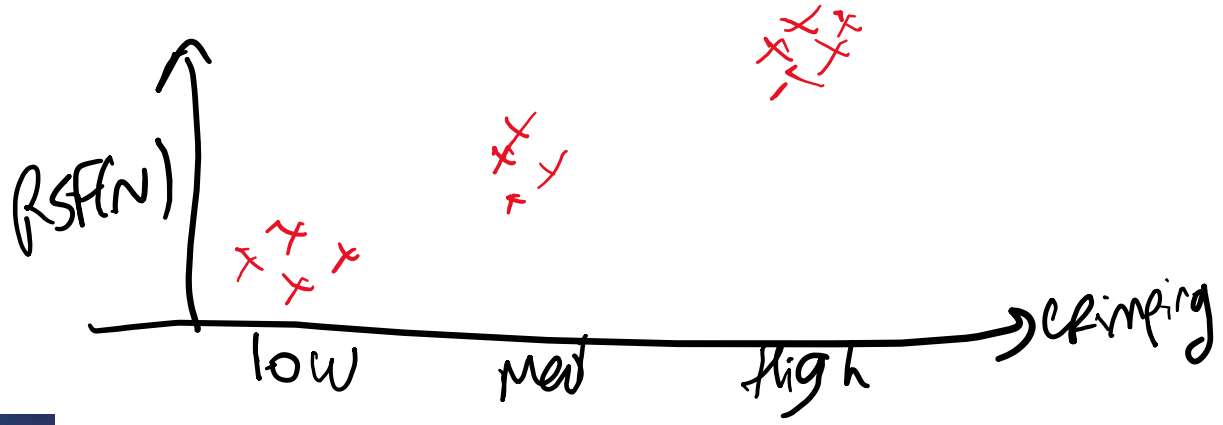
Headspace Analysis

- Allows for CCI evaluation at in-use conditions
  - Incorporates temperature
  - Apply known shipping & shelf life constraints

- -78 ℃, headspace underpressure
- Stopper loose elasticity, interface gaps
- CO_2 in headspace
- Warm up, stopper reseals
- CO_2 trapped

Development: Seal Quality Test

Main Goal: Establishing the correlation between residual seal force (RSF) (seal quality test) and CCI



Developing a Readily Available Primary Packaging System for Use in an Ultra-Cold Chain for COVID19 Vaccine Global Distribution – Using a Scientific Approach

Co-presenters:
Michael Edey, Pfizer
Derek Duncan, Lighthouse Instruments

2021 PDA Parenteral Packaging Conference

See Suzanne's presentation

Scale Up: Approach

Shift the focus from systemic to residual risk

- Transition from design → process
- Emphasize control strategy development
  - Consider incoming, filling, and transit
  - Incorporate 2º packaging?
- Employ statistical powering

Scale Up: Structural Integrity

Hazards

- Liquid expansion at phase change
- Freeze/thaw at shipping nodes
- Mechanical stresses
  - Vibration and Drop during shipment
  - Glass to glass contact at filling

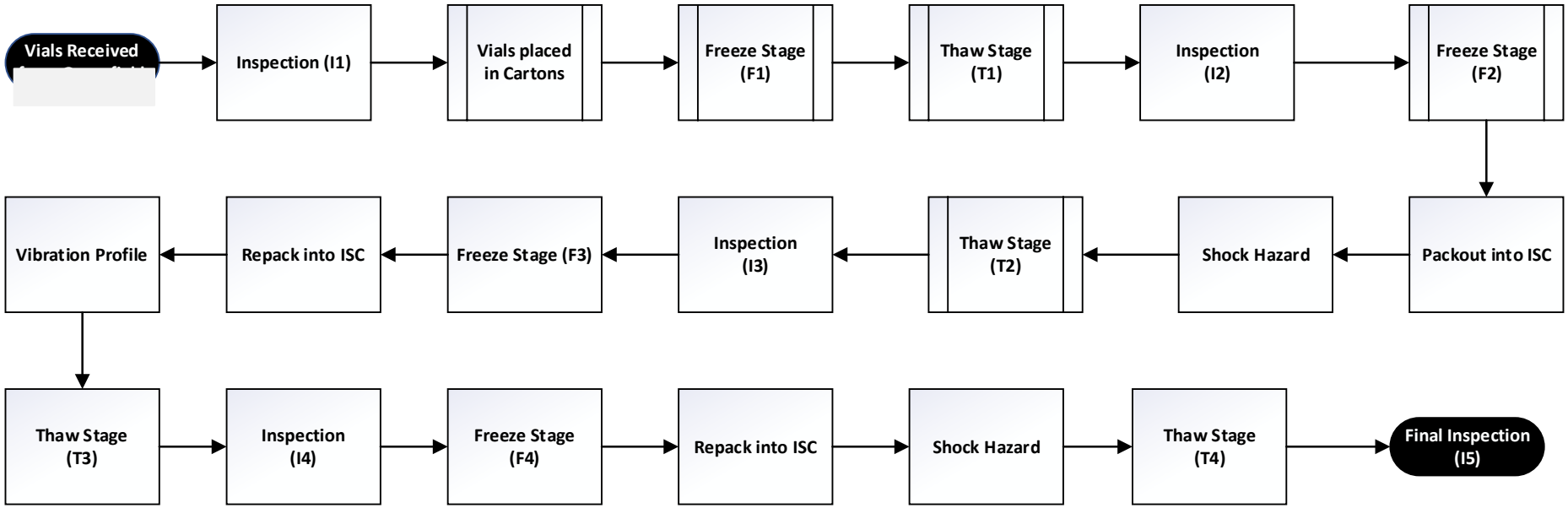
DOE considerations

- Storage Temperature/orientation
- Shipping conditions: temperature, method, e.g. dry ice
- Fill volume, CCS size
- Best outputs (RSF, CCI)

