Pre-filled Syringe Container Closure Integrity in Deep-Cold Storage Conditions: Correlating Predictive Modeling with Empirical Data

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Purpose and Background

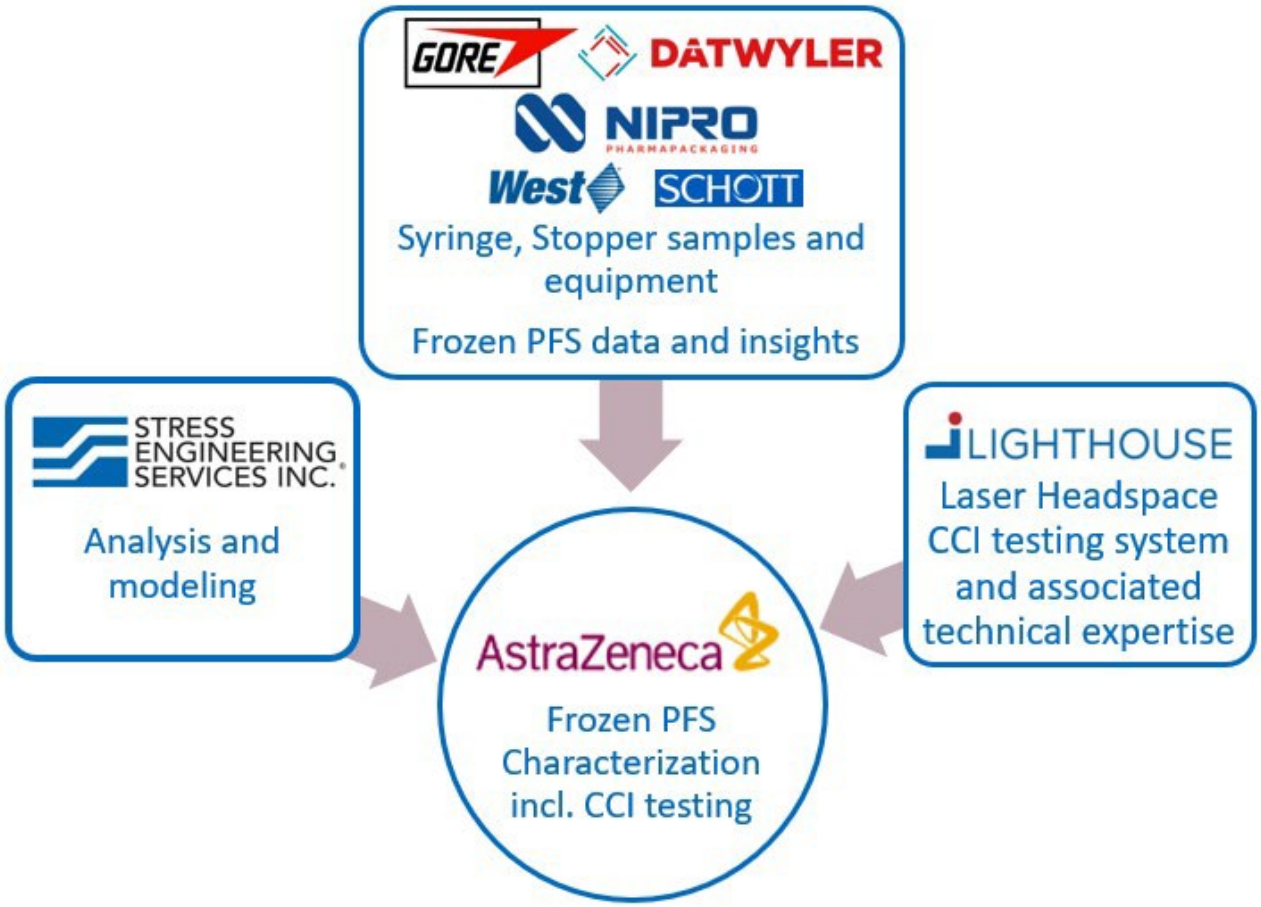
Pre-filled syringes (PFS) are widely used for pharmaceutical products; however rarely when frozen storage is required due to heightened concerns over **Container Closure Integrity (CCI) risks.**

Our project team **combined theoretical modelling with empirical testing to characterize CCI performance of PFS** at storage temperatures down to -80C.

The team established an **effective method to evaluate PFS CCI under frozen stored conditions** and the factors impacting CCI and used **theoretical modeling and in-situ imaging** to inform and support the empirical testing.

