Developing Cryogenic Parenteral Packaging Solutions

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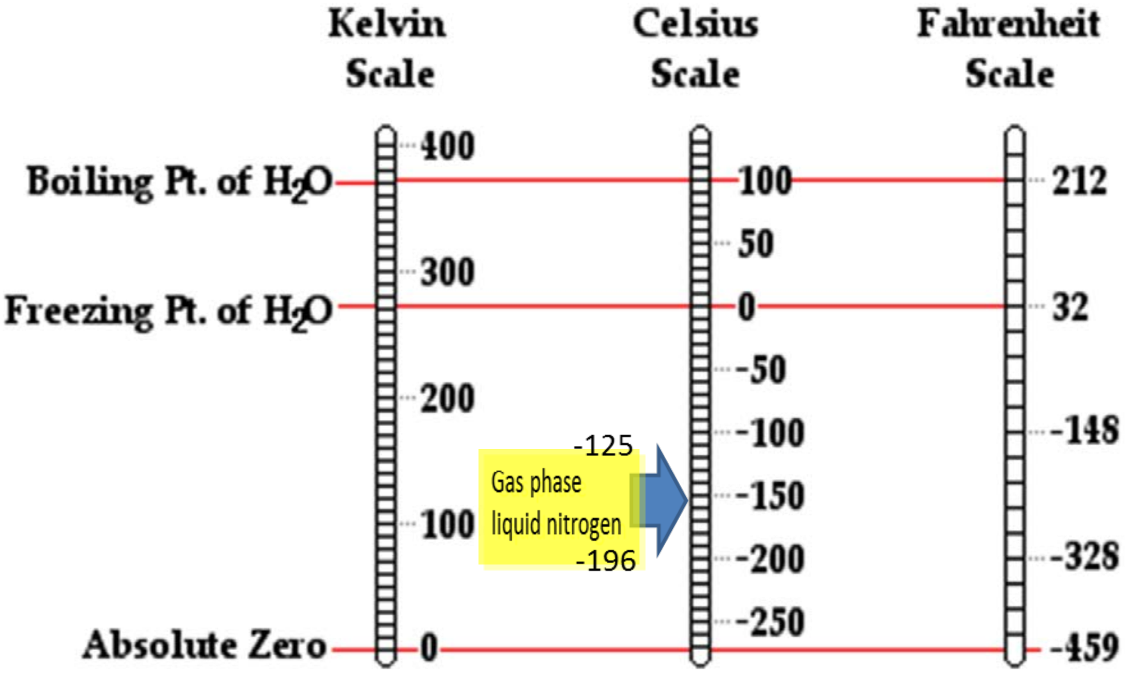
Cryogenic Packaging

…protecting products at very low temperatures.

Dry ice temperatures are approximately -60 to -80 degrees C.

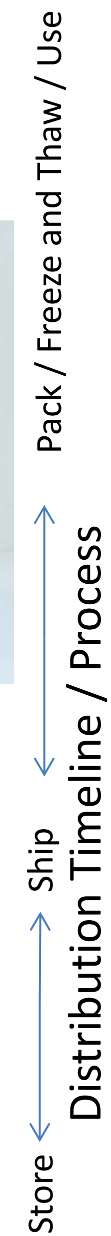
CP can be considered both dry ice and LN2.



