Strategies to Evaluate CCI of Vial and Syringe Systems over Time and Temperature

Amy Gindhart, Louis Brasten, Amy Kim, Jennifer Roark

West Pharmaceutical Services, Inc.

Background / Strategy

Proper characterization of container closure integrity (CCI) of vial and syringe systems is essential

Aid pharmaceutical manufacturers to determine if a system is suitable for a drug product

Determine if a system can meet the maximum allowable leakage limit (MALL)

No single method is suitable for all systems

Proper characterization strategy should employ multiple methods

Long-term case studies using tracer gas detection vacuum mode (helium leak detection) and laser-based gas headspace analysis (oxygen and carbon dioxide)

Glass/elastomer vial combinations over 2 years at room temperature

Polymer/elastomer vial combinations over 2 years at room temperature, ultra-cold, and cryogenic, including carbon dioxide atmosphere

Glass syringe combinations

Discussed also are the specific utilities of each method

Techniques Used

Techniques combined offer more complete picture of CCI and aid in determining if MALL is met

Residual Seal Force (complementary method)

- Quantifies compression of stopper against vial

Tracer Gas detection vacuum mode with Helium (He Leak)

- Measures stopper/vial seal integrity
- Deterministic – endorsed by USP <1207>

Laser-Based Gas Headspace Analysis (O_2 & CO_2)

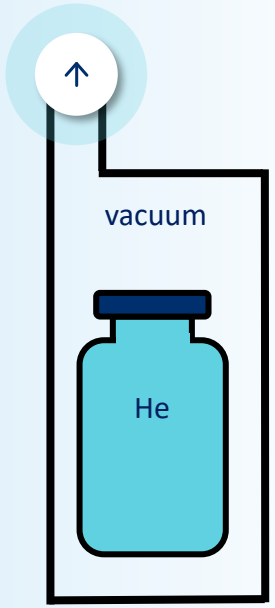
- Measures diffusion/effusion through vial, stopper, and interface
- Deterministic – endorsed by USP <1207>

Residual Seal Force (RSF)

- Equipment: Genesis Model AWG RSF Tester
- RSF is a measurement of the seal tightness of the stopper against the vial in the stopper/seal/vial combination resulting from the sealing process
- Indirectly measures the force exerted by the stopper on a vial's land surface
- Sealed vial is placed into the instrument holder with an appropriately sized cap anvil on top of the vial
- Pressure is applied to the sample; the machine calculates the force (pounds-force) required to dislodge the crimp seal from the underside of the vial crown.

Helium Leak

mass spectrometer



Room Temperature, Ultra-low & Cryogenic Temperatures

Equipment: Leak Detection Associates (LDA)/Packaging Technologies and Inspection (PTI) 1284+ Seal Integrity Monitoring System (SIMS)

2 modes of operation

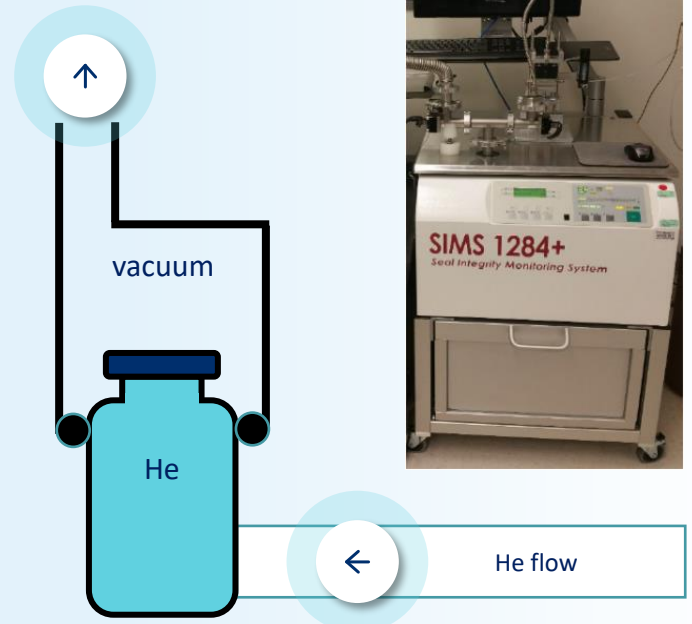
- Standard (room temperature, -80°C and -180°C)
- Continuous flow (room temperature)

Mass spec measures level of Helium and reports as leak rate (mbar-L/s)

Advantages

- Highly sensitive
- Quantitative leak size determination
- Non-destructive
- 100% testing feasible

mass spectrometer

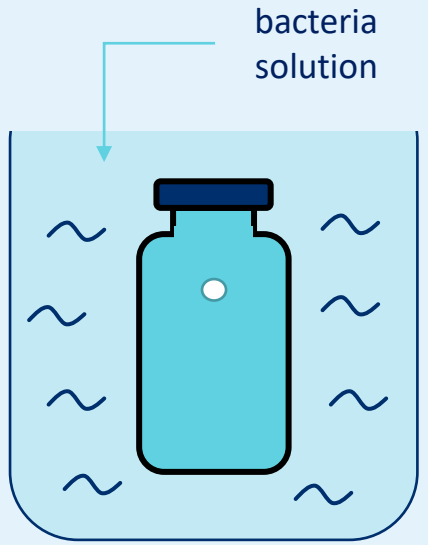


Room Temperature

Kirsch Limit

Often used as a valuation standard for CCI performance

Hole Diameter (μ)	**He-Leak** (cm^3/s @ STP)	**- log (He-Leak)**	**Microbial Ingress Rate** (%)
2	1.0×10^{-3}	3.0	70
0.7	2.0×10^{-4}	3.7	65
0.4	9.0×10^{-6}	5.0	11
---	6×10^{-6}	5.2	8 - 10
0.3	2.0×10^{-6}	5.7	7
0.2	2.2×10^{-7}	6.6	0
0.1	1.0×10^{-7}	7.0	0

