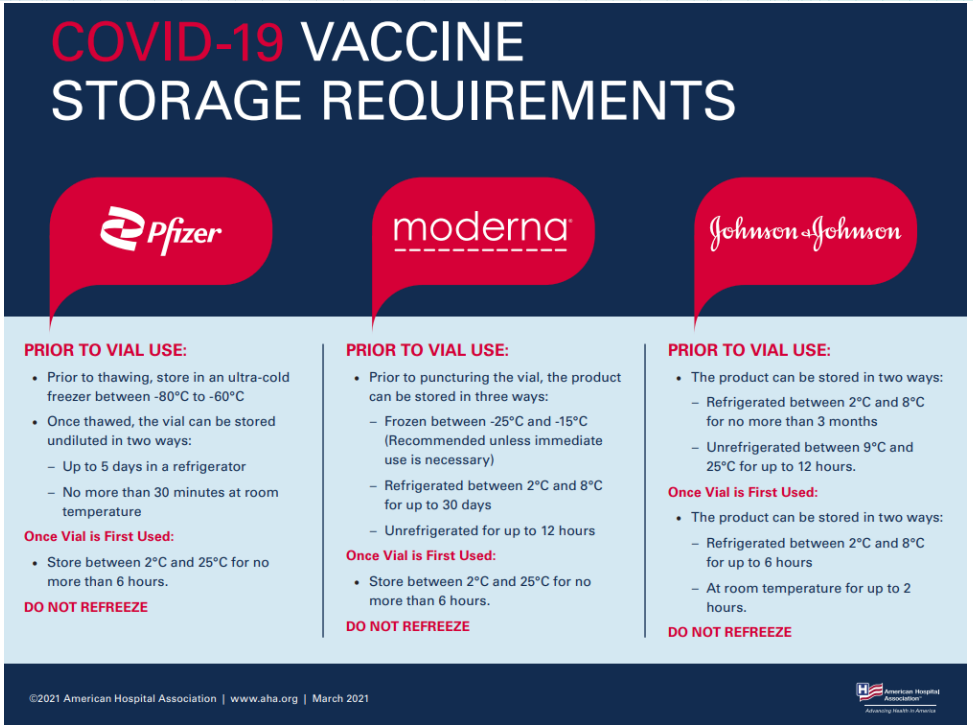
Case Study: Systemic Evaluation of Vial Container Closure System Suitability at Frozen Conditions

- Christiana Oh, Ph.D., Eli Lilly and Company
- 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

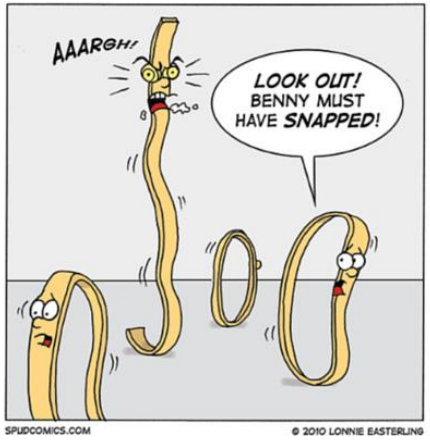
- Loss of elastomer elasticity below Tg
- Increased risk for breakage due to liquid expansion
- Difference of CTE (coefficient of thermal expansion)

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



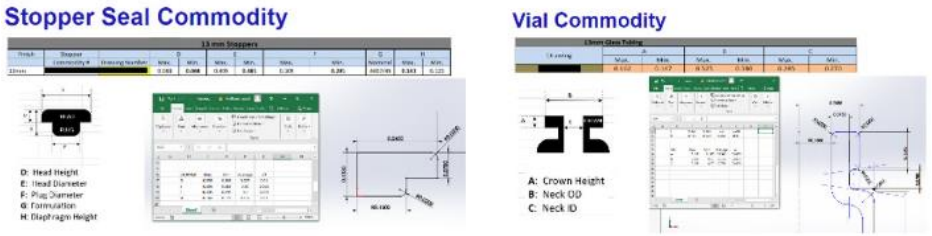
Risk Assessment: Phased Approach

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** **Ph 3/ Primary Stability**			
Focus	**Design and Systemic Risk with Focus on Patient Safety** **Process Suitability and Business Risk**			

