SiO2

MATERIALS SCIENCE℠

Next Generation Vials for COVID-19 vaccines and cell and gene therapies.

Millrock Webinar

Chris Weikart & Peter Sagona

April 8th, 2021

Challenges with COVID-19 Vaccines and Gene Therapy Drugs

- **Biologic Based Drugs/Vaccines**
  - Complex molecules
  - Inherently unstable in liquid formulations

- **Currently requires cryogenic storage to meet shelf life**

- **Efforts ongoing to Lyophilize (Freeze Drying) drug to eliminate cold storage.**

Technology

Hybrid Parenteral Vials – Materials of Construction

❑Primary Container (polymer)

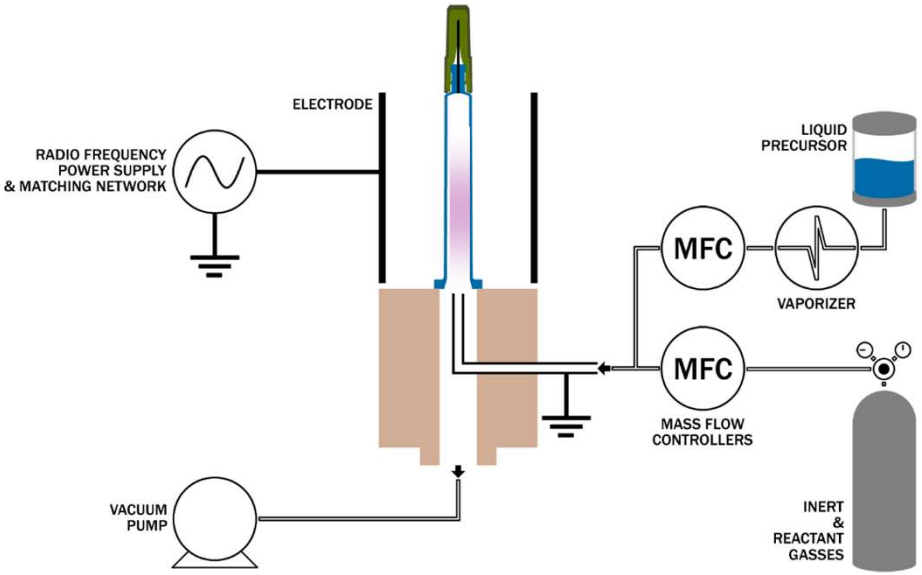
- Injection Stretch Blow Molded
- Medical Grade Cyclic Olefin Polymer (COP/COC)
- Low dimensional Variability
- Optically clear & shatter resistant
- High barrier to water vapor

❑Barrier Coating System (glass-like)

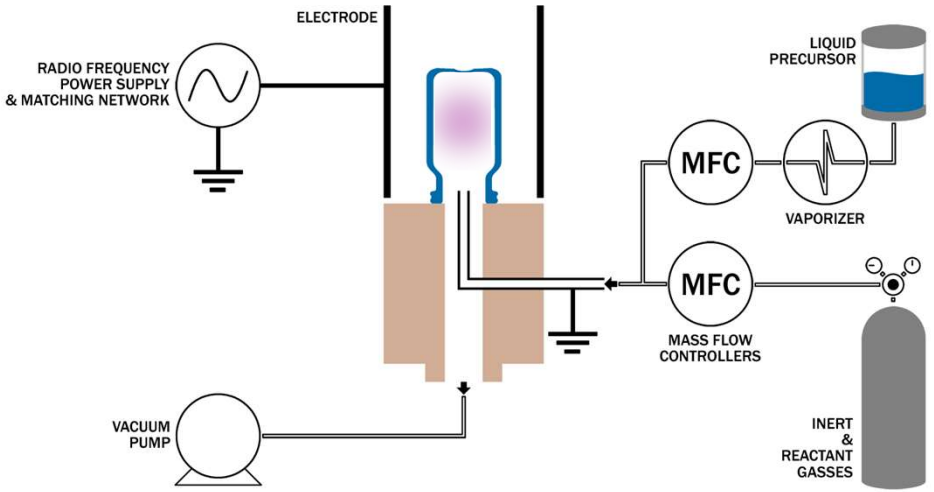
- Plasma Enhanced Chemical Vapor Deposition
- Silicon-based coating
- High barrier to oxygen
- Inert No extractable/no leachables
- Barrier to label adhesives/polymer additives
- Optically clear

Proprietary Technology Applied to Any Container Geometry

- Plasma enhanced chemical vapor deposition (PECVD)
- Coating applied to the inside of syringes, vials, cartridges of all geometries
- Inert drug contact surface is equivalent irrespective of container



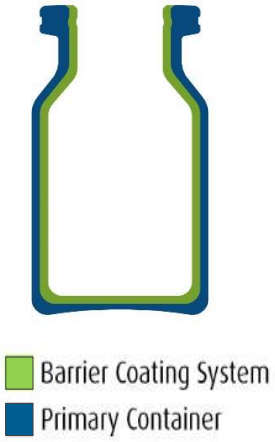
1mL staked needle syringe



6mL vial

Characteristics of Barrier Coating System

- ❑ Chemically Inert & hydrophobic
  - o Hydrolytically resistant (low Si dissolution)
  - o pH resistant (no ion migration)
- ❑ Covalently bound to polymer
- ❑ Barrier to gases
  - o Oxygen
  - o Ethylene oxide