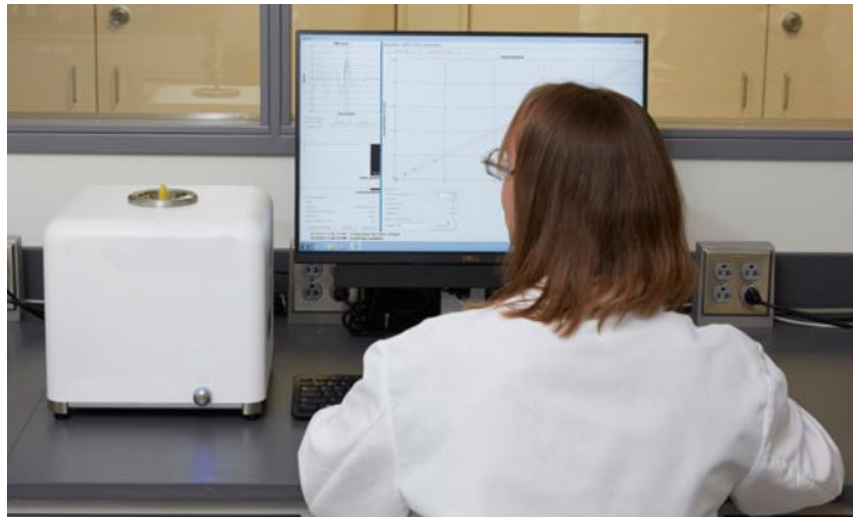


[1] L. E. Kirsch, et al. (University of Iowa) *Pharmaceutical Container/Closure Integrity II: The Relationship between Microbial Ingress and Helium Leak Rates in Rubber-Stoppered Vials.* PDA Journal of Pharmaceutical Science & Technology, 51 (5), 195-202 (1997).

Headspace Analysis

Equipment: Oxygen Headspace Analyzer, FMS-760 by Lighthouse Instruments

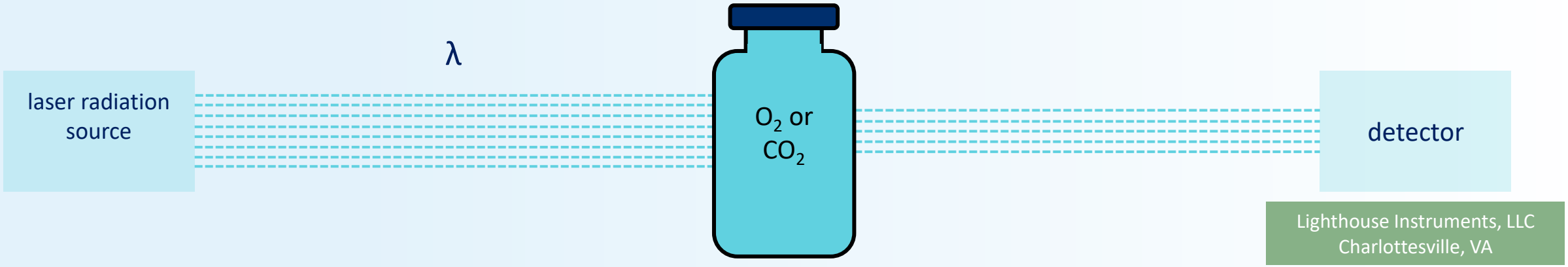
Amount absorbed correlates to concentration



Uses near-IR radiation wavelength that is absorbed by gas of interest

Advantages

- Rapid testing time
- Non-Destructive
- Highly sensitive
- No sample preparation



Lighthouse Instruments, LLC
Charlottesville, VA

Glass Vial / Stopper / Seal Combinations

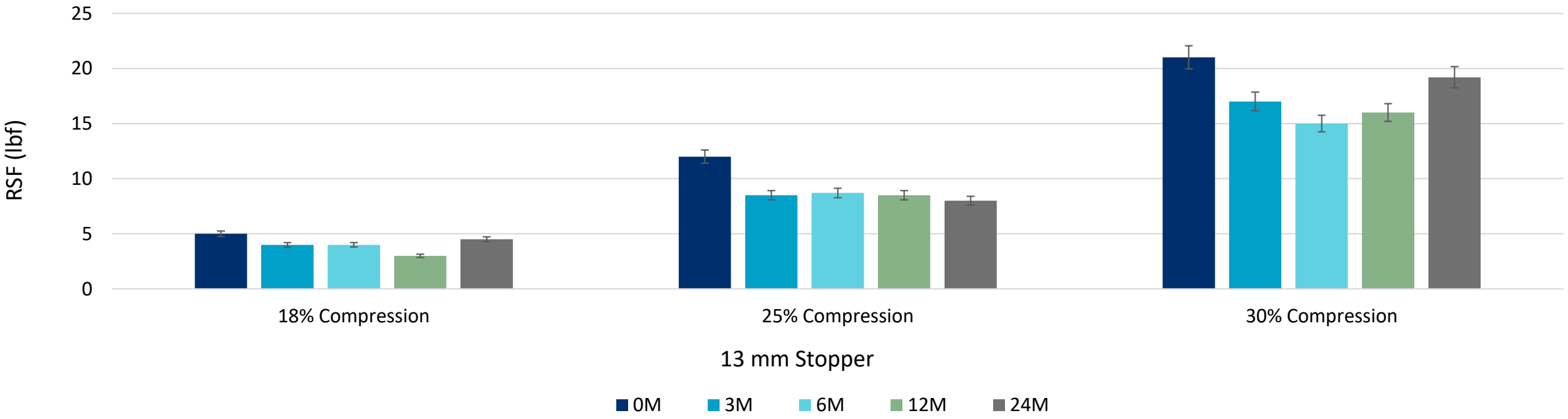
He leak and O_2 headspace routinely used at West to quantify performance of vial/stopper/seal combinations varying in:

- Vial: size, blowback, supplier
- Stopper: size, configuration/design, elastomer, post-treatment
- Assembly: compression level, seal

Example Presented:

- 13 mm serum bromobutyl elastomer stopper
- 2R straightwall glass vial

Residual Seal Force at Ambient Temperature



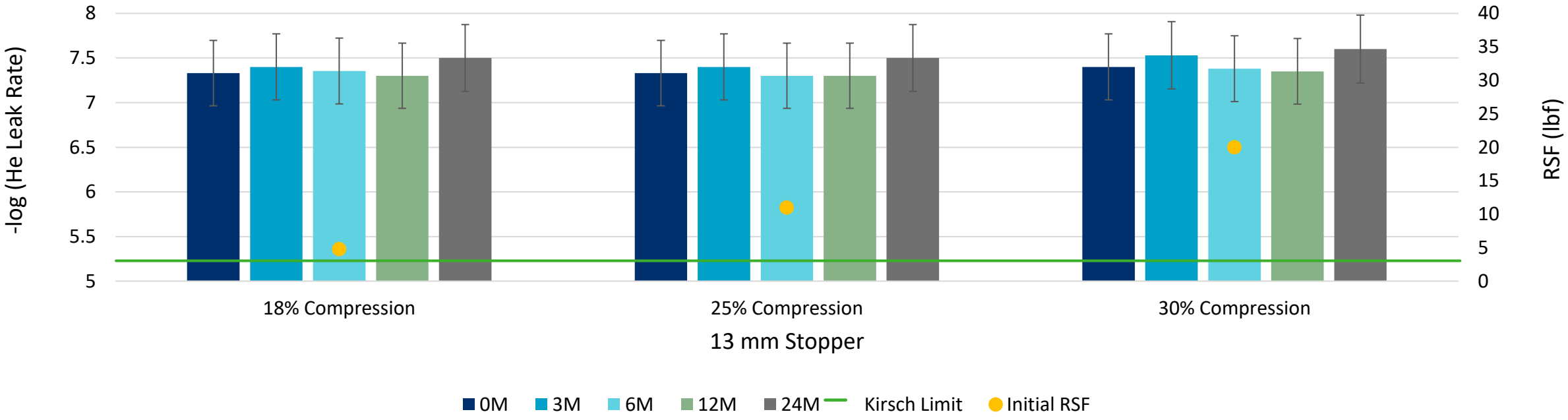
2R straight wall glass vial with 13mm serum bromobutyl elastomer stopper

Increases with compression level as expected

Reduces in value quickly at 3M and then remains constant over 24M due to the relaxation of the elastomer

Gehrmann, Long-Term Study of Container Closure Integrity of Rubber-Glass Vial Systems by Multiple Methods. PDA J Pharm Sci Technol. 2020 Jan-Feb;74(1):147-161. doi: 10.5731/pdajpst.2019.010223

Helium Leak at Ambient Temperature



There was no change in helium leak values observed over 24M

Data demonstrates excellent sealing integrity

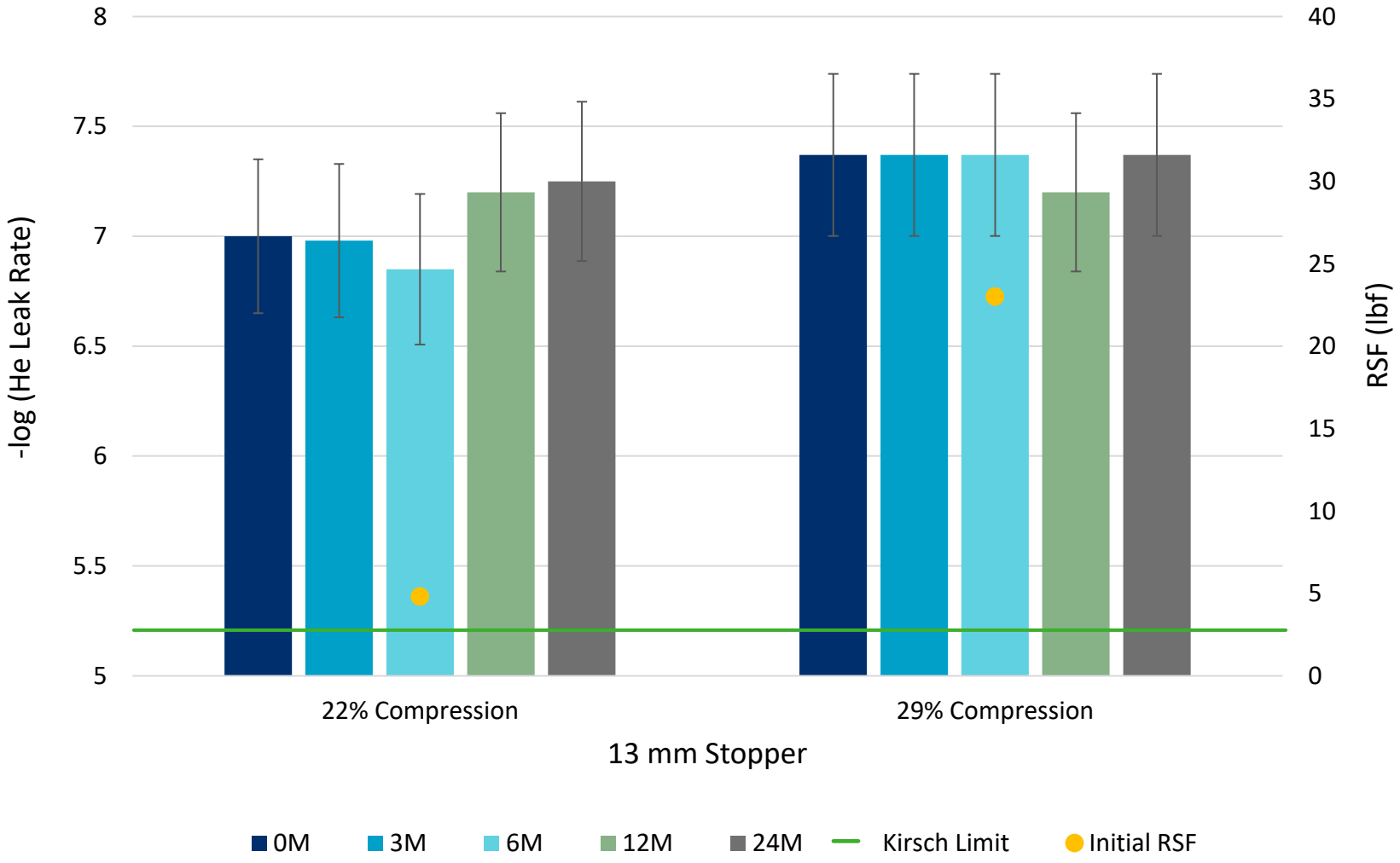
Values correspond to 0% microbial ingress per Kirsch limit

Gehrmann, Long-Term Study of Container Closure Integrity of Rubber-Glass Vial Systems by Multiple Methods. PDA J Pharm Sci Technol. 2020 Jan-Feb;74(1):147-161.
doi: 10.5731/pdajpst.2019.010223

Helium Leak at Ambient Temperature (Low Compression)