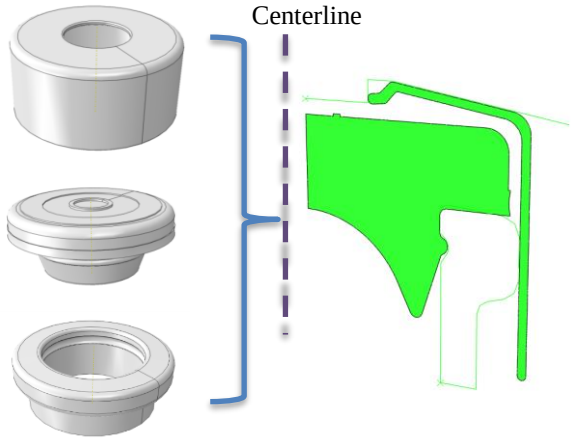
- *Right size the approach*
- *Gate transitions between phases*
- *Expand the system boundaries*

Screening: Form / Fit + Computed Aided Engineering

Form fit: Component Stack Tolerances



CAE / Modeling: characterize component Materials of Construction as inputs

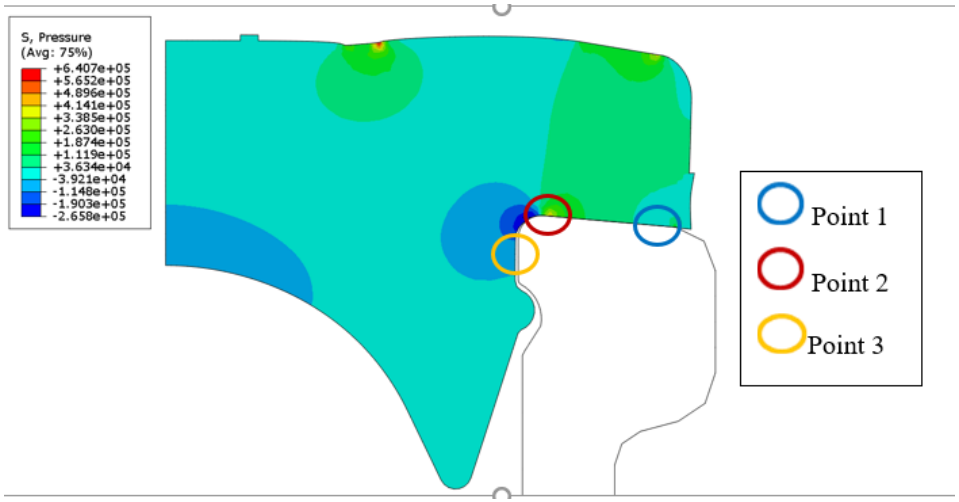


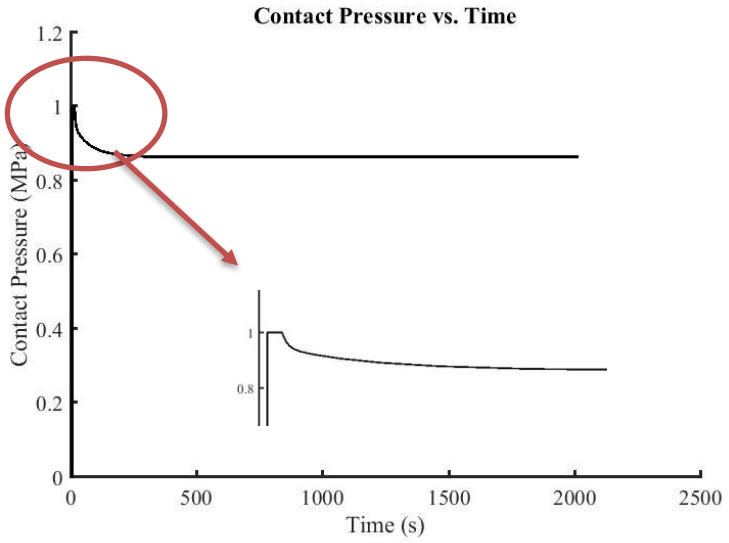
Vials	***Elastomer***	***Seals***
Assumed to be a rigid body	• Viscoelastic characterization > T_g • Elasto-plastic characterization < T_g	• T_g • CTE • Poisson

