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Correlating Vial Seal Tightness to Container Closure Integrity at Various Storage Temperatures

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Presentation Outline

- What happens to CCI during deep cold storage?
- How does vial seal tightness correlate to maintaining CCI?
- What should you do if you have product requiring deep cold storage?

  (live viral vaccines, gene/cell therapy)

Glass transition temperature T_g

- Only polymers have a glass transition temperature.
- When the polymer is cooled below this temperature, it loses elasticity and becomes hard and brittle, like glass.
- 'Rubbery state' vs. 'glassy state'

If container closure integrity depends on the elasticity of the rubber stopper, one might expect potential sealing issues below T_g of the rubber stopper.

Identified CCI issues in deep cold storage

Because deep cold storage (-80 ˚C to cryo) is colder than the $\mathbf{T}_g$ of most rubber stopper formulations (-50 to -70 ˚C), there is an increased risk of losing CCI if:

- An appropriate vial / stopper combination is not used
  - Vial / stopper design (blowback, non-blowback, etc.)
  - Vial / stopper fit (relative dimensions stopper plug, inner vial neck)
- Capping / crimping is not done properly
  - ‘Tight’ vs. ‘Loose’

REF: Container/Closure Integrity Testing and the Identification of a Suitable Vial/Stopper Combination for Low-Temperature Storage at -80 C

Brigitte Zuleger, Uwe Werner, Alexander Kort, Rene Glowienka, Engelbert Wehnes, Derek Duncan
PDA J Pharm Sci and Tech 2012, 66 453-465

Leakage in deep cold storage

- Air filled vial at 1 atm at RT
- At low T, initial headspace condenses and creates **underpressure**
- Stopper can lose elastic properties & closure can be lost
- Cold dense gas from storage environment fills headspace
- Warming container to RT, stopper regains elasticity and **reseals**

Leakage in deep cold storage

- Cold dense gas now trapped inside, expands as temperature goes up, creating **overpressure**
- **Maintenance** of this **overpressure** can be monitored over time to verify that the **leak was temporary**.

The analytical tool

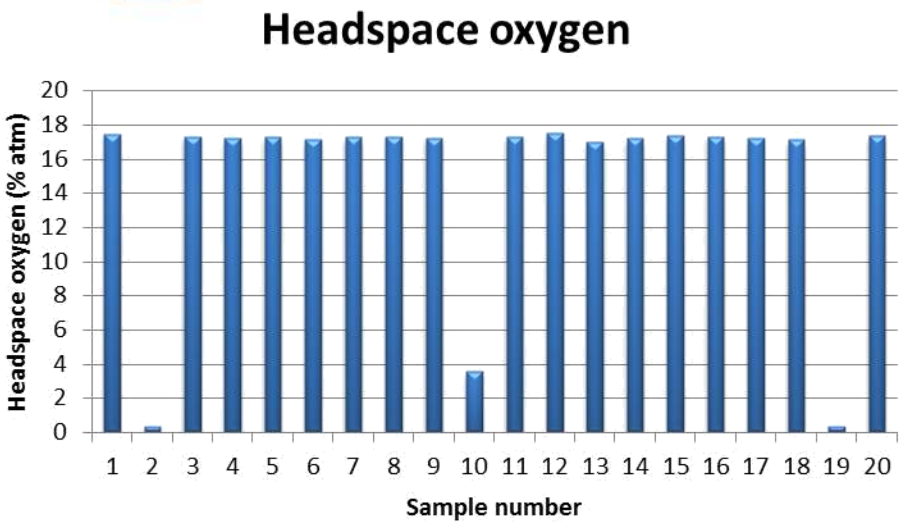
Rapid non-destructive analytical method for measuring headspace O_2, H_2O, CO_2, and pressure levels

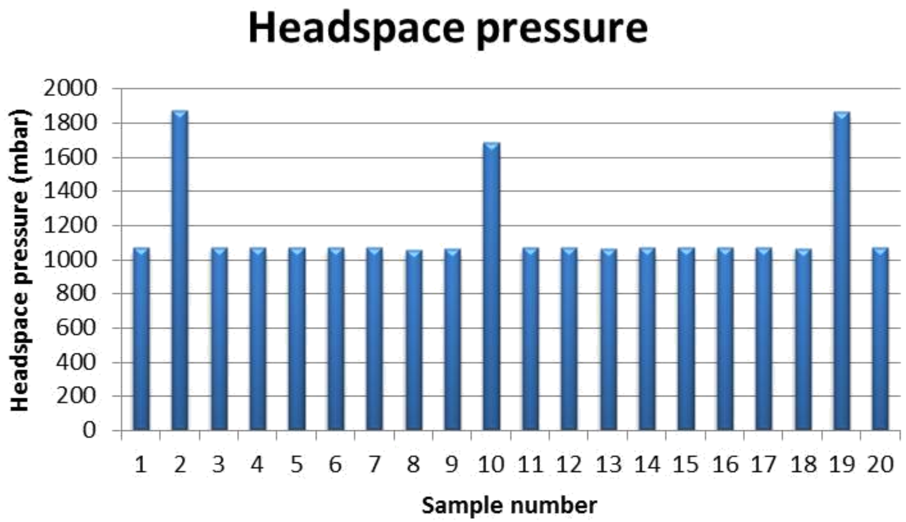
Quantifying the physical headspace conditions with **Laser-based Headspace Analysis** enables identification of CCI dynamics during deep cold storage