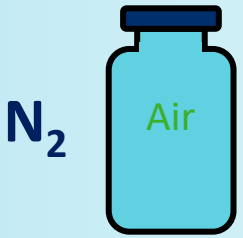
Helium leak can indicate compression levels that are not optimal

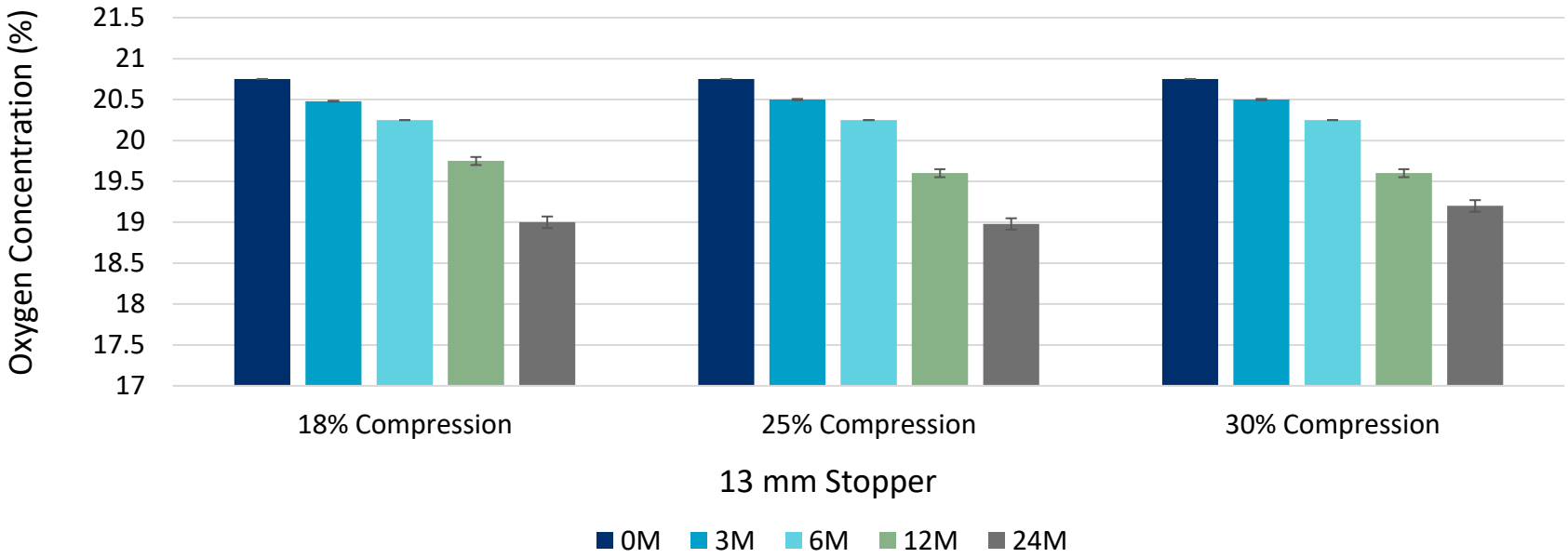
- Including standard deviation



Gehrmann, Long-Term Study of Container Closure Integrity of Rubber-Glass Vial Systems by Multiple Methods. PDA J Pharm Sci Technol. 2020 Jan-Feb;74(1):147-161.
doi: 10.5731/pdajpst.2019.010223

Headspace Analysis (O_2) at Ambient Temperature





There was some egress of O_2 and ingress of N_2 over time not predicted by the helium leak data.

Rubber is known to be gas permeable

Egress was on avg 1.7% O_2 after 24M.

Gehrmann, Long-Term Study of Container Closure Integrity of Rubber-Glass Vial Systems by Multiple Methods. PDA J Pharm Sci Technol. 2020 Jan-Feb;74(1):147-161. doi: 10.5731/pdajpst.2019.010223

Conclusion of Glass/Elastomer Vial Combinations

Combined He leak and O_2 headspace analyses give a more complete view of CCI and better enables understanding if MALL can be met

For the present example (13 mm stopper and 2R vial)

- Seal integrity over 2 years is excellent
- All He leak values are better than the Kirsch limit (correspond to ~ 0% microbial ingress)
- O_2 headspace values show some quantified permeation through the rubber over time

Reason for Low Temp Interest in Polymer Vials

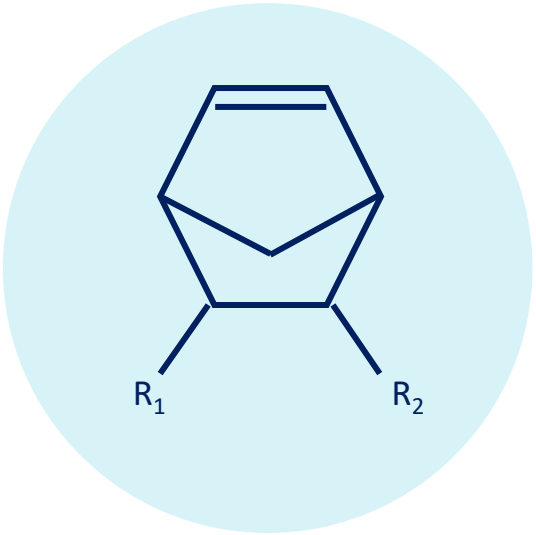
Gene and cell therapies require storage at -80°C (ultra-low) and below -130°C (cryogenic).

The vial/stopper/seal combinations selected must be able to maintain container closure integrity (CCI) during long-term storage at said temperatures.

