Elastomeric Closures for Lyophilization Applications

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PDA Freeze Drying in Practice, Osterode, Germany

Agenda

- Considerations for Elastomeric Stoppers for Lyophilization
- Challenges & Solutions: Stopper pop-up
- Challenges & Solutions: Stoppers sticking to the Lyo Shelf
- Challenges & Solutions: Moisture Uptake and Transmission
- Vial System Considerations
- New Stopper for Lyophilization Applications

Considerations for Lyophilization Closures: Elastomer Formulation

- Low absorption and adsorption characteristics
- Low extractable volatiles
- Low oxygen transmission
- Low moisture absorption
- Low moisture permeation
- Easy to dry
- Low particulates

- Low coring/fragmentation
- Good resealing
- Optimum container closure integrity
- Good machineability

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Considerations for Lyophilization Closures: Design

Legged Design

- More flexible during insertion
- Symmetric: keeps horizontal position during freeze drying
- Twining effect of stoppers possible

Igloo Design

- More stable in the vented position due to more contact with the glass vial and a less flexible plug part
- Asymmetric balance point: can get out of vertical axis during stoppering
- Igloo design prevents twinning

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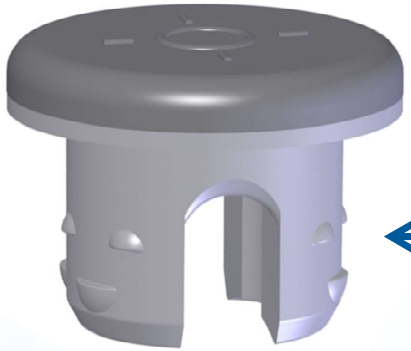
Challenges & Solutions: Stopper Pop-Up/Pop-Off

Check list:

- ✓ Blowback features
- ✓ Interference fit of the stopper plug and vial neck
- ✓ Siliconization of the stopper and vial

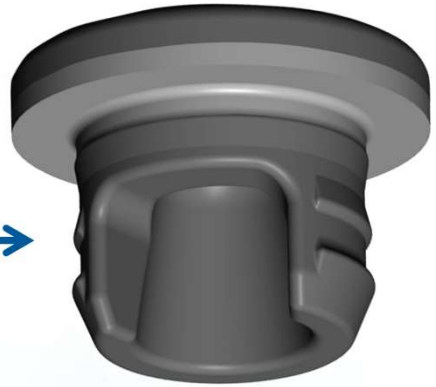
Challenges & Solutions: Stopper Pop-Up/Pop-Off
Blowback features

Non-blowback stopper



protruding nubs or rings
for stopper positioning

Blowback stopper



Blowback feature

Challenges & Solutions: Stopper Pop-Up/Pop-Off

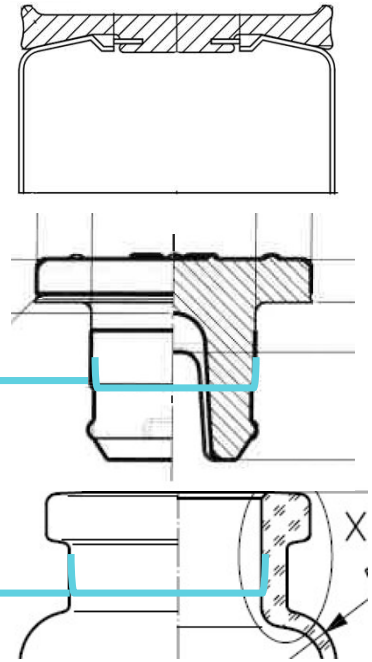
Interference Fit of stopper plug and vial neck

Interference Fit : Analysis which shows the dimensional interference between stopper plug and vial inner neck

Stopper plug outer diameter [mm]	13.10
Vial neck inner diameter* [mm]	12.60
Nominal Interference Fit [%]	**3.8**

Industry Standard is 2 - 10%

Consider min and max values!



$$Interference\ fit\ [\%] = 100 \bullet \frac{[(stopper\ plug\ outer\ diameter) - (vial\ inner\ neck\ diameter)]}{(stopper\ plug\ outer\ diameter)}$$

* According to ISO 8362-1:2009 Injection containers and accessories — Part 1: Injection vials made of glass tubing

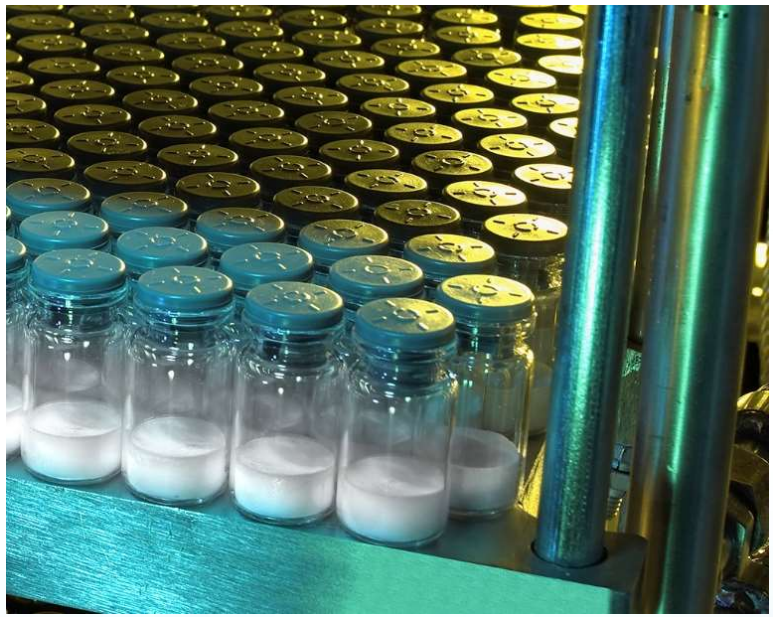
Holistic Considerations in Optimizing a Sterile Product Package to Ensure Container Closure Integrity. Fran L. DeGrazio. PDA Journal of Pharmaceutical Science and Technology Jan 2018, 72 (1) 15-34; DOI: 10.5731/pdajpst.2017.007658

Challenges & Solutions: Stoppers Sticking to the Lyo Shelf

The closure surface can stick to the lyo shelf and lift the whole vial when closing the vials after lyophilization

Solution: FluroTec® film to prevent sticking

- Eliminate sticking to the lyo chamber shelf
- Reduce clumping/sticking and twining issues
- Minimize adsorption and absorption
- Minimize extractable volatiles from the elastomer
- Increase lubricity and thus ensuring a smoother transport in the filling line, leading to higher throughput
- Base elastomer formulation remains the same - regulatory burden for change is smaller



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Challenges & Solutions: Moisture Uptake and Transmission