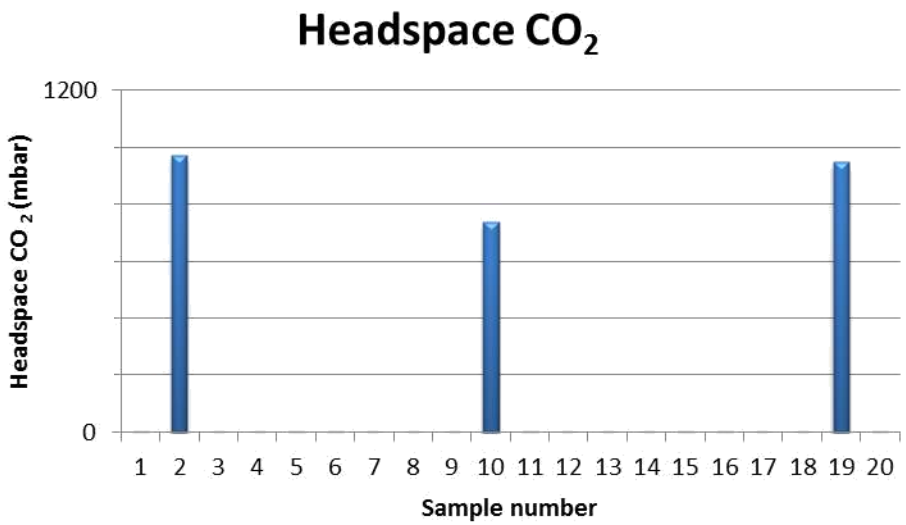
Example: CCI of media filled vials stored on dry ice

- 2R clear tubing vials containing media.
- Initial headspace conditions: 1 atm of air
- Stored on dry ice for 7 days.
- Thawed to room temperature (RT).
- Headspace conditions analyzed.
- Any change in the headspace conditions is a direct sign that closure was lost during deep cold storage resulting in headspace gas exchange.

Example: CCI of media filled vials stored on dry ice for 7 days







Three different headspace measurements identify the same 3 vials as having CCI issues.

Example: CCI of media filled vials stored on dry ice

Some important comments on these results:

- The maintenance of overpressure in the leaking samples over time at RT means the **vial has resealed** at temperatures **above the T_g** of the rubber stopper.

- **Leaks** during deep cold storage are **temporary**!

- **Other CCI methods** (blue dye, microbial ingress, pressure decay) that test these vials after thawing **will NOT identify these vials as having leaked**.

Elastomeric Closure

- Elastomers are amorphous polymers that exist above their Glass Transition Temperature (Tg) and exhibit viscoelastic behavior (interchangeable with the term rubber).

- Rubber Formulations for closures to seal pharmaceutical containers have Tg s that are usually in the range -50 to -70 ˚C.

Elastomeric Closure (continued)

- In sealing rubber components, the elastic property is important. An applied stress (sealing force) induces a corresponding strain which creates a contact stress. This stored internal energy is the Residual Seal Force (RSF).

- The viscous property of rubber is also important. It allows considerable segmental motion or flow. This movement can fill gaps and voids in the sealing surface.

Quantifying vial seal tightness

Residual seal force

- RSF is the stress a compressed elastomeric closure flange continues to exert on a vial land Sealing surface after application of an aluminum seal (crimping)
- Quantifying the RSF is a test method for the indirect estimation of elastomeric closure compression
- Sufficient compression is essential to seal integrity.

Objectives this cold storage study

- Quantify capping & crimping parameters
  - Three capping pressures defined
  - Measured with Residual Seal Force

- Direct comparison different storage temps
  - Empty capped vials
  - RT, -20˚C, -80 ˚C, and cryogenic (-178 ˚C) storage