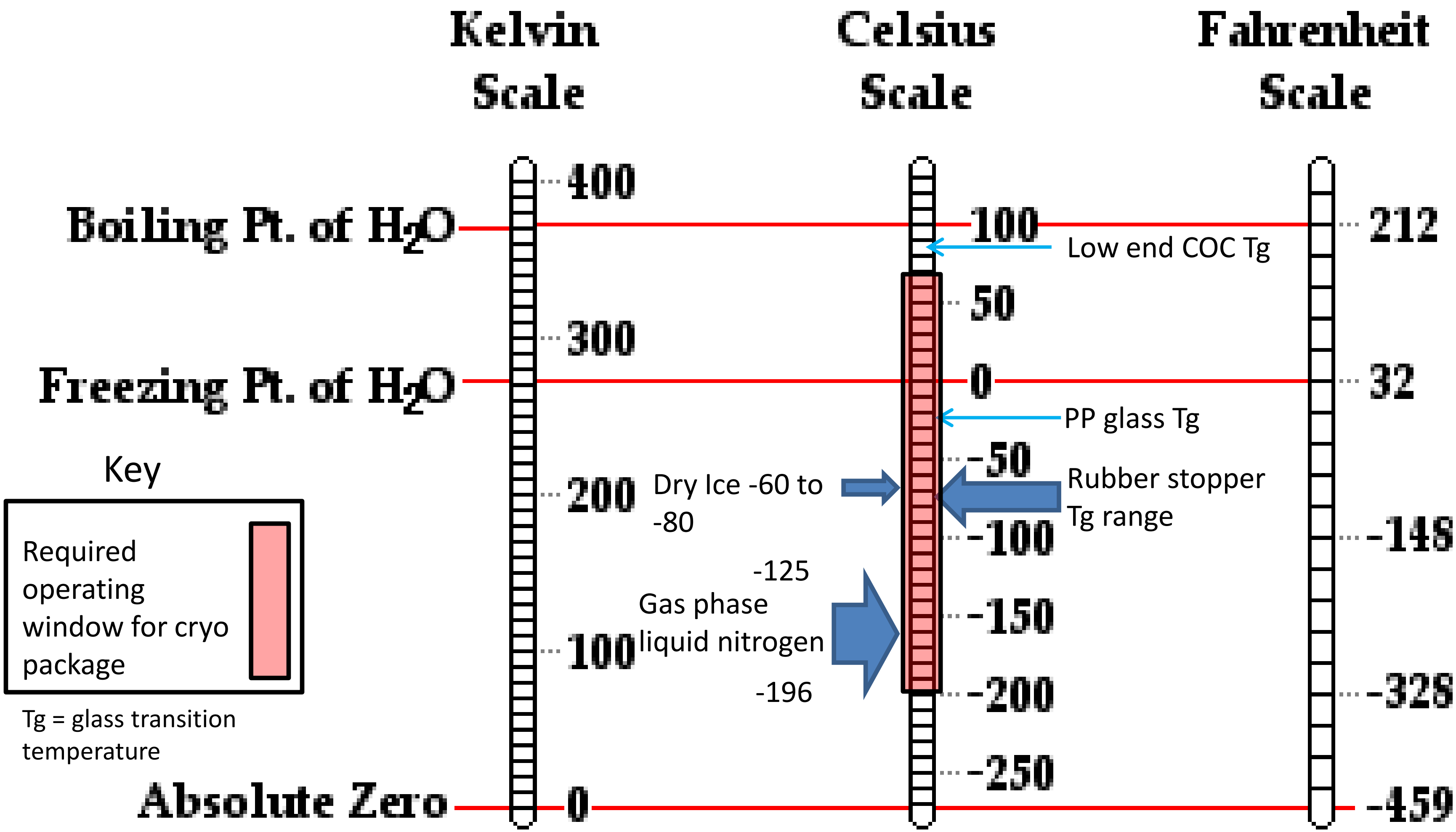
- Common CP issues: <u>labels don't adhere, pouch seals separate, parenteral vials lose integrity</u>
- Three primary uses for CP: primary cell, stem cell, and immunotherapy
- Overall, the CP industry is estimated to be growing at an annual rate of <u>20-35%</u>

Cryogenic Packaging

- Primary – specialized packages that are moved and stored in active and passive systems
- Dewer – thermos-like passive storage and transportation
- Cryofrig – active



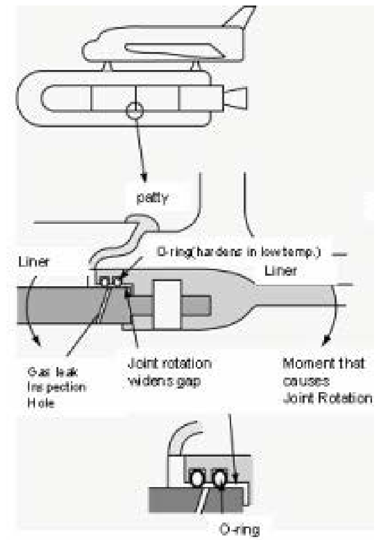
Physical Effects of Extreme Low Temperatures



