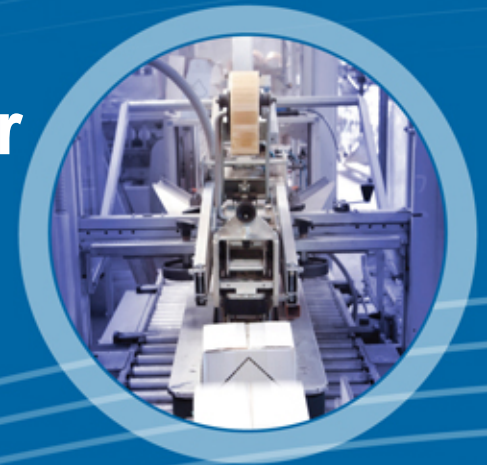




Connecting People, Science and Regulation®

Elastomeric Components and Innovative Plastic Caps for Container Closure Systems for Lyophilization Applications

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Agenda

- Lyophilization stoppers and their impact on moisture content in lyophilized drug products
- New generation of elastomeric materials for parenteral applications
- Clean seals and new plastic closures for lyophilized drug products

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Lyophilization stoppers and their impact on moisture content in lyophilized drugs

Configuration of Lyo stoppers



- **Most common elastomers**
 - Butyl, Bromo- and Chlorobutyl (halobutyles)
- **Most common designs**
 - Igloo
 - Split- / two-leg
- **Protruding dots**
 - Stopper positioning before and during lyophilization
- **Stopper retention feature**
 - Without blowback or with blowback ring
- **Sealing Areas**
 - Sealing area before capping = the stopper neck
 - Primary sealing area after capping = the stopper flange





Potential Sources for Moisture Ingress into a Container System

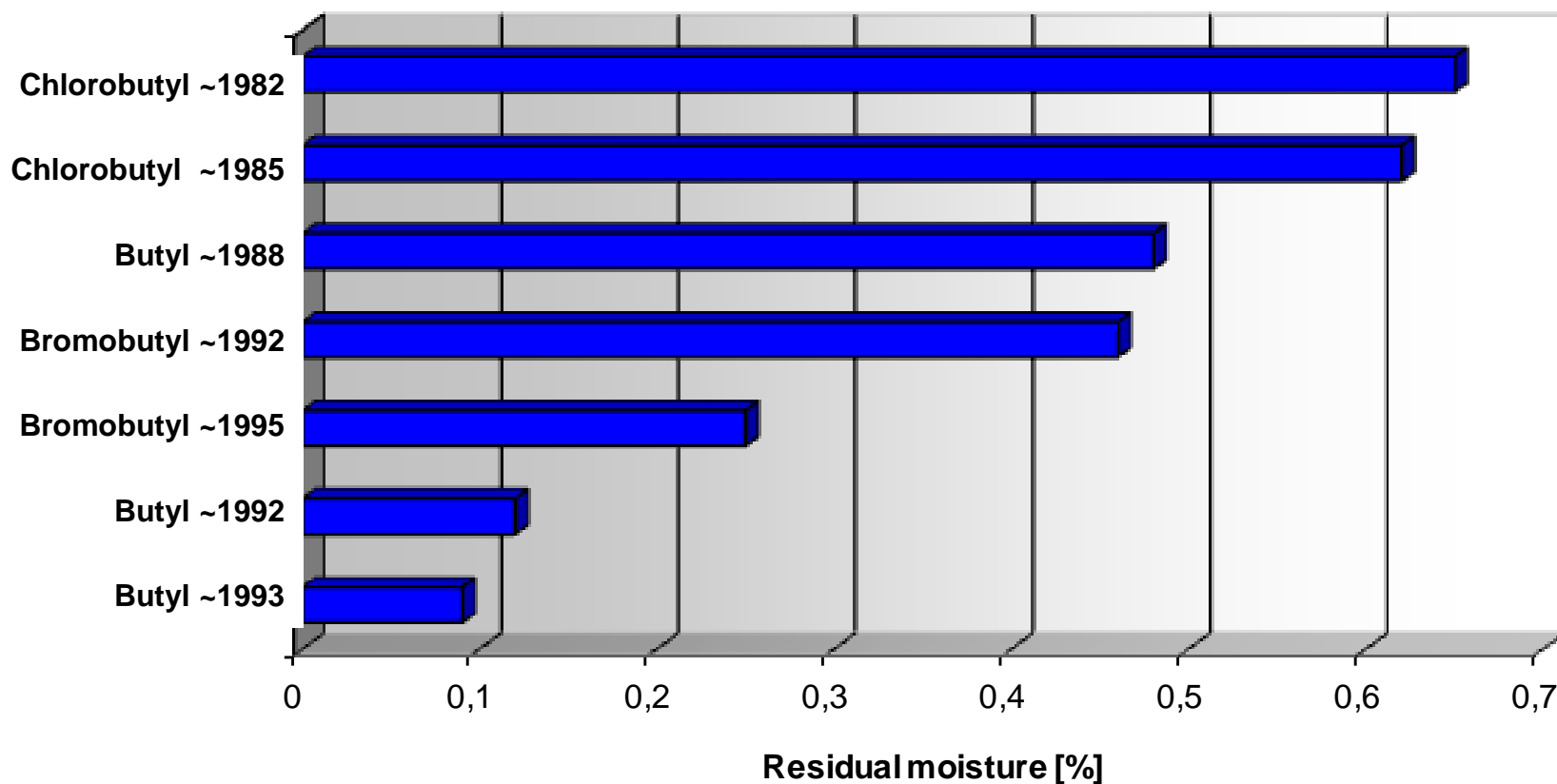
- **Potential Lack of Container Closure Integrity**
 - Permeation through stopper-vial interface
- **Specific moisture vapor transmission rates (MVTR) of elastomeric formulations**
- **None appropriate steam sterilization and drying processes for the elastomeric closures**
- **Specific moisture content of an elastomeric stopper formulation (potential release into container)**