This presentation is intended to provide broad, general conclusions about frozen storage of glass pre-filled syringes and **does not make any recommendations for specific components or storage temperatures**.

An Industry Collaboration Initiated and Led by AstraZeneca



Theoretical Sealing for Pre-Filled Syringes

An **effective seal** requires adequate

1. Stopper contact stresses
2. Stopper contact width

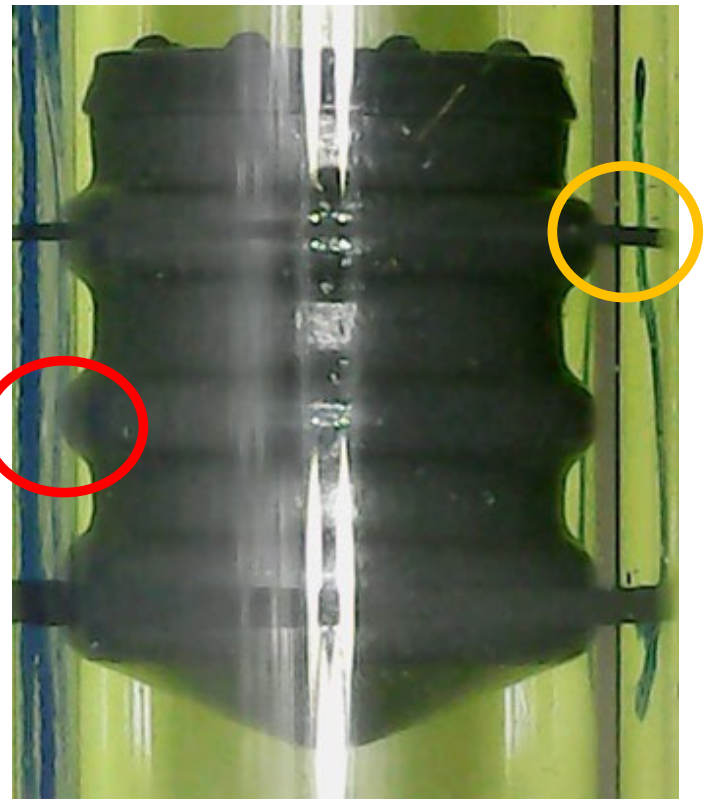
And be **robust** to

1. Dimensional and manufacturing specifications and tolerances
2. Materials properties (e.g. Thermal expansion, stiffness, compression recovery etc.)
3. Manufacturing, assembly, storage, transportation, etc.

Deep cold storage further challenges robustness

1. Reduced contact, complex material property changes, etc.
2. Risk of transient CCI failures

Seal Interface Visualization

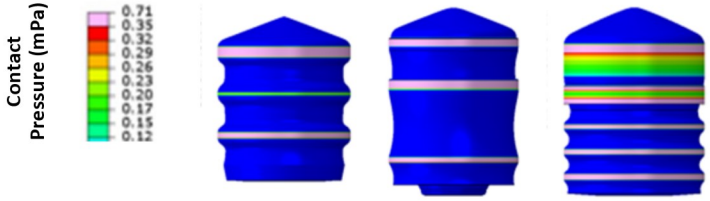


Incremental Theoretical Approach

- **Level 1 – Stopper interference**
  - Based on critical component diameters, tolerances, Coefficient of Thermal Expansion (CTE), static properties, etc.

$$\text{Diametric Interference} = \frac{OD_{stopper} - ID_{barrel}}{ID_{barrel}}\,\%$$

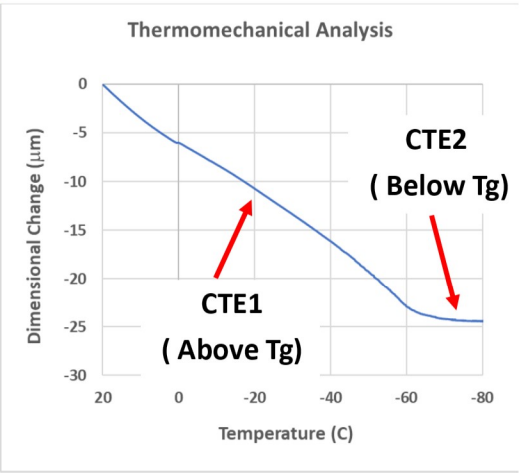
- **Level 2 – Contact pressure**
  - Level 1 + stopper geometry + materials properties

