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

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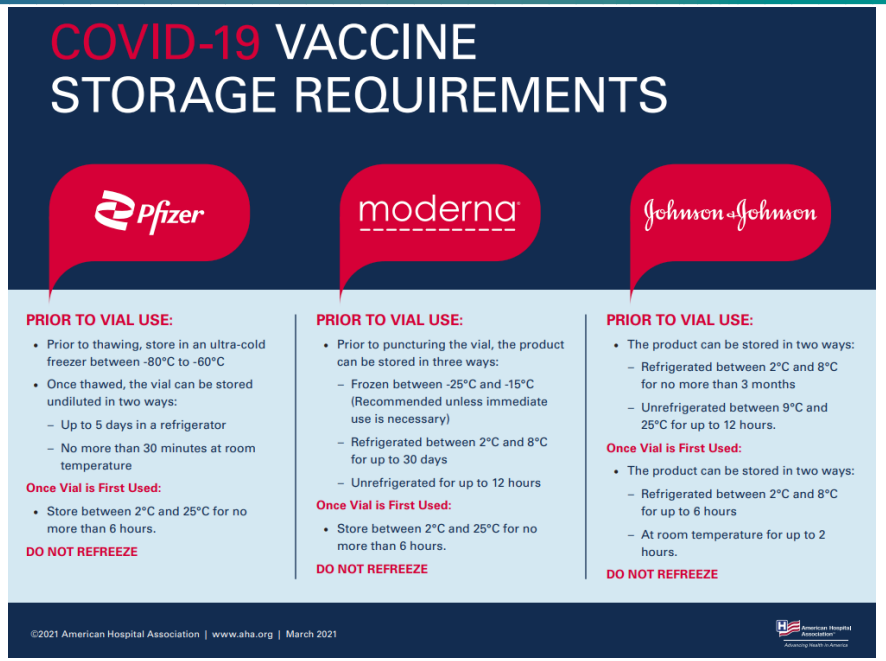
Agenda

- 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

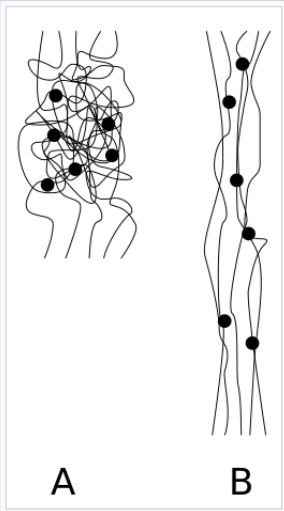
- Loss of elastomer elasticity below Tg
  - Sealing failures are temporary
- Increased risk for breakage due to liquid expansion

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*

Risk Assessment: Phased Approach

Screen for Form/Fit issues at 'standard' conditions

- Machinability studies
- Stacked Tolerance Analysis

Confirm & Develop frozen use conditions

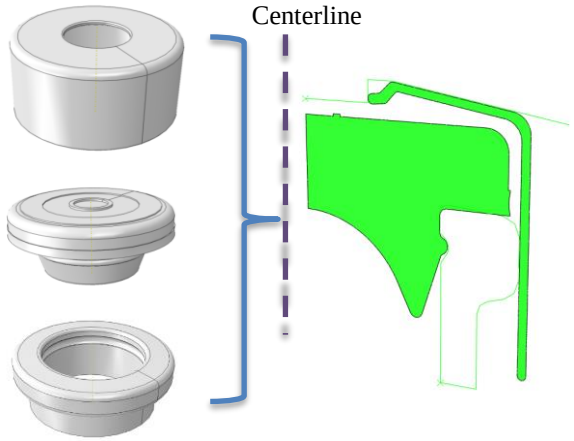
- Identify lower temp. bound in storage and shipping
- Understand supply chain risk points
  - Impact of Shipping Hazards
  - Temperature transitions

Apply a world view in the scale up process

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

Screening: CAE

Characterize component Materials of Construction as inputs to computer aided engineering and modelling

