

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

- 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

Opportunities for extended expiry

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

COVID-19 VACCINE STORAGE REQUIREMENTS

Pfizer

moderna

Johnson & Johnson

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.

DO NOT REFREEZE

PRIOR TO VIAL USE:

- 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 25°C for no more than 6 hours.

DO NOT REFREEZE

PRIOR TO VIAL USE:

- The product can be stored in two ways:
 - 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 ways:
 - Refrigerated between 2°C and 8°C for up to 6 hours
 - At room temperature for up to 2 hours.

DO NOT REFREEZE

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Risk Assessment: Suitability Hazards

Protection Risk

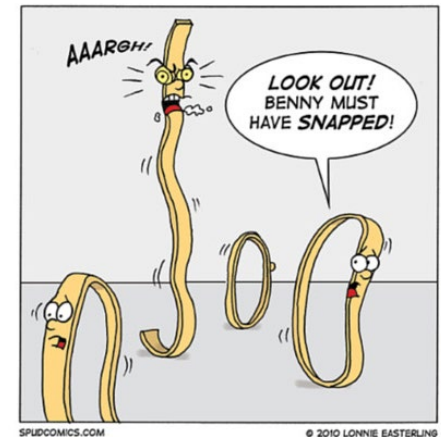
- Loss of elastomer elasticity below T_g
- Increased risk for breakage due to liquid expansion
- Difference of CTE (coefficient of thermal expansion)

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				
Focus				

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

Screening: Form / Fit + Computed Aided Engineering

Form fit: Component Stack Tolerances

Stopper Seal Commodity



Vial Commodity



CAE / Modeling: characterize component Materials of Construction as inputs

Vials

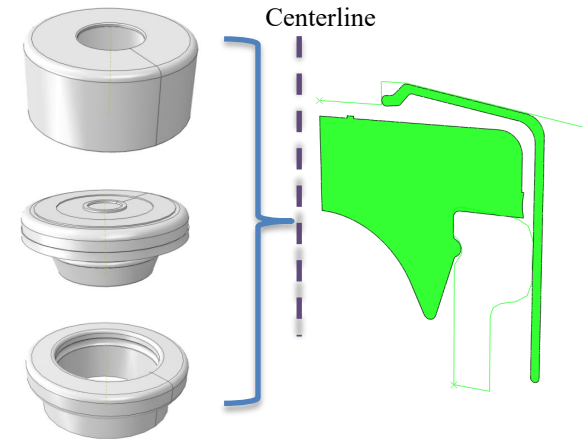
Assumed to be a rigid body

Elastomer

- Viscoelastic characterization $> T_g$
- Elasto-plastic characterization $< T_g$