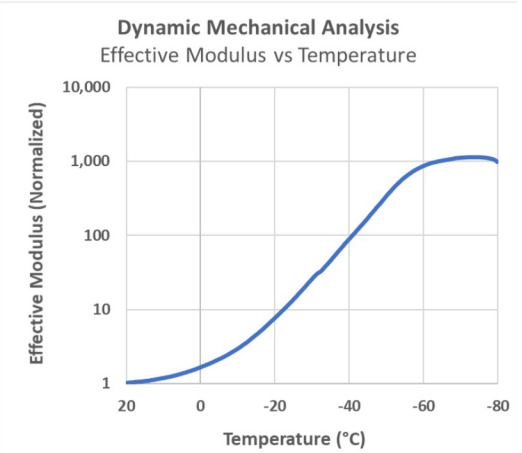


- **Level 3 – Dynamic modeling**
  - Level 2 + time dependent / dynamic materials properties, etc.

Model Inputs

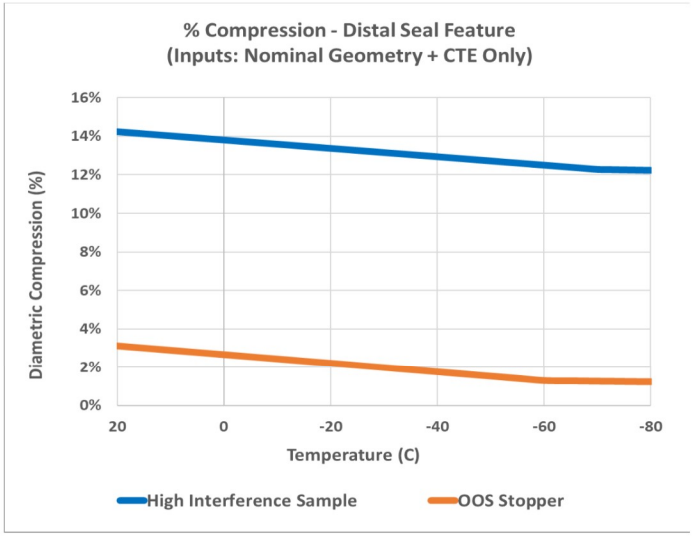
Experimental material properties



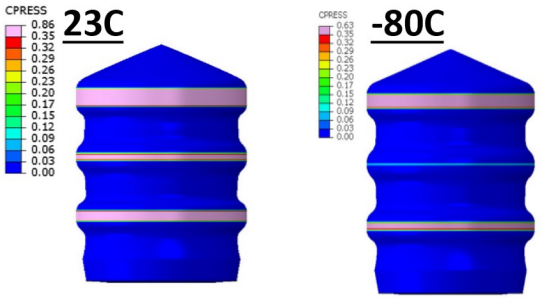


Level 1 and 2 Modeling: Results and Limitations

Level 1
Stopper interference



Level 2
Contact pressure



Level 1 and 2 model predictions

- % compression and contact pressure decline proportionally with temperature
- Inflection point associated with the elastomer Tg
- Significant % compression and contact pressure even as low as -80C (all stoppers)
- Leads to assumption that larger OD stoppers will perform better in frozen conditions

Empirical testing results **diverge** from the model predictions for temperatures **lower than Tg**

Level 3 modeling needed to incorporate more complex material property changes (e.g. dynamic / time dependent properties) **lower than Tg**

Measuring CCI of PFS in Frozen Storage Conditions

Sample Conditioning

System fully characterized for CO2 and temperature uniformity

Temperature cycler outfitted with **CO_2 purge** to condition test samples

- ~1atm CO_2 achievable
- Adjustable freeze and thaw rates

Repeatable and robust

- Glass luer 1mLL PFS (with and without silicone oil)
- Range of different stopper manufacturers and designs (coated and uncoated)
- OOS components*
- Room Temperature to -80C

Increasing outer diameter

*Component specially made & intended to be Out Of Specification (OOS)

CCI Testing

Laser headspace analysis (CO_2) method utilized for CCI testing due to its well-established capability to evaluate **transient CCI breaches during cold storage**.