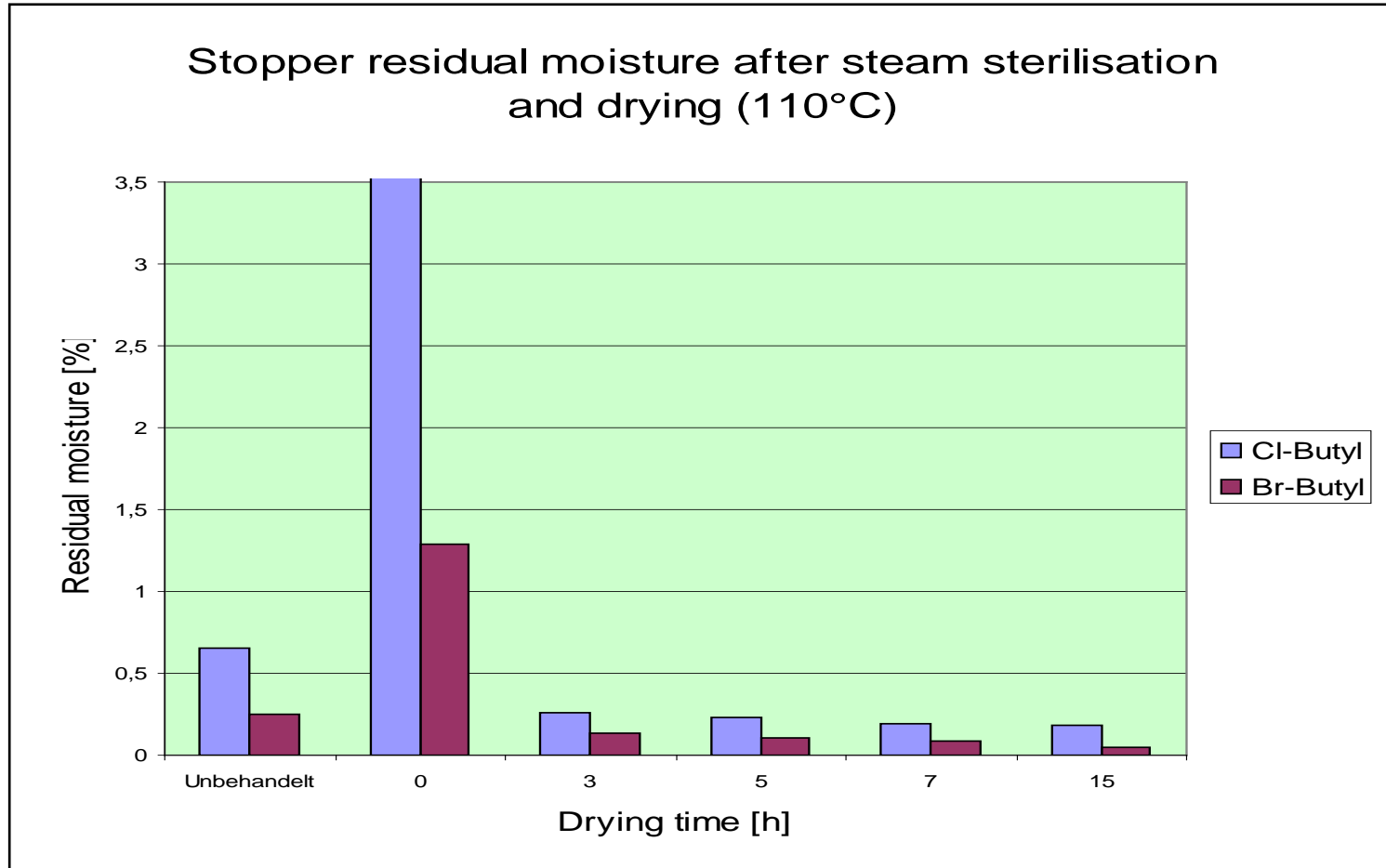




Residual Moisture Content in Elastomers

Residual moisture content in rubber stoppers before steam sterilization





This slide only represents two formulations and cannot be seen as a general information about all bromo- and chlorobutyle stoppers



Some insights from former studies with Iyo stoppers

- There is no direct correlation between stopper residual moisture content and the specific water vapor permeation rate
- Determination of moisture using Karl-Fischer method provides no information about potential moisture gradient inside the stopper
- The lyophilization process itself has no significant drying effect on the stoppers
- Applying a fluoropolymer lamination drastically reduces the amount of subvisible silicone oil particles but they are not a barrier for water vapor

But there are more questions to answer...



Study to determine the influence of stopper residual moisture on lyo cake properties

Scope of the lyophilization study at West

1. Monitoring the residual moisture content of the lyophilization cake and the stopper over a 3-year time period
2. Gain information about the impact of different elastomeric materials on moisture content in lyo cakes
3. Evaluate the impact of different stopper drying times on long term moisture content in lyophilized drugs



Study to determine the influence of stopper residual moisture on lyo cake properties

Materials used

- **Placebo**
5% lactose solution (2 ml solution resulting in about 100mg Lyocake)
- **Stoppers**
Four different elastomeric stoppers were used for the study
 - Butyl stopper
 - Chlorobutyl 1 stopper
 - Chlorobutyl 2 stopper
 - Bromobutyl stopper
- **Vials**
Borosilicate Type I vials (10ml/8ml)