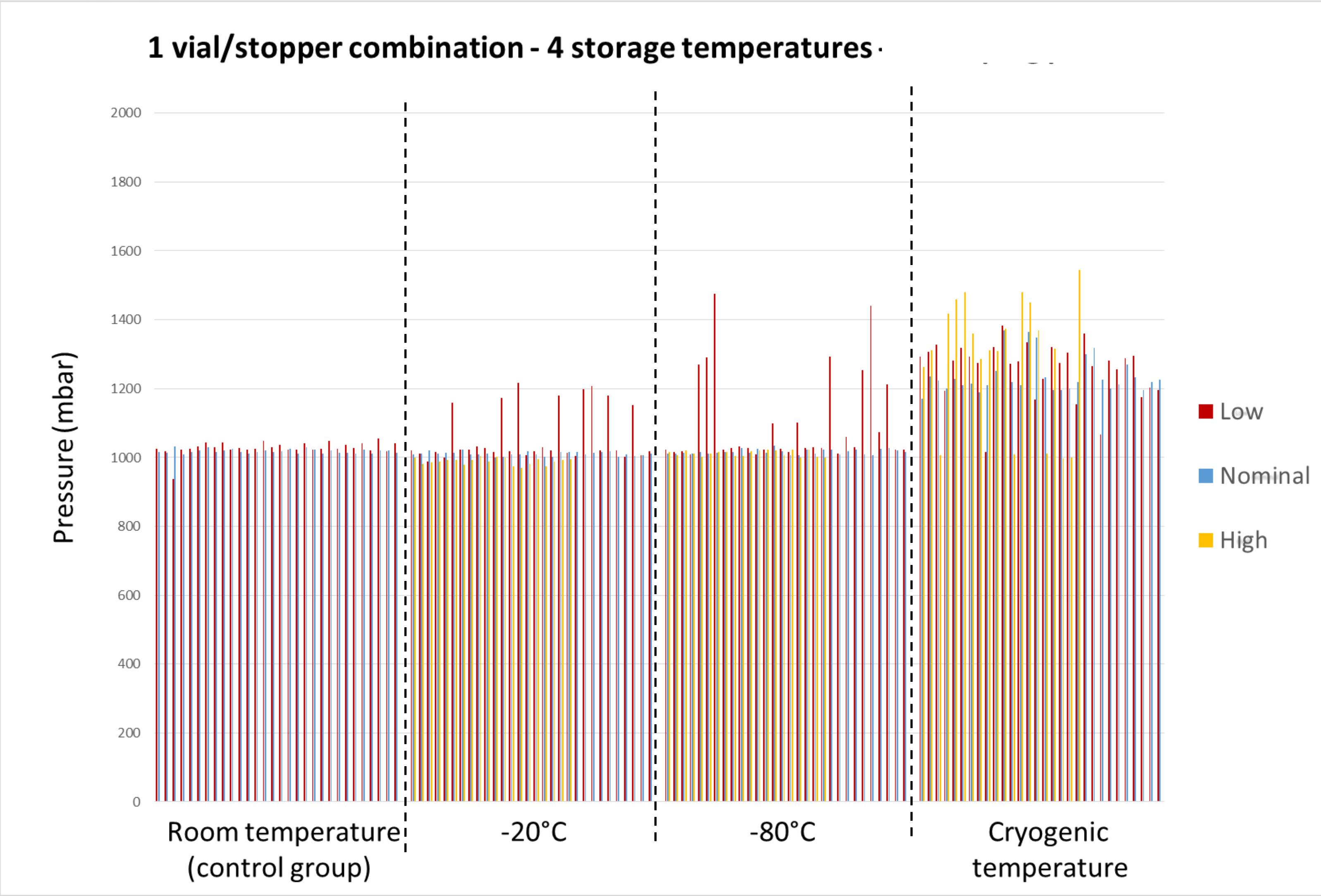
Experimental parameters

- **Stopper/vial combinations**
  - Five different stopper/vial combinations
  - 30 samples of each combi at each temperature and each capping pressure (1800 total)

- **Crimping parameters**
  - Genesis RW-50 capper (rail technology)
  - Crimping pressures (force differentials):
    - Low: 45 N; Med: 98 N; High: 151 N
  - Measured RSF