Physical Effects of Extreme Low Temperatures – Glass Transition Temperature

Glass Transition Temperature – Tg

- The <u>reversible</u> temperature at which polymers go from flexible to brittle
- Elastomers
- Plastics

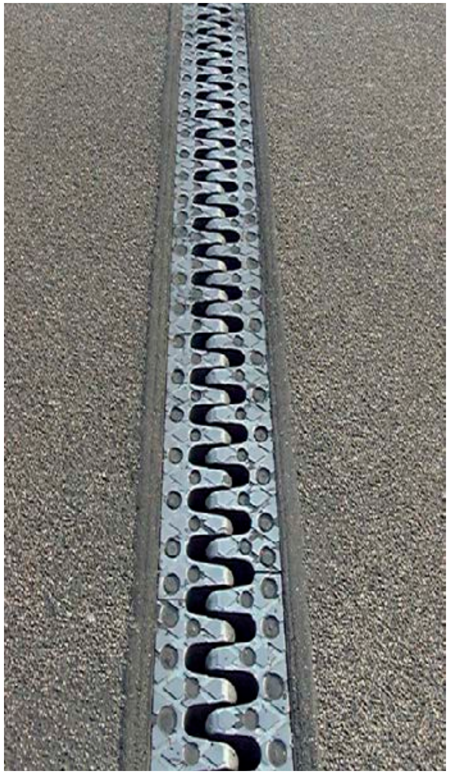


Material	Temperature (degrees C)
Common Stopper Elastomers	-60 to -80
Polypropylene	-20
Copolymer	-95
Cyclic Olefin Copolymer (COC)	80 to 180

Physical Effects of Extreme Low Temperatures – Thermal Expansion

Coefficients of Thermal Expansion

Material	Approximate Linear Temperature Expansion (Contraction) Coefficient (10-6 m / (m K))
Glass	4 - 9
Polypropylene	100 -200
Polyethylene	200?
COC / COP	60 – 70
Elastomer	115 -185
Aluminum	22.2

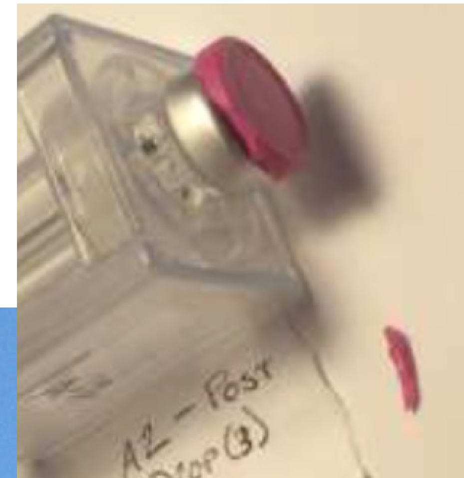


Physical Effects of Extreme Low Temperatures – Common Components

- Vial (plastic or glass)
  - Below Tg
  - Low shrinkage factor (glass)
  - Residual stress, scratching, and thermal shock
- Stopper
  - Starts above Tg
  - <u>Shrinkage greater than vial</u>
- Seal
  - Shell shrinks slightly greater than both vials
  - Button becomes brittle
  - Bridges?

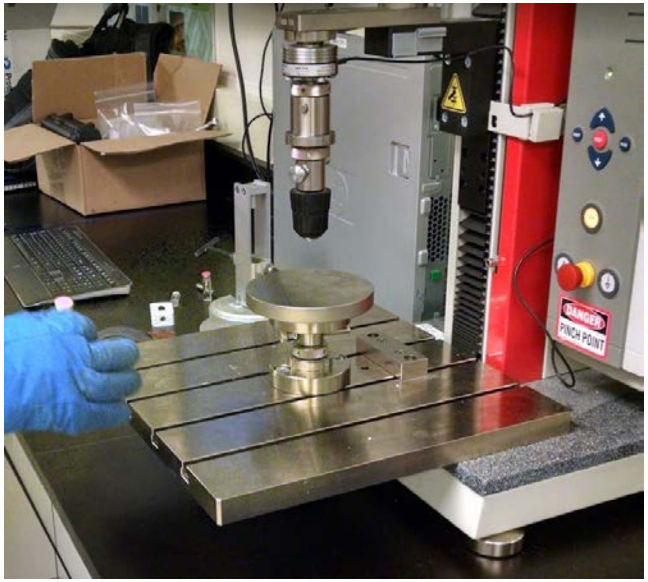
Physical Effects of Extreme Low Temperatures – Seal

