

# *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



### 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**

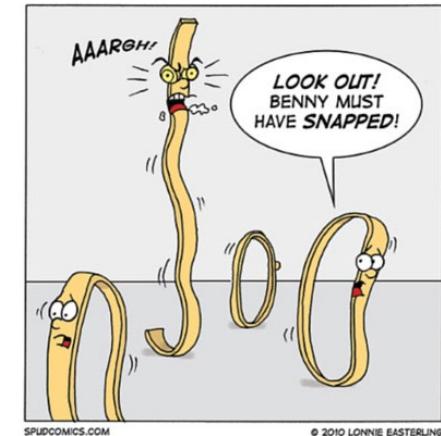
- Loss of elastomer elasticity below Tg
- Increased risk for breakage due to liquid expansion
- Difference of CTE (coefficient of thermal expansion)

## **Performance Risk**

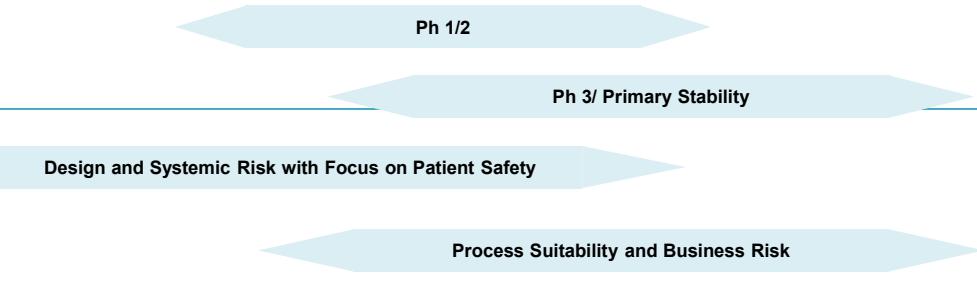
- Mechanical/thermal stresses of shipping
- Thermal stresses of processing streams
- In-use performance after thawing

## **Safety & Compatibility**

- Frozen conditions favorable for DP stability and E/L



# Risk Assessment: Phased Approach

Stage Description	Screen	Confirm	Develop	Scale Up
<b>Activities</b>	<ul style="list-style-type: none"> <li>• Form/Fit Concerns</li> <li>• Finite Element Analysis</li> </ul>	<ul style="list-style-type: none"> <li>• In-Use conditions</li> <li>• CT X-Ray</li> <li>• Inherent Leak (HeLD)</li> </ul>	<ul style="list-style-type: none"> <li>• Head Space Analysis</li> <li>• Stability</li> <li>• Shipping Hazards</li> </ul>	<ul style="list-style-type: none"> <li>• Process Mapping</li> <li>• Structural Integrity</li> </ul>
<b>Phase</b>				
<b>Focus</b>	 <p>Design and Systemic Risk with Focus on Patient Safety</p> <p>Process Suitability and Business Risk</p>			

- 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

The screenshot shows the Livin' Item Tailor software interface. On the left, a 3D model of a necktie is displayed with dimensions A, B, and C labeled. On the right, a table of dimensions is shown:

Dimension	Min.	Max.	Min.	Max.	Min.	Max.
B (Neck ID)	0.167	0.255	0.538	0.745	0.172	0.272