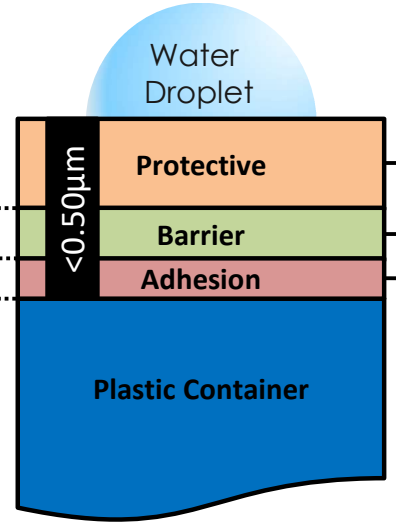


"Covalent" Interfacial Bonds

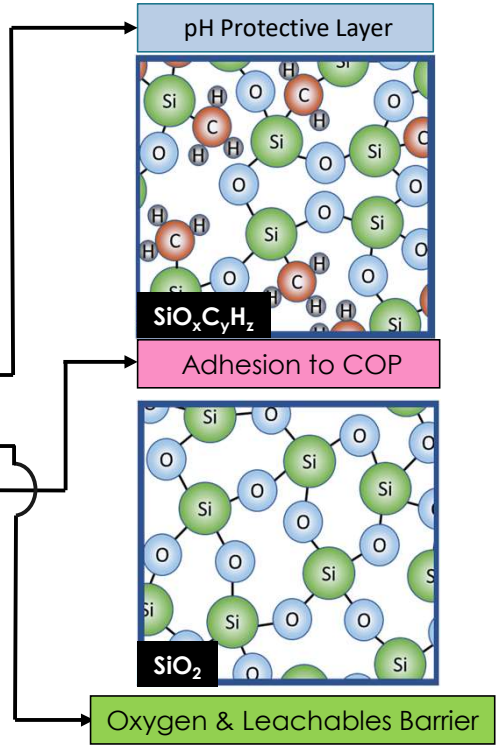
- Si-O-Si
- Si-CH_x

- O_3-Si-C
- Si-O-C
- Si-C
- Si-CH_x

"Hydrophobic" Surface Wettability



"Organosiloxane" Coating Chemistry



Lyophilized Drugs/Vaccines

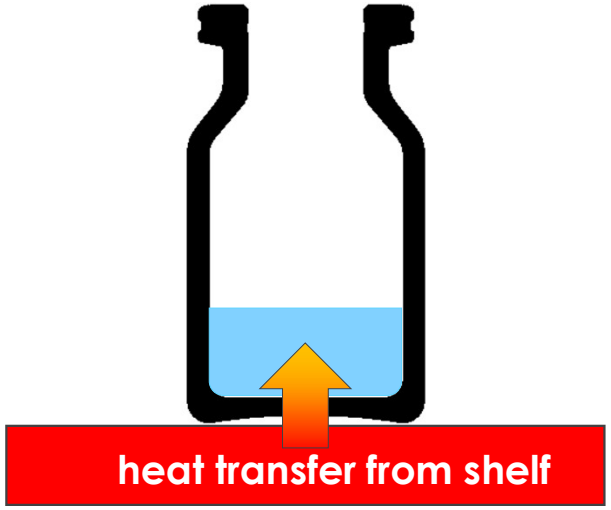
Exploiting SiO2 Hybrid Vials for Lyo

	Borosilicate Glass	SiO_2 Medical Products
No Breakage	• Freezing expansion/contraction • Filling, handling & transport	• **Shatter resistant hybrid material** • **Breakage eliminated at high fill**
Lower Particles	• Wall Shear from freeze expansion • Glass particles injected into patient	• **Covalent bonding** • **Lower shear force** • **Eliminates glass particles**
Drying Consistency	• Variability in mass and dimensions • Higher heat transfer variability	• **Lower mass and dimensional variation** • **Flatter bottom vials**
No Wall Residue	• Hydrophilic surface • Solution wicks & cake sticks to wall	• **Consistent hydrophobic surface** • **No cake sticking or wicking**
Less Protein Aggregation	• Higher shear stress on proteins • Protein denaturing & aggregates	• **Lower protein shear forces** • **Lower aggregates & denaturing**
Higher Fill Volumes	• Fill volumes kept below 50% • Risk of breakage	• **100% fill volumes possible** • **No breakage**

Polymer Thermal Conductivity and Vial Base Reduces Heat Transfer

Heat transfer coefficient of vials (K_V) is dependent on:

- ❑ Thickness & mass of vial wall
- ❑ Thermal conductivity (h) of material
  - COP/COC – 0.13 W/m K
  - Glass – 1.20 W/m K
  - Air – 0.023 W/m K
- ❑ Contour of vial base