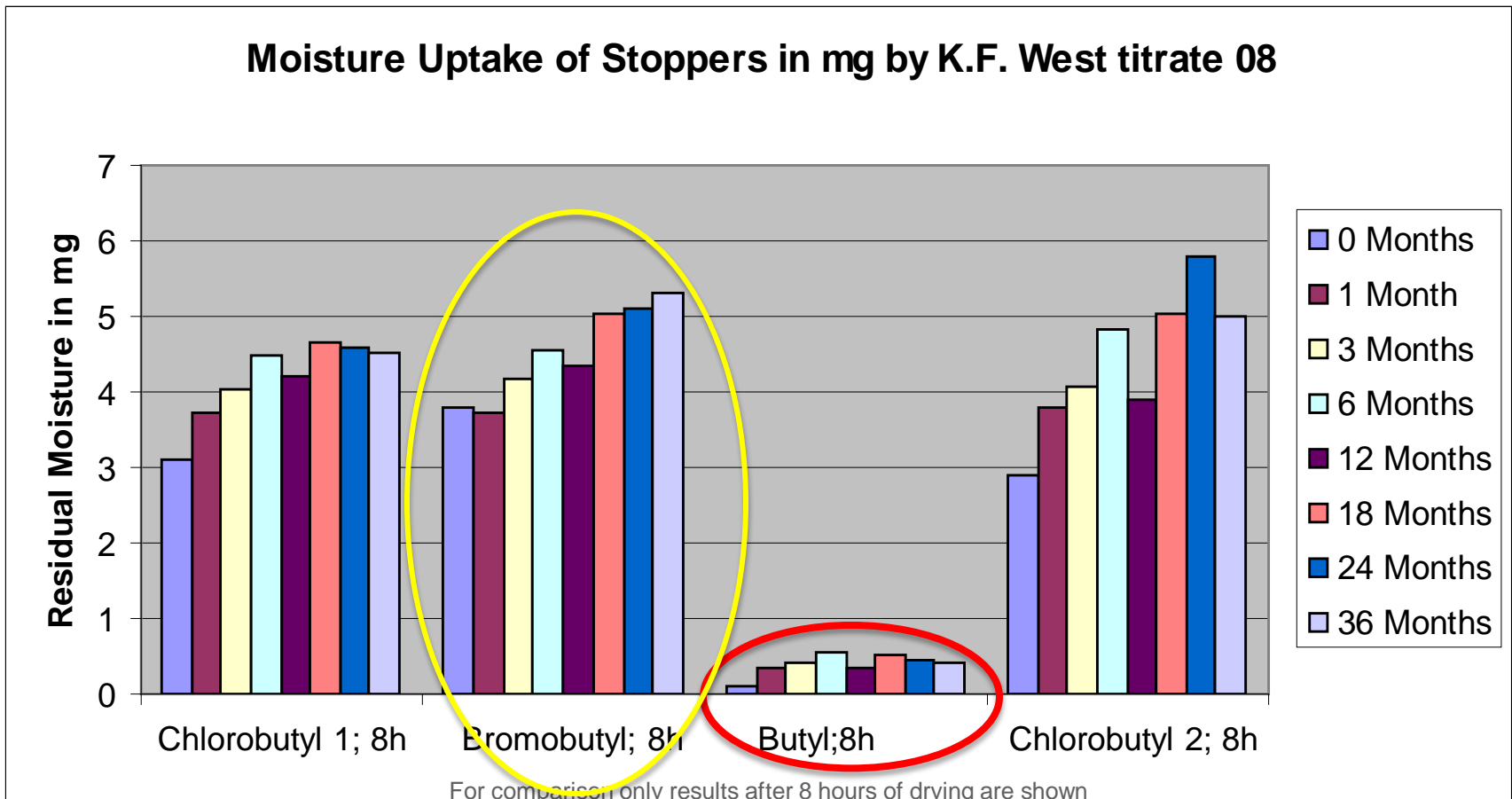
Study to determine the influence of stopper residual moisture on lyo cake properties

Methods

- Steam sterilization of stoppers in steribags for 60 min at 121 ° C
- Drying of stoppers at 105 ° C for 1h, 4h or 8h
- Seal integrity checked using Helium-Leakage-Method with an acceptance criteria of $AHLR < 6 \times 10^{-6} \text{ std} \cdot \text{cm}^3/\text{sec}$
- Storage of lyophilized product vials for 3 years at 25 ° C/60% RH
- Sample pulls: 0,1,3,6,12,18,24 and 36 months



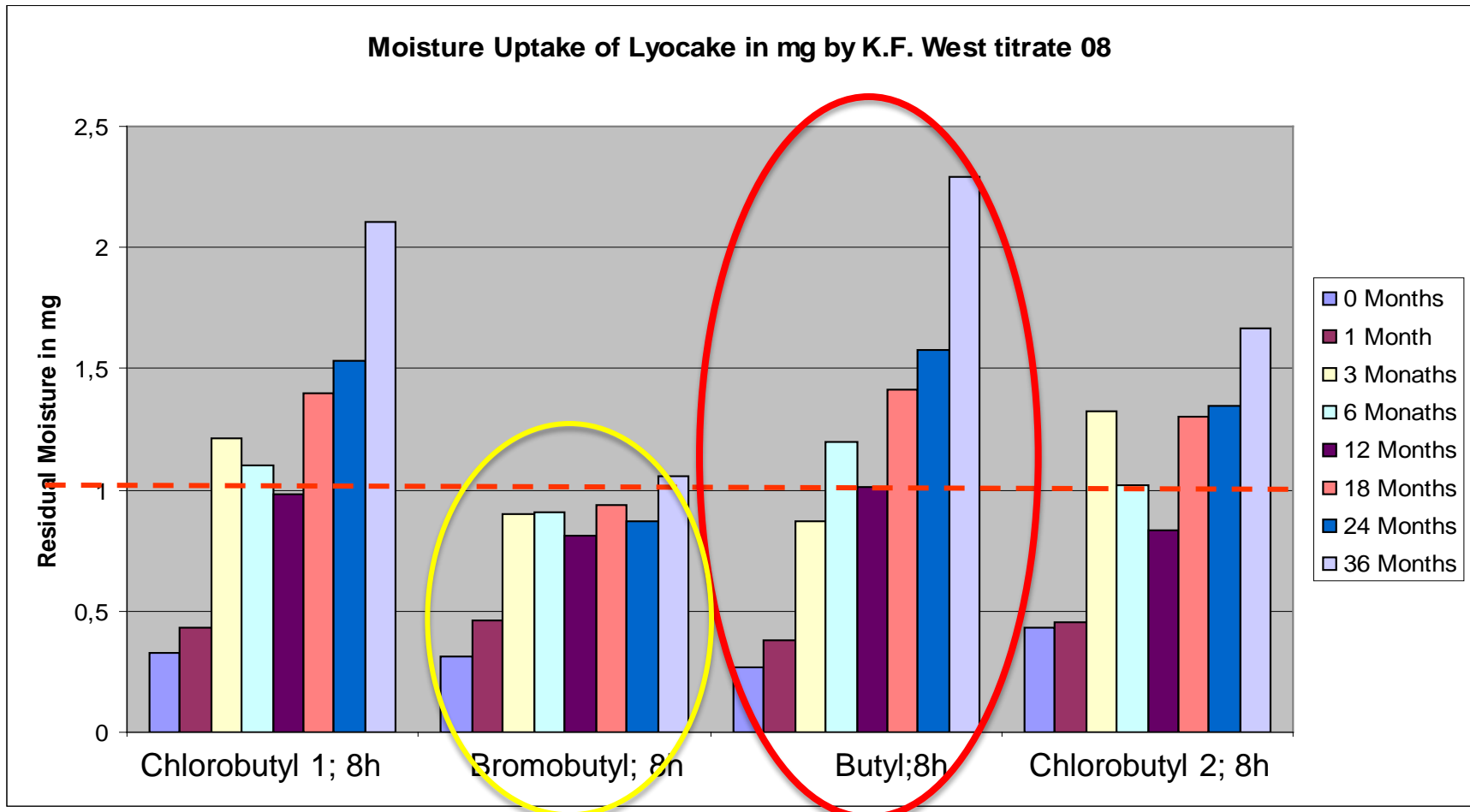
Study to determine the influence of stopper residual moisture on lyo cake properties