4000+ samples measured across temperatures and PFS configurations

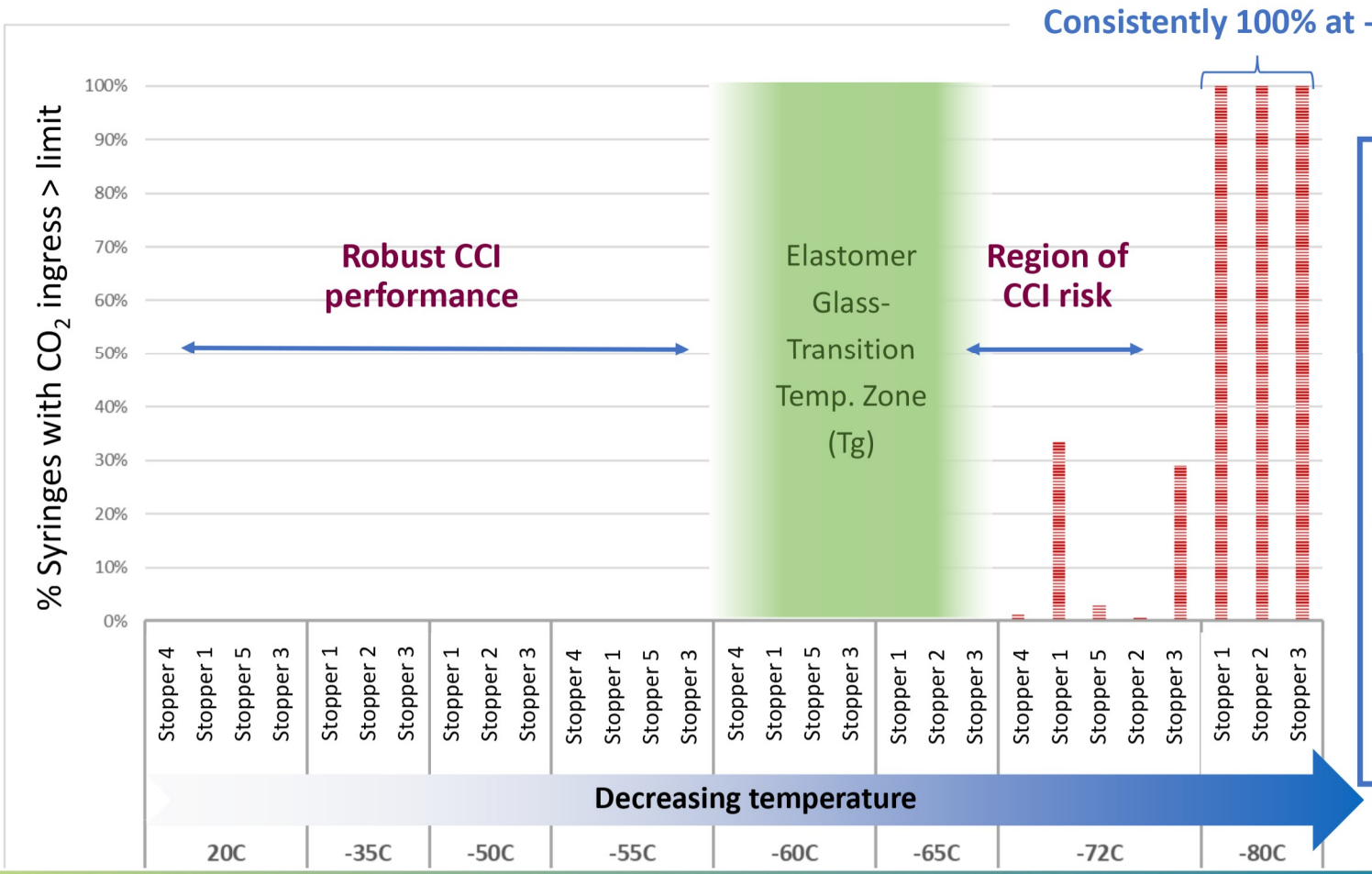
CO_2 Ingress Limit

A limit of **60 torr** limit was defined for this study

- Positive controls with **3 µm laser drilled defect** measured **~350 torr CO_2**
- Equipment Limit of Quantification of **~10 torr**
- **Not intended as a criteria for any other CCIT method**

[Stock images courtesy of LightHouse and Tenney]