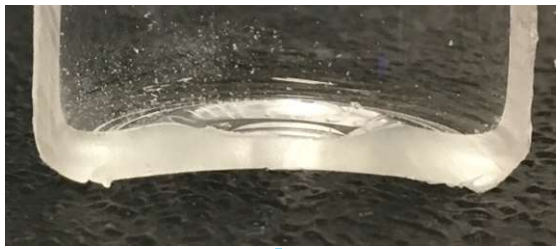


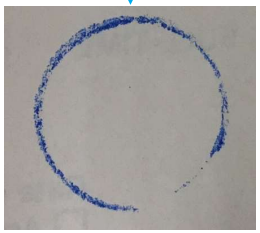
$$K_v \approx h/\text{thickness}$$

Improving COP/COC Vial Heat Transfer

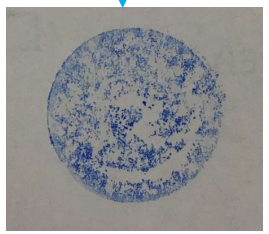
Base of SiO2 Vials

Standard





Flat-Bottom



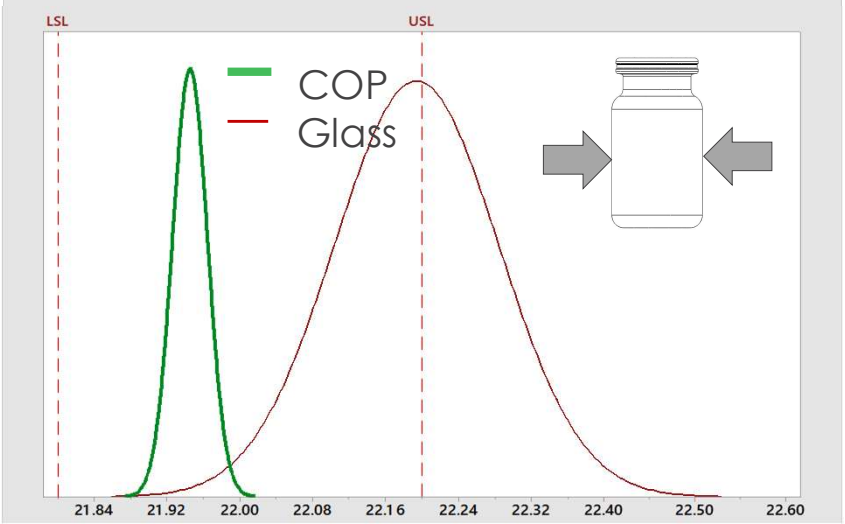
Ink-blot test for flatness

Lower Dimensional and Mass Variability

Mass Variability

Vial Type	Mass (g)
Glass	11.708 ± 0.085
COP	6.726 ± 0.006
Coated COP	6.728 ± 0.005

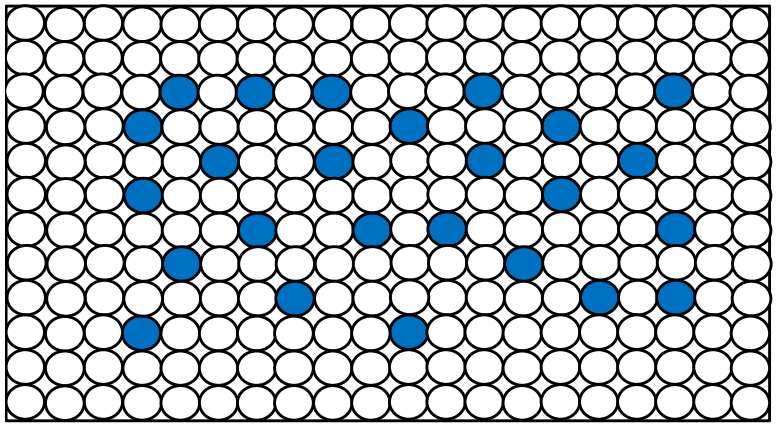
Dimensional Variability



Outside Diameter (mm)

Improved Heat Transfer and Less Batch Variability

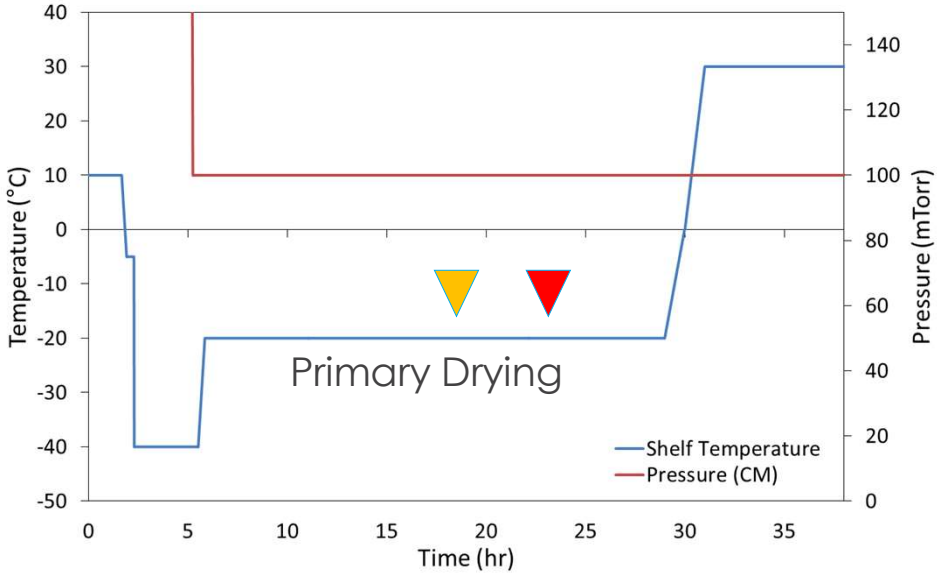
Tray Capacity (240 10ml Vials)



Tested vials

Vial Type	Kv *10^4 (cal/s/cm^2/^{o}C)	Standard Deviation
Glass	4.23	± 0.19
Coated COP	3.18	± 0.07
Coated COP (Flat Bottom)	3.56	± 0.07

Lower Moisture Loss Variability Within Batch



Relative Std Dev (% water lost)		
Vial Type	**18 hrs**	**23 hrs**
Glass	6.5	0.2
Coated COP (Flat Bottom)	1.7	0.5

- Glass has more water loss variability during primary drying (sublimation).
- Ensures more consistent lyo product quality.