## *CAE / Modeling: characterize component Materials of Construction as inputs*

## Vials

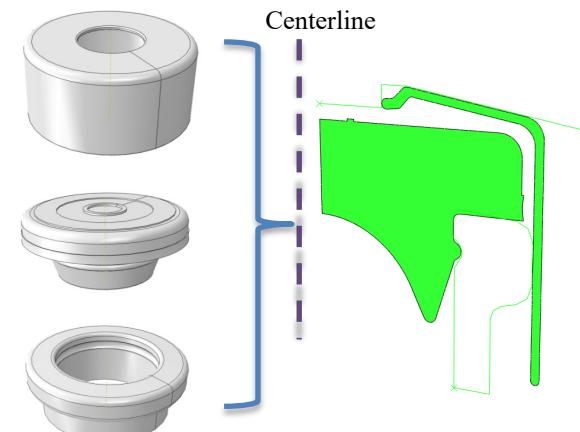
Assumed to be a rigid body

## **Elastomer**

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

## Seals

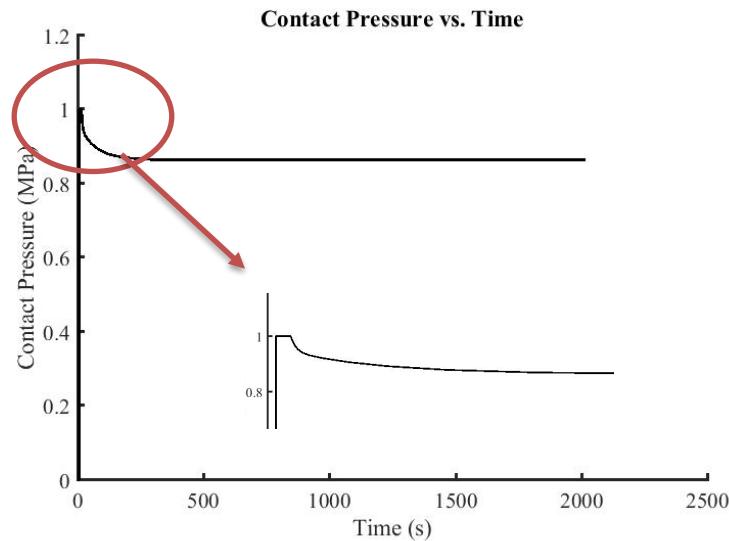
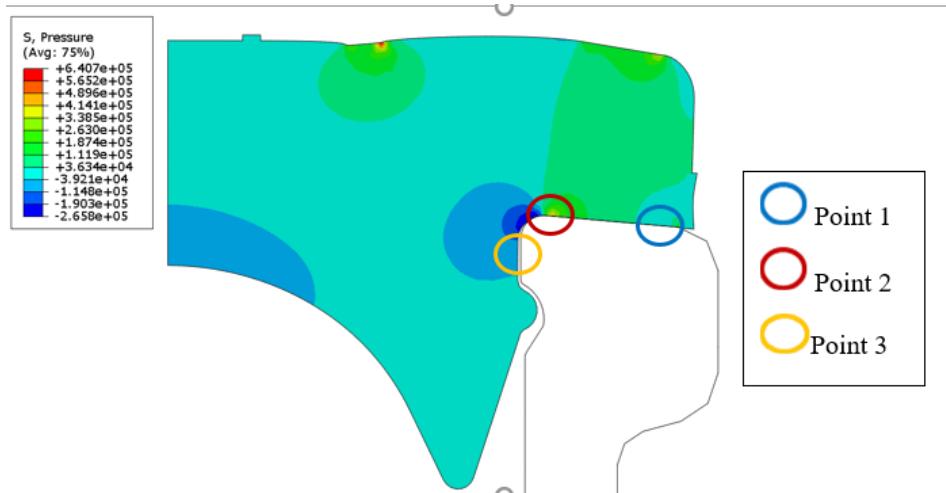
- $T_g$
- CTE
- Poisson



# Screening: CAE

## ***Evaluate contact pressure***

- Consider shelf life
- Consider temperature



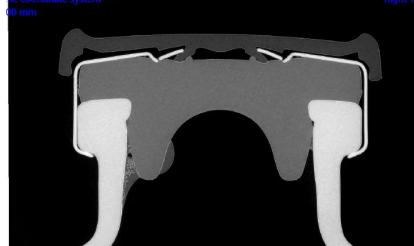
	Contact pressure (MPa)	Contact force (N)
Maximum	1	25.7
Relaxed	0.864	22.2

# Development: CT Imaging

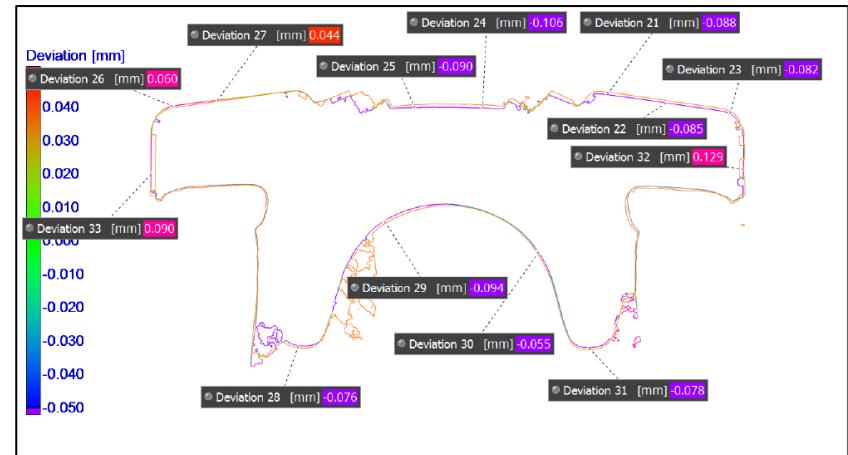
***Confirm modeling assumptions via CT x-ray***