- **Storage**
  - RT, -20˚C, -80 ˚C, liquid nitrogen

Results: Overpressure vs Temp

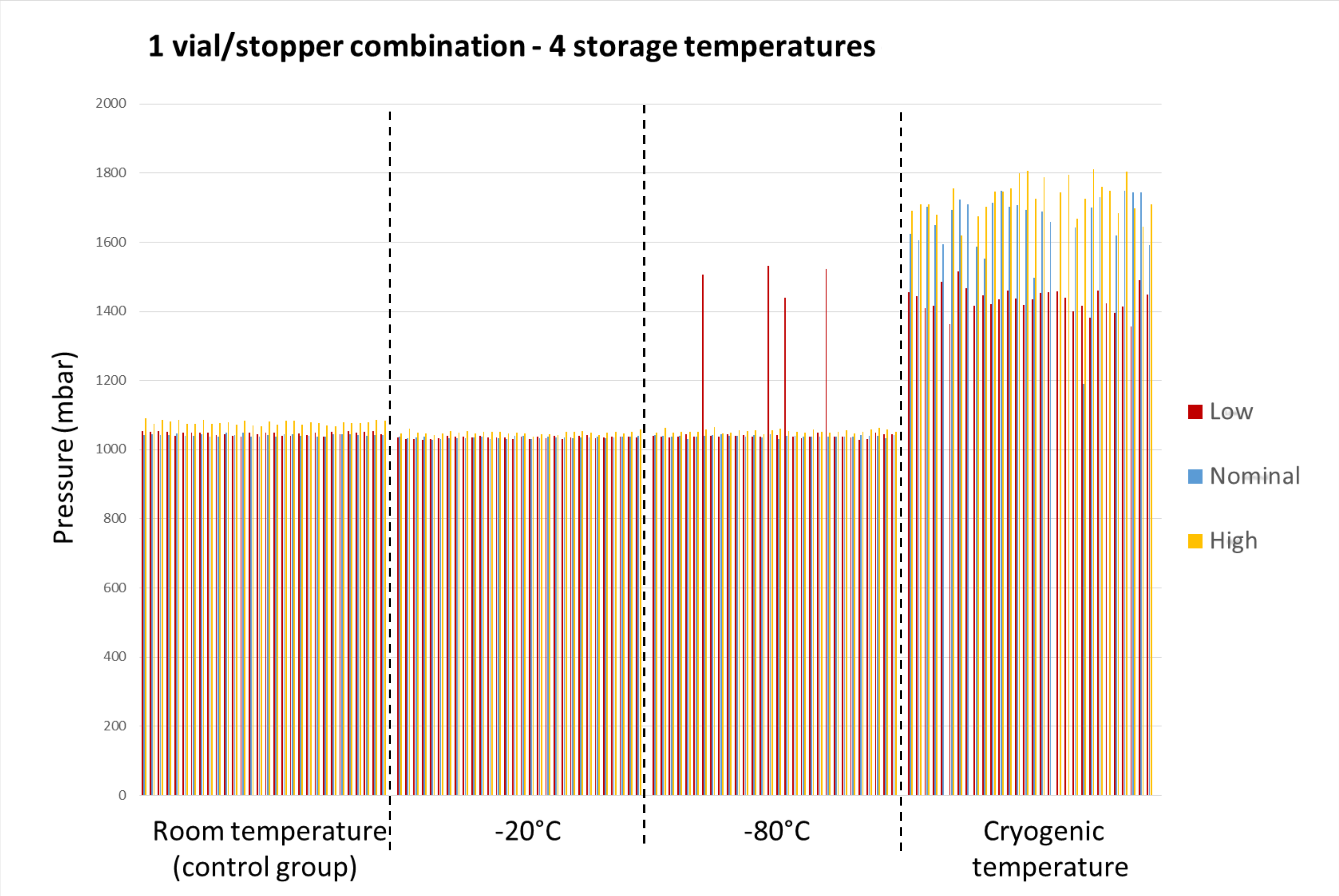


Stopper
13mm serum

Vial
2 ml EU BB

3 crimping pressures (RSF)

Results: Overpressure vs Temp

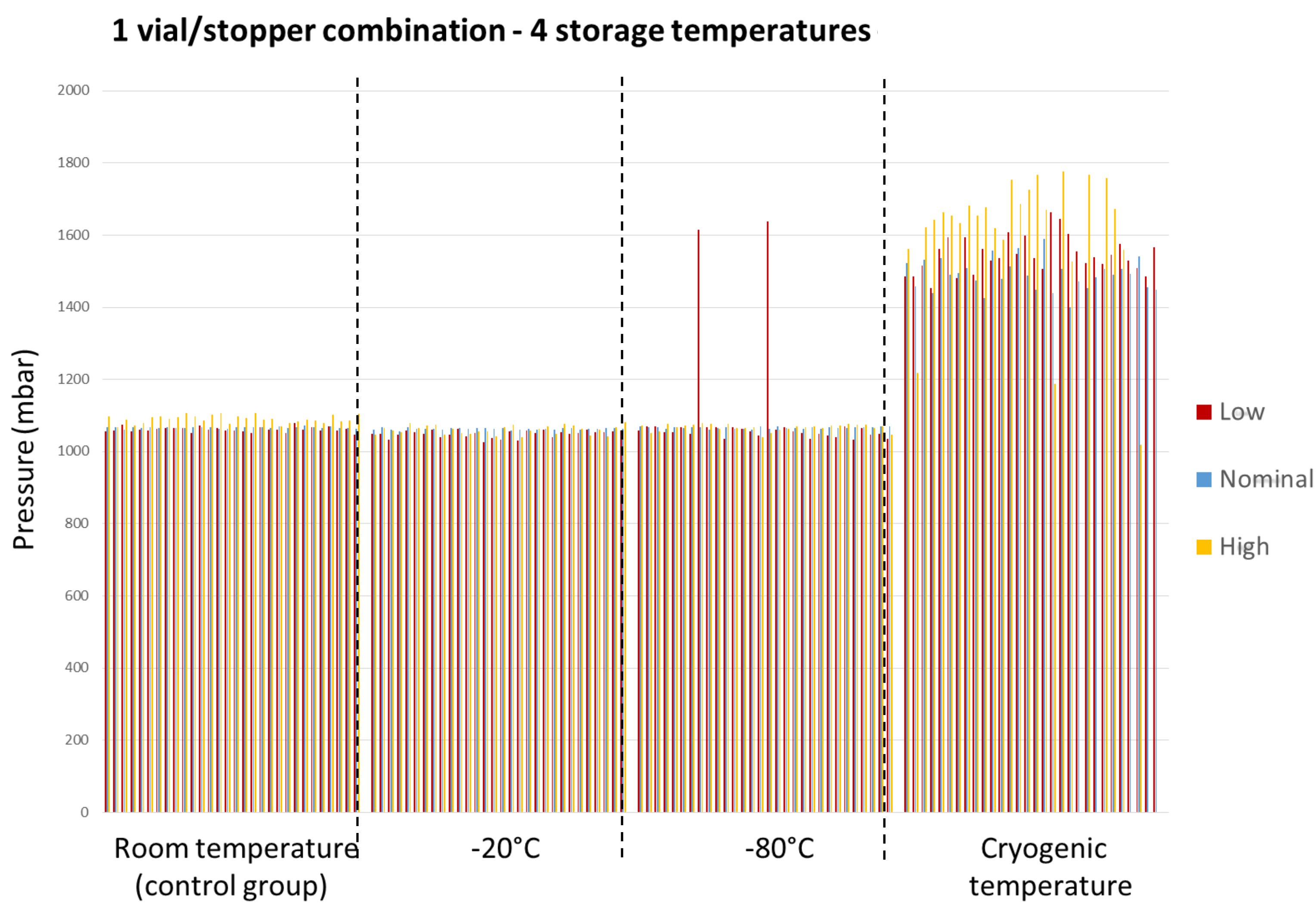


Stopper
13mm Serum

Vial
2 ml EUBB

3 crimping pressures (RSF)