No Breakage Irrespective of Fill Volume

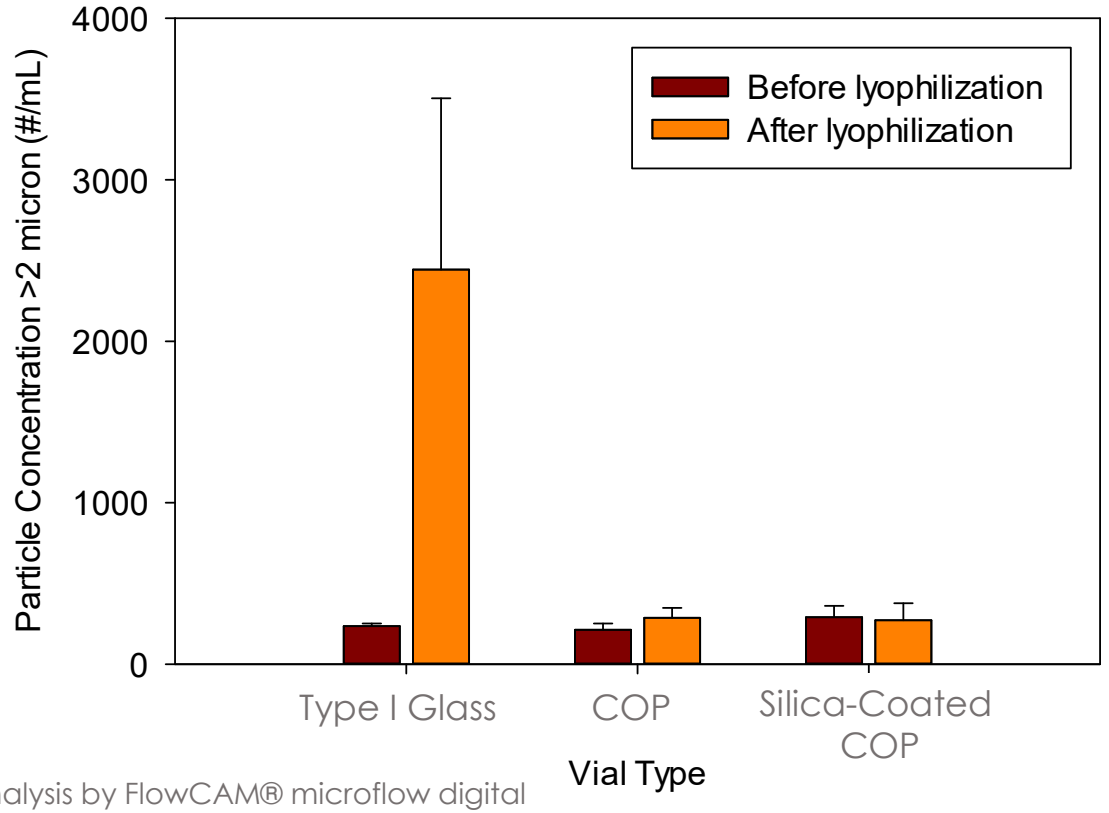
Fill Volume (mL)	Fill Percentage (%)	Glass		SiO2	
		# Broken	%	# Broken	%
10	100	4/12	33	0/16	0
8	80	5/27	19	0/37	0
6	60	1/38	3	0/38	0
4	40	0/35	0	0/38	0

- Vials filled with 10% w/v mannitol solution
- Freezing: Shelves were cooled to -40°C at a rate of 1°C/min and held for two hours to freeze
- Drying: Chamber pressure was reduced to 150mT and the shelf was warmed to 5°C at 0.5°C/min.

NOTE: Conducted at Millrock Technology

Fewer Subvisible Particles after Reconstitution

(10% Mannitol Solution/6ml fill Volume)



*Particle analysis by FlowCAM® microflow digital imaging which detects particles between 2 -100 µm

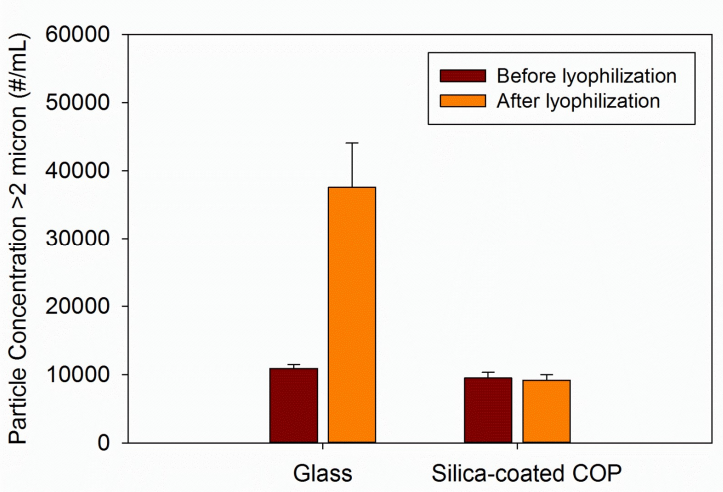
Similarities and Improvements Compared to Glass

Lyo Formulation:

1 mg/ml IVIg
10mM glycine
5% w/v sucrose
0.02% v/v polysorbate 20

SiO2 Coated

- **Similarities:** Initial residual moisture content, cake appearance, reconstitution time, and protein recovery.
- **Improvements:**
  - 4X Lower particle levels in reconstituted formulations in coated COP.
  - Less variable Kv and drying rates.