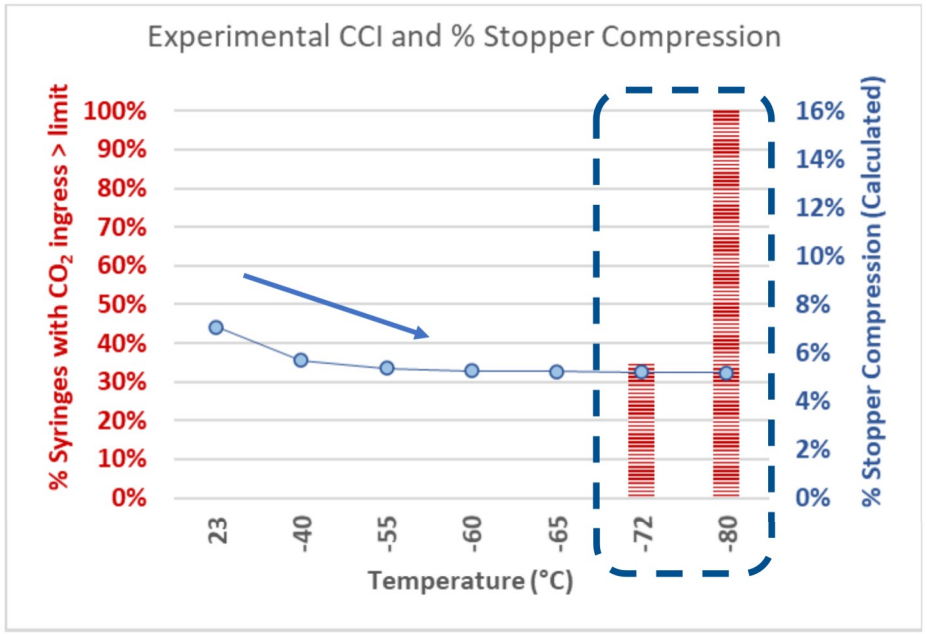
Overall CCI Performance

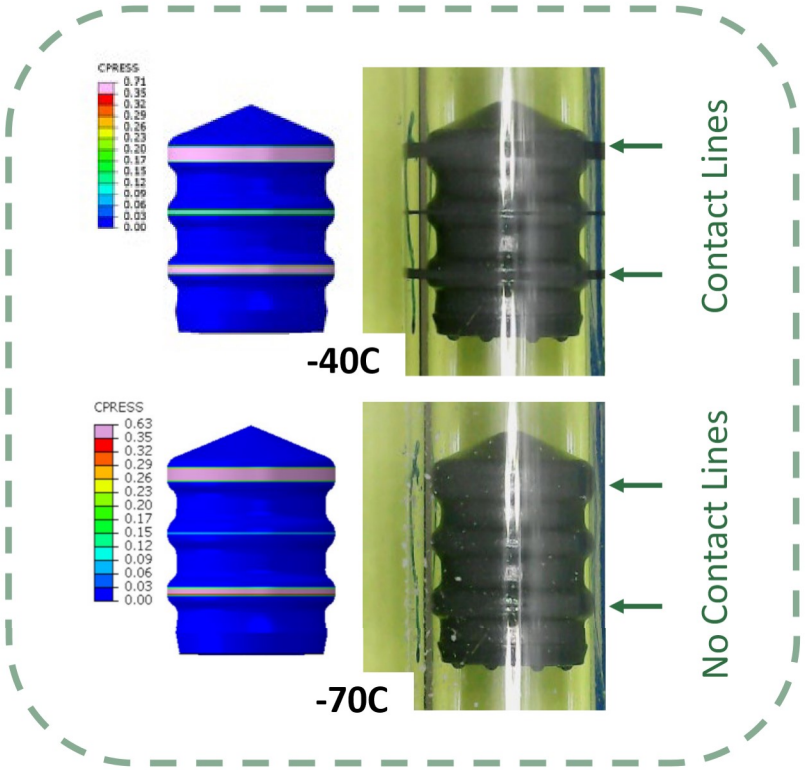


KEY FINDINGS

- All stoppers maintained CCI down to -60C
- CCI risk region just below Tg with significant CO_2 ingress seen from -72C
- 100% of samples had CO_2 ingress above limit at -80C
- NOTE: Results from testing with glass syringe barrels only. With polymer (COC) syringe barrels, CCI performance at -80C stopper dependent (Data not shown).