Polymer-based vial/stopper/seal combinations have lower risk of loss of CCI at low temperature

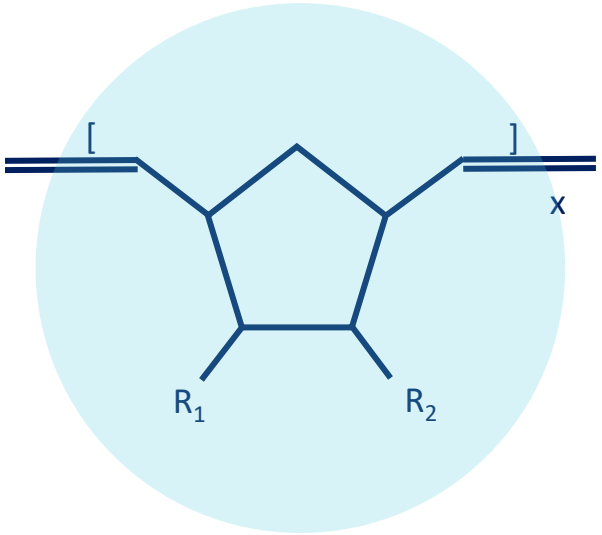
- Based on better match of Coefficient of Thermal Expansion (CTE)

Polymer Vial-Stopper-Seal Combinations

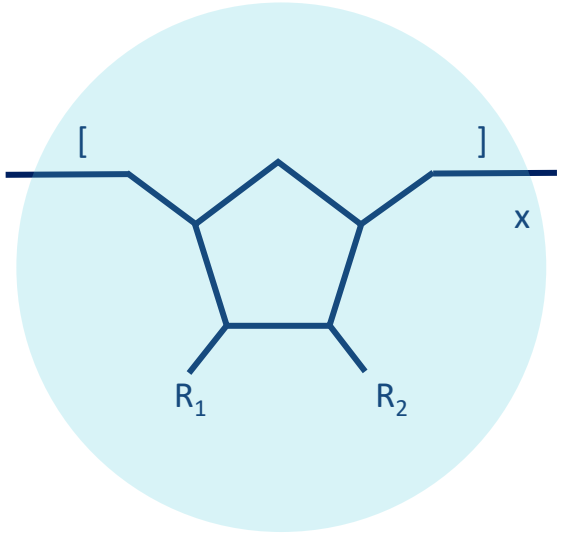


2005 Nobel Prize

Ring-Opening Metathesis Polymerization
e.g., $Ru[P_2C_3H_2(C_6H_5)_8]Cl_2$



Hydrogenation



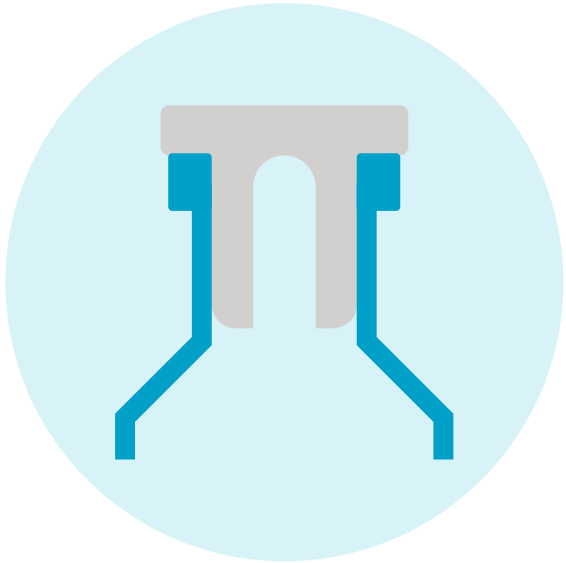
Mw ~ 7×10^4
PD ~ 2

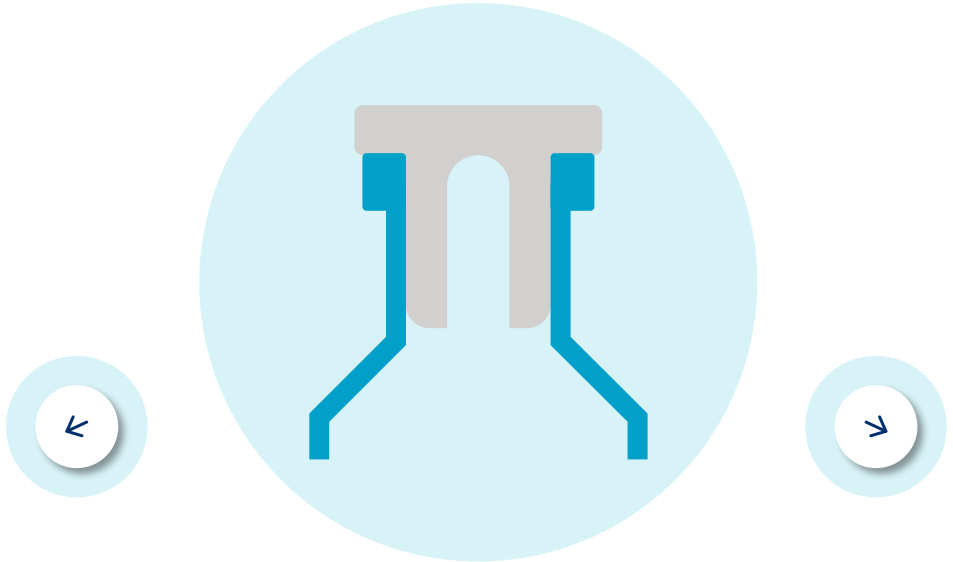
Daikyo Crystal Zenith® Cyclic Olefin Polymer (COP)

J. Edwards, W. Wolf, R. Grubbs. The synthesis of cyclic polymers by olefin metathesis: Achievements and challenges. J. Polym. Sci., Part A: Polym. Chem. 2019, 57, 228–242.