Scale Up: Process Mapping

Process Mapping

- Understand temperature transitions
- Build in high-volume production hazards
- Adopt a statistical approach and foundation



Takeaways

Risk Assessment Strategy
Use a right sized, phase approach

***Screen* for Form/Fit issues at 'standard' conditions**

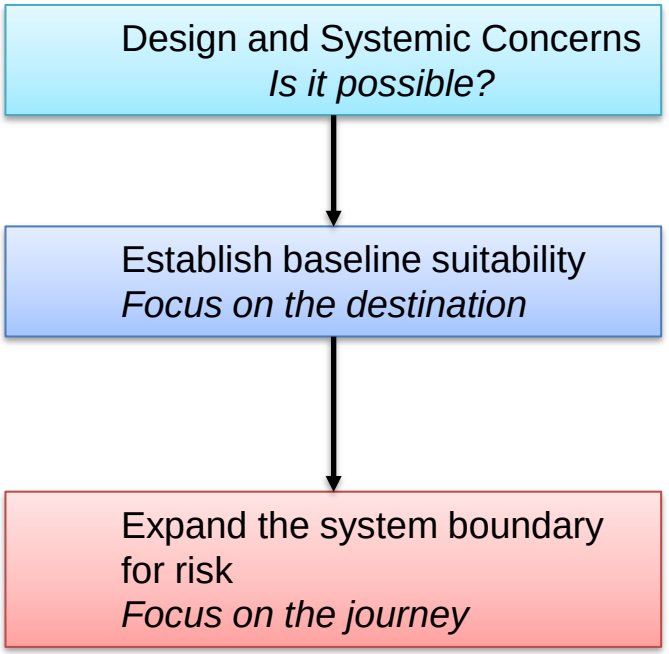
- Machinability studies
- Stacked Tolerance Analysis

***Confirm & Develop* frozen use conditions**

- Identify lower temp. bound in storage and shipping
- Understand supply chain risk points
  - Impact of Shipping Hazards
  - Temperature transitions

Apply a world view in the scale up process

- Transition to outcomes thinking
- Propagation of stresses means propagation of risk



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

A Prefilled Syringe Case Study

Container Closure Integrity: Regulations, Test Methods, Application

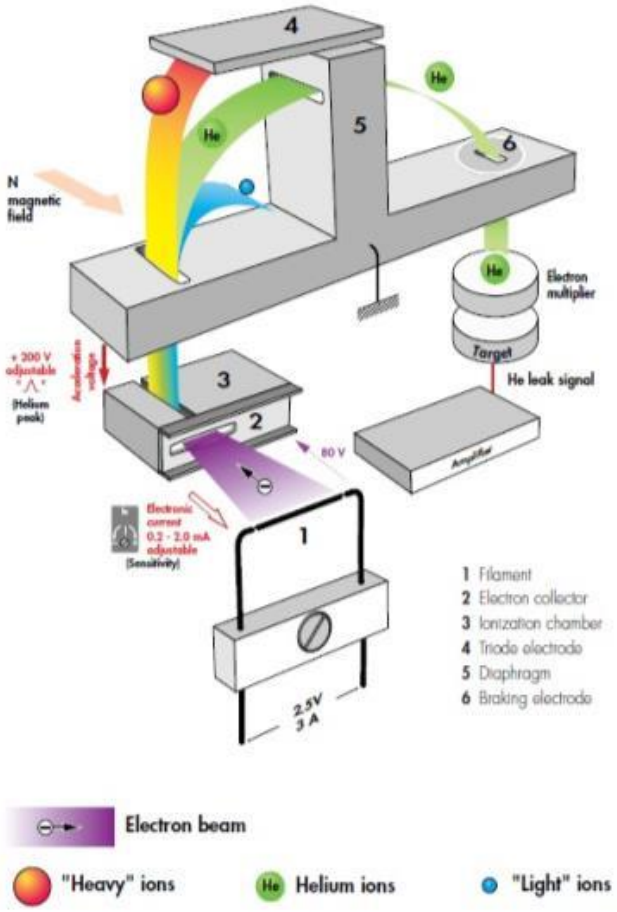
Coralie Richard
Lei Li
Eli Lilly and Company

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

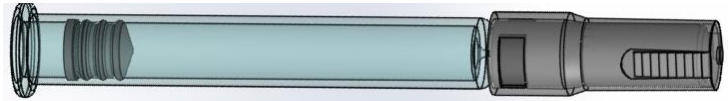
Introduction – Helium Leak Detection

- **Sensitivity & Quantitative**
  - Mass spectrometer as detector
- **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**