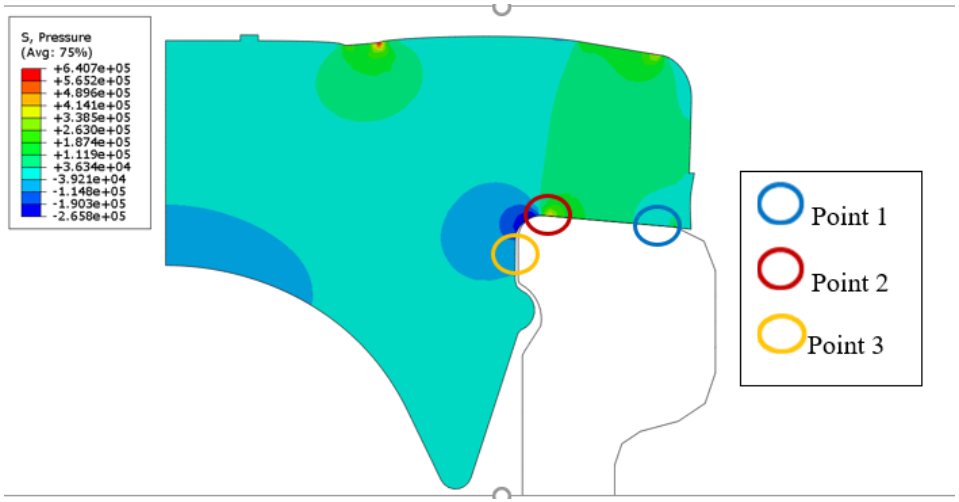


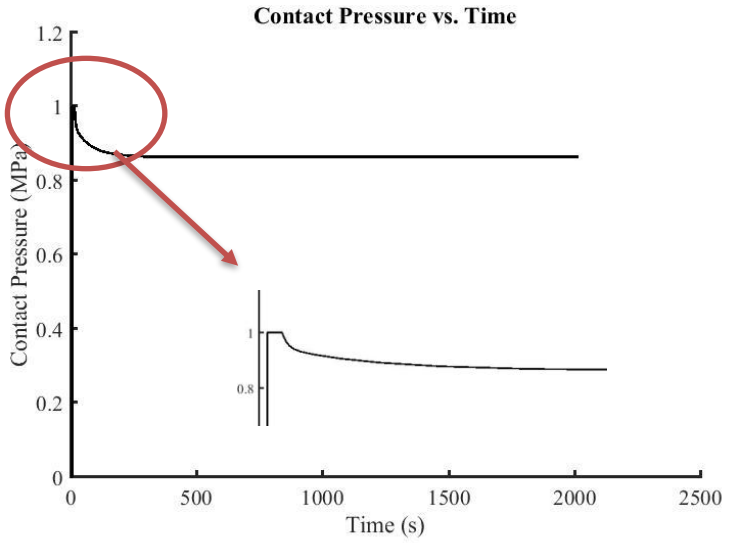
Vials	***Elastomer***	***Seals***
Assumed to be a rigid body	• Viscoelastic characterization > T_g • Elasto-plastic characterization < T_g	• T_g • CTE • Poisson

Screening: CAE

Evaluate contact pressure

- Include lower temperature bound
- Consider shelf life





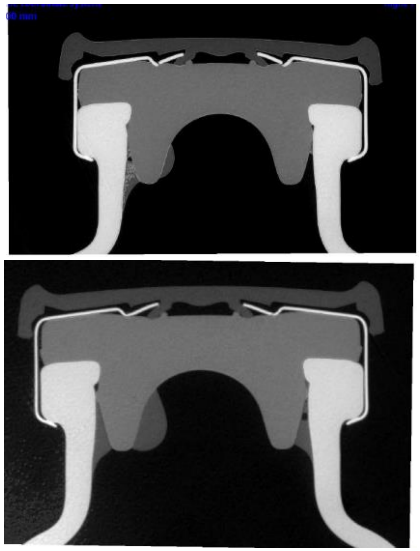
	Contact pressure (MPa)	Contact force (N)
Maximum	1	25.7
Relaxed	0.864	22.2

Development: CT Imaging

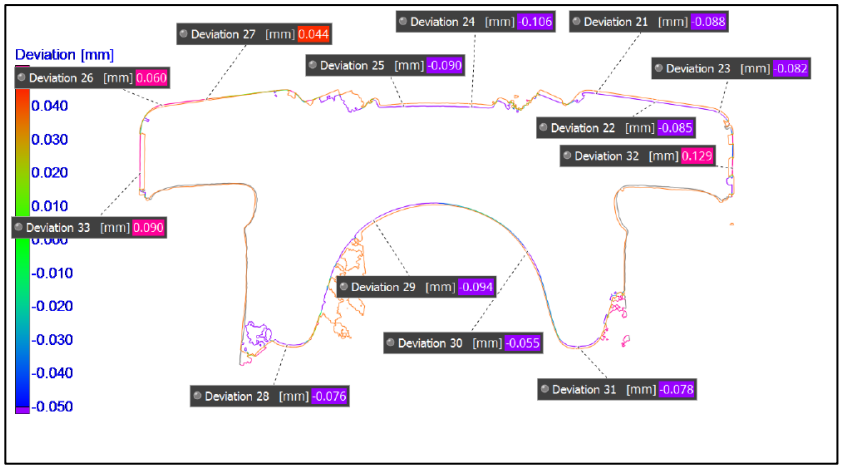
Confirm modeling assumptions via CT x-ray