- Moisture Vapor Transmission Rate (MVTR) can be measured
- For most drugs, the target residual moisture is < 1% lyophilized product
- Contributions to moisture include
  - Washing procedure
  - Sterilization cycle
  - Drying parameters dependent
  - Migration through the stopper

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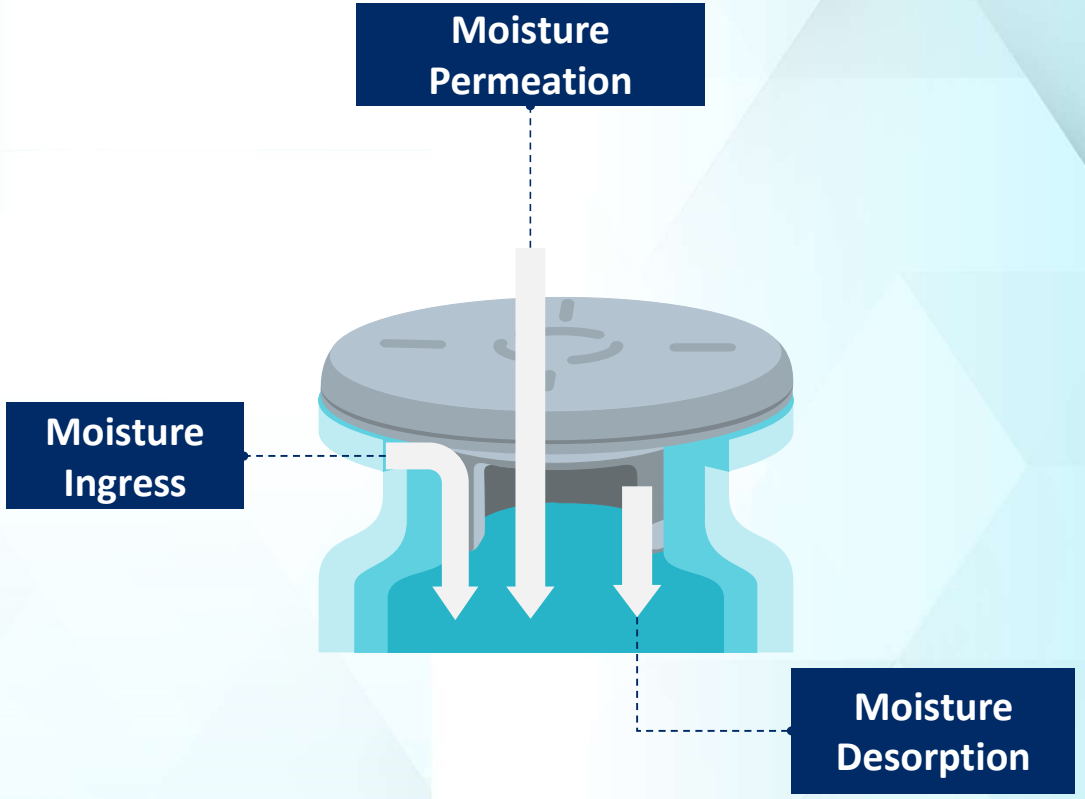
Challenges & Solutions: Moisture Uptake and Transmission

- Container closure integrity (CCI):
  Moisture ingress via the stopper-vial interface when lacking intact seal
- Moisture Vapor Transmission Rate (MVTR):
  Water vapor permeates from the environment through the stopper during long-term storage
- Residual moisture in the closure:
  Desorbs or releases from the stopper after processing (washing and steam sterilization)



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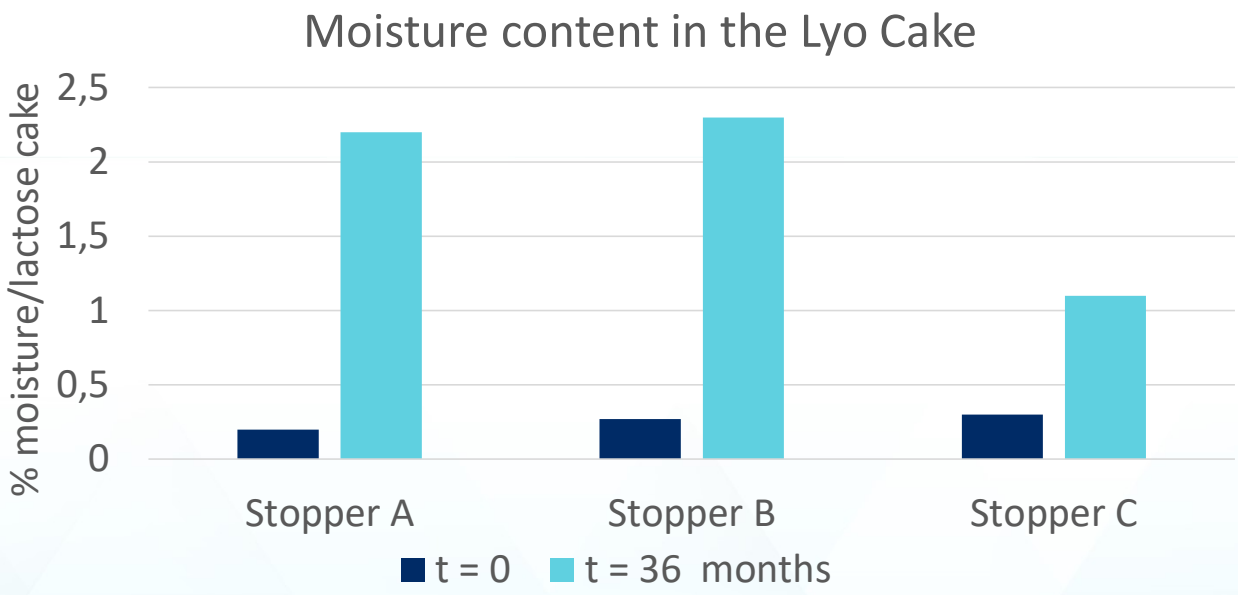
Challenges & Solutions: Moisture Uptake and Transmission

Case Study: MVTR and moisture uptake by the lyophilization cake

- Autoclaving: 60 min, 121^{0}C
  Drying: at 105^{0}C for 8 hours
- Filling: 2 mL of 5% lactose in water solution
- Storage of lyophilized product vials for 3 years at 25^{0}C/60% RH for 36 months



Moisture uptake by the lyo cake correlates with the MVTR of the rubber formulation

WEST Technical Report 2007/116: Lyophilization Stoppers and End Product Moisture Evaluation