Leak Detection Associates, Blackwood, NJ

Prefilled Syringe System



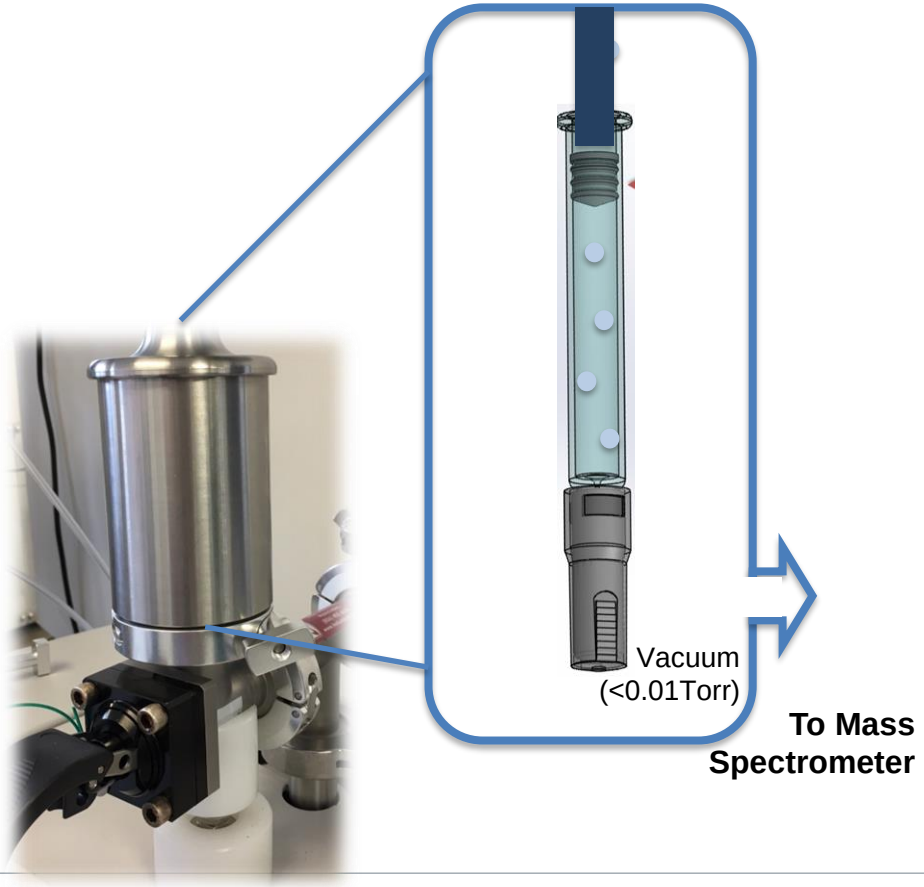
“Weak links”

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

Preliminary Testing

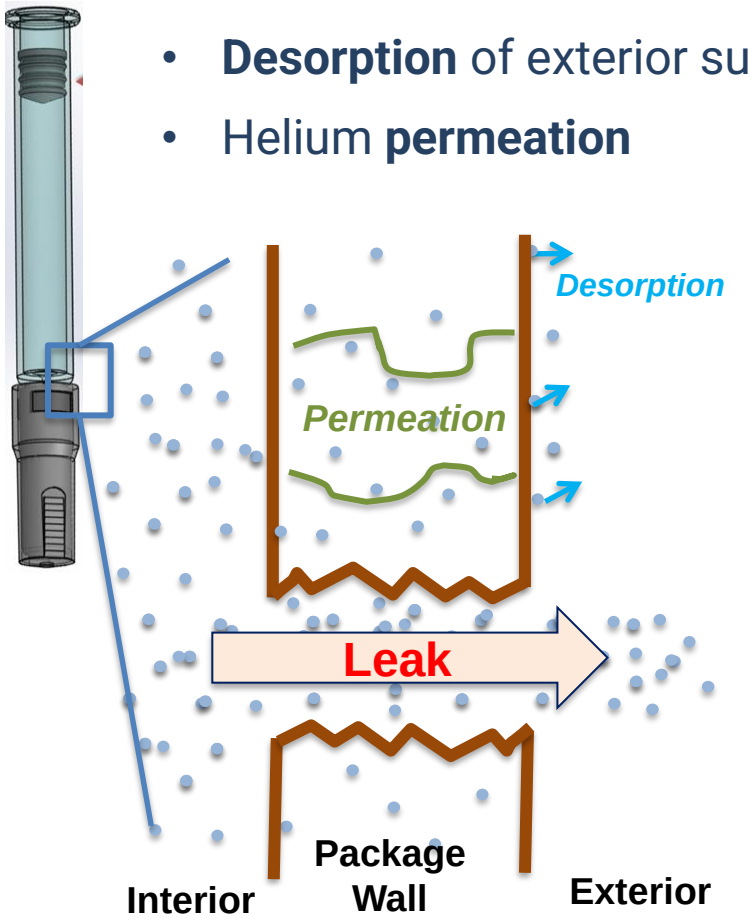
1. **Filling**: syringes charged with helium and plungered in a glove box

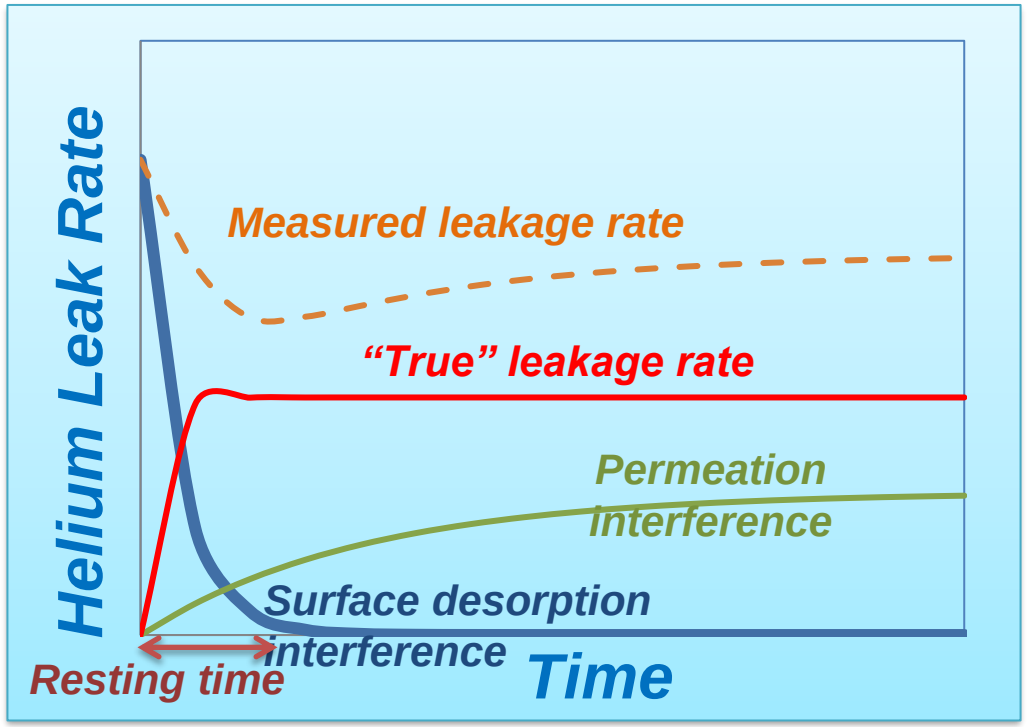
2. **Testing**: filled syringe is placed in a sample chamber for testing
   - A plunger rod is used to retain plunger during testing