Source: 3 Year Residual Moisture Study on Lyophilized drugs with different elastomeric closures; West Pharmaceutical Services



Study to determine the influence of stopper residual moisture on lyo cake properties

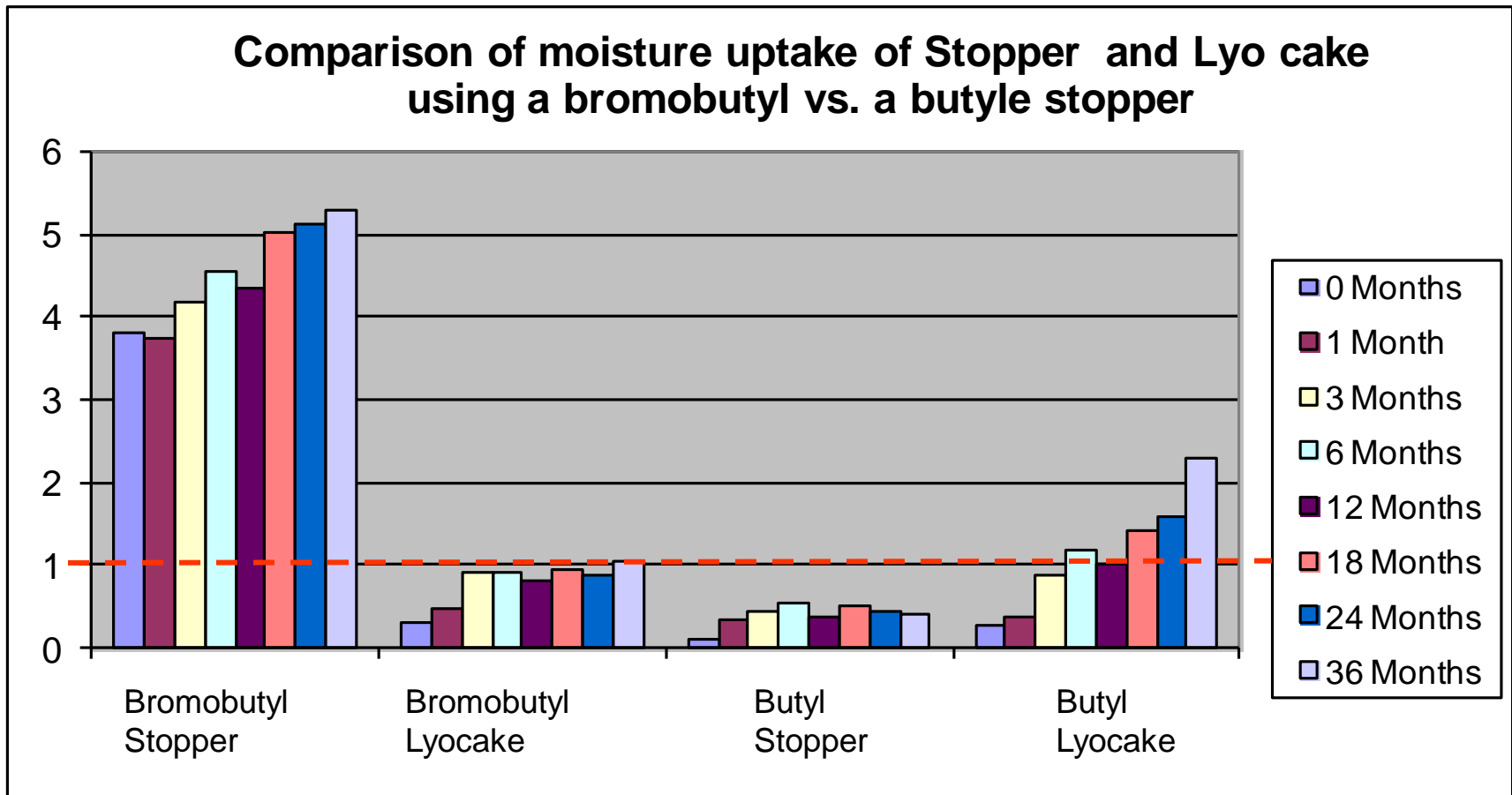


For comparison only results after 8h drying are shown

Source: 3 Year Residual Moisture Study on Lyophilized drugs with different elastomeric closures; West Pharmaceutical Services



Study to determine the influence of stopper residual moisture on lyo cake properties



For comparison only results after 8h drying are shown

Source: 3 Year Residual Moisture Study on Lyophilized drugs with different elastomeric closures; West Pharmaceutical Services



Interpretations based on the performed study

- Elastomeric components take up moisture over time up to an equilibrium level being specific to each rubber formulation
- Rubber stopper impact on cake moisture is specific for elastomeric formulations
- Moisture uptake of the lyophilisation cake does not correlate to the moisture uptake of the stopper
- The drying of a stopper has more short term than long term impact on the moisture content of a lyo cake
- Amount of initial stopper moisture is less important to the lyo cake than it was assumed
- For long term stability it is crucial to evaluate the MVTR of an elastomeric formulation