Differences in Coefficient of Thermal Expansion

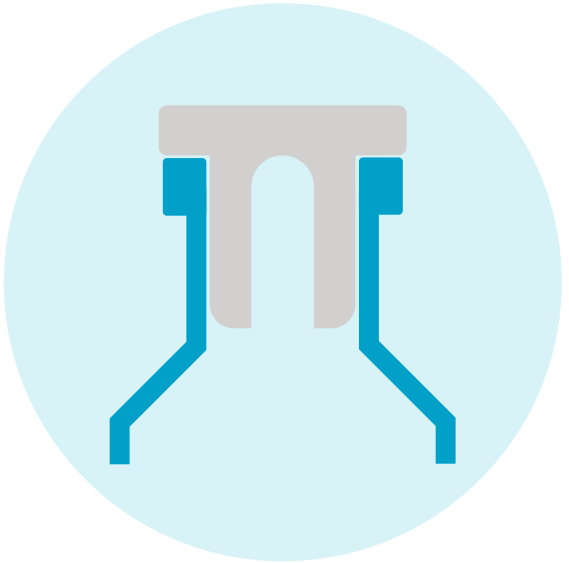
Polymer Vial
-180°C





Room Temperature

Glass Vial
-180°C

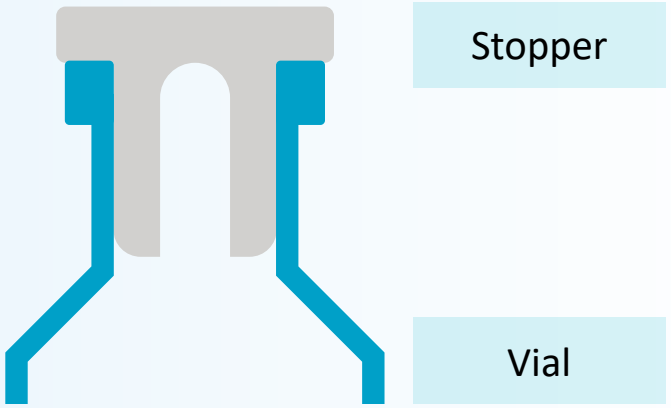


polymer and rubber shrink at ~ same rate

M. R. Gehrmann, et al. Long-Term Study of Container Closure Integrity of Rubber-Glass Vial Systems by Multiple methods. PDA Journal of Pharmaceutical Science & Technology, 74, 147-161 (2020)

Differences in Coefficient of Thermal Expansion

Room Temperature

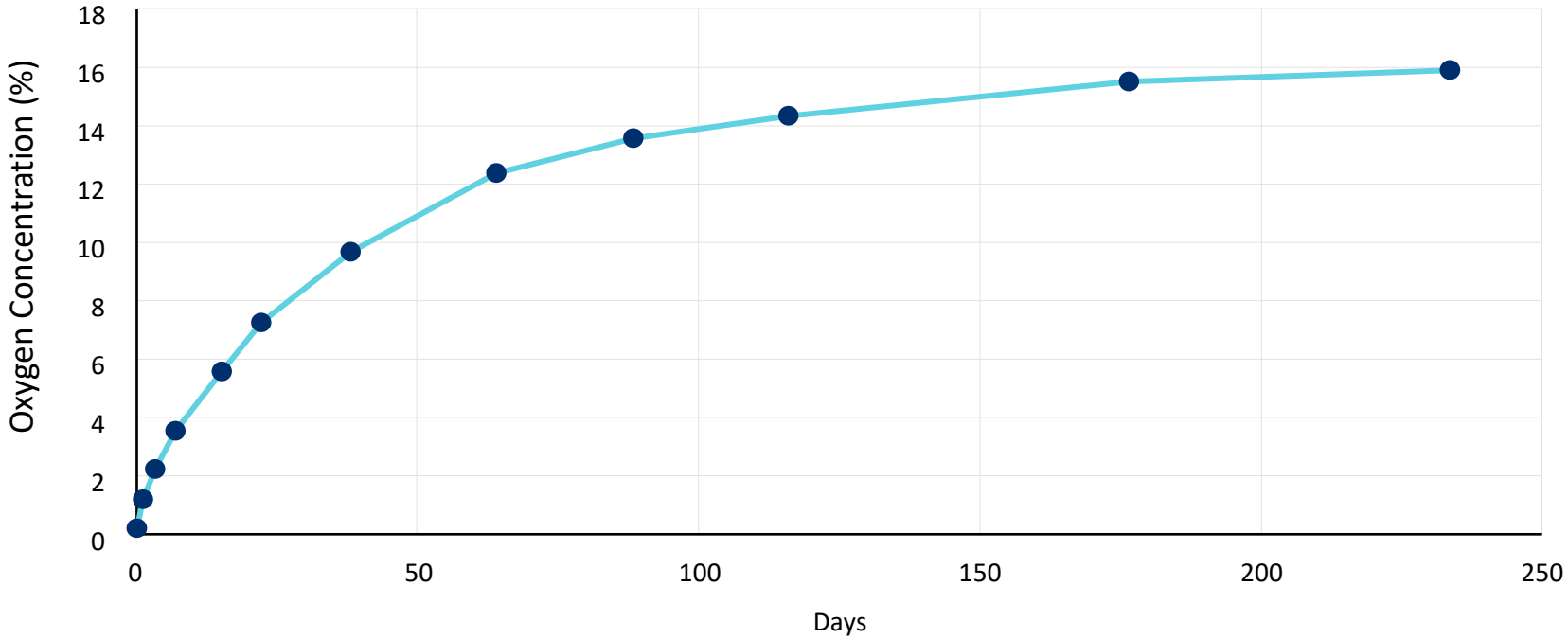


	Coefficient of Thermal Expansion[1] (10^{-6} cm / cm – K)	Volume Shrinkage (%) (room temperature to -180°C)
Glass	4	0.2
Rubber	77	4.5
COP	70[2]	4.1

[1] Thermal Expansion-Linear Expansion Coefficients: http://www.engineeringtoolbox.com/linear-expansion-coefficients-d_95.html
[2] Characteristics of Daikyo Resin CZ, Daikyo Seiko, Ltd. Technical Report DS-CZ-E017, January 2022.