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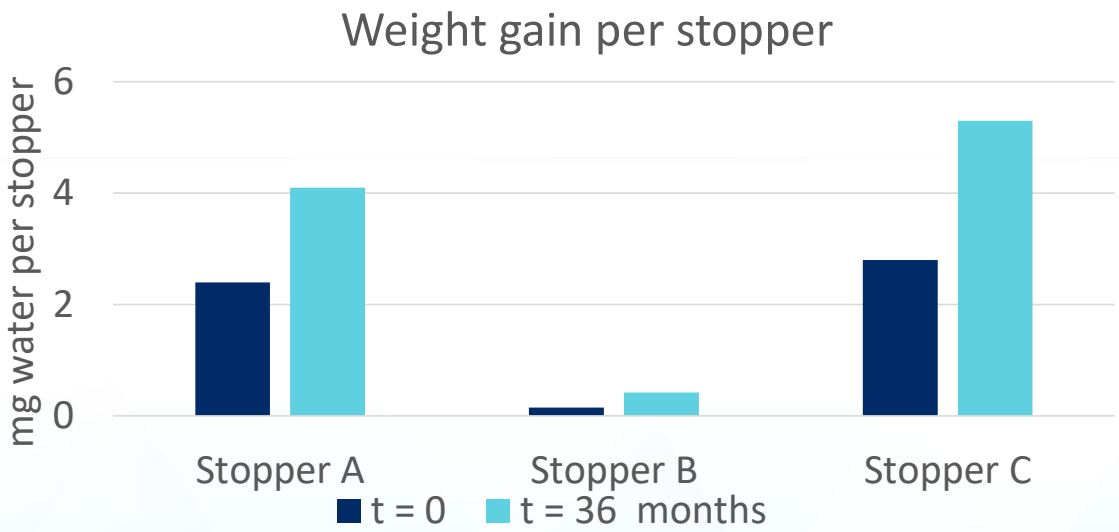

Stopper B has the highest MVTR

MVTR does not correlate to the moisture absorption capacity

WEST Technical Report 2007/116: Lyophilization Stoppers and End Product Moisture Evaluation

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Challenges & Solutions: Moisture Uptake and Transmission

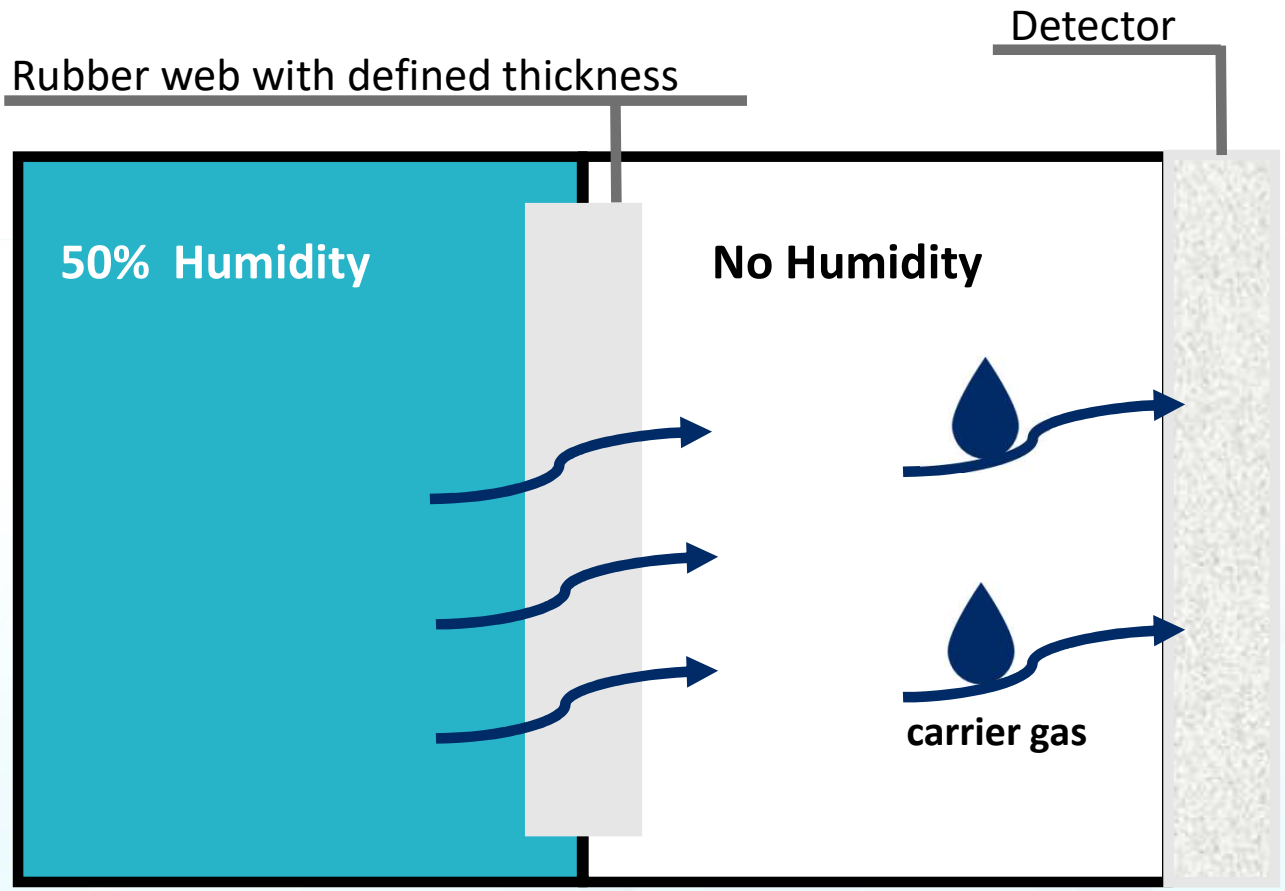
Reference: ISO 15106-3:2005, ASTM F1927

- **Critical Parameters:** temperature, humidity, thickness, flow rate, gas concentration