Results: Overpressure vs Temp

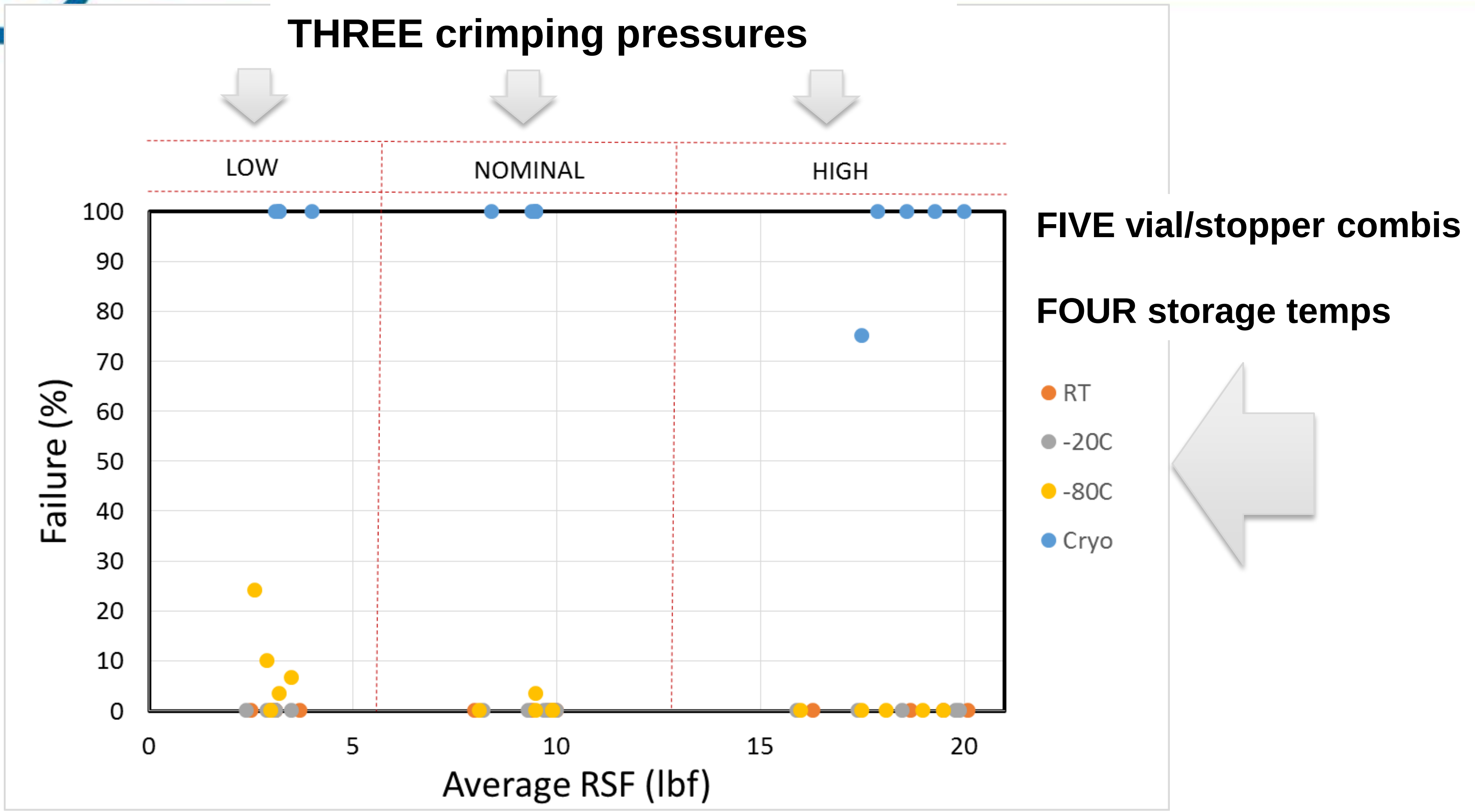


Stopper
13mm solid plug

Vial
2 ml NonBB

3 crimping pressures (RSF)