Potential Interferences

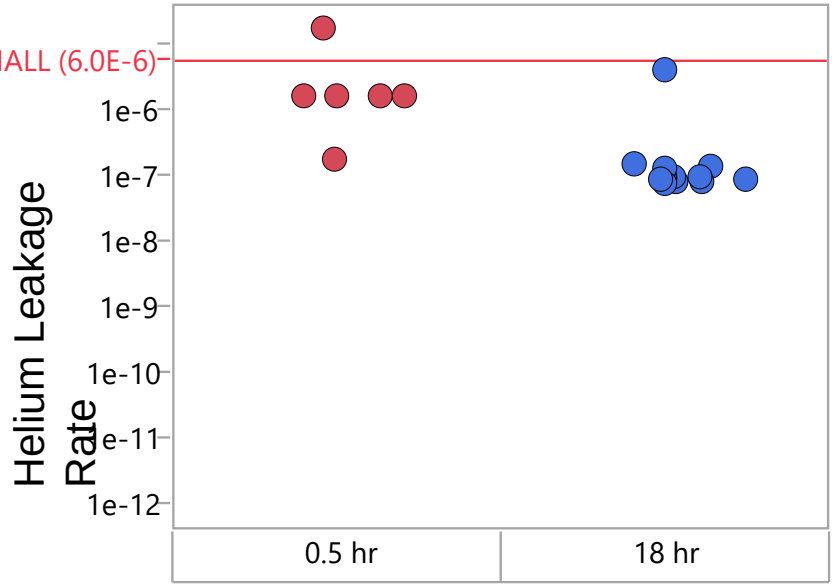
- **Desorption** of exterior surface-adsorbed helium
- Helium **permeation**





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

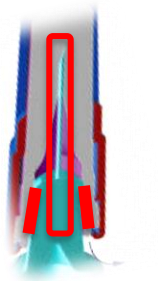
Method Improvement Strategy

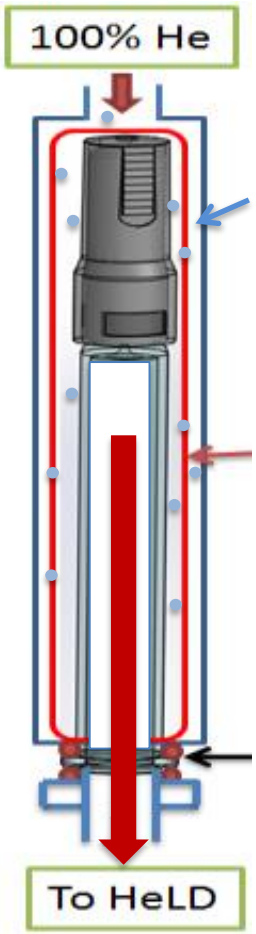
- ❑ "**Fast and Clean**" helium charging
  - **Fast**: allow testing to start prior to significant permeation
  - **Clean**: eliminate helium contact with interfering sample surfaces

- ❑ "**Divide and Conquer**" critical seal elements
  - Isolate critical seal elements for independent assessment

Key Enabler: Sample Fixture Design

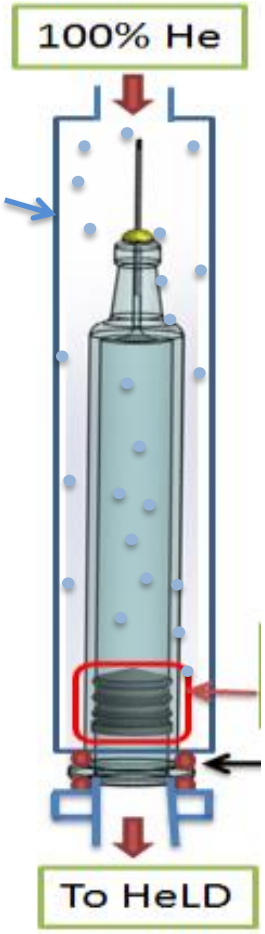
Testing Fixture Design





Sample Chamber (1 atm Helium)