- Test item: Web
- Equilibrium needed before analysis

- MVTR is a material constant but is dependent on stopper design

- Typical data range: 0.06 – 6 g/m*day

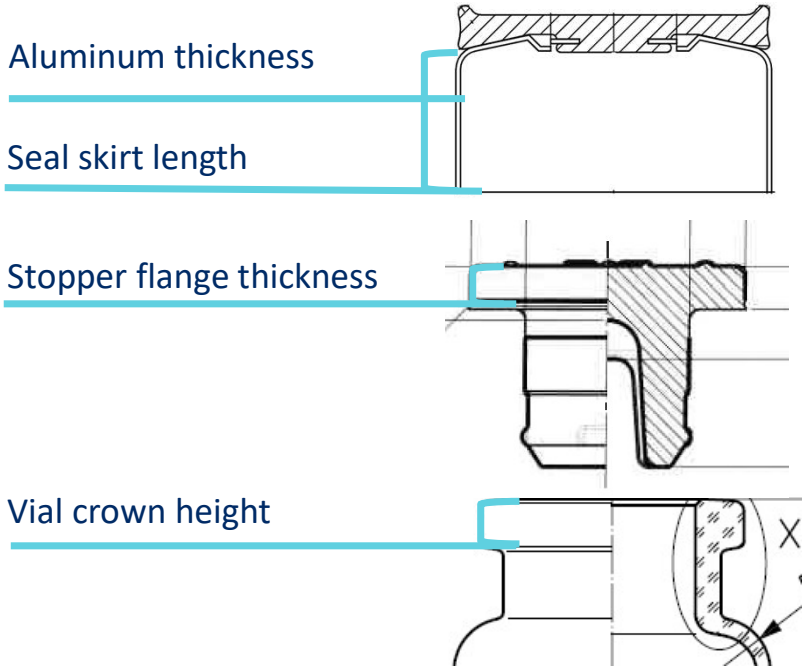


Vial System Considerations: Stack-Up Analysis of Vial, Stopper and Crimp Seal

Stack-Up Analysis: Shows the stack-up of vial, stopper and seal

Seal skirt length [mm]	7.5
Stopper flange thickness [mm]	3.43
Vial crown height * [mm]	3.60
Nominal excess skirt length ** [mm]	**1.04**

Industry Standard is 0.76 – 1.3 mm

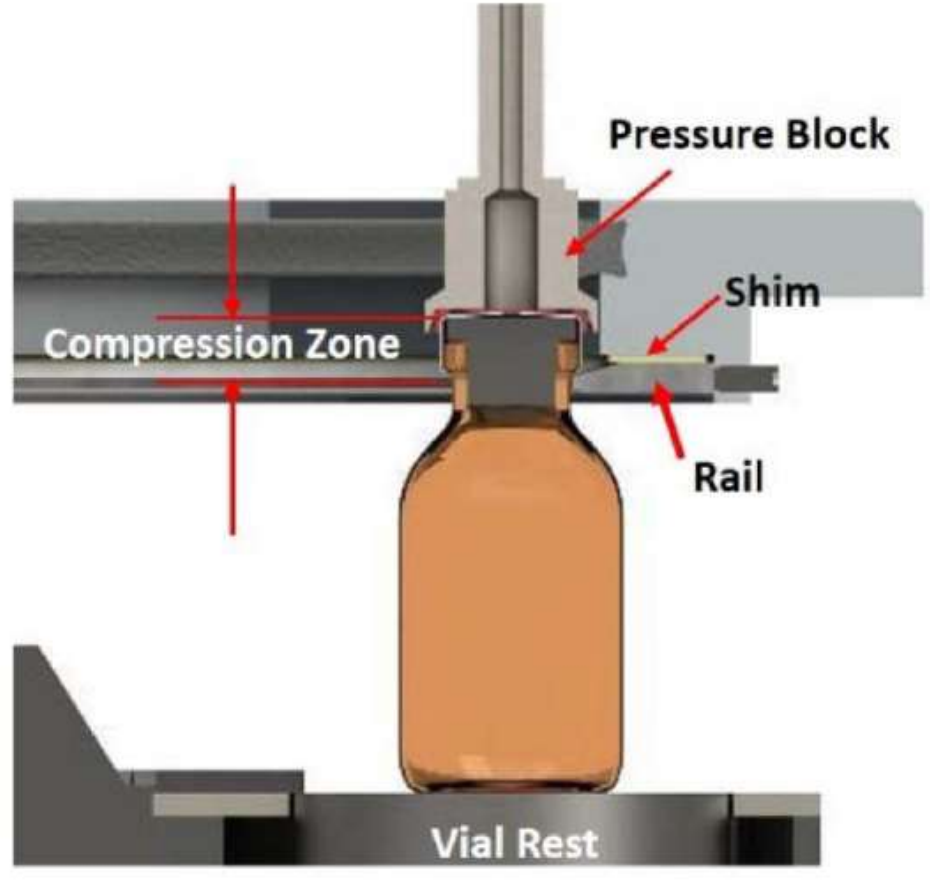


Excess skirt length =
(seal skirt length) – (aluminum thickness) – (vial crown height) – [(stopper flange thickness) • (1 – % stopper compression)]

* According to ISO 8362-1:2009 Injection containers and accessories — Part 1: Injection vials made of glass tubing
** at 20% compression, aluminum thickness 0.2 mm

Vial System Considerations: Crimping Process

- Capper Parameter Variables for Sealing Rail Capper
- Head height
- Pressure block
- Vial rest position
- Pre-compression force
- Sealing rail vertical position
- Sealing rail lateral position
- Sealing rail angles and angle contour
- Compression zone
- Applied top spring force



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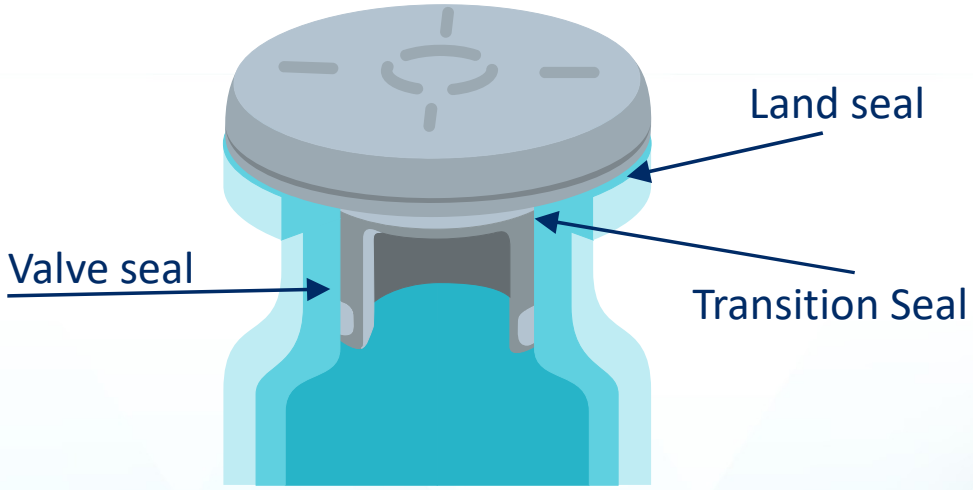
Vial System Considerations: Container Closure Integrity

- For an optimal CCI - use interference fit and stack up assessment
- The land seal is the main sealing surface
- An integral container closure system supports a low MVTR
- Methods to measure CCI, e.g., in USP <1207> CCI Testing