- Shell shrinks between plastic and glass vials
- Button becomes brittle
- Bridges



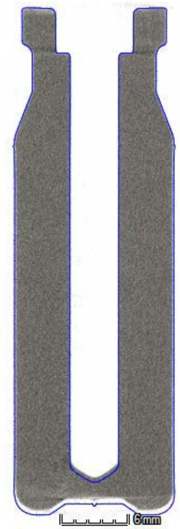
Gross Vial Cap Button / Bridge Breakage

- 20 Placebo Filled Vials
- Cryocart / Zwick Tester
  - 200 lbs for 5 seconds
    - Screw Head
    - Finger
    - Plate



Physical Effects of Extreme Low Temperatures – Vial

- Plastic or glass at ambient; <u>already</u> below Tg
- Low shrinkage factor versus “soft” plastic and elastomer
- Vial cracking: residual stress, scratching, and thermal shock

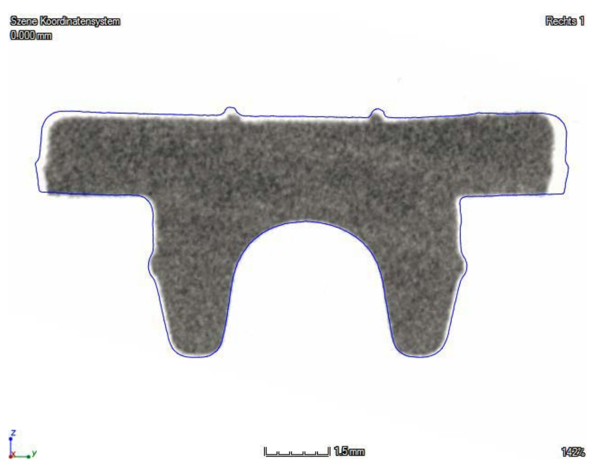


X-ray tomography image

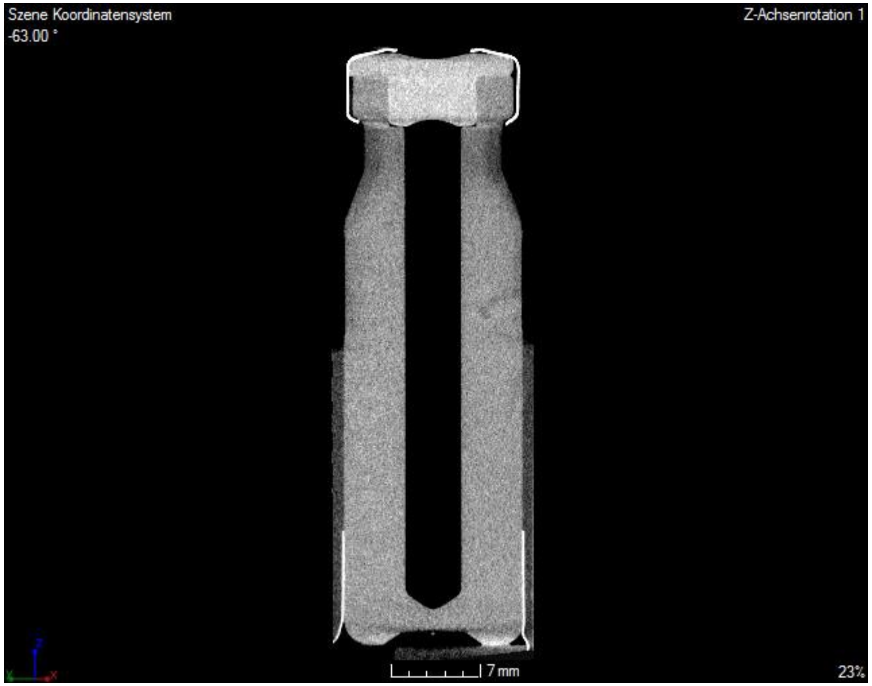
Cracked vial from extreme use conditions