Mass Spec <0.01Torr

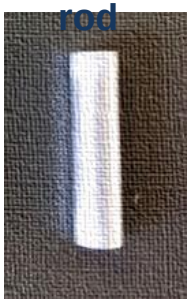


Needle Shield – Barrel

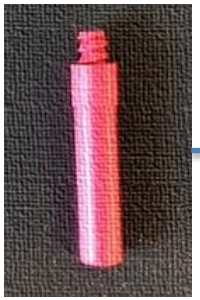
Plunger-Barrel

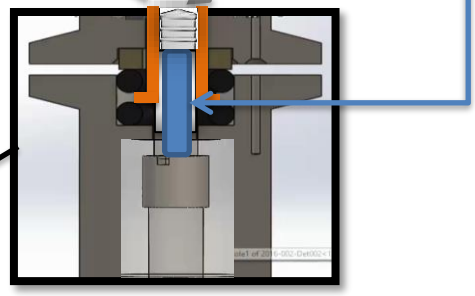
Plunger Support

Blunt rod



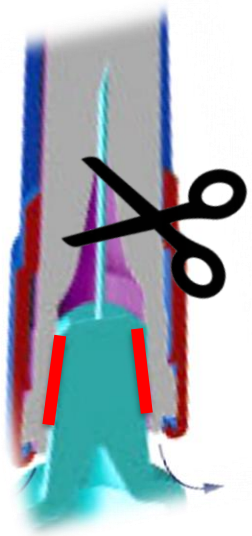
Threaded rod

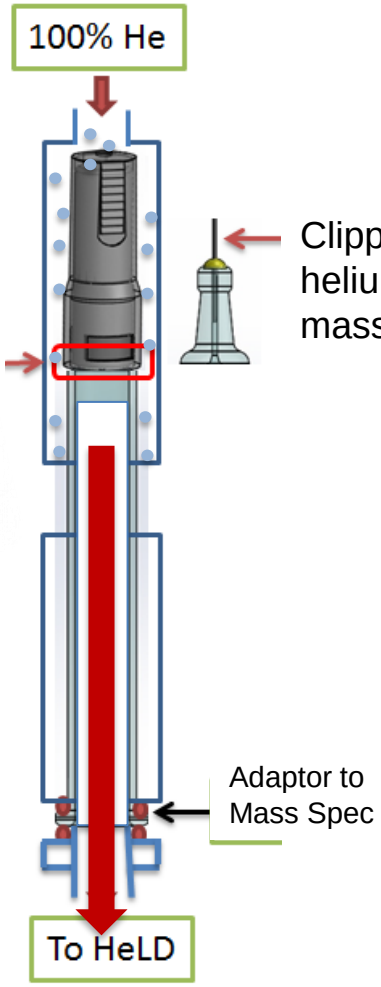




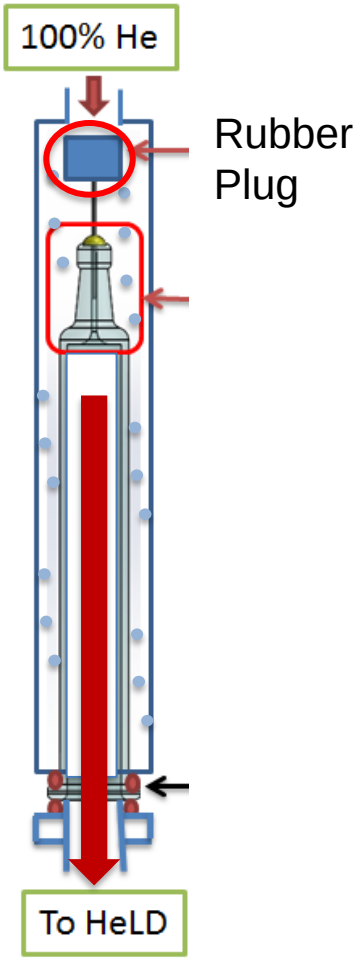
Two plunger support types based on common syringe injection device designs

Testing Fixture Design





Needle Shield – Barrel head Seal



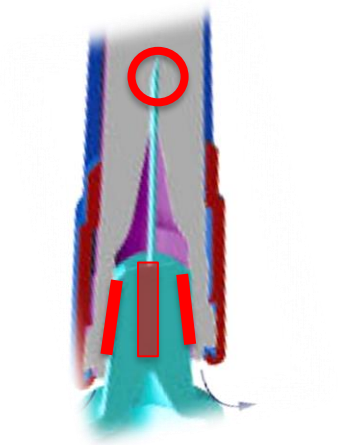
Needle Stem Seals

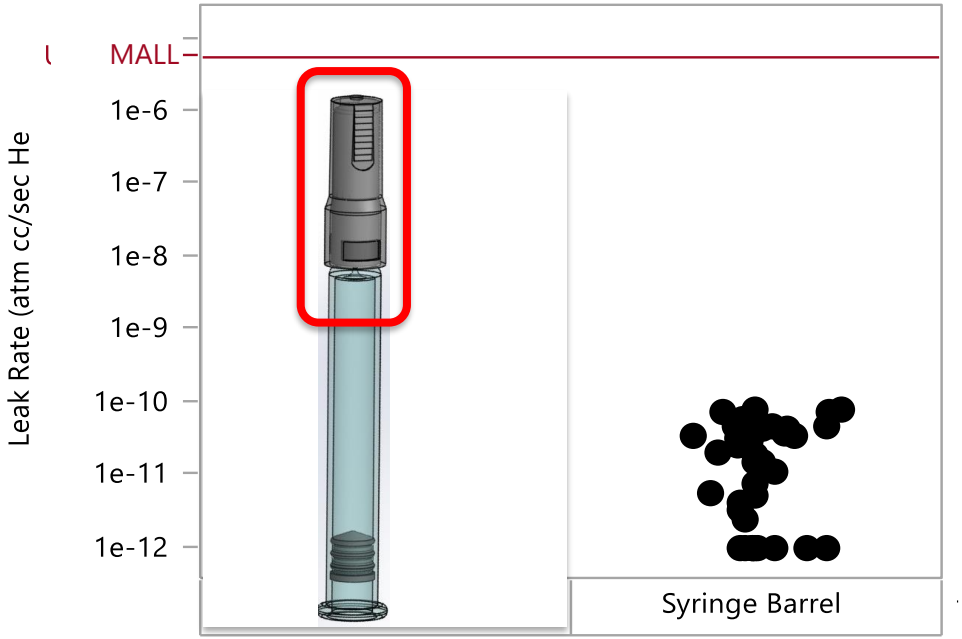
Evaluation of Needle Shield – Barrel Seal