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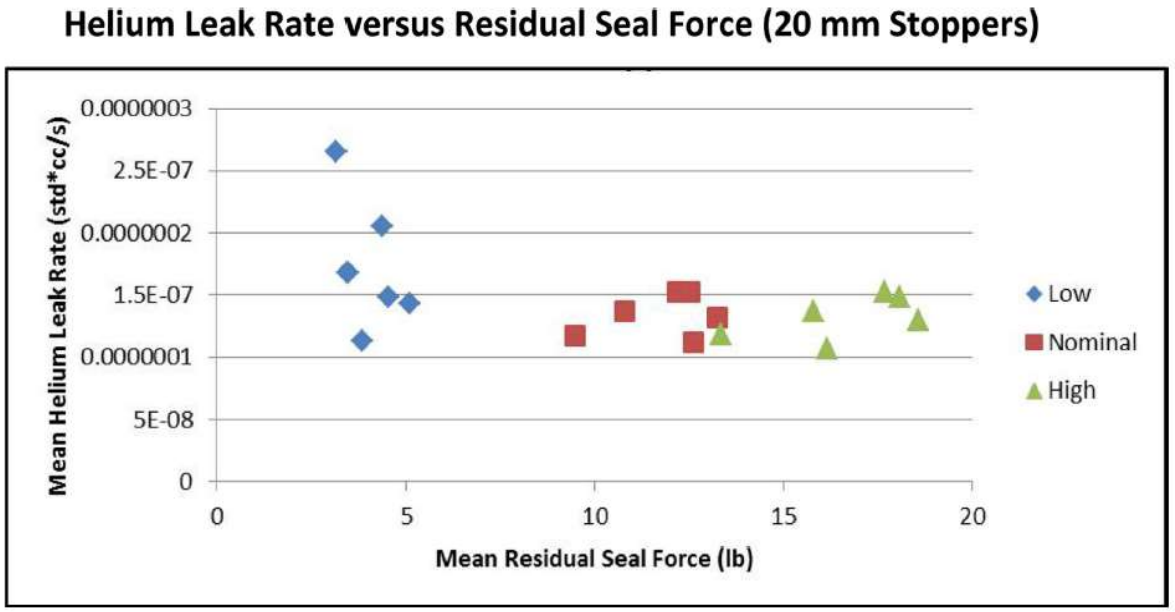
Vial System Considerations: Residual Seal Force

Residual Seal Force (RSF) is the stress a compressed elastomeric closure flange continues to exert on a vial land seal after crimping

- The stopper acts like a “compressed spring”
- Quantifying the RSF is a test method for the indirect estimation of elastomeric closure compression
- Sufficient compression is essential to seal integrity



RSF can be correlated to CCI, but needs to be evaluated for each specific container/closure/seal combination

Roger Asselta, Parenteral Vial Sealing & Integrity, PDA Europe Parenteral Packaging, Barcelona, Spain, 2017

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Vial System Considerations: Volatile Leachables

Reconstituted solutions might show haze formation

- Volatiles from the rubber composition can adsorb to the solid cake
- Antioxidants, oils, waxes, oligomers, low molecular weight PDMS, …
- This is more likely with legacy formulations than with modern formulations
- FluroTec® barrier film can help prevent leachables issues
- A “low extracting” rubber formulation might help as well …

Blue area: FluroTec® film coverage

Blue is for illustration purposes only

New Stopper for Lyophilization Application: 4040/40 V-50-I, S-87-I LyoTec® Stopper

At a Glance:

Formulation:

Chlorobutyl 4040/40

Design:

V-50-I, S-87-I, Igloo LyoTec® Stopper

Westar® washed
Ready-to-Sterilize and Ready-to-Use
Steam and Gamma compatible
Envision™ verification

Overview of 4040/40 LyoTec® Stoppers

Designed with the Future in Mind

Ultra-low extractables & leachables protect product quality while providing broad drug compatibility

Well-characterized extractables inform decision-making & enable risk assessment

Low level of particulates achieved through both raw material selection & West processing

Formula optimized for **low moisture content** to prevent cake degradation

Optimized drying properties improve steam sterilization throughput & save time

Compatibility with steam sterilization or gamma irradiation provides processing flexibility

Risk-mediated supply with strong inventory positions & qualified alternative sources of raw materials

Platform portfolio & global supply network strategy with strong West commitment

Closed System Transfer Device (CSTD) compatibility testing performed

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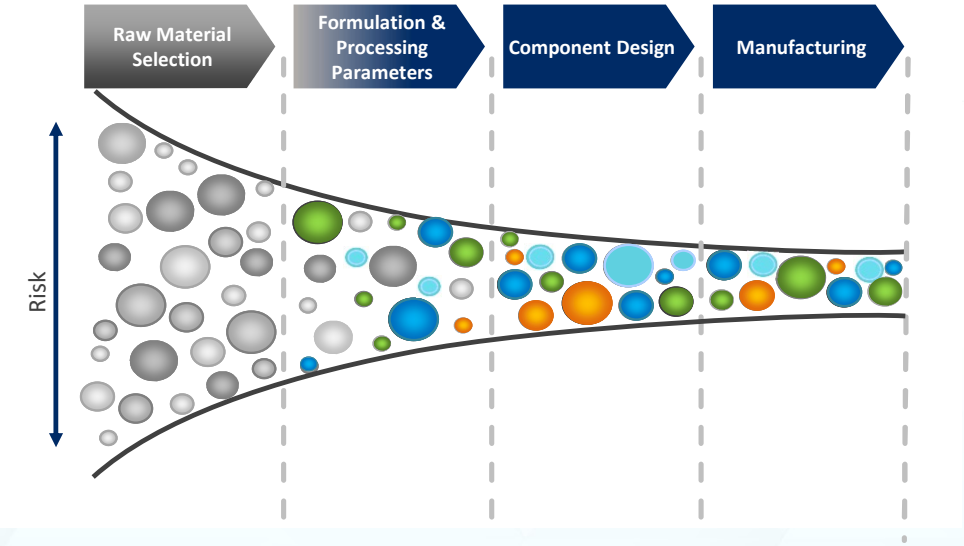
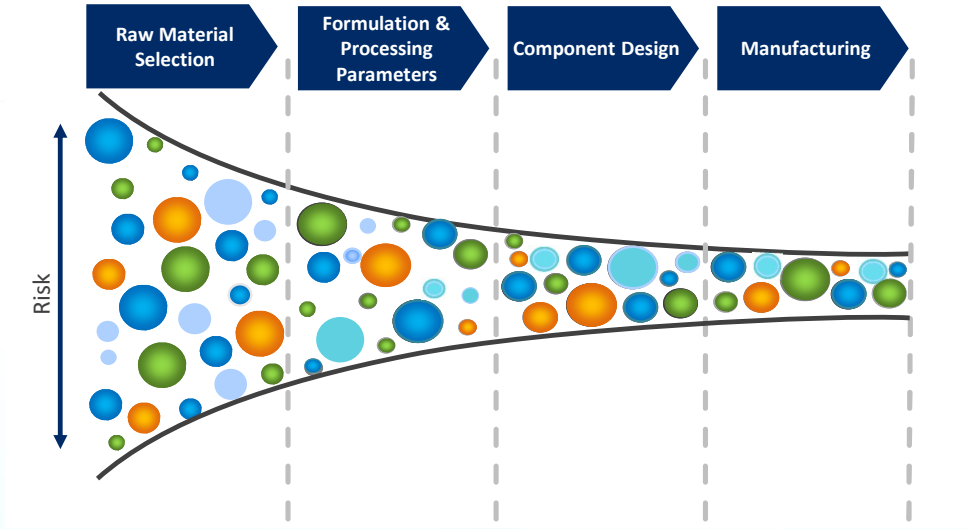
Quality by Design Approach: 4040/40 Development