Combining Modeling with In-Situ Imaging & Experimental CCI



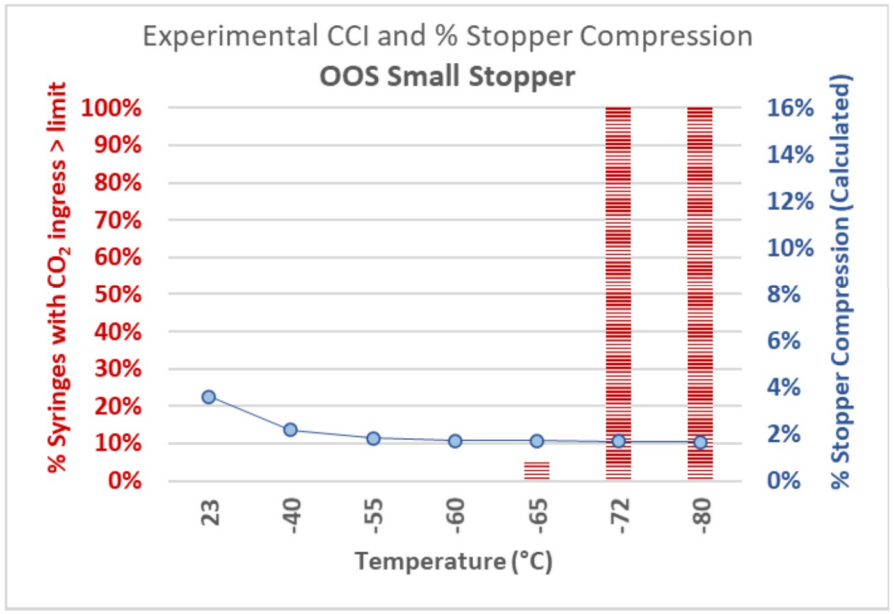


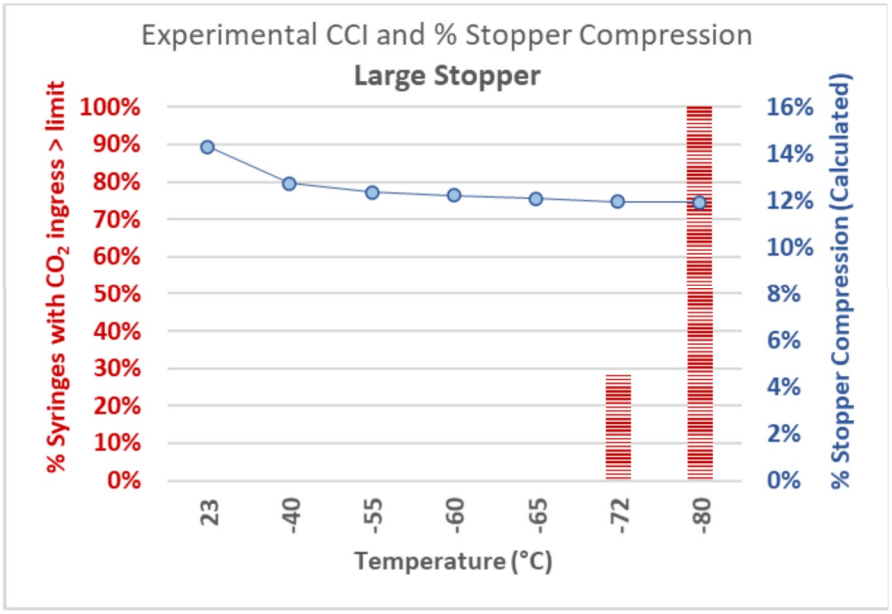
% Stopper compression reduces with temperature but is still theoretically adequate even down to -80C

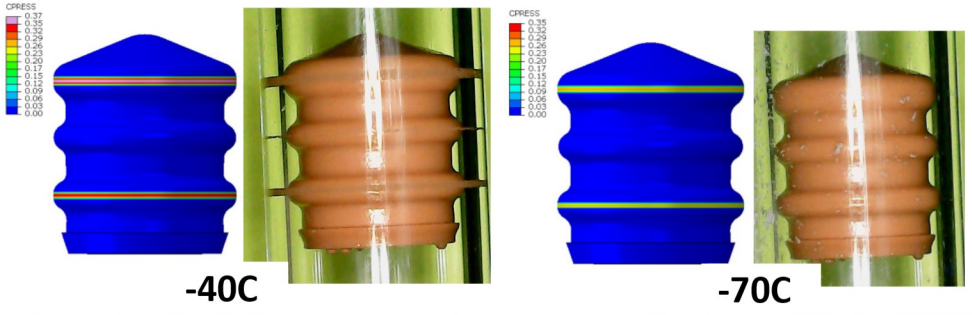
Significant CO_2 ingress at -72 C and below