Oxygen Headspace Room Temperature

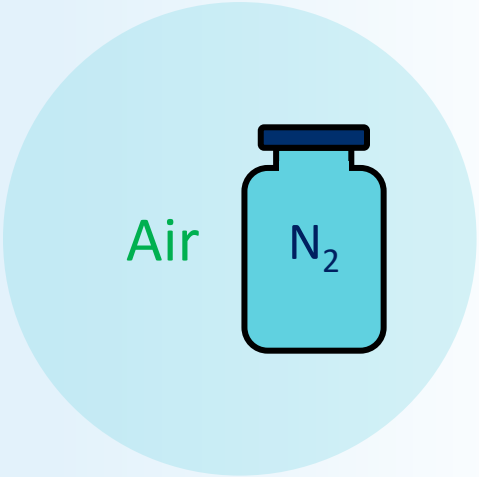
2 ml COP - RT



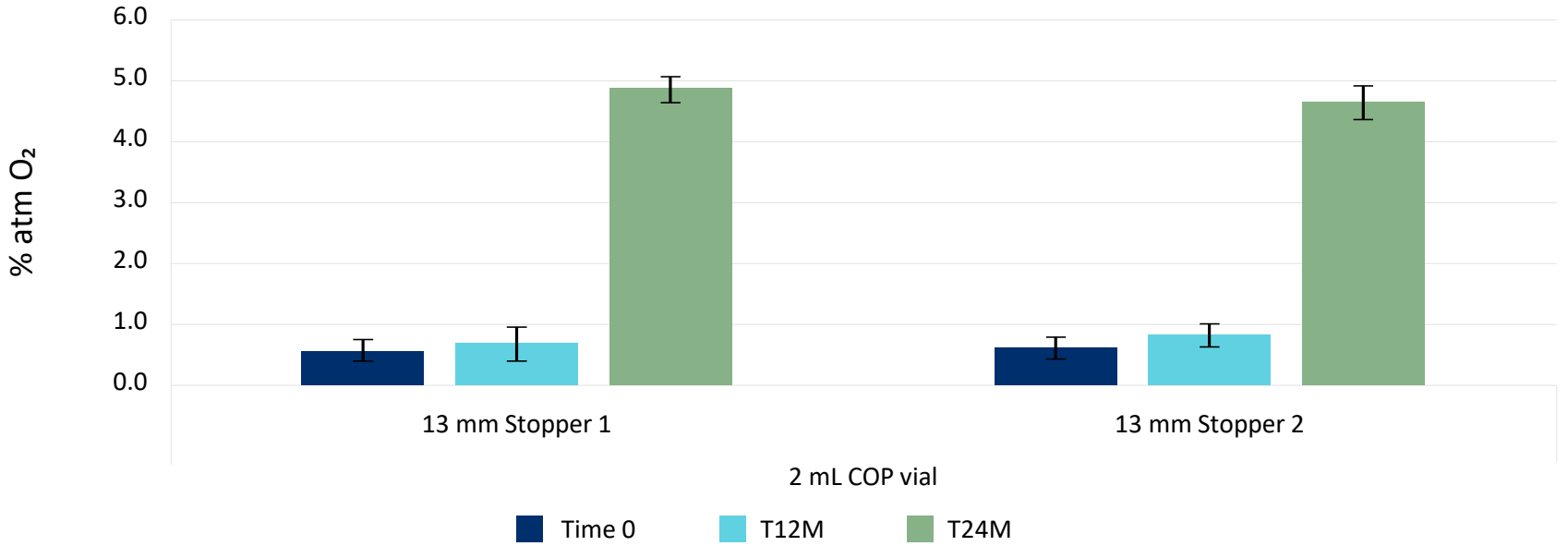
- 2 ml COP vial and 13 mm serum stopper
- Significant permeation of O_2
- Expected –polymers are gas permeable

Ingress of Gases into Cyclic Olefin Polymer Vial-Based Container Closure Systems at -80°C, West Pharmaceuticals Service Inc. Technical Report 2019/028
M. Gehrmann, O. Laskina, L. Fang, P. McAndrew. Challenges in Low-Temperature Storage of Cell Therapy Drug Products. PepTalk 2020, San Diego, CA, January 20, 2020.

Oxygen Headspace -80°C Storage



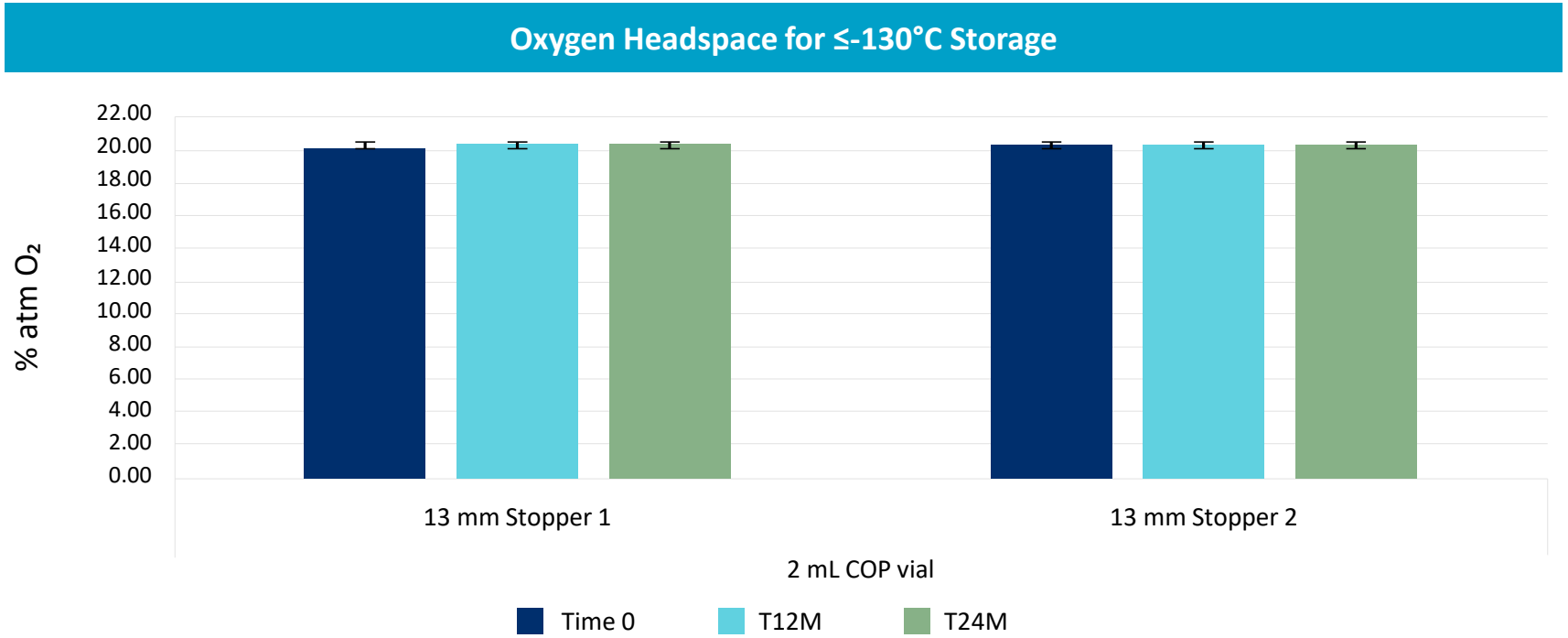
Oxygen Headspace for -80°C Storage (N_2 filled vials)



- 2 ml COP vial and 13 mm serum stopper
- Essentially no ingress of O_2 over 12 M
- Low level of ingress of O_2 over 24 M

Long-Term Container Closure Integrity Testing of Vial-Stopper-Seal Combinations Comprising Daikyo Crystal Zenith® Vials at Ultra-Low and Cryogenic Temperatures, West Pharmaceuticals Service Inc. Technical Report 2023/261