Historical Approach



4040/40 Portfolio Approach



West's deep elastomer expertise & Quality by Design approach to development of the 4040 portfolio has focused on mitigating risk from raw material selection of the formulation to the final product

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4040/40 Ultra-Low Extractables & Leachables

Results:

- Ultra-low volatile extractables for 4040 LyoTec® stoppers
- Extractables were as expected & reflected our QbD approach to elastomer development

Impact:

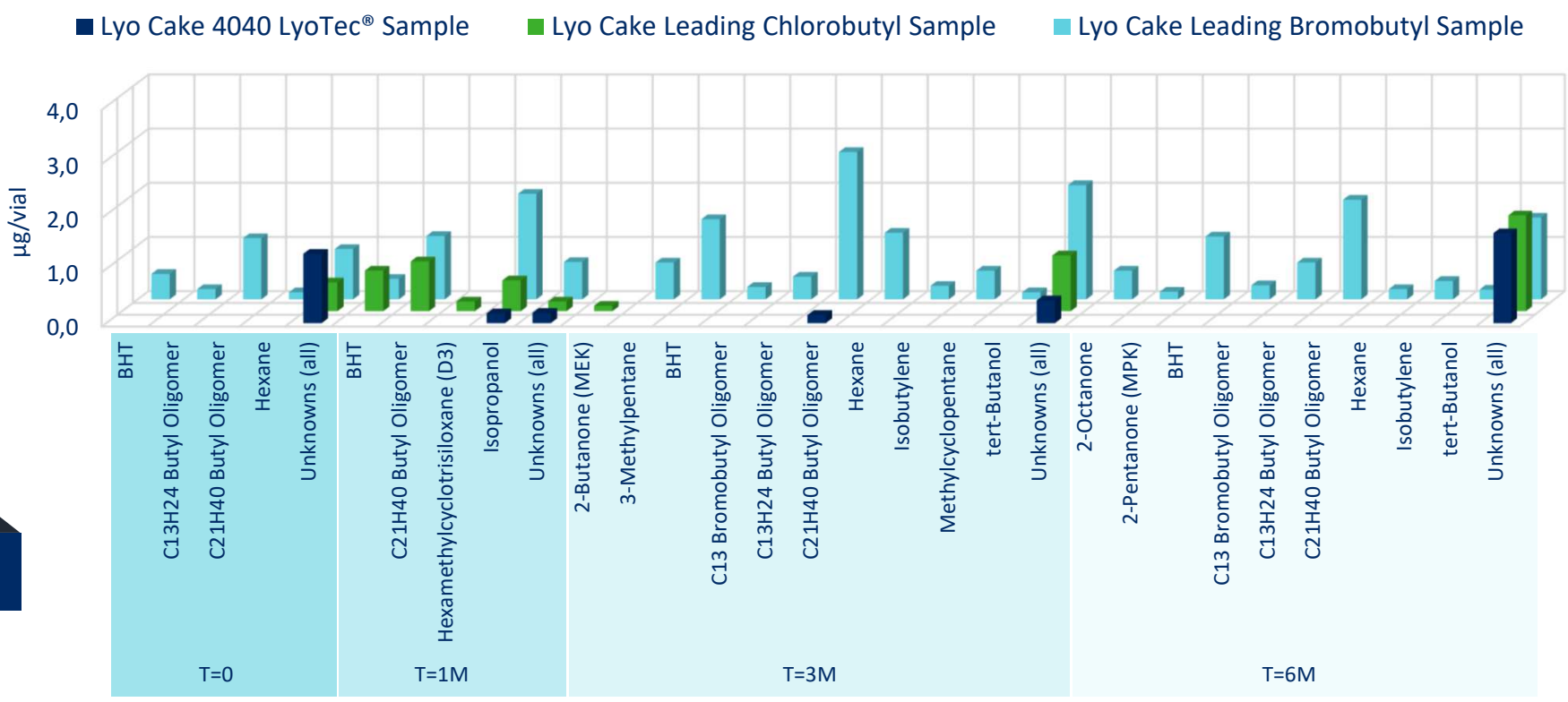
- Provides broad drug compatibility & protects drug product quality
- Proven reduction of potentially problematic extractables – no BHT*, no bromo-oligomers
- Extractables data demonstrates: no nitrosamines above the reporting threshold of 1 ng/g elastomer & no heavy metals above the reporting threshold of 0.05 µg/g of component**

Well-characterized extractables reinforced that deliberate raw material selection & a QbD approach results in reduced risk with 4040 LyoTec® stoppers

*BHT = Butylated hydroxytoluene or also known as dibutylhydroxytoluene
**Data available at West - Extractable Elements Data Sheet & Nitrosamines Data Sheet

4040/40 Leachables Over Time with Comparators

Volatile Leachables Lyo Cake Gas Chromatography–Mass Spectrometry (GC-MS) Headspace Reporting Threshold ≥ 0.1 µg/g