Seals

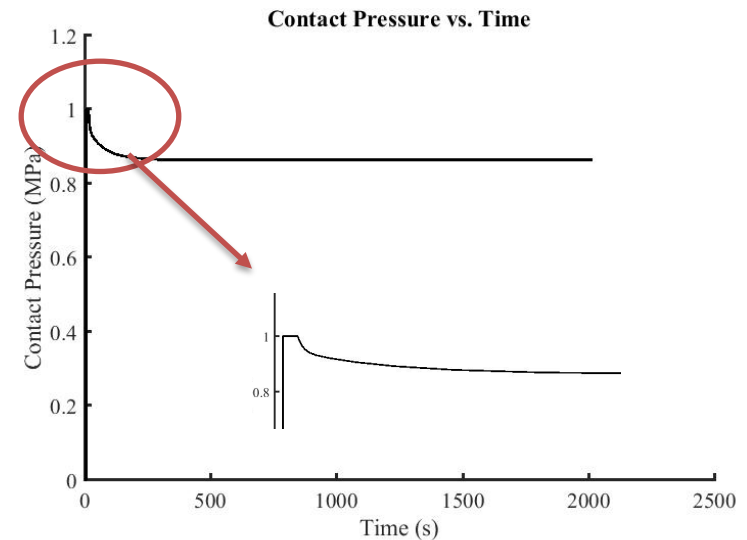
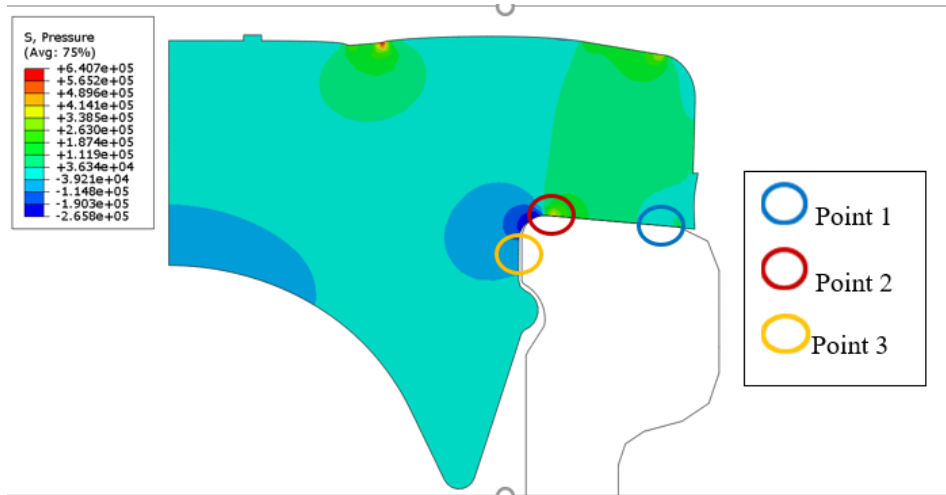
- T_g
- CTE
- Poisson



Screening: CAE

Evaluate contact pressure

- Consider shelf life
- Consider temperature



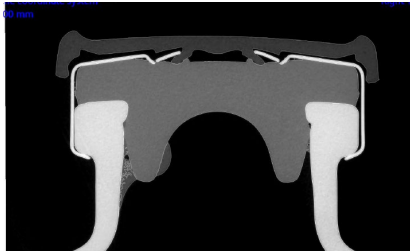
	Contact pressure (MPa)	Contact force (N)
Maximum	1	25.7
Relaxed	0.864	22.2

Development: CT Imaging

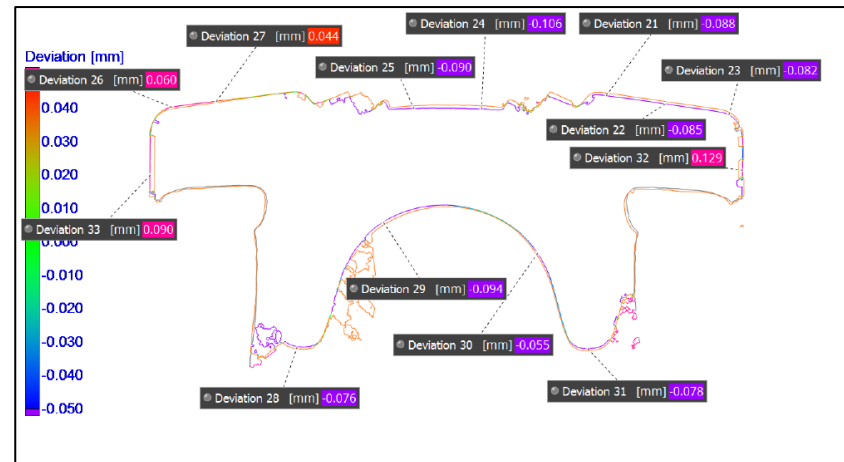
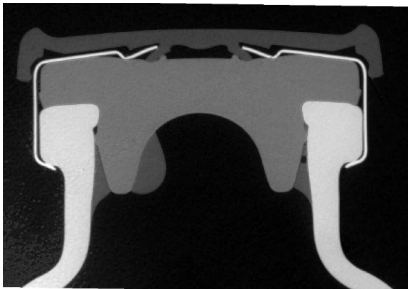
Confirm modeling assumptions via CT x-ray

- 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 °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 → 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

