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

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COVID-19 VACCINE STORAGE REQUIREMENTS

P fizer	moderna	Johnson Johnson
PRIOR TO VIAL USE:	PRIOR TO VIAL USE:	PRIOR TO VIAL USE:
 Prior to thawing, store in an ultra-cold freezer between -80°C to -60°C Once thawed, the vial can be stored undiluted in two ways: Up to 5 days in a refrigerator No more than 30 minutes at room temperature Once Vial is First Used: Store between 2°C and 25°C for no more than 6 hours. 	 Prior to puncturing the vial, the product can be stored in three ways: Frozen between -25°C and -15°C (Recommended unless immediate use is necessary) Refrigerated between 2°C and 8°C for up to 30 days Unrefrigerated for up to 12 hours Once Vial is First Used: Store between 2°C and 28°C for no 	 The product can be stored in two way Refrigerated between 2°C and 8°C for no more than 3 months Unrefrigerated between 9°C and 25°C for up to 12 hours. Once Vial is First Used: The product can be stored in two way Refrigerated between 2°C and 8°C for up to 6 hours
DO NOT REFREEZE	DO NOT REFREEZE	 At room temperature for up to 2 hours. DO NOT REFREEZE



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Risk Assessment: Suitability Hazards

Protection Risk

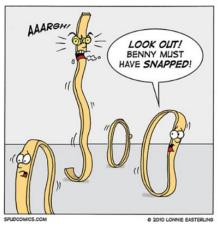
- Loss of elastomer elasticity below Tg
- Increased risk for breakage due to liquid expansion
- Difference of CTE (coefficient of thermal expansion)

Performance Risk

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

Safety & Compatibility

- Frozen conditions favorable for DP stability and E/L







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				
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 **Stopper Seal Commodity** Vial Commodity

Form fit: Component Stack Tolerances

CAE / Modeling: characterize component Materials of Construction as inputs

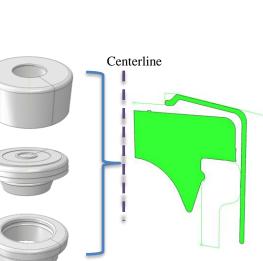
<u>Vials</u> Assumed to be a rigid body

Elastomer Viscoelastic characterization > T_{a} Elasto-plastic

characterization $< T_{a}$



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3: Neck DD

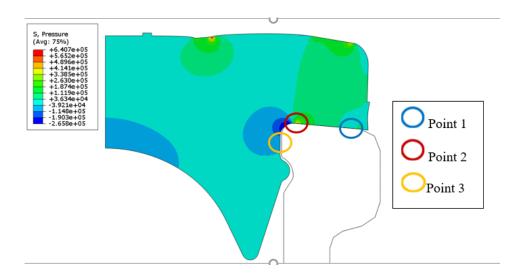


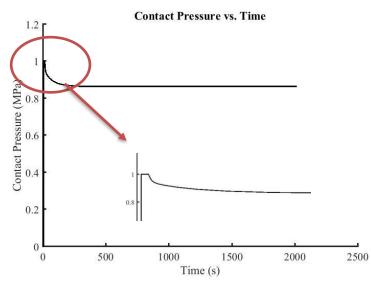


Screening: CAE

Evaluate contact pressure

- Consider shelf life
- Consider temperature





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

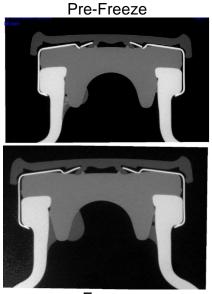


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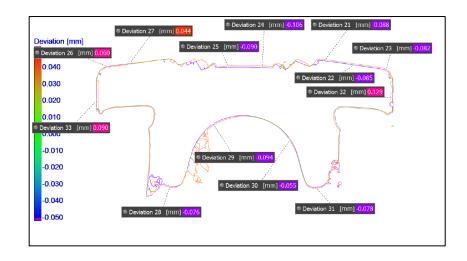
Development: CT Imaging

Confirm modeling assumptions via CT x-ray

- Look for variance between normal conditions and frozen



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 °C, headspace underpressure
- Stopper loose elasticity, interface gaps
- CO₂ in headspace
- Warm up, stopper reseals
- CO₂ trapped





Scale Up: Approach

Shift the focus from systemic to residual risk

- Transition from design \rightarrow process
- Emphasize control strategy development
 - Consider incoming, filling, and transit
 - Incorporate 2° 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)

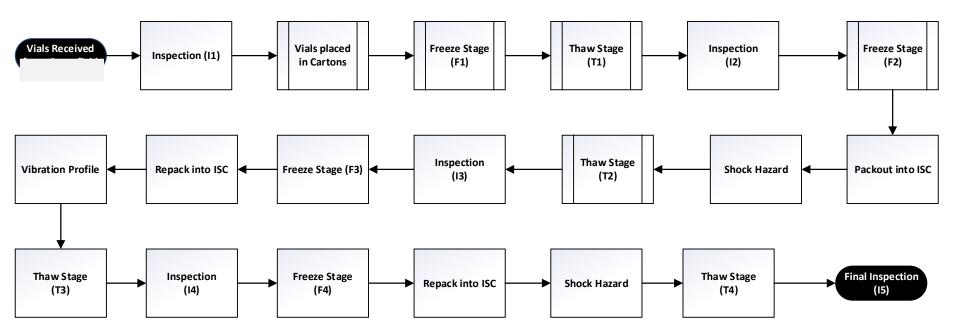




Scale Up: Process Mapping

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

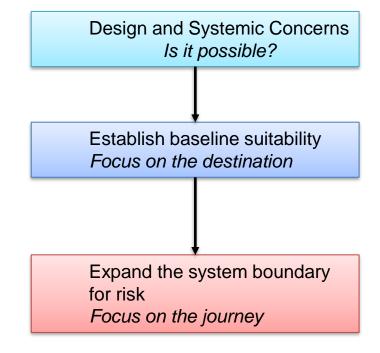
- Machinability studies
- Stacked Tolerance Analysis

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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