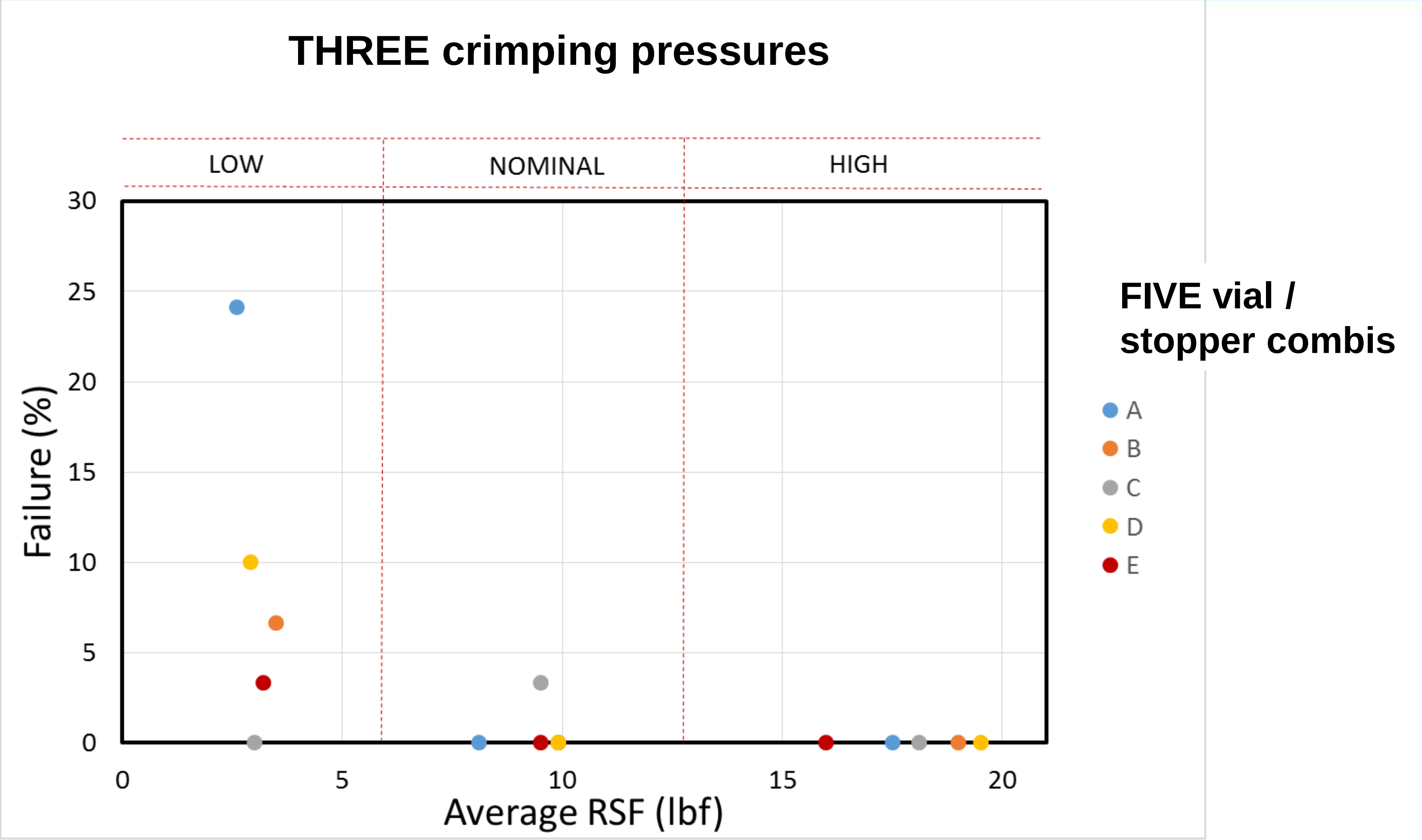
Results: Failure rate vs. RSF



LOW RSF CLEARLY CORRELATES TO HIGH CCI FAILURE DURING DEEP COLD STORAGE

NOTE: Actual avg RSF of low crimped vials is lower, since some RSF were too low to measure (<2lbf)

Results: Failure vs. vial / stopper combination at -80 C

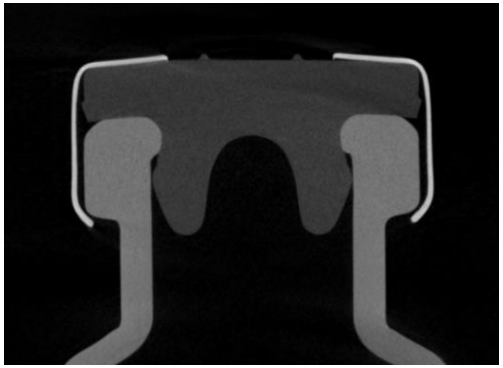


Retaining CCI during cold storage is also a function of vial-stopper combination

NOTE: Actual avg RSF of low crimped vials is lower, since some RSF were too low to measure (<2lbf)

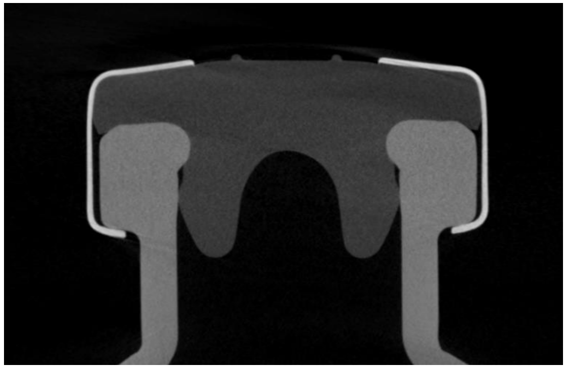
Results: X-ray imaging

Compression Examples Group E



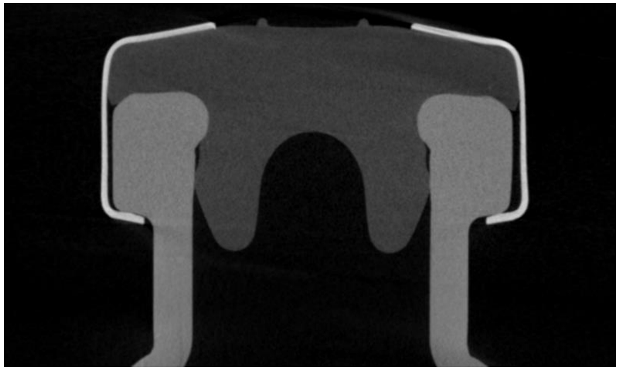
Low crimping pressure

10.3% Compression avg.
3.1 lbs RSF avg



Nominal crimping pressure

22.7% Compression avg.
9.6 lbs RSF avg



High crimping pressure

27.4% Compression avg.
16.5 lbs RSF avg

Images by Micro Photonics Inc. Allentown, PA USA using Bruker Micro CT SkyScan 1173