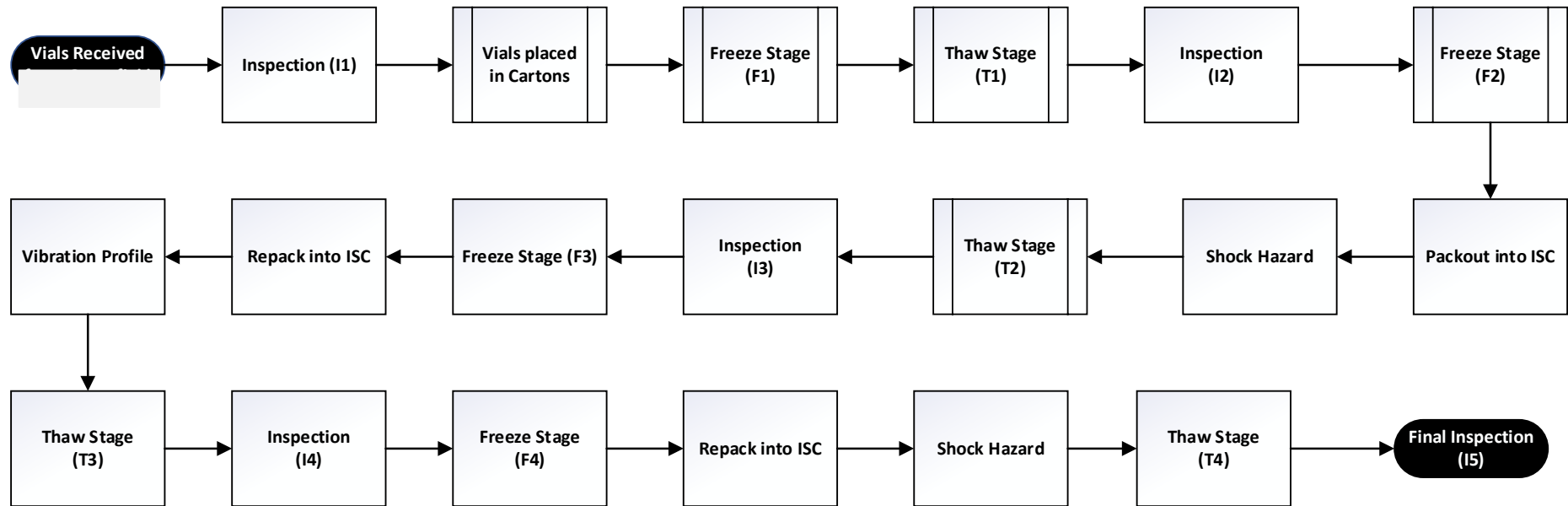
DOE considerations

- 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

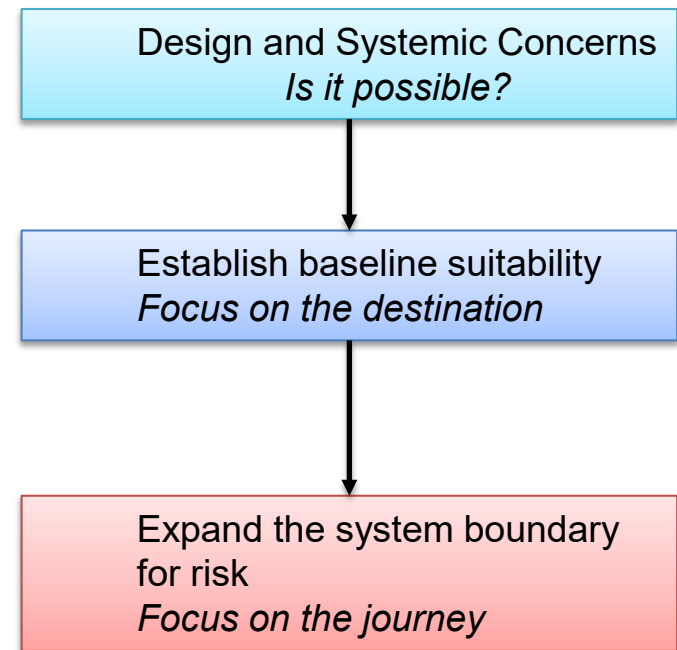
- Machinability studies
- Stacked Tolerance Analysis

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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