New Generation of Elastomeric Materials for Parenteral Applications



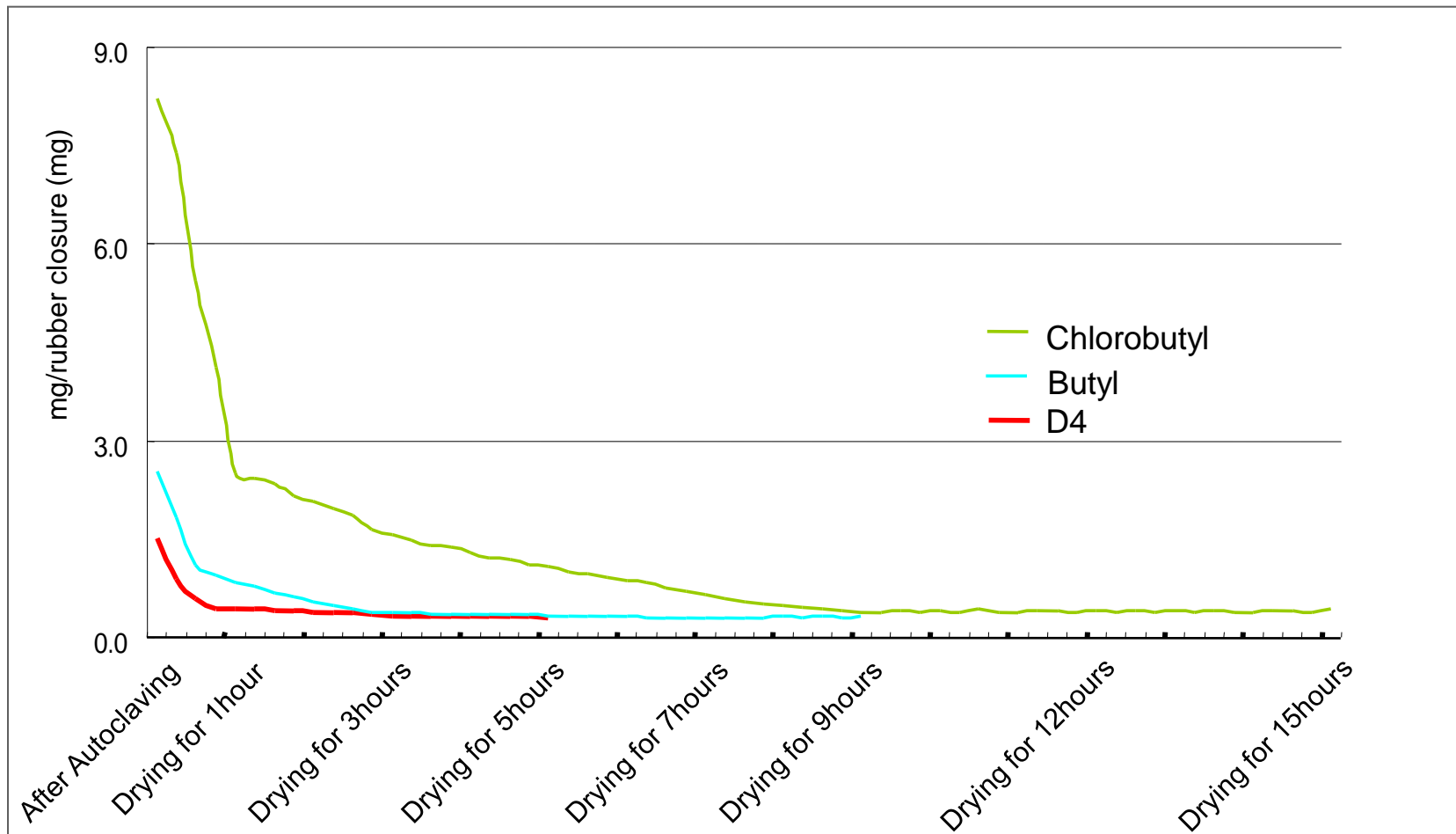
New Packaging Solutions for Lyophilized Drug Products

- New Daikyo elastomeric material called D4
- Ultra low in extractables
- Eliminates carbon black
- Extremely soft – needle sharpness
- Designed for vision inspection
- Lyophilization - extremely fast drying
 - Drying up to 10 times faster than conventional rubber to equal level





Improved Drying through Innovative Elastomer Composition



Source: Moisture testing in different elastomeric compositions; Daikyo Seiko Ltd.



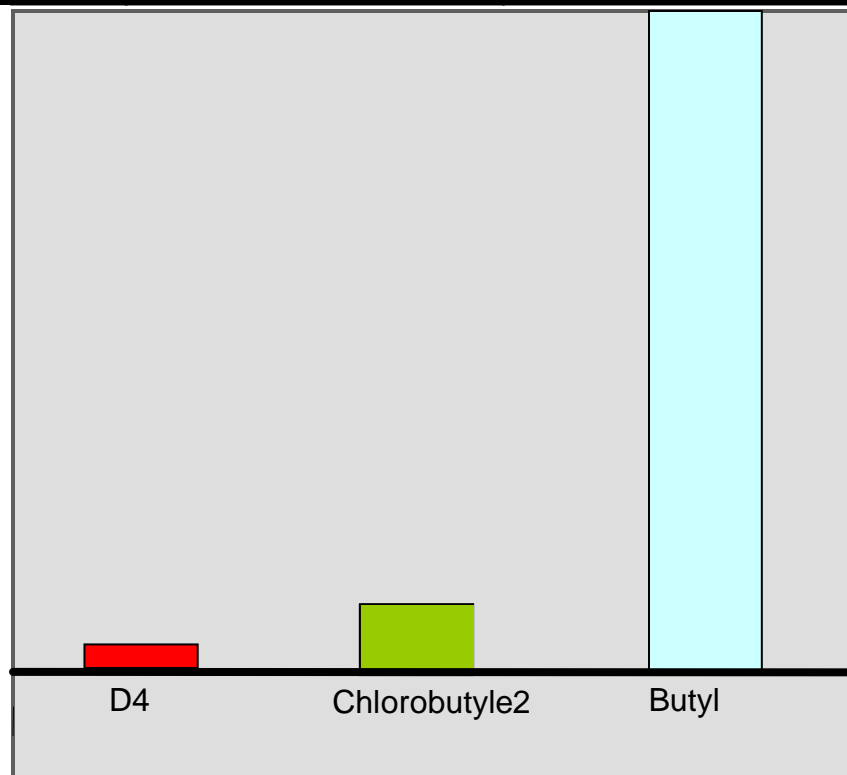
Improved Cleanliness through Innovative Elastomer Composition

	Sample formulation		
Injection volume: 250µl	D4	Chlorobutyl 2	Butyl
Total Area	85	2636	247026
Market release year	2008	1998	1992

Sample:
20mm serum, both side lamination;
No coating

Measurement condition:
Model: Shimadzu GC-14A
Detector: FID
Column: Gaskuropack54 60/80
Glass 3φ × 2m

Column Temp: 150°C
Injection Temp: 170°C
Detector Temp: 190°C
Flow Rate: H₂ 0.5Kg/cm²
Air 0.5Kg/cm²
N₂ 42mL/min
Range: 10²





Alternatives to Freeze Drying Systems

New Daikyo elastomeric material for deep frozen storage

- § Good low-temperature properties
à $T_g = -105^\circ \text{C}$
- § Fluoropolymer lamination: ETFE
- § Meets PhEur, USP and JP requirements
- § O_2 and MVT typical for butadiene rubber
- § For liners and stoppers