Eliminates Wall Residue – Hydrophobic Coating

- Placebo Formulation:
  - hemophilia
  - high salt content
  - polar solution
- Wall Residue
  - Silica-coated vials: NONE
  - Glass: Significant
- Conclusion: hydrophobic coating surface reduces wall residue for some formulations.

Cold Storage

Exploiting SiO2 Hybrid Vials for Cell & Gene Therapies

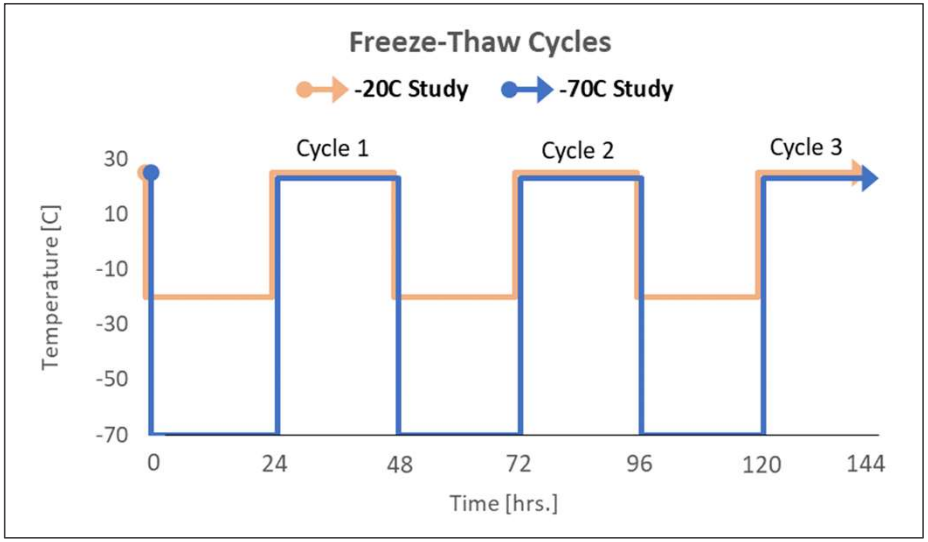
- ❑ No CCI Leakage at Cryo Temps (-196°C)
- ❑ Low Particles
- ❑ No Organic or Inorganic Leachables
- ❑ Barrier to Oxygen
- ❑ No Breakage
- ❑ Serialization – Track & Trace
- ❑ Ready-to-use

Freeze-Thaw Study Design (-20°C & -70°C)

Experimental:

- Vials filled with various volumes of high purity water and enclosed with rubber stopper and aluminum crimp
- Vials then placed in freezer, one group at -20C and another group at -70C
- After a 24-hour at temperature, vials were removed from freezer and held at room temp for 24 hours.
- Freeze-thaw cycle repeated 3 times with visual inspections after each cycle (cycle = low temp + room temp)

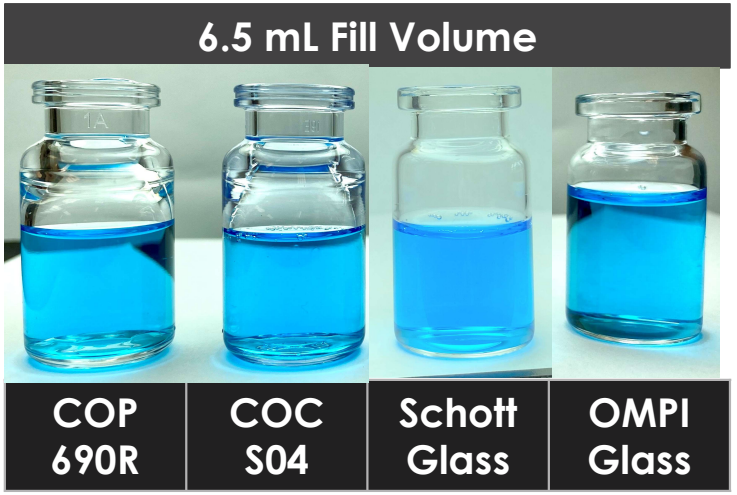
10 mL Vial Fill
(representative)



No Breakage Observed for SiO2 Vials at-70C

Low temp. to room temp. (24 hr. soak at each temp, no ramp between)

Manufacturer	Material	Fill Volume	# Failures (n = 50)			
			Cycle 1	Cycle 2	Cycle 3	TOTAL
-70C Cycling						
SiO2	COP 690R	6.5 mL	0	0	0	**0**
SiO2	COC S04	6.5 mL	0	0	0	**0**
Schott	Glass	6.5 mL	0	**3**	**1**	**4**
OMPI*	Glass	6.5 mL	**2**	**1**	**2**	**5**