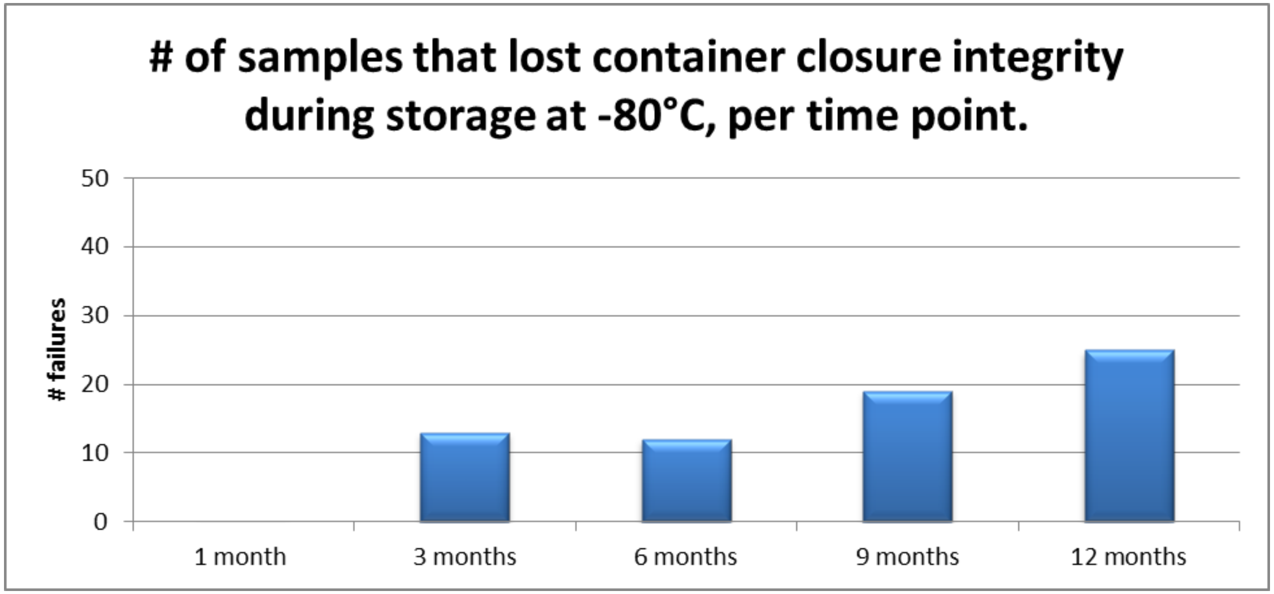
Conclusions

- There is **risk for CCI failure** at storage temperatures **below the T_g** of the rubber stopper formulation.
- CCI failures can be mitigated by **ensuring appropriate vial / stopper** combination and **capping & crimping** parameters
- **RSF measurements** can be a useful tool in quantifying seal tightness and predictive of CCI failure at low temps
- **Laser Headspace Analysis** is a suitable non-destructive method to detect (temporary) leaks in cold storage

Recent stability results: Failures over storage time

Customer wanted to compare CCI of two stopper vial combinations over 12 months of deep cold storage

- **400 samples of each combination prepared**
- **50 samples taken out of storage and measured at each time point**



- **One combination held CCI over 12 months of storage at -80 ˚C**
- **For other combination, failures started to appear at 3 month time point**

Alternative container solutions for deep cold storage?

- If rubber stoppers have a $\mathbf{T}_g$ warmer than -80° C, are traditional stoppered vials fundamentally the wrong container to consider for deep cold storage?

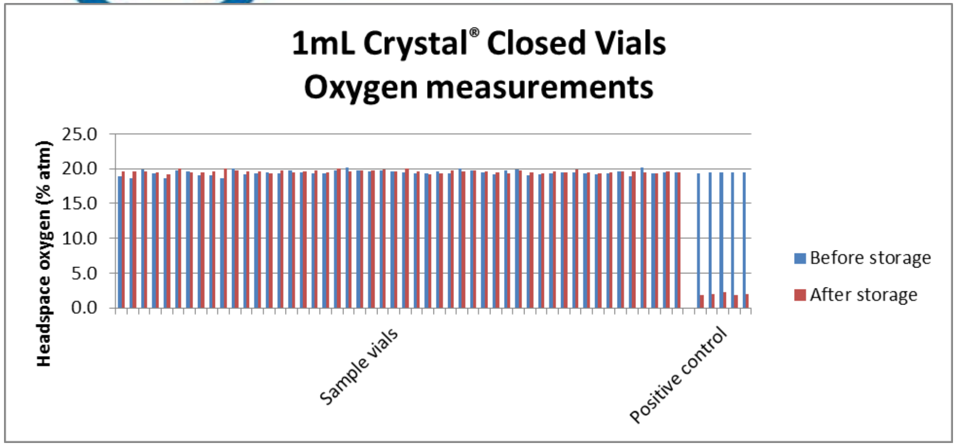
- Are there alternative container solutions?