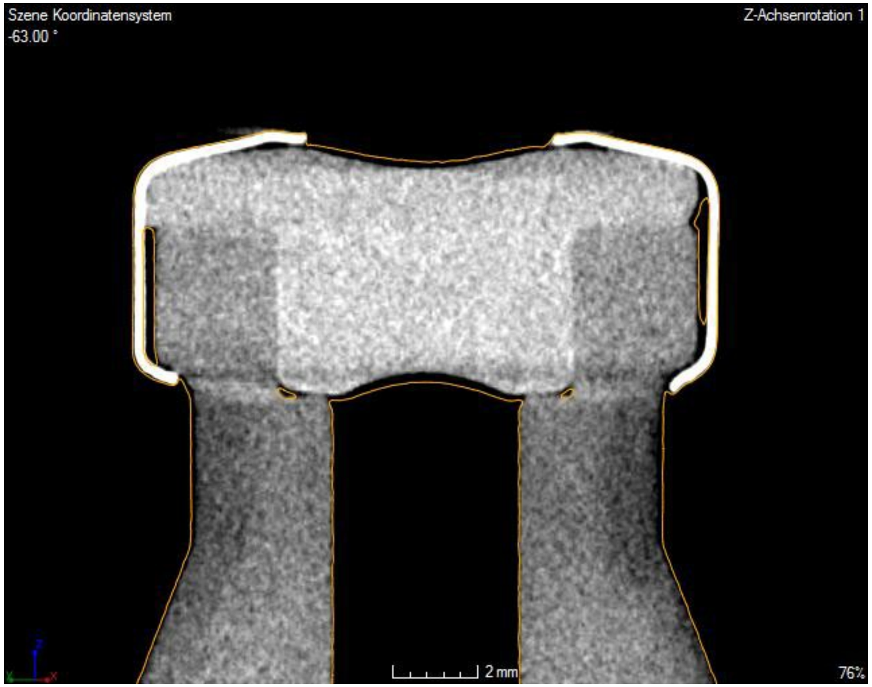
Physical Effects of Extreme Low Temperatures – Stopper

- Starts above Tg but drops below
  - Viscoelastic properties; flow and compression
  - Rose video
- Expansion / Shrinkage greater than vial



Physical Effects of Extreme Low Temperatures – Package





- X-ray tomography cross-section
- Composite image at ambient and cryo temps

Maximizing Vial-Stopper-Seal Cryo Performance - Simulation

- Two-Part Finite Element Analysis* w/ nominal components
  1. Compression / Capping**
  2. Freezing – from ambient to LN2

* - work performed by Cedric Gysel, Janssen

** - Thawing not simulated

Cryo Leak and Reseal Timeline

Freezing

- Package exposed to cryo temperatures
  - Temperature and pressure delta
- Elastomers and certain plastics reach Tg
- Gas pathways between inside and outside of package may develop
- Cold dense gas outside vials displaces warm gas inside vials
- Frozen - steady state

Thawing

- The air outside the vials is warmed or is replaced with warm / ambient air
- The elastomers and plastics warm, expand, and reseal
  - Temperature and pressure delta
  - contents