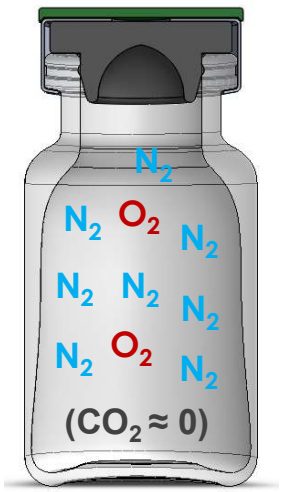


No Breakage for any vials at -20°C cycling

*Ompi vials are 8 mL vial geometry

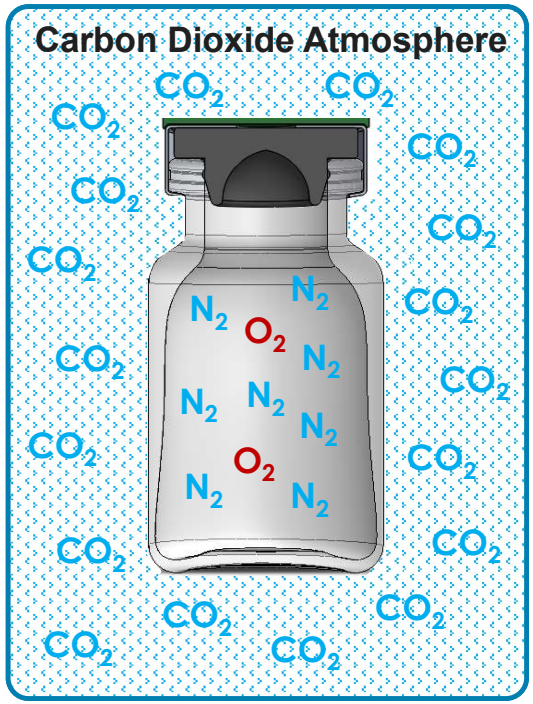
Deep Cold Storage CCI Experimental

CO_2 Headspace Analysis @ **-80C**



Sample sealed at ambient conditions (Air) and headspace CO_2 measured

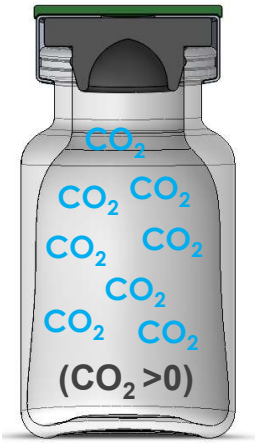
Storage

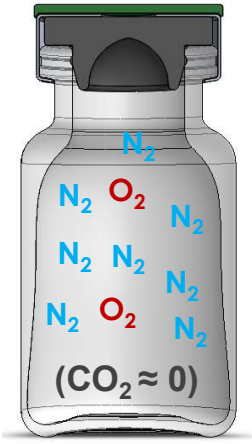


Loss of seal integrity equals increase of CO_2

At each timepoint headspace measured again

Preservation of seal integrity equals preservation of air headspace





Driving Force

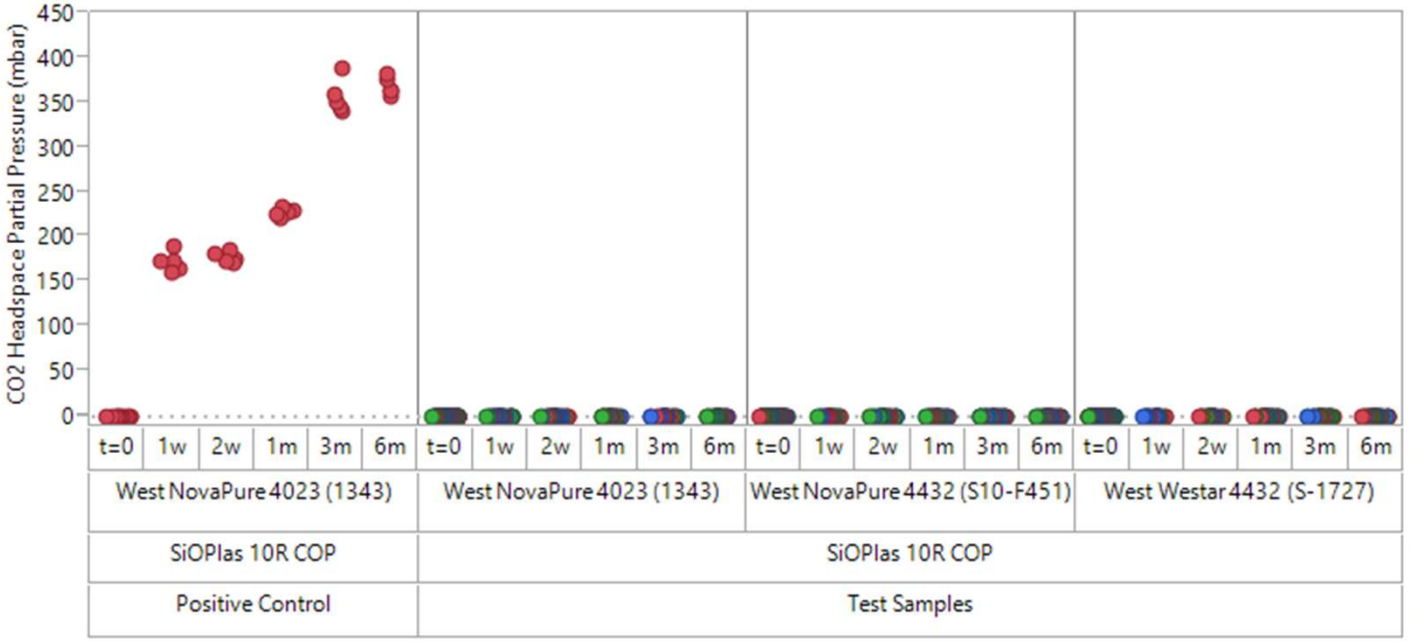
Carbon Dioxide (CO_2) rich atmosphere ensures a concentration gradient between the chamber atmosphere and the container headspace