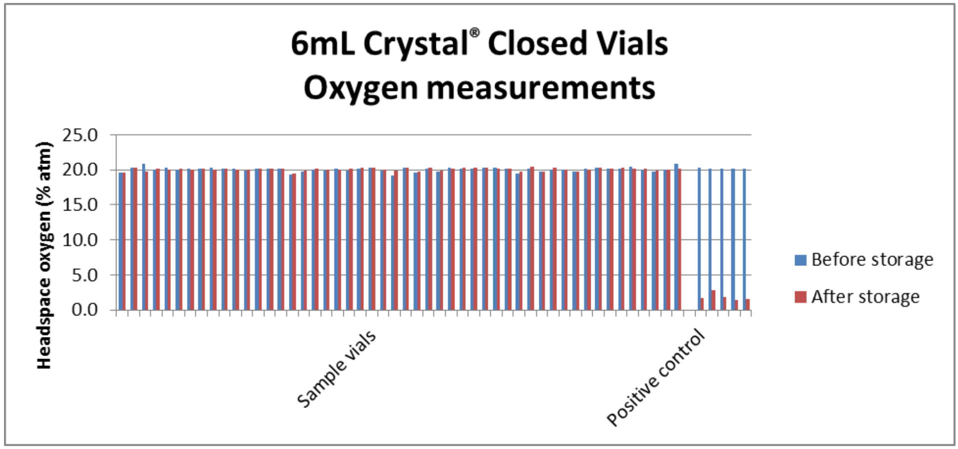
Alternate container: Crystal® Closed Vials

- Supplied by Aseptic Technologies

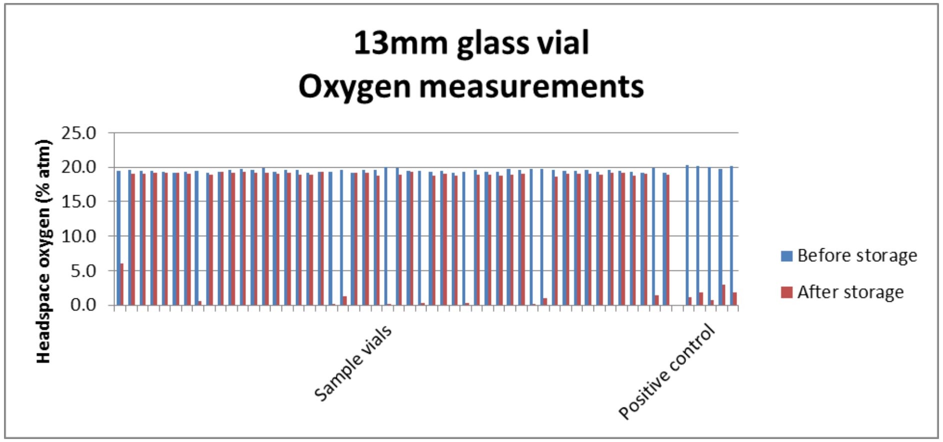
- Study performed with **cryogenic storage temp**:
  - 1ml and 6ml Crystal® Closed Vials
  - 13mm stoppered tubing vial (semi-automatic crimper targeting > 30% stopper compression)
  - 20mm stoppered molded vials (hand-crimped)

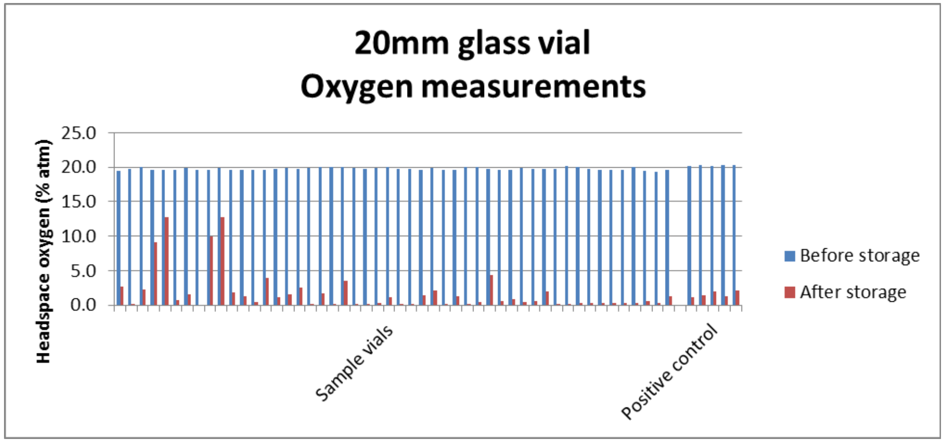
Crystal® Closed Vials vs. Stoppered glass vials





No CCI failures in Crystal® Closed Vials during cryo storage





High CCI failures in stoppered glass vials

Acknowledgements

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Thank you for your attention!

For further discussion please come by the LIGHTHOUSE or Genesis Exhibits

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Past references

- *"Dry ice should not be used in shipping rubber-stoppered vials because the low temperatures can lead to shrinkage of the rubber with subsequent ingress of (unsterile) air and carbon dioxide."*

  Reference: "Recommendations on the Control and Monitoring of Storage and Transportation Temperatures of Medicinal Products", John Taylor (Medicines Control Agency UK), The Pharmaceutical Journal (Vol. 267), 28 July 2001, p.129

- **Effect of Low Temperatures on Parenteral Vial Seal Integrity**

  Asselta, R.; Smith, E.; Sunderland, W.; Trappler, E. Presented at the PDA Annual Meeting, Las Vegas, NV, 2007.

Recent references

- **Identification of a Suitable Vial/Stopper Combination for Low Temperature Storage at -80C**
  Dr. Brigitte Zuleger, Bavarian Nordic, Presented at the PDA Parenteral Packaging Meeting, Berlin, 2012.

- **Container/Closure Integrity Testing and the Identification of a Suitable Vial/Stopper Combination for Low-Temperature Storage at -80 C**
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