USP 1207 Guideline and Leak Effects

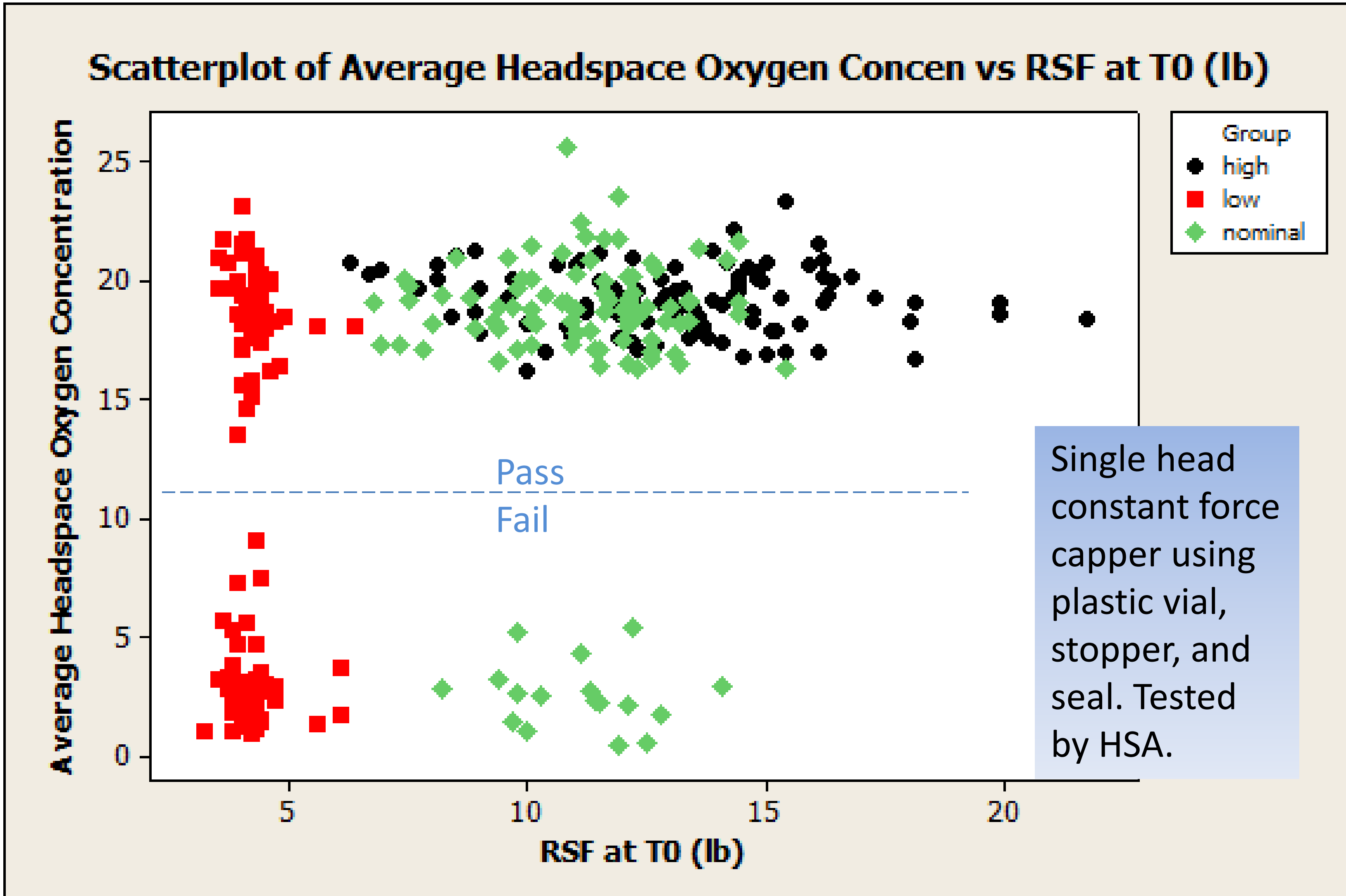
- “Sterility and Product Formulation Content must be Preserved; Gas Headspace Content Preservation is not Required”
- Nitrogen replacement of vial headspace
- Gas vs microbial leaks
  - Dry ice / CO2
  - LN2

Maximizing Cryo Performance

- "Critical factors for the maintenance of container closure integrity included appropriate design of the vial stopper and plug, relative dimensions of the stopper and vial neck giving a tight fit, as well as an appropriately tight capping and crimping process. The dimensional variability found between different vial and stopper lots as well as different specifications for the 13 mm stopper……motivates a careful selection of components. …rubber formulations with a Tg below -80 degrees C. might also have a positive effect."