Screening: CAE

Evaluate contact pressure

- Consider shelf life
- Consider temperature





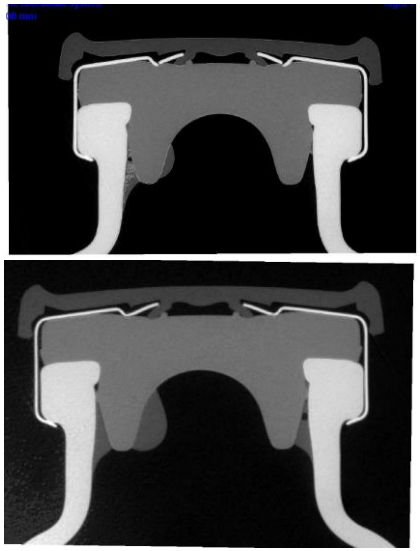
	Contact pressure (MPa)	Contact force (N)
Maximum	1	25.7
Relaxed	0.864	22.2

Development: CT Imaging

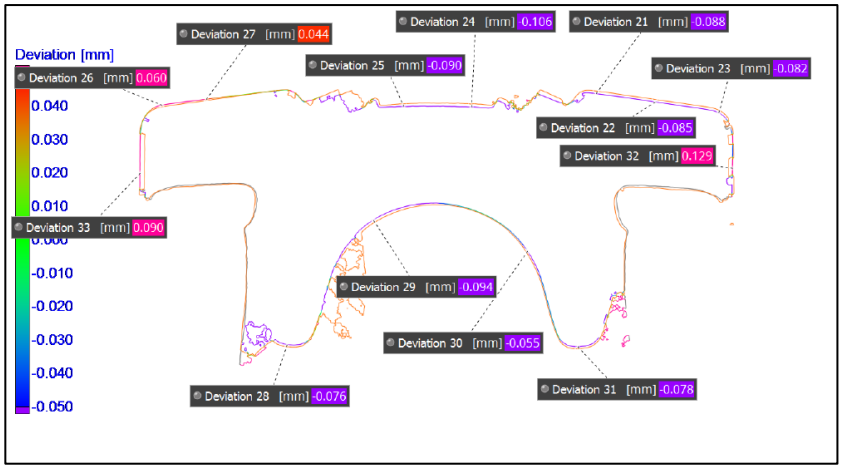
Confirm modeling assumptions via CT x-ray