Oxygen Headspace ≤-130°C Storage



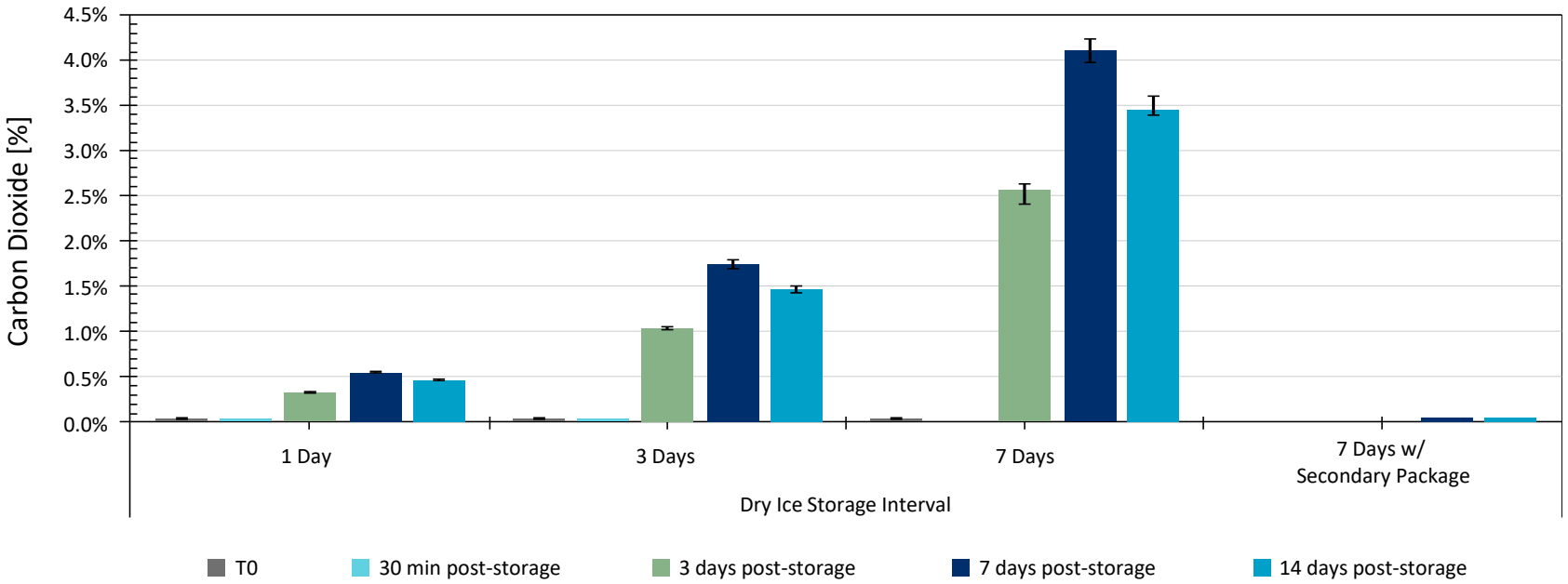
2 ml COP vial and 13 mm serum stopper

No ingress of N_2 over 24 M

Long-Term Container Closure Integrity Testing of Vial-Stopper-Seal Combinations Comprising Daikyo Crystal Zenith® Vials at Ultra-Low and Cryogenic Temperatures, West Pharmaceuticals Service Inc. Technical Report 2023/261

CO_2 Headspace at -78°C (Dry Ice Storage)

2R COP vial and 13 mm serum stopper



Upon storage on dry ice and thaw small amount of CO_2 appears – results from dissolution/permeation of CO_2 in COP

Level is low and quantified

Prevented by secondary packaging (poly(ethylene terephthalate-based sealed bag)

Ingress of Gases into Cyclic Olefin Polymer Vial-Based Container Closure Systems at -80°C, West Pharmaceuticals Service Inc. Technical Report 2019/028
M. Gehrmann, O. Laskina, L. Fang, P. McAndrew. Challenges in Low-Temperature Storage of Cell Therapy Drug Products. PepTalk 2020, San Diego, CA, January 20, 2020.

Conclusion of Polymer/Elastomer Vial Combinations

For COP-based systems, gas permeation is quantified:

- Significant at room temperature
- Substantially reduced at -80°C
- Eliminated at ≤ -130°C

For COP-based systems stored on dry ice:

- Small level of CO_2 ingress occurs
- Can be addressed with a secondary package

Summary

Combining techniques (RSF, tracer gas analysis and headspace analysis) enables a more complete and quantified measure of CCI for vial and syringe combinations to enable judgement if MALL can be met

Acknowledgements / References

Project Managers & Analytical Laboratory Staff:

- V. Gupta, B. Jacobs, E. Crouch, G. O'deens, A. Chapman, A. McLean

References:

- L. E. Kirsch, et al. (University of Iowa) *Pharmaceutical Container/Closure Integrity II: The Relationship between Microbial Ingress and Helium Leak Rates in Rubber-Stoppered Vials.* PDA Journal of Pharmaceutical Science & Technology, 51 (5), 195-202 (1997).
- Gehrmann M.R., McAndrew T.P. Long-Term Study of Container Closure Integrity of Rubber-Glass Vial Systems by Multiple Methods. PDA J Pharm Sci Technol. 2020 Jan-Feb;74(1):147-161. doi: 10.5731/pdajpst.2019.010223
- J. Edwards, W. Wolf, R. Grubbs. *The synthesis of cyclic polymers by olefin metathesis: Achievements and challenges.* J. Polym. Sci., Part A: Polym. Chem. 2019, 57, 228–242.
- Ingress of Gases into Cyclic Olefin Polymer Vial-Based Container Closure Systems at -80°C, West Pharmaceuticals Service Inc. Technical Report 2019/028
- Long-Term Container Closure Integrity Testing of Vial-Stopper-Seal Combinations Comprising Daikyo Crystal Zenith® Vials at Ultra-Low and Cryogenic Temperatures, West Pharmaceuticals Service Inc. Technical Report 2023/261
- M. Gehrmann, O. Laskina, L. Fang, P. McAndrew. Challenges in Low-Temperature Storage of Cell Therapy Drug Products. PepTalk 2020, San Diego, CA, January 20, 2020.
- Characteristics of Daikyo Resin CZ, Daikyo Seiko, Ltd. Technical Report DS-CZ-E017, January 2022.