PDA Journal, 2012, 66 453-465, Container / Closure Integrity Testing and the Identification of a Suitable Vial / Stopper Combination for Low-Temperature Storage at -80 degrees C, Zuleger, Werner, Kort, et al.

Maximizing Cryo Performance - Compression



Single head constant force capper using plastic vial, stopper, and seal. Tested by HSA.

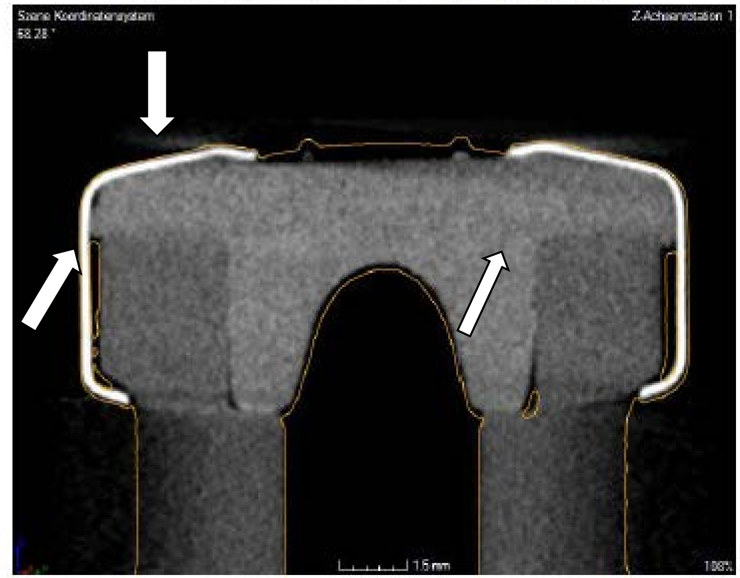
Compression Level Comparison by X-ray Tomography

Frozen vial vs. vial at RT (red line)

Phase 1b/2a Process

Vial: COC
Stopper: two-material
Cap: long skirt
RSF: <4 lbs

Frozen vial vs. vial at RT (yellow line)



Process Development- First attempt

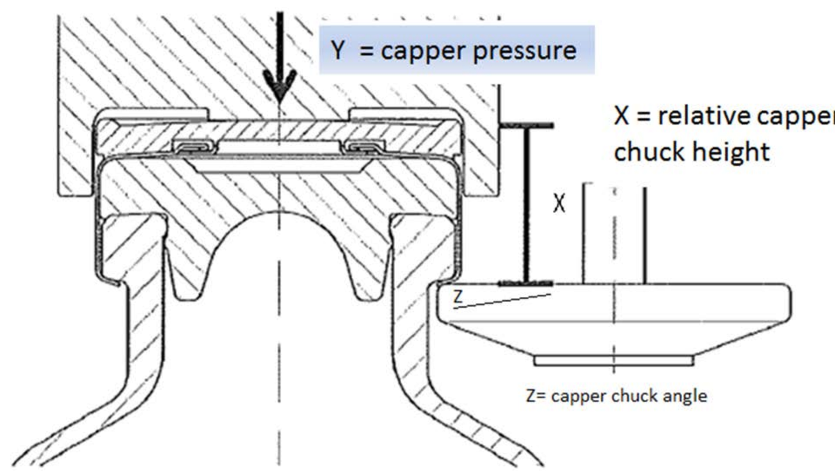
Vial: COC
Stopper: two-material
Cap: short skirt
RSF: **8-17 lbs**

Capping study performed at Genesis; X-ray tomography performed at Cilag

Maximizing Parenteral Cryo Performance – Design Equipment and Package

- Equipment variation
  - Number of heads
  - Constant force vs constant distance
  - Head angle
- Package
  - Torturous path and v-ring
  - Welding?
  - Variability
    - Injection molding vs compression
    - Number of cavities

Hooke's law for springs (rubber)
F=kx where F is force, x distance, and k the spring coefficient



Maximizing VSS Cryo Performance – Size, Tg, and Fluid Effects

- 20 mm vs 13 mm
  - Tolerance
- Glass transition
  - Elastomer facts
    - Not viscoelastic below Tg
    - Parts are smaller at LN2 temp than at ambient
  - Rubber theories
    - Shrinks when heated / grows when chilled
    - Shrinkage starts at Tg
    - Shrinkage stops at Tg

<u>20 mm flange > 13 mm flange</u>
20 mm tolerance = 13 mm tol

10 mm / 2mm = 20 percent
8 mm / 2 mm = 25 percent!
Variability of 13 mm is greater

?