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

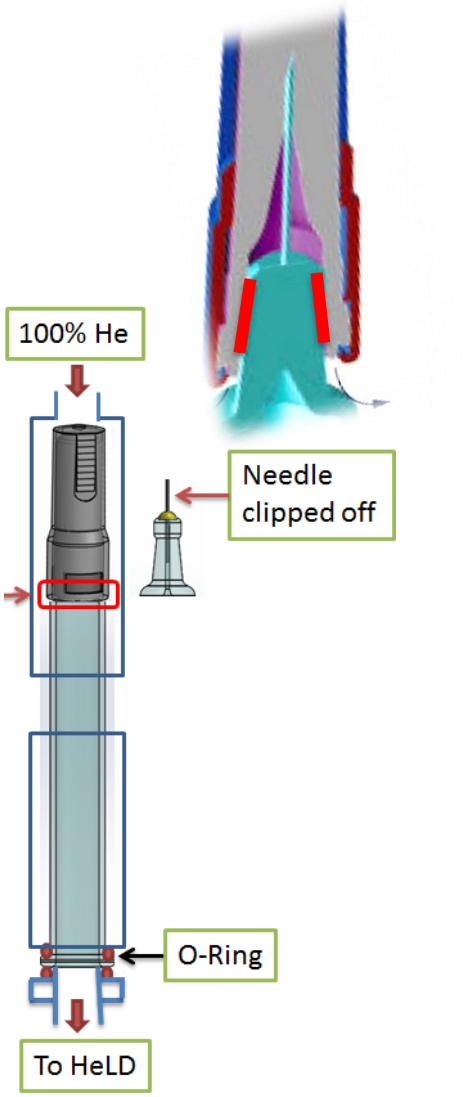




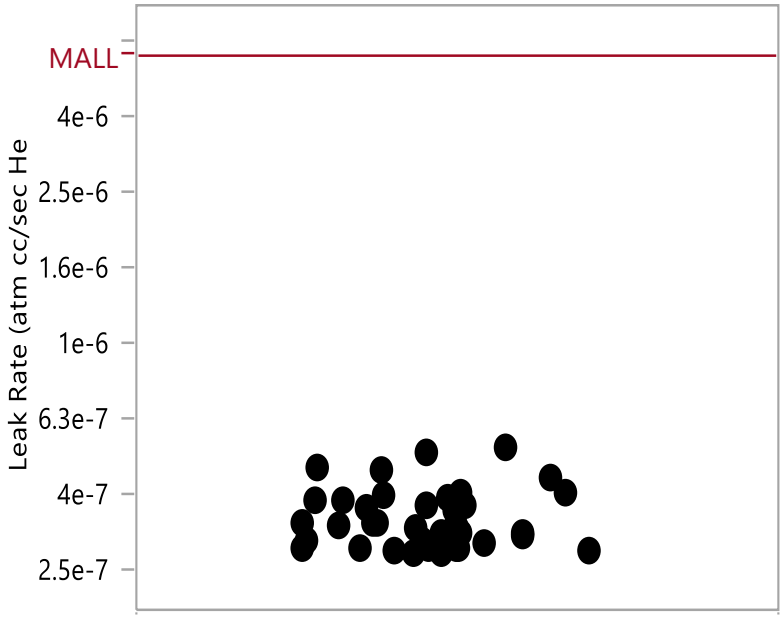
Leakage Rate <= 8 x 10^{-11} atm-cc/sec

- Confirm to MALL for preserving sterility and product formulation content

Evaluation of Needle Shield – Barrel Head Seal



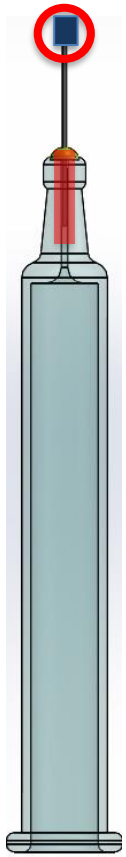
- **Physically mated (compression) seal**
  - Critical to needle stem sterility protection
  - Contributes to DP compartment seal