Clean Seals and New Plastic Closures for Lyophilized Drug Products

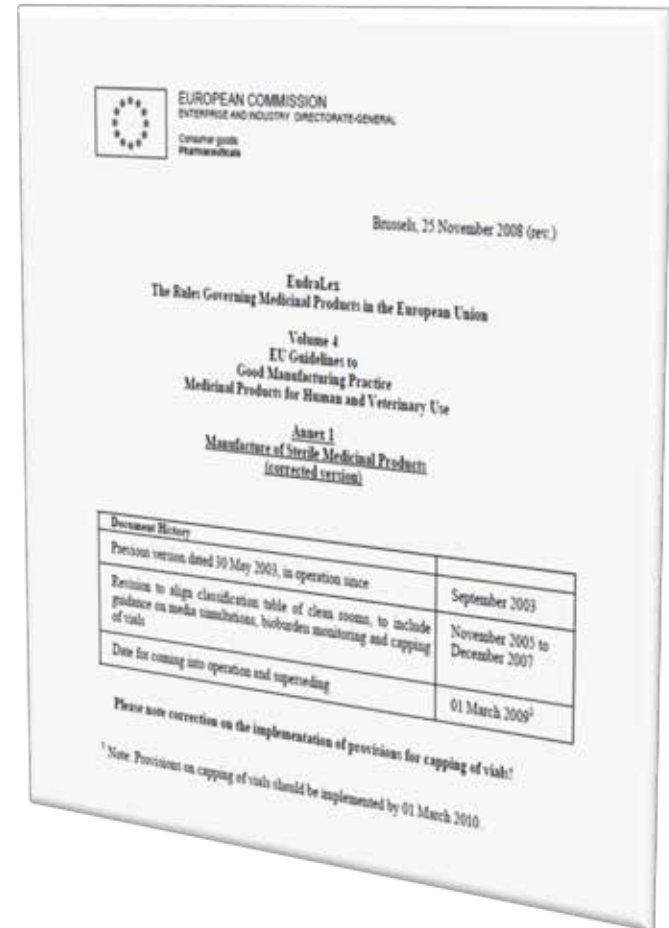


Requirements for capping are increasing

Example: The EU GMP Annex 1

Key Points for capping related procedures:

- 118. The container closure system for aseptically filled vials is not fully integral until the aluminum cap has been crimped into place on the stoppered vial. ...
- 120. Vial capping can be undertaken as an aseptic process using sterilized caps or as a clean process outside the aseptic core....
- 121. Vials with missing or displaced stoppers should be rejected prior to capping...
- 122. Restricted access barriers and isolators may be beneficial in assuring the required conditions ...
- 123. Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period....



Source: EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use (EU GMP Annex 1; Manufacture of Sterile Medicinal Products)



Clean Capping Solutions for Improved Capping Cleanliness

Option	Potential Solution
Vial crimping in Class 5 environment (aseptic core)	Clean Certified and Sterilized Seals
Integration of crimping process into RABS / Isolator / grade A air supply	Clean Certified and Sterilized Seals
Capping inside Freeze Dryer	Plastic Caps



Clean Crimping Concept – Clean Certified Sterilized Seals

- Buttons are washed prior to the assembly process
- Aluminum is silicone-coated in order to minimize particle abrasion
- Assembly takes place under controlled environment
- Seals are gamma sterilized
- Bioburden and particulate levels are specified
- Clean seals provide a capping solution for meeting cleaner manufacturing standards (e.g. according to GMP Annex 1)



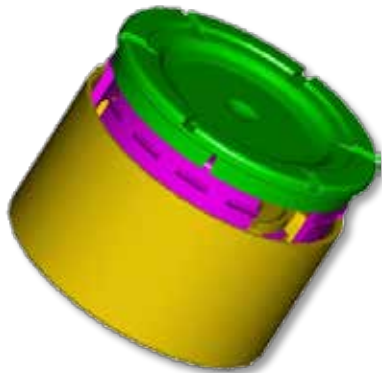


Concerns with Existing Capping Concepts

- Vacuum loss due to poorly inserted lyo stoppers before crimping
- Potential sterility loss due to pop up issues before crimping
- Cracked glass vials caused by stoppers sticking to freeze dryer shelves
- Set up and maintenance of a post lyophilization capping station
- Creation and control of aluminum particles created during the crimping process
- Difficulties regarding usability of current seals with new nested vial concepts



New Capping Concepts



LyoSeal®



PlasCap®

New Capping Concepts are full plastic seals as e.g. the PlasCap® and the LyoSeal® plastic cap with following advantages:

For lyophilized drug products

- Capping in the freeze-dryer directly after the lyophilization process

For liquid drug products

- Capping immediately after stoppering, on the filling line
- Capping of nested vials without de-nesting

LyoSeal® is a registered trademark from Biocorp Recherche and Development Company
PlasCap™ is a trademark of Daikyo Seiko Ltd., Japan