Maximizing VSS Cryo Performance – Size, Tg, and Fluid Effects

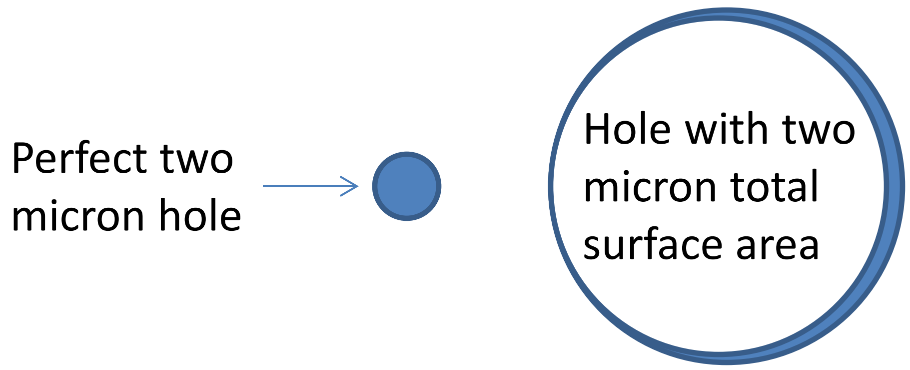
- The effect of cryo cooled contracting and expanding liquids was tested under extreme conditions (< -196 degrees C.) in a plastic vial with existing stresses

Liquid	Percent of vials cracked
Distilled water (expanding)	50 - 65
Anhydrous ethanol (contracting)	40 - 55

- Due to small sample size only large effects could be detected

Maximizing VSS Cryo Performance – Other Options

- Gas phase liquid nitrogen microbe viability?
- Filtered nitrogen?
- Tortuous and crescent vs circle path
  - Positive control holes are not real world holes
  - Gas exchange does not equal microbial ingress



Available Cryo Packages

- Thermo Scientific Nunc Cryotube
  - PE screwtop w silicone gasket
  - Polypropylene bottom
  - One-handed fill with no equipment
- Aseptic Technologies
  - COC body
  - TPE plug / stopper
  - Plug bonded to body
  - Arrive sterile and require new filling technology
- Conventional Ambient Vial / Stopper / Seal
  - Glass / plastic (COC)
  - Wide range of stoppers / seals
  - Well-known equipment and filling technology

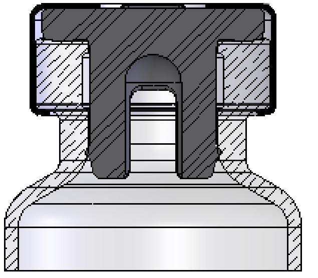
Practical Test Methods

- Equipment functionality
  - No equipment can function across range of cryo temps
  - Effects of leaks can be detected after cryo exposure
- HSA – light that passes through the vial identifies gas contents of vial
- Overpressure – in vials with reasonable head space trapped gases create increased pressure
- Helium Leak Detection – only validated to -140 which makes it acceptable for dry ice packaging
- Residual Seal Force – a tool that can measure sealing force which is positively correlated to good seals

Questions?

Residual Seal Force

- Container closure integrity of parenteral vial system, cappers, and components
  - Stopper and vial flange and compression
  - Seal failure correlation with RSF



- RSF – the reciprocal force the seal continues to exert
  - Spring
  - Compression set
- RSF Tester – exerts ^ force until stopper compresses
- Limitations
  - Doesn't measure leakage
  - Not application force
  - Total variation = component var + capper var + tester var