West Stability Report 741-SSR, Mar21

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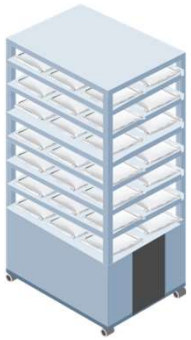
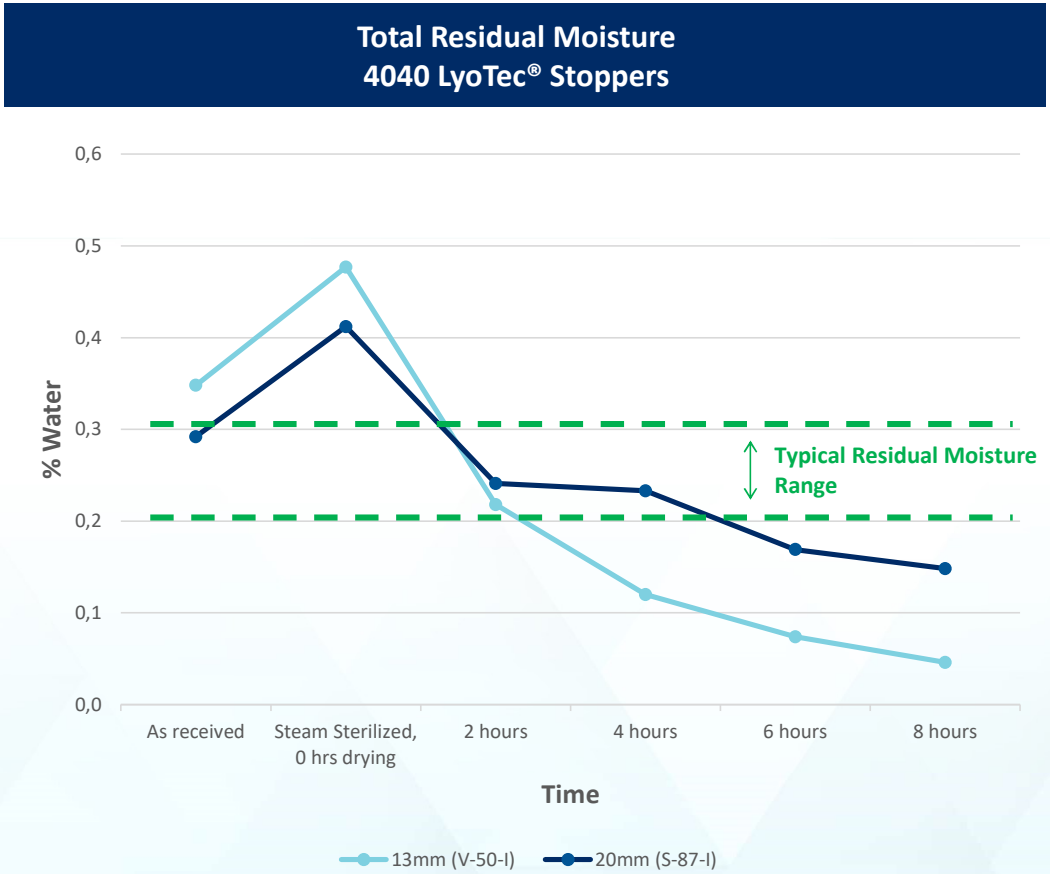
4040/40 Optimized Properties: Low Moisture Content



Sterilization of Stoppers

- Ready-to-sterilize (RS) product
- Steam sterilized @ 121°C for 1 hr
- Oven-dried @105°C
- Improve steam sterilization throughput with optimized drying properties
- Total Residual Moisture ≤ 0.2% H_2O for Lyophilization Stoppers



West Technical Report 2021/236: Evaluation of Ready-to-Sterilize 4040/40 Gray Lyo Stopper Water Content vs Comparators Post-Steam Sterilization and Drying

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4040/40 Optimized Properties: Compatible Across ISO Glass Vial Blowback Types

TESTING PROGRAM

ISO standard tested	13mm (V-50-I)	20mm (S-87-I)
European blowback (EBB)	Compatible	Compatible
No blowback (NBB)	Compatible	Compatible
American blowback (ABB)	Compatible	Compatible

Simplify global supply chain management with stopper designs compatible with various glass blowback geometries

West Technical Report 2019/211: Evaluation of Container Closure Integrity for 4040/40 Lyophilization Stoppers

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4040/40 Demonstrated Container Closure Integrity

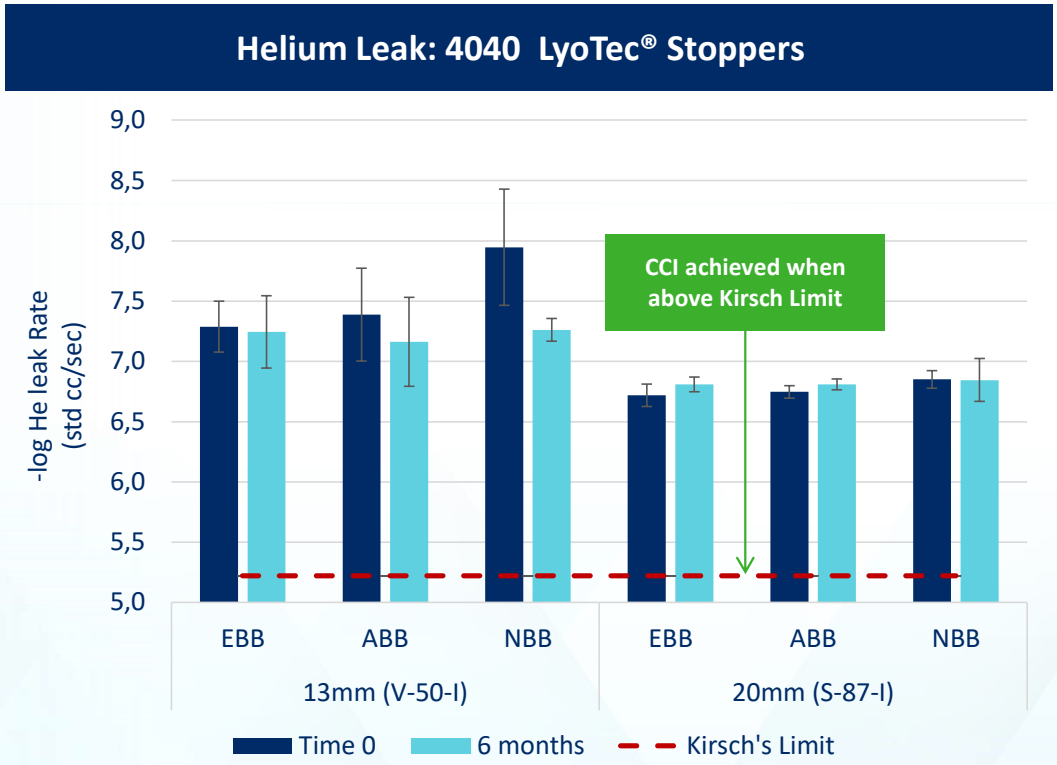
- 13mm (V-50-I) & 20mm (S-87-I) ready-to-use (RU) stoppers
- Stoppers (only) were aged in ambient conditions (unassembled)
- ISO 2R & 10R glass vials: EBB, ABB & NBB vials
- n = 20 per size/blowback geometry/aging timepoint
- All vials passed the Kirsch Limit of 6 x 10^{-6} mbar*L/s (dashed line)

"selecting this conservative maximum allowable leakage limit will ensure a low risk of microbial ingress…"‡

Simplify global supply chain management with **stopper designs compatible with differing glass blowback geometries**

European blowback (EBB,) American blowback (ABB,) & no blowback (NBB) vials

‡ USP-NF <1207> Package Integrity Evaluation – Sterile Products



Container closure integrity was achieved over time with a variety of glass blowback options

West Technical Report 2019/211: Evaluation of Container Closure Integrity for 4040/40 Lyophilization Stoppers