CCI Study Design **(-80°C)**

Set	Type	Conatainer Closure System (CCS)			Vial-Closure	Seal	Storage	Time Points						Total Meas.
		Vial	Cap	Stopper	Finish (mm)	Compression (RSF-lbf)	Temp. (C)	t=0	1 week	2 weeks	1 month	3 months	6 months	12 months	
1	Test Samples	SiOPlas 10 mL COP Vial	West Flip-Off Seal (Aluminum Crimp)	West NovaPure 1343, 4023/50	20	Low	-80	360	20	20	20	20	20	20	720
						Mid			20	20	20	20	20	20	
						High			20	20	20	20	20	20	
2	Test Samples	SiOPlas 10 mL COP Vial	West Flip-Off Seal (Aluminum Crimp)	West NovaPure S10-F451-4432/50	20	Low	-80	360	20	20	20	20	20	20	720
						Mid			20	20	20	20	20	20	
						High			20	20	20	20	20	20	
3	Test Samples	SiOPlas 10 mL COP Vial	West Flip-Off Seal (Aluminum Crimp)	West Westar RU (non-Flurotec coated) S-1727, 4432/50, B2-42	20	Low	-80	360	20	20	20	20	20	20	720
						Mid			20	20	20	20	20	20	
						High			20	20	20	20	20	20	
4	Positive Controls	SiOPlas 10 mL COP Vial (5µm Laser Drilled)	West Flip-Off Seal (Aluminum Crimp)	West NovaPure 1343, 4023/50	20	High	-80	30	5	5	5	5	5	5	60

- All test samples stoppered and crimped at Genesis Packaging Technologies under ambient conditions
- Positive controls samples, 5 µm laser drilled SiOPlas 10 mL COP vials, prepared by Lighthouse Instruments
- All headspace CO_2 measurements via FMS-Carbon Dioxide Headspace Analyzer performed by Lighthouse Instruments

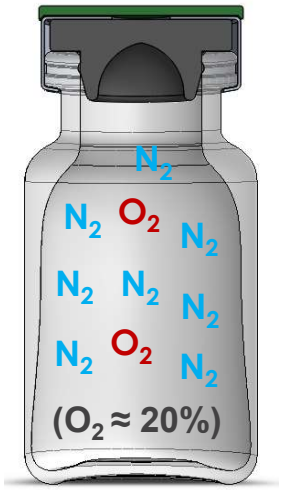
No measurable changes in headspace observed after 6 months at **-80°C**



Initial Residual Seal Force Setting (RSF)
- High (~16 lbf)
- Mid (~10 lbf)
- Low (~6 lbf)

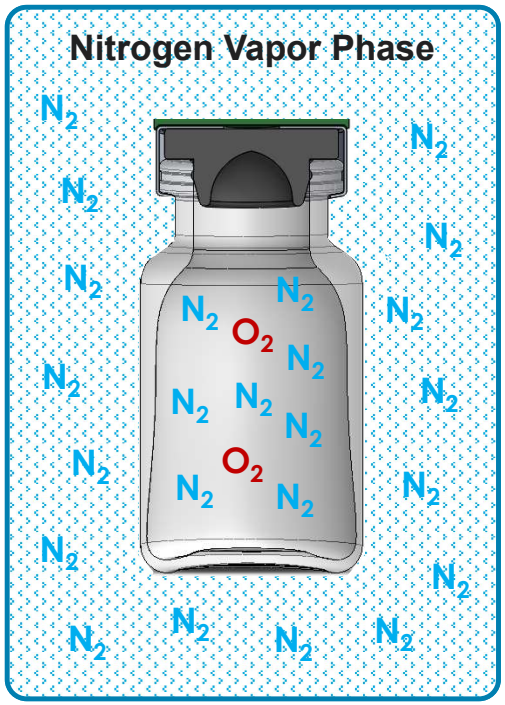
Cryogenic Storage CCI Experimental

O_2 Headspace Analysis @ **-180C**



Sample sealed at ambient conditions (Air) and headspace O_2 measured

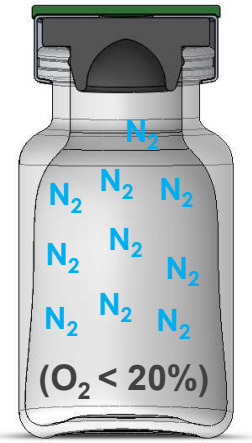
Storage



Driving Force

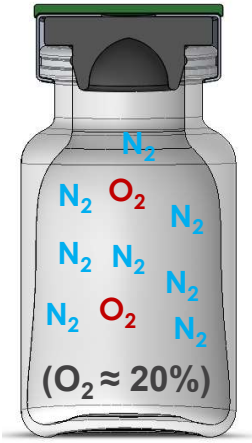
Nitrogen (N_2) rich atmosphere ensures a concentration gradient between the chamber atmosphere and the container headspace