– Look for variance between normal conditions and frozen

Pre-Freeze



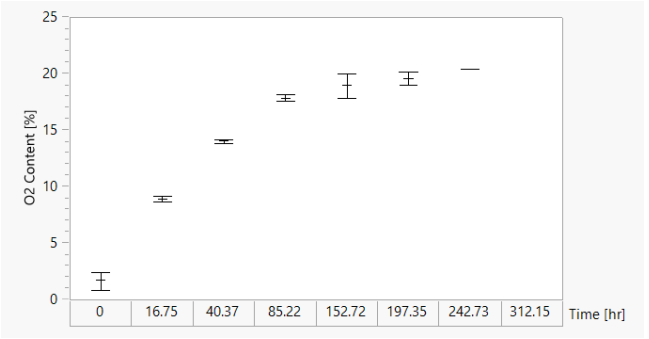
Frozen



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

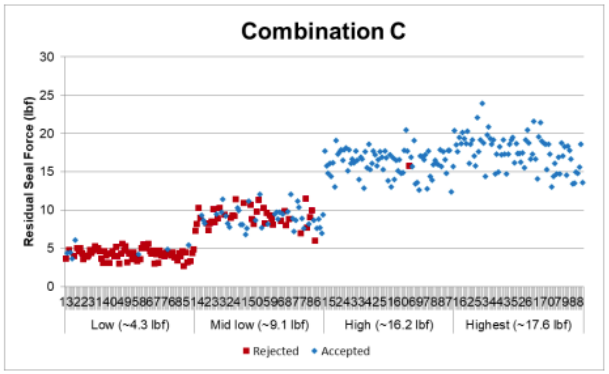
Development: Seal Quality Test

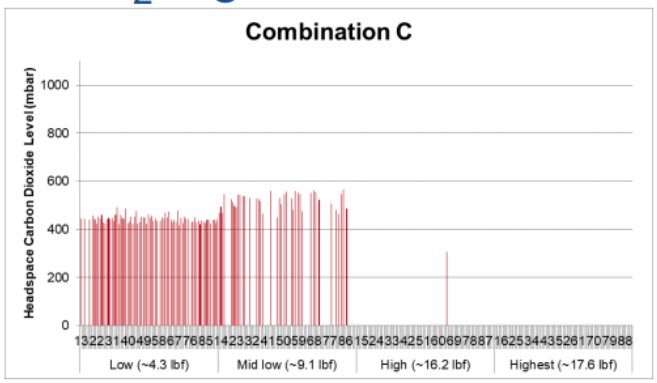
Developing a Readily Available Primary Packaging System for Use in an Ultra-Cold Chain for COVID19 Vaccine Global Distribution – Using a Scientific Approach

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

2021 PDA Parenteral Packaging Conference

Combination C: RSF and CO_2 ingress results





- Vial-stopper combination C: 1 week storage at -80 C in a CO_2 rich environment
- 73 of 80 samples *(lowest capping setting)* 38 of 80 samples *(mid low capping setting)*, and 1 of 80 samples *(high capping setting)* measured increased CO_2 levels, indicating loss of CCI during cold storage

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

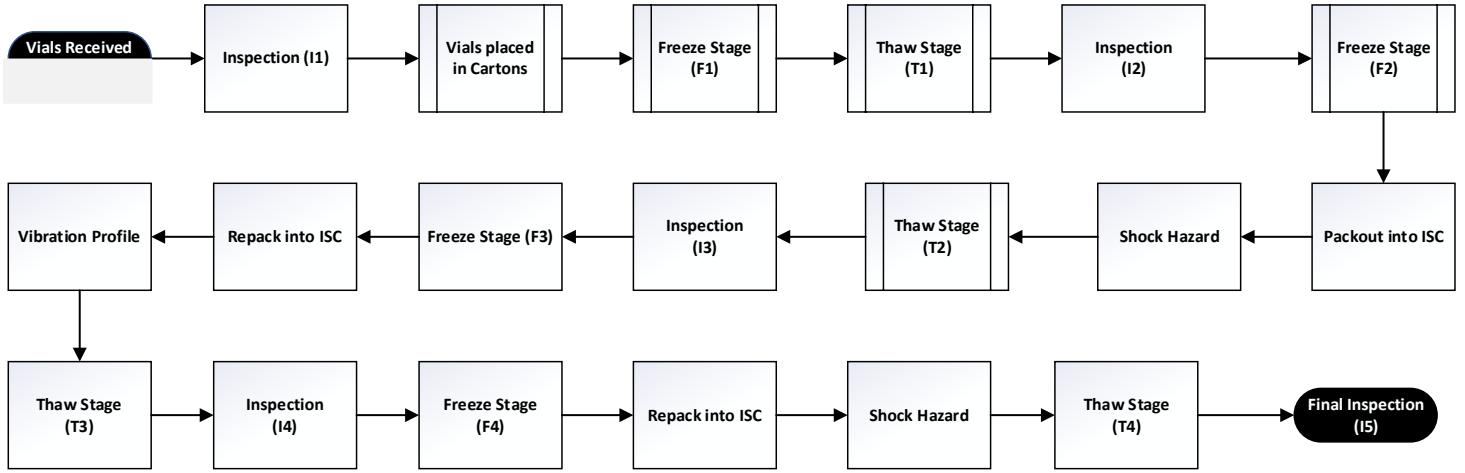
DOE considerations

- 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
  - Design and Systemic Concerns
  - Is it possible?
- Confirm and develop
  - Establish baseline suitability
  - Focus on the destination
- Scale up
  - Expand the system boundary for risk
  - Focus on the journey

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