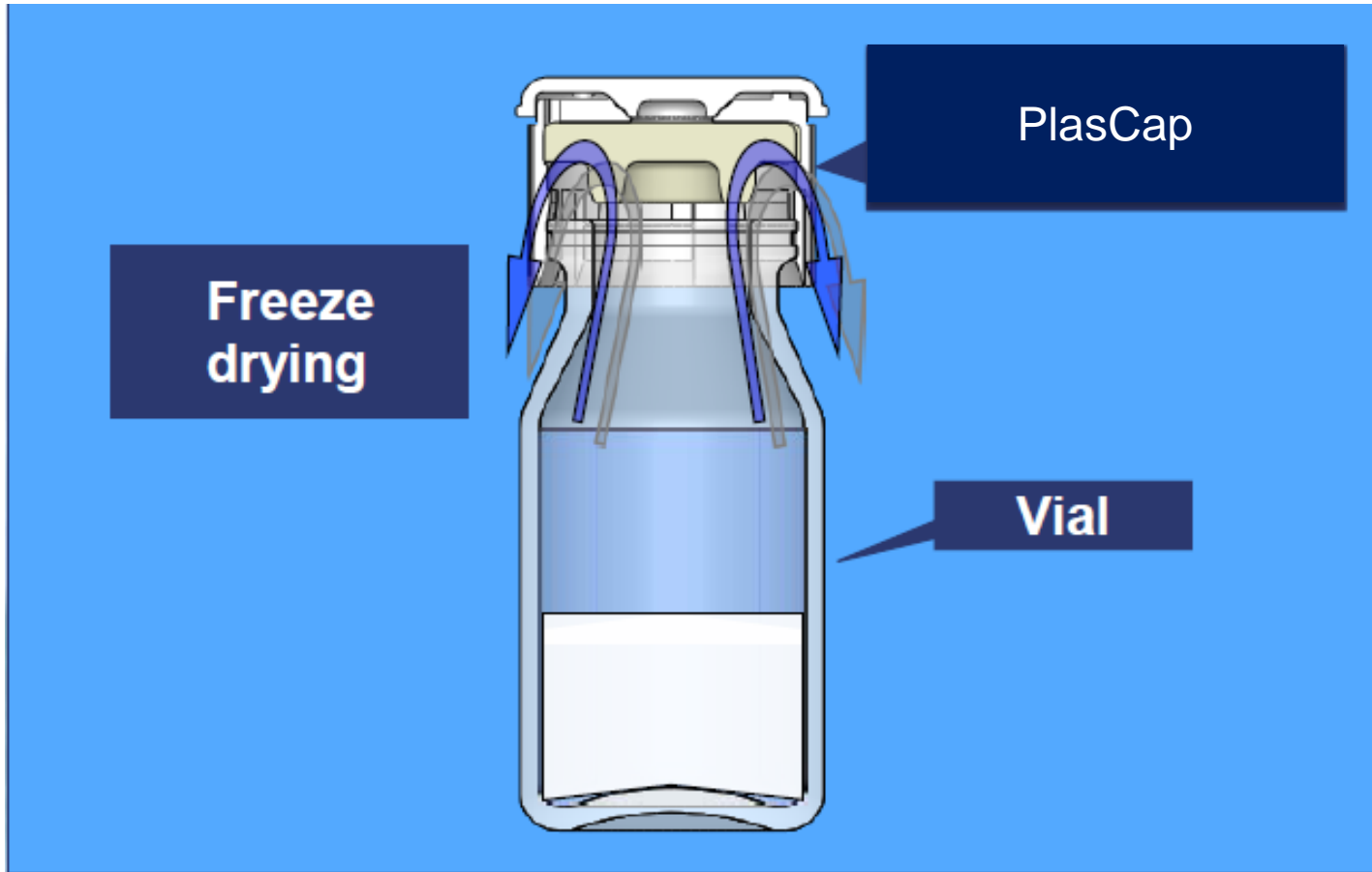


New Capping Concepts

- Daikyo PlasCap closure
- Facilitates compliance with EU GMP Annex1
- Easy disposal/total incineration
- 13mm, 20mm and 32mm
- Currently under evaluation with plastic and glass vials
- Resistance to irradiation