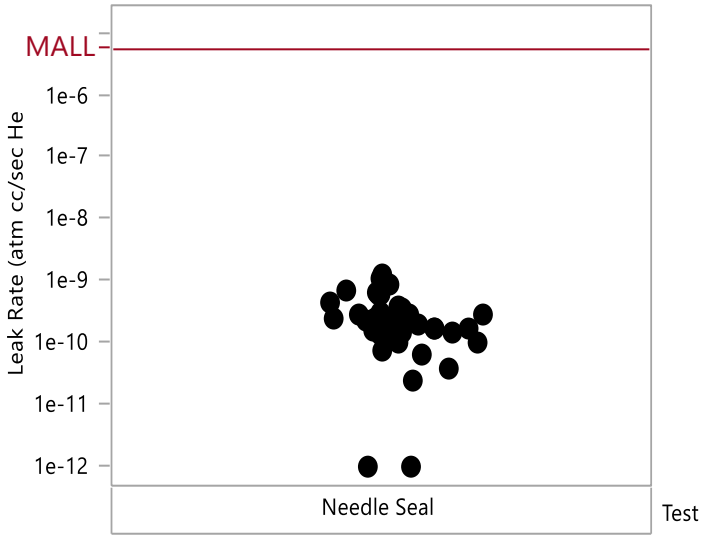
Leakage Rate <= 6×10^{-7} atm-cc/sec

- 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



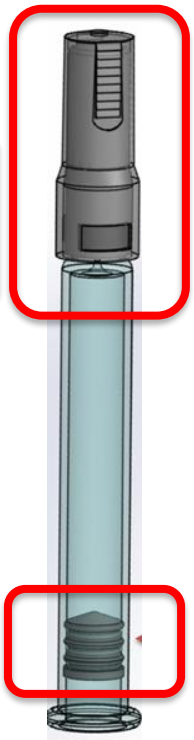
Leakage Rate <= $2x10^{-9}$ atm-cc/sec

- Confirm to MALL for preserving sterility and product formulation content

Inherent Package Integrity Summary

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

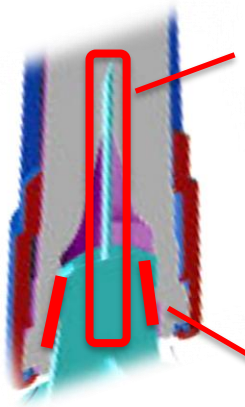
8x10^{-11} atm-cc/sec



4x10^{-10} atm-cc/sec

"Layered" seal design in needle shield significantly lowers overall leakage rate

– Added protection to drug product



2x10^{-9} atm-cc/sec

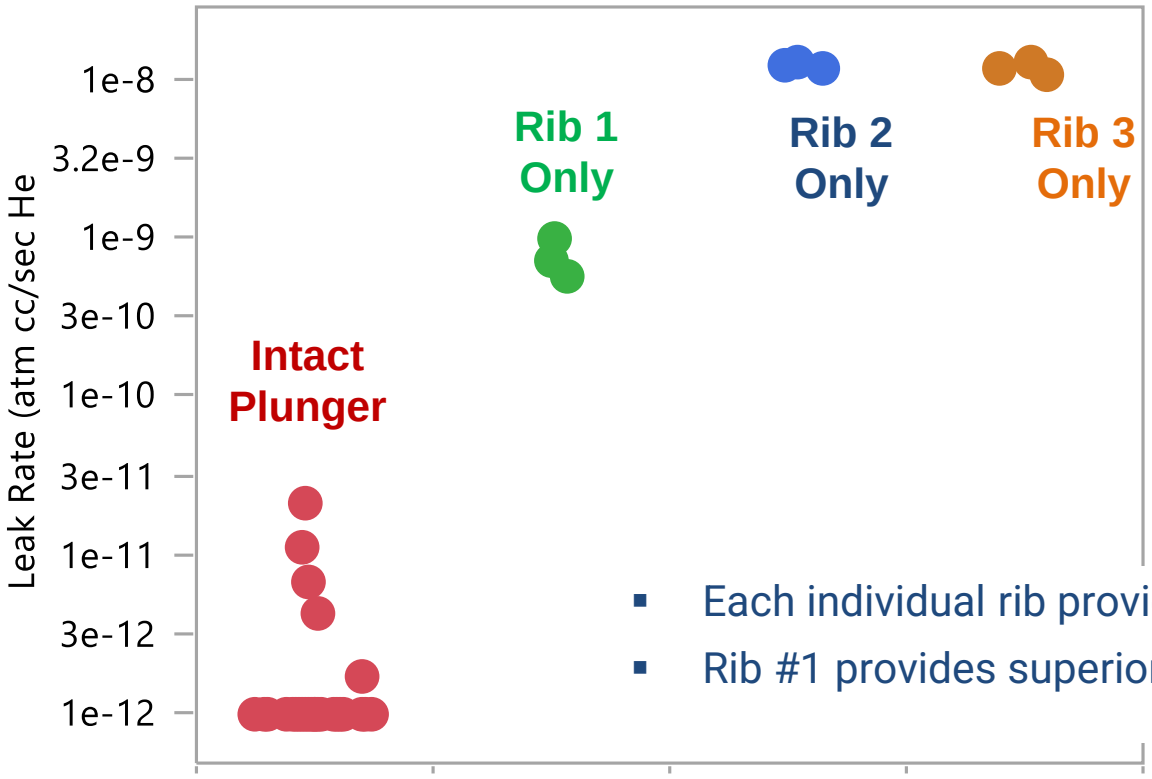
6x10^{-7} atm-cc/sec

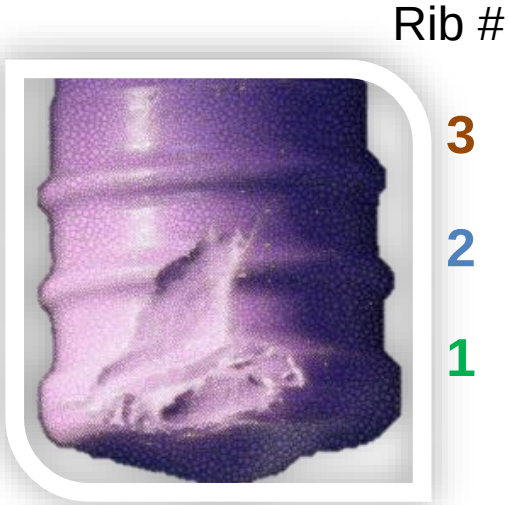
The needle shield – barrel head seal is the weakest among all seals