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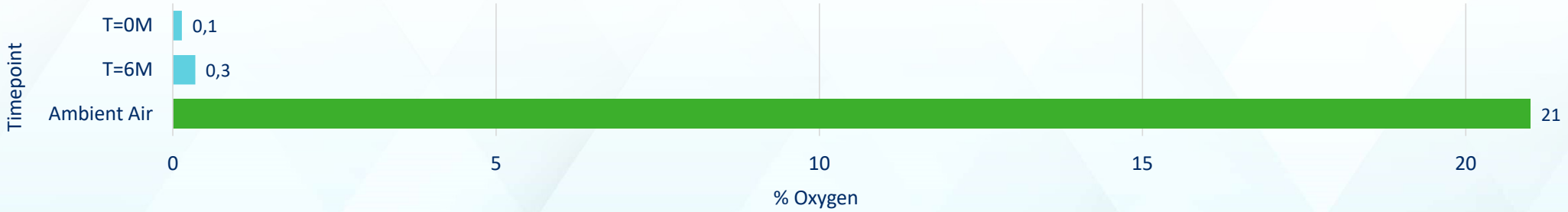
4040/40 Oxygen by Frequency Modulated Spectroscopy

Headspace oxygen measurement performed on vials of lyophilized drug product:

- 4040/40 LyoTec® 20mm igloo lyo stoppers
- ISO 10R ABB tubular glass vials
- Mannitol excipient

- Vials filled, lyophilized & sealed by Lyophilization Technology, Inc. (LTI)
- Vials stored at 20°C - 25°C
- Oxygen concentration in vials determined at T=0 & 6M
- n=15 (non-destructive test)

Average % Oxygen in Vial Headspace



Container closure integrity was maintained over time as demonstrated by non-destructive oxygen headspace testing

West Stability Report 741-SSR, Mar21

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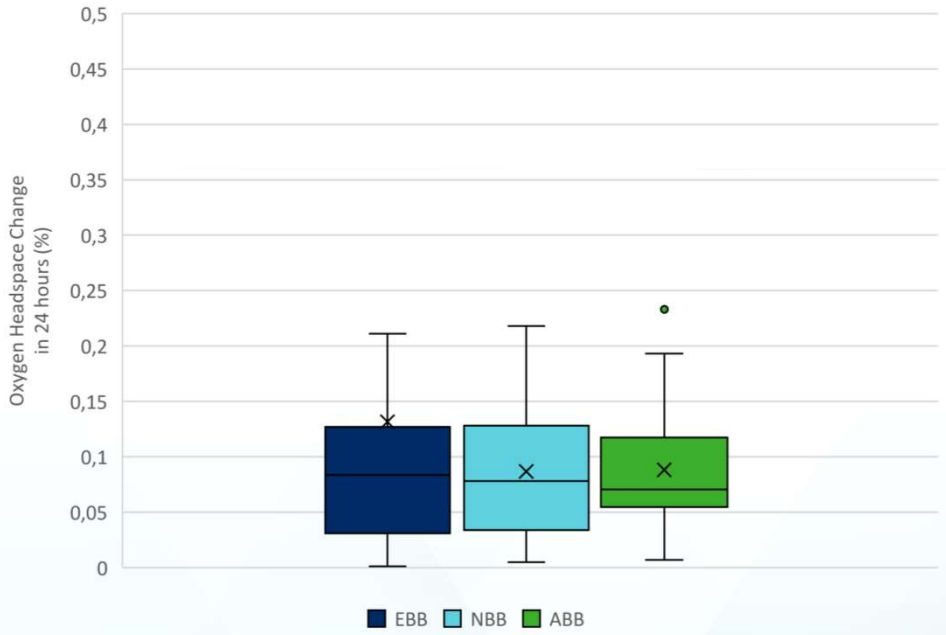
4040/40 Optimized Properties: Raised (Pop-Up) Stopper Evaluation

- CCI testing performed on packaging system using 4040 LyoTec® ready-to-use (RU) stoppers representing final processed state
- Raised stopper evaluation performed on packaging system using:

  4040 LyoTec 13mm (V-50-I) & 20mm (S-87-I) stoppers
- ISO 2R & 10R tubular glass vials with blowback geometries: EBB, ABB & NBB vials
- Stoppers were aged in ambient conditions (unassembled)
- Stoppers inserted in the vent position, simulated lyo processing to fully seat stoppers without crimp seal
- Measured headspace change in vials at 0h & 24h after assembly
- Visual inspection & oxygen headspace testing
- Acceptance criteria: no visual pop-up & < 2% oxygen headspace change
- Result: **No pop-up, maintains closure integrity**

20mm (S-87-I)



European blowback (EBB,) American blowback (ABB,) & no blowback (NBB) vials

Testing suggests low risk of vacuum loss within 24 hrs post-stoppering without capping

West Technical Report 2019/211: Evaluation of Container Closure Integrity for 4040/40 Lyophilization Stoppers

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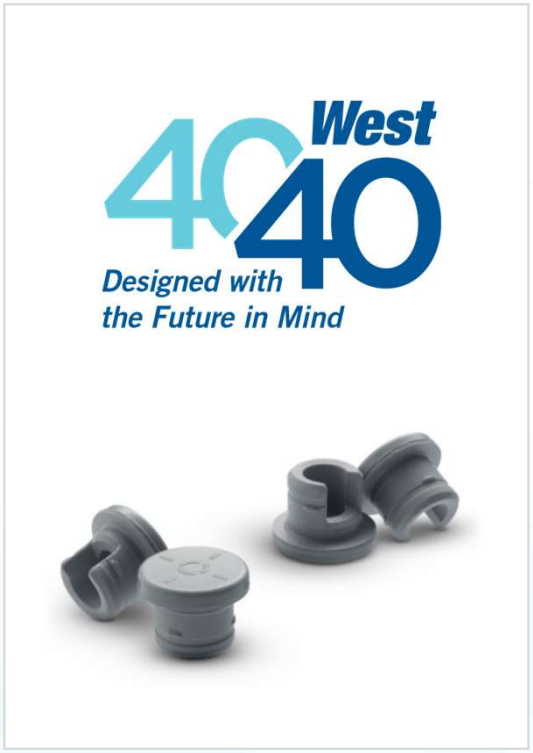
4040/40 LyoTec® Portfolio



Size	STERILIZABLEBAG™ Packaging	Ported Bag Packaging	Finish	Quality Process
13mm (V-50-I)	X	X	Ready-to-Sterilize	Westar® Select Envision™ Verification
			Ready-to-Use	Westar® Select Envision™ Verification
20mm (S-87-I)	X	X	Ready-to-Sterilize	Westar® Select Envision™ Verification
			Ready-to-Use	Westar® Select Envision™ Verification

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