– Look for variance between normal conditions and frozen

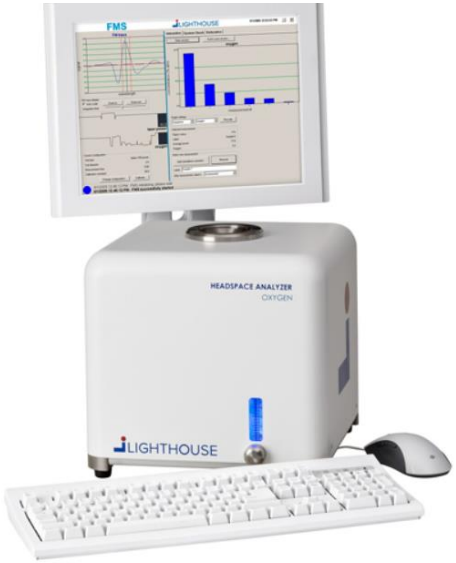
Pre-Freeze



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

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

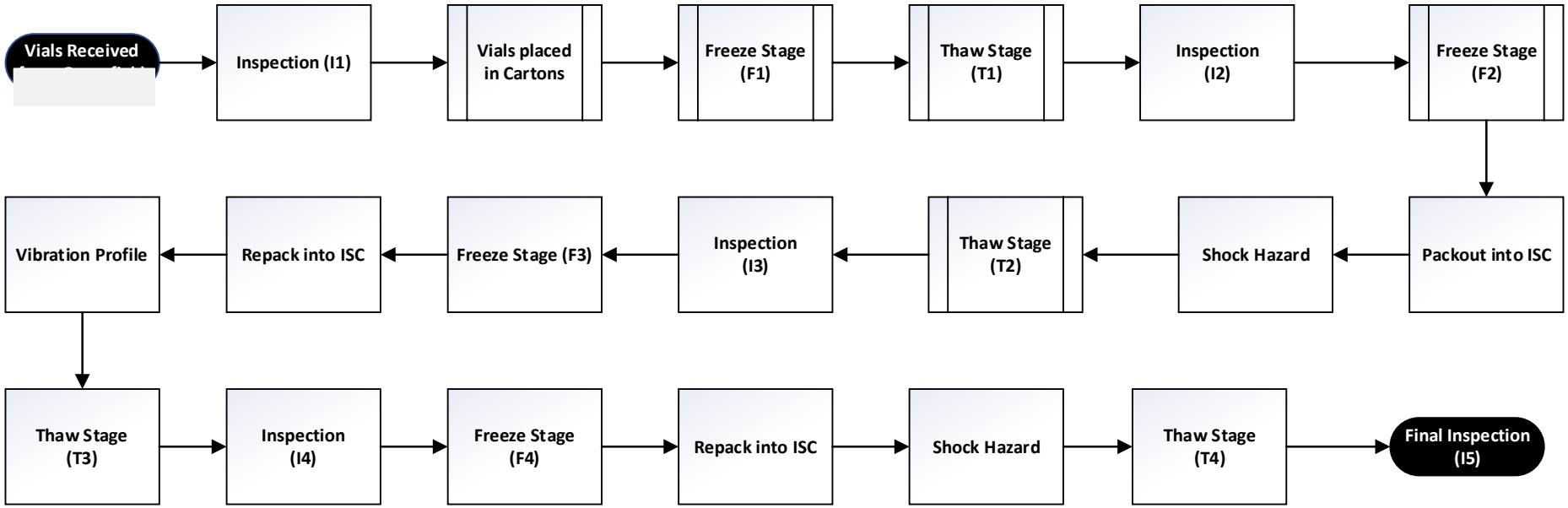
DOE considerations

- 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**

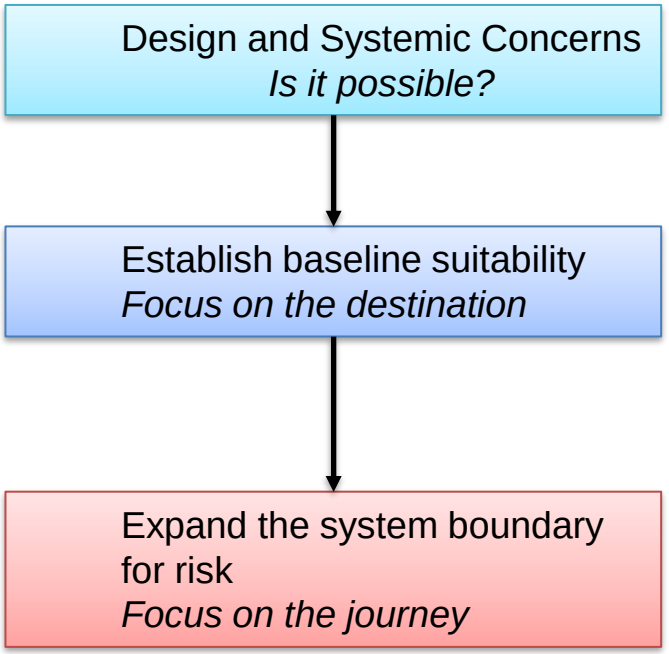
- Machinability studies
- Stacked Tolerance Analysis

***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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