– Look for variance between normal conditions and frozen

Pre-Freeze



Frozen



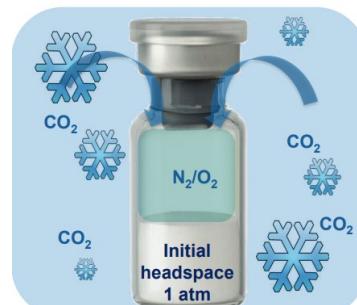
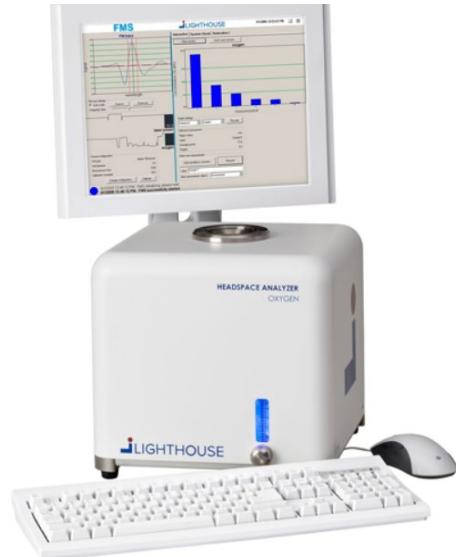
# Development: CCI

## 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



- $-78^{\circ}\text{C}$ , headspace underpressure
- Stopper loose elasticity, interface gaps
- $\text{CO}_2$  in headspace
- Warm up, stopper reseals
- $\text{CO}_2$  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

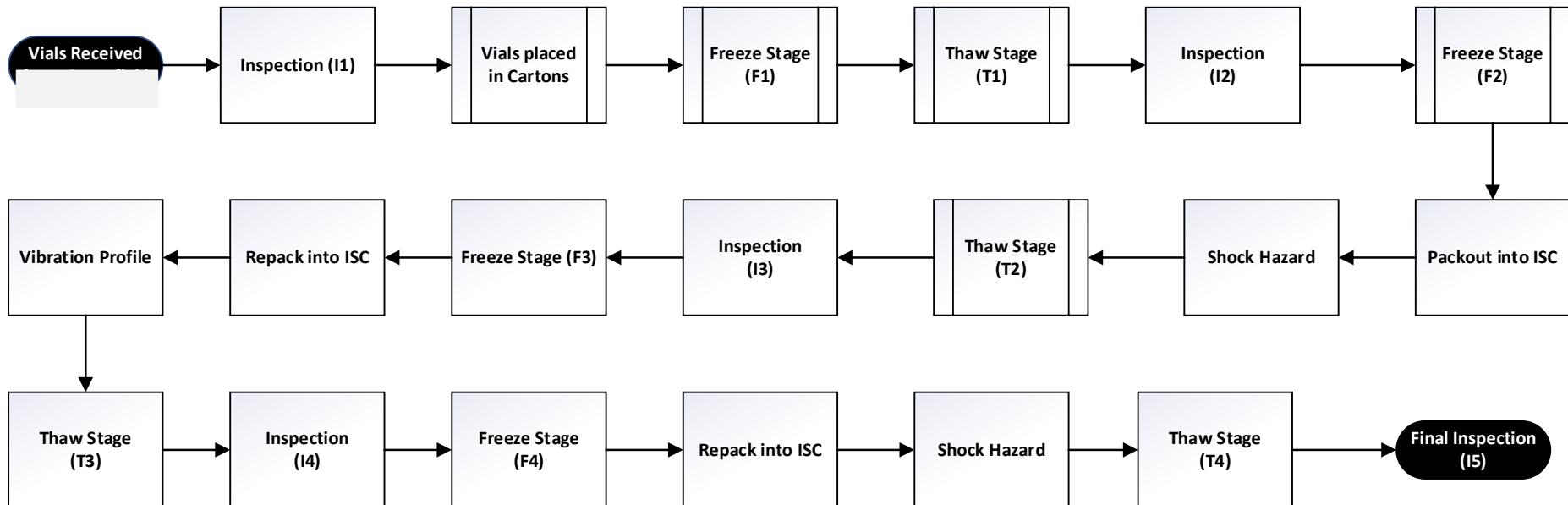
## ***DOE considerations***

- 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

Design and Systemic Concerns  
*Is it possible?*

Establish baseline suitability  
*Focus on the destination*

Expand the system boundary  
 for risk  
*Focus on the journey*

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