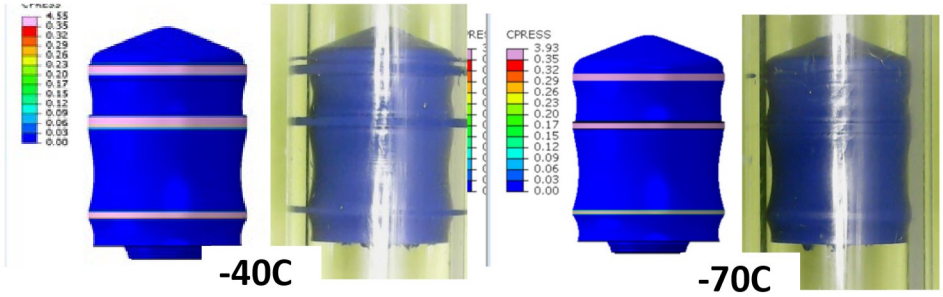
Stopper imaging at target temperatures supports CO_2 ingress results
Finite Element Analysis modeling fails to model the stopper behavior below elastomer Tg

Comparable Results for the Range of Stoppers Tested







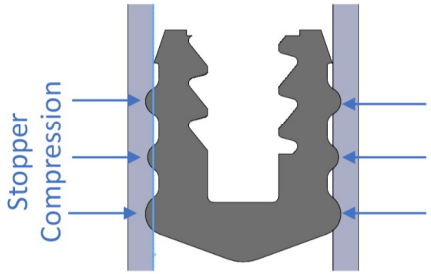


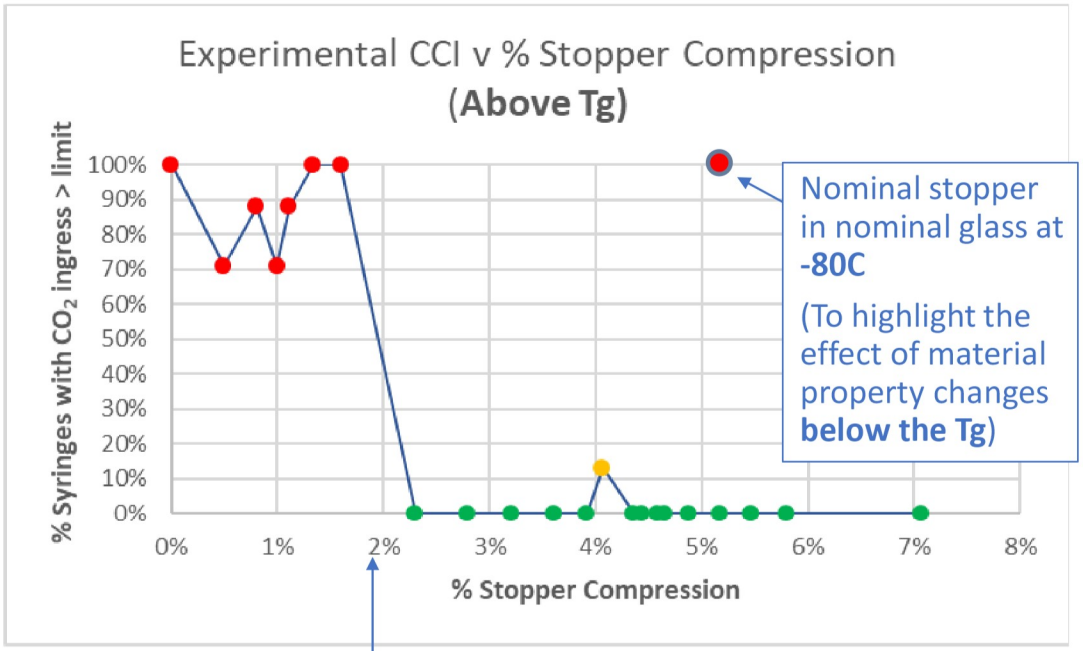
CCI Failure Can Result From Either Inadequate Stopper Compression or Material Property Shifts Related to Tg

Reduced stopper compression simulated using:

- OOS* larger diameter glass barrels
- Nominal and OOS* smaller stoppers
- Lowering temperature above Tg.

*Component specially made & intended to be Out Of Specification (OOS)





Sources of Variability Much More Significant Below Tg

Potential sources of variability in CCI performance were evaluated above and below the glass transition temperature (Tg)