Loss of seal integrity equals loss of O_2



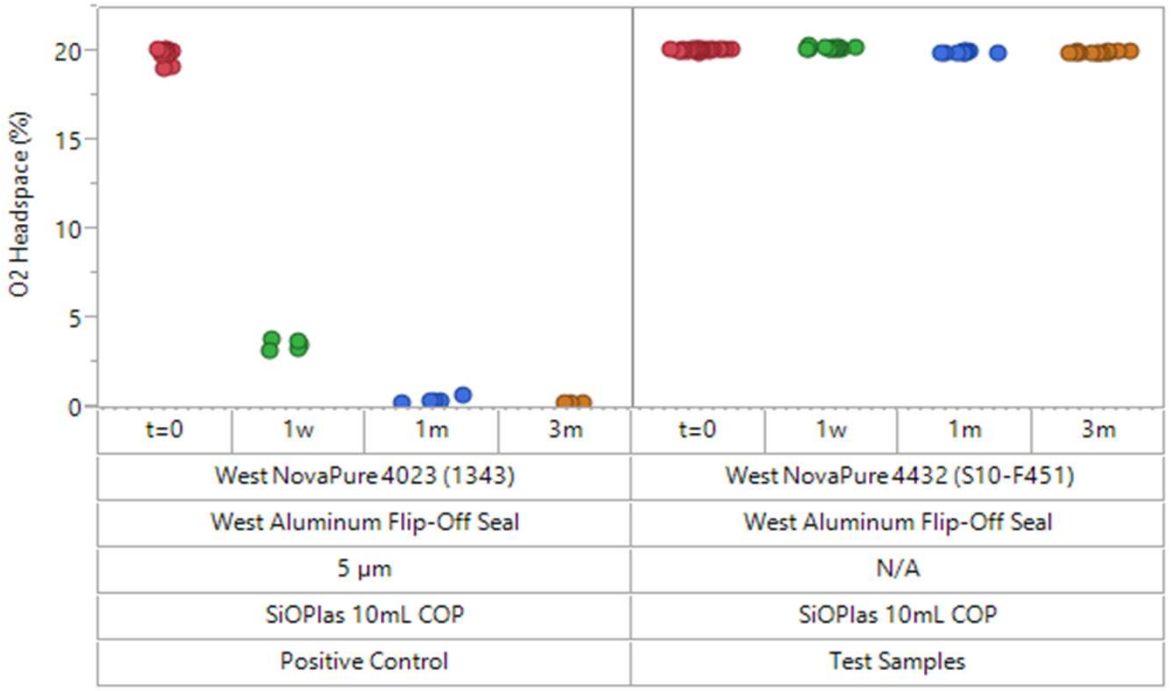
At each timepoint headspace measured again

Preservation of seal integrity equals preservation of O_2



Results: 10 mL Vial Headspace O_2 Concentration (%) after 3 months at **-180°C**

West NovaPure 4432 Stopper + Aluminum Crimp



Test Samples: n=15
Positive Controls: n=5

Conclusion: No measurable changes in headspace observed after 3 months at -180°C

Cell & Gene Therapy Company Using SiO2 (-80°C Cold Storage)

- Peptide-based viral vector formulation
  - soluble adaptor to redirect human T cell engineered to express an universal chimeric antigen receptor UniCAR against PSMA expressing solid tumors
  - Packaged in 2mL SiO2 Vials
  - 1+ year into 3-year cold storage (i.e. -80°C) stability study.
- Eliminated borosilicate glass as a packaging option due to problems with ion migration into drug product.

Demonstrated Drug Stability in SiO2 2mL Vial (1+ years @ -80°C Storage)

Purpose/Parameter	Method	Acceptance criteria	t0	1 m	3 m	6 m	9 m	12 m
[illegible]				[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Appearance	Ph. Eur. 2.1.1./ Ph. Eur. 2.2.2.	colorless and clear	colorless and clear	colorless and clear	colorless and clear	colorless and clear	colorless and clear	colorless and clear
Identity	^{1}H-NMR	For information only	conforms	conforms	conforms	conforms	conforms	conforms
Purity	RP-HPLC	For information only	97.5*	97.4	97.5	97.1	97.6#	98.5#
Potency/Identity	Standardized cellular flow assay	50-150 %	94	105	79	101	101	125
Content	UV (280 nm)	0.6 mg/mL ± 10 %	0.60	0.60	0.60	0.61	0.60	0.61
pH	Ph. Eur. 2.2.3.	4.5 ± 0.2	4.4	4.5	4.5	4.4	4.5	4.4
Sterility	Ph. Eur. 2.6.1.	Sterile, no microbial contamination	Sterile	-	-	-	-	-
Particulate contaminants (sub-visible particles)	Ph. Eur. 2.9.19.	≥ 10 µm: < 6000 per container ≥ 25 µm: < 600 per container	64 2	-	-	-	-	43/container 0/container
Endotoxins	Ph. Eur. 2.6.14	< 5 EU/mL	0.15 EU/mL	-	-	-	-	-
Test for integrity	According to ASTM E 515 – 2011	no leakage detected		-	-	-	-	-

Summary – SiO2 Hybrid Vials

- ❑ Developed for Lyophilized Drug/Vaccine products
  - Lower heat transfer variability → Lower freezing/drying variability
  - No breakage and no wall residue
  - Fewer particles and aggregates compared to glass
- ❑ Demonstrated to withstand extreme cold storage requirements.
  - No CCI leakage down to -180°C
  - Drug stability with a viral vector formulation stored at -80C for 1+ years