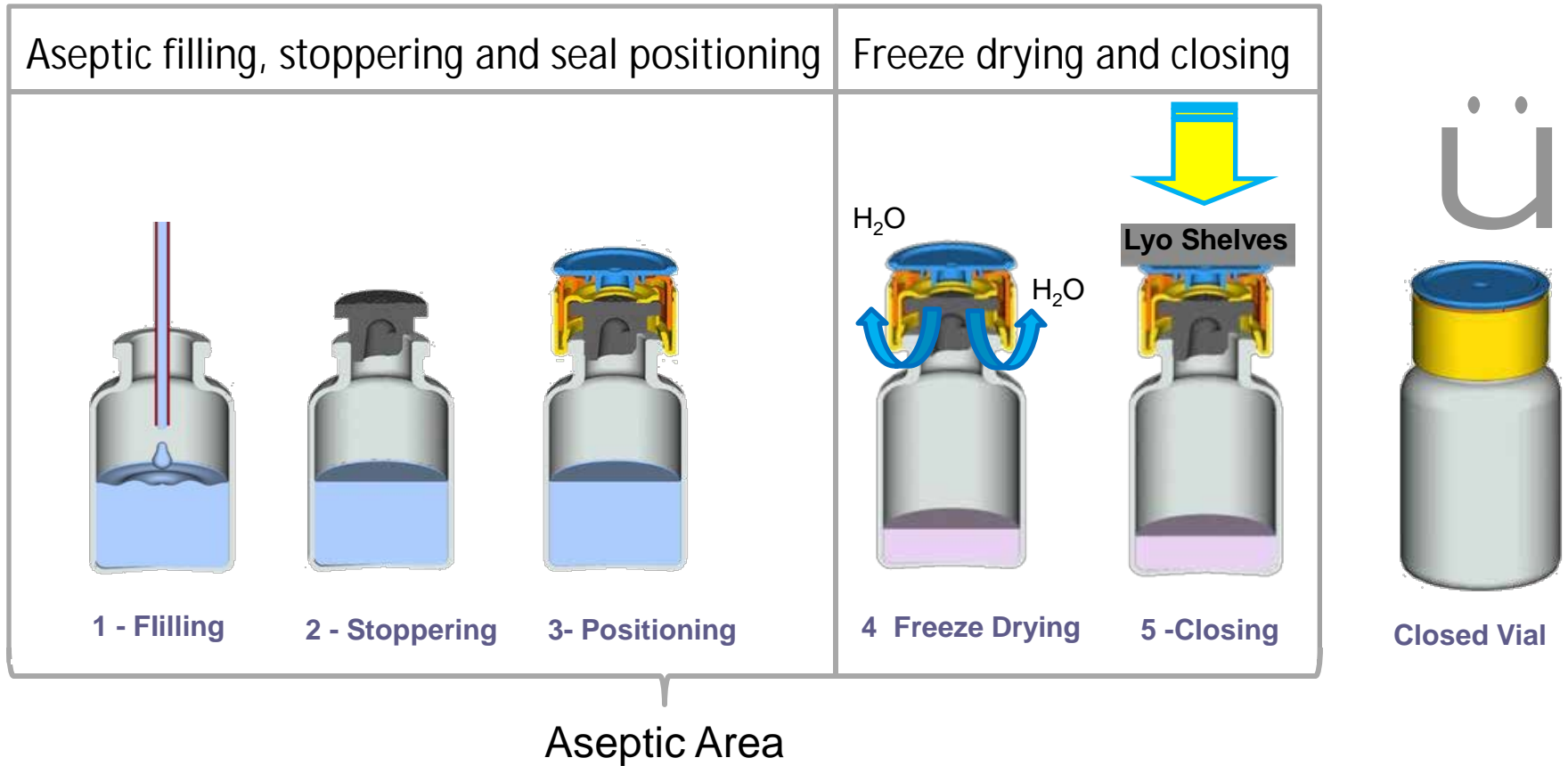


Plastic Cap with pre assembled stopper inside





LyoSeal Cap Functionality in a Freeze Dryer

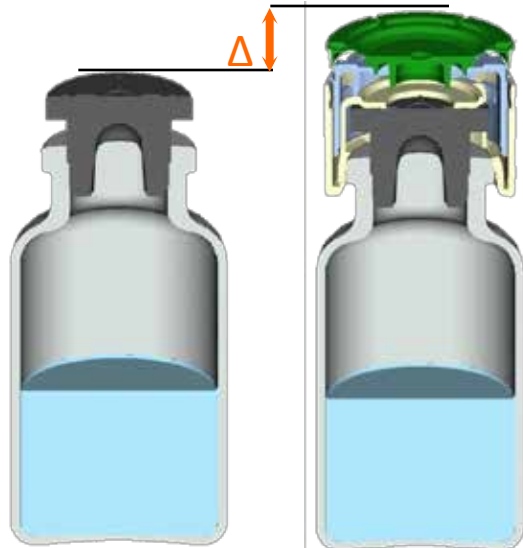




Height Comparison between LyoSeal® Cap and Flip-Off® Seal

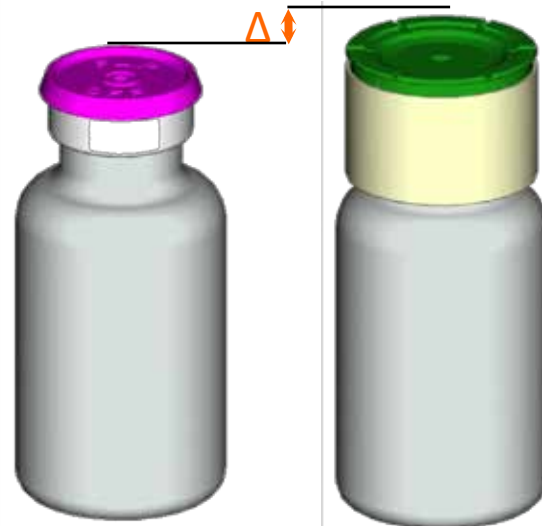
Height difference during freeze-drying process:

Typical $\Delta = +9.8\text{mm}$



Height difference after crimping:

Typical $\Delta = +4.3\text{mm}$





LyoSeal® Performance in a Freeze Dryer

Different Freeze Dryers Capabilities

Compatibility trials with some Freeze-Dryers using defined capping forces have shown good results:

LyoSeal 20mm	Surface Area [m ²]	Capping Pressure [kg/cm ²]	Crimping Success
GEA Lyofill	2	Nominal	100%
Klee	Pilot scale	Nominal	100%
Heraus	20	Nominal	100%
GEA Lyofill	20	0.7	99.73%
Steris	35	1.4	99.5%
Telstar	45	1.2	100%

Existing freeze-dryer equipment can be used in most cases



Microbial Challenge Test

- Microbial challenge test with LyoSeal caps and representative vials and stoppers demonstrates container closure integrity

Helium test

- Comparative studies between LyoSeal® caps crimped on vials and vials crimped with standard aluminum caps demonstrate equivalence

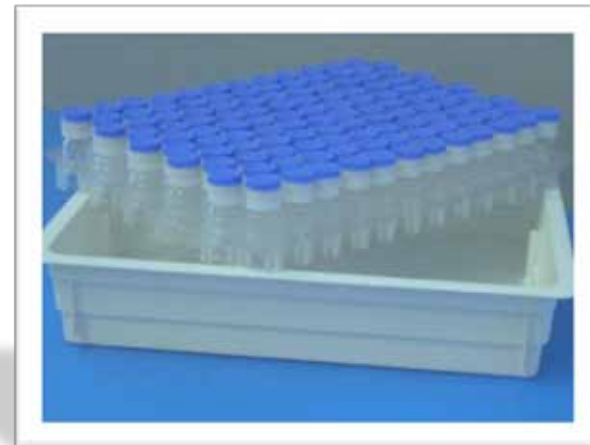
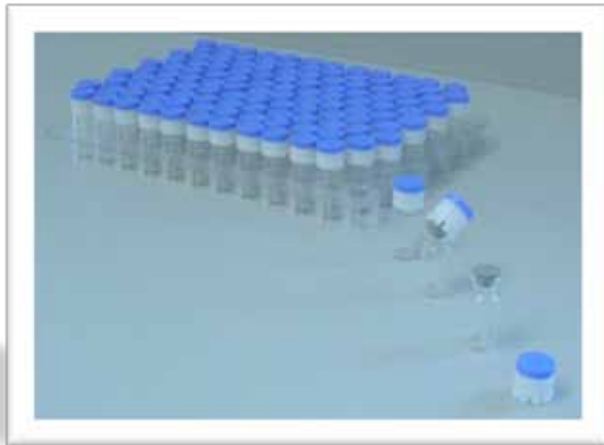
Vacuum Decay Test

- Vacuum decay tests (Wilco) demonstrate container closure integrity of LyoSeal® caps crimped on vials upon aging (ongoing study)



Outlook – Solution for Nested Vials

- § Nested vial systems allow vial filling in flexible machine settings that can be used with prefillable syringe and injectable container systems
- § A plastic cap allows capping of vials directly inside a nest
 - § Complex and time intensive de-nesting of vials can be eliminated
 - § For manual and semi-automatic handling the LyoSeal plastic cap is an easy capping solution





Advantages of Plastic Capping Concepts

Improvements in operational efficiency can be achieved in the following areas:

Lyophilization:

- à No post-lyophilization capping station is necessary
- à Additional clean room environment for capping can be avoided
- à The container system is fully closed before unloading of the freeze dryer
- à Eliminate glass breakage caused by sticking stoppers to the freeze dryer shelves
- à Higher security for operators in case toxic substances are packed

Usage of nested vial systems:

- à Fast and reliable capping directly inside the nest
- à No de-nesting of vials necessary for capping

Usage in an R&D or small scale setting:

- à A container systems can be closed without additional tools and machinery



!!Thanks for your attention!!

We would be happy to welcome you at our
booth for further discussion