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

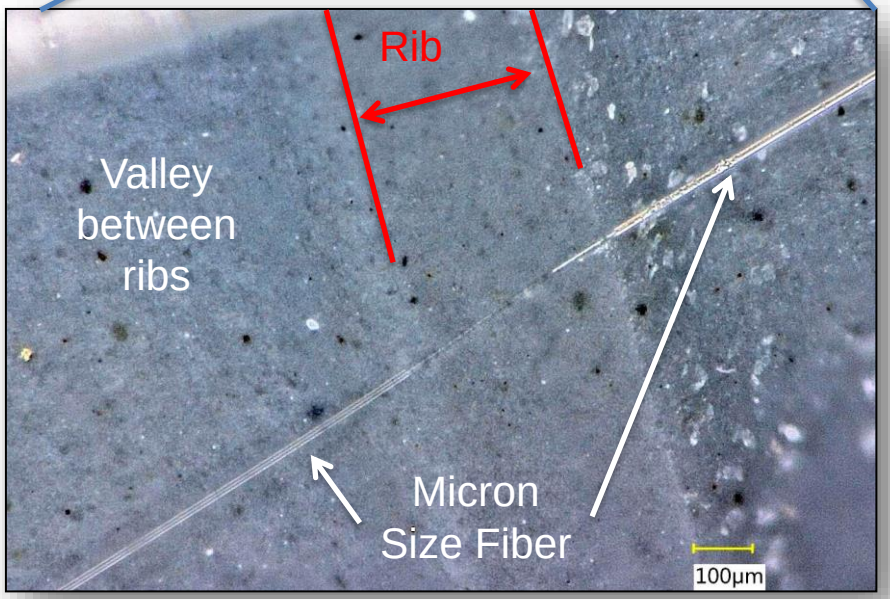




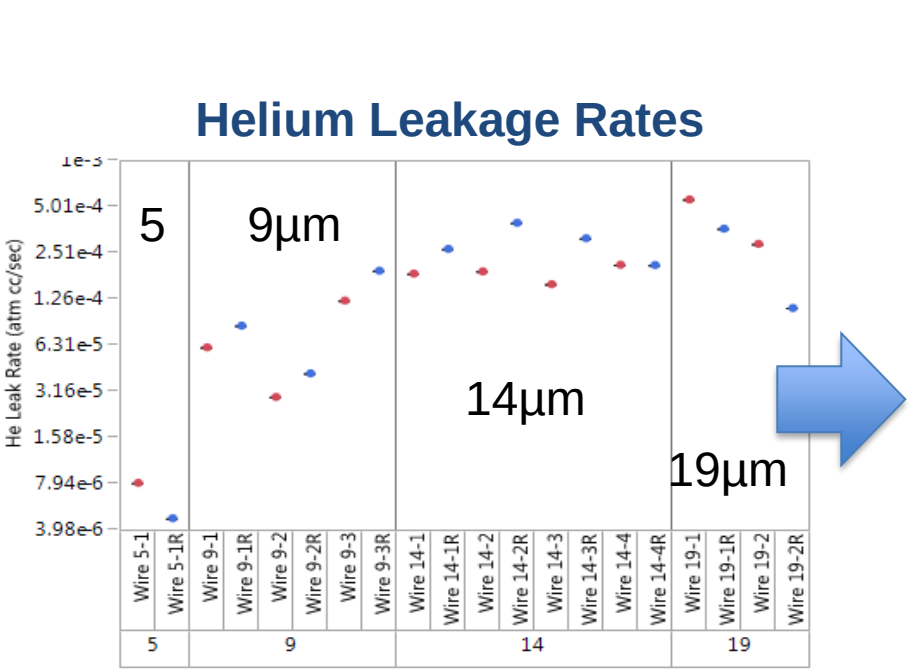
- Each individual rib provides adequate seal
- Rib #1 provides superior sealing performance

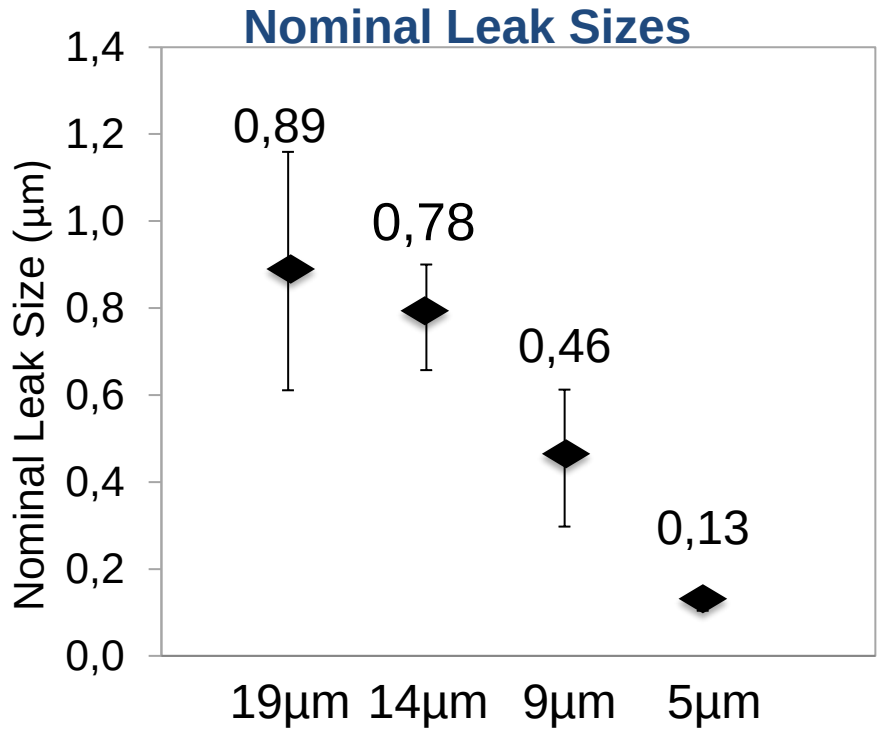
Design Robustness: Fiber Interference

- Fiber Intereference 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

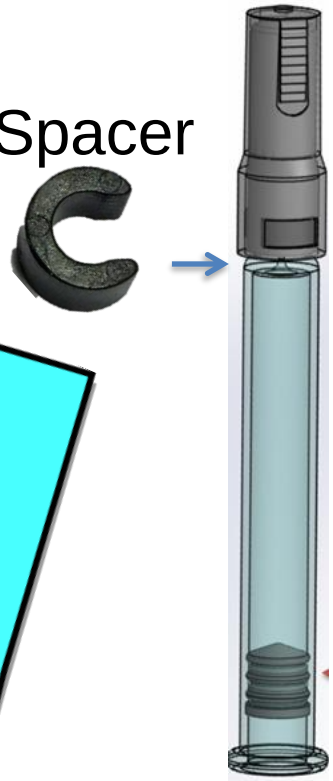




- Presence of interfering fibers could compromise plunger seal integrity
- Interfering fibers provide a practical means for fabricating sub-micron defects
  - Enable development of other CCI testing technologies

Potential Opportunities

Spacer



Needle Shield Gap Study

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

" CCI Capability"

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

Component aging study

How does the seal performance change over time?

Conclusions

- Understand Instruments + Methods + Results
  - Not a black box
  - Fixture design and helium charging critical for method development

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

References