For sterile products manufacturing, Lyoseal is an innovative technology to improve quality problems with final drug product due to crimping issues and inadequate stopper seating. It eliminates aluminum particles from process, meets more stringent requirements for capping process according to cGMP expectations.

“Lyoseal: Introducing a New Capping Solution for Freeze Dried Products” presented by Mr. Tony Bouzerar from BioCorp offers us detailed introduction on Lyoseal from technology, process, application and validation.

It offers us an alternative capping solution for freeze dried products.
Lyoseal®: Introducing a New Capping Solution for Freeze Dried Products

Speaker: Tony Bouzerar, LyoSeal® Customer Support Manager, BioCorp

PDA Conference: Stoppers & Elastomers, Rennes, 6th & 7th April 2011
Purpose presentation: Lyoseal®

Lyoseal – Product Description

- Lyoseal
- Standard Stopper
- Standard Vial
- Single Step Freeze-Dry-Seal
- Class A Crimp-Sealed Vial
Agenda

1. **Introduction: market drivers**
2. **Technical Challenge:**
   1. how to crimp a large population of vials in one single operation?
   2. The solution: LyoSeal®
3. **LyoSeal® description**
4. **Case study:**
   1. Implementation at a customer: Modification of the manufacturing process
   2. Process validation
   3. Container Closure Integrity
5. **Conclusion**
Introduction: Market Drivers

- When speaking about sterile products manufacturing, issues are:
  - Quality problems with final drug product due to crimping issues and inadequate stopper seating
    - Lack of sterility
    - Loss of vacuum in vial
    - Cracked glass vials
    - Cosmetic defects
    - Stoppers sticking to Lyo chamber shelves
  - Elimination of aluminium particles from process
  - More stringent requirements for capping process according to EU GMP Annex 1
Introduction: Market drivers

- Options to meet GMP Annex 1

<table>
<thead>
<tr>
<th>Option</th>
<th>Example of Product Offering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crimping in Class 5 environment</td>
<td>West Flip-Off® CCS/ Clean Seals</td>
</tr>
<tr>
<td>Integration of crimping process into RABS/ Isolator</td>
<td>West Flip-Off® CCS/ Clean Seals</td>
</tr>
<tr>
<td>Capping in Freeze Dryer</td>
<td>LyoSeal®</td>
</tr>
<tr>
<td>In-Line Oxygen head-space inspection on finished product</td>
<td>Several In-line control Systems</td>
</tr>
</tbody>
</table>
Introduction: Market drivers

- Options to meet GMP Annex 1 + elimination of aluminium

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5. Conclusion
2: Technical Challenge

• The Challenge:
  – How to crimp a large population of vials in a freeze-dryer?

• Main Issues:
  – Pressing force from the FD machine versus crimping force needed for x vials
  – Tolerances of the freeze-dryer shelves flatness
  – Stacking tolerances of vials and stoppers
2: Technical Challenge

- Compression curve of a typical 20mm lyo stopper, in down position (equipment used: Lloyd; stoppers from main suppliers)

For more details, please contact info@lyoseal.com or Dial +33 47355 7050
2: Technical Challenge

• Compression curve of a 20mm LyoSeal, in down position (measurement equipment used: Lloyd)

For more details, please contact info@lyoseal.com or Dial +33 47355 7050
2: Technical Challenge

• Assuming a Normal Distribution of dimensions of 1800 vial and stoppers on a single shelf in a Freeze-Dryer machine

\[ \Delta = 1.5 \text{ mm} \]

For more details, please contact info@lyoseal.com or dial +33 47355 7050

18.7 T
2: Technical Challenge

• Assuming a Normal Distribution of dimensions of 1800 vials and stoppers on a single shelf in a Freeze-Dryer machine

For more details, please contact info@lyoseal.com or
dial +33 47355 7050

equ. 26,9T
2: Technical Challenge

For more details, please contact info@lyoseal.com or dial +33 47355 7050

equ. 18 T
2: Technical Challenge

For more details, please contact info@lyoseal.com or dial +33 47355 7050
2: Technical Challenge: summary

- Compression of 0.5mm of 1800 units of typical rubber lyo stoppers on top of vial:
  - average 82kN
- Compression of 0.5mm of 1800 crimped vials with LyoSeal:
  - Estimated extra force needed = 0N!
- Conclusion:
  - LyoSeal may compensate a moderate dispersion of dimensions including stopper dimensions, and allow a 100% crimping
Compatibility trials with some Freeze-Dryers from the market and capping force used: 
=Most FD can be used as they are.

<table>
<thead>
<tr>
<th>LYOSEAL 20mm</th>
<th>Surface Area (m²)</th>
<th>Capping Pressure (kg/cm²)</th>
<th>Crimping Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEA Lyofill</td>
<td>2</td>
<td>Nominal</td>
<td>100%</td>
</tr>
<tr>
<td>Klee</td>
<td>Pilot scale</td>
<td>Nominal</td>
<td>100%</td>
</tr>
<tr>
<td>Heraus</td>
<td>20</td>
<td>Nominal</td>
<td>100%</td>
</tr>
<tr>
<td>GEA Lyofill</td>
<td>20</td>
<td>0.7</td>
<td>99.73%</td>
</tr>
<tr>
<td>Steris</td>
<td>35</td>
<td>1.4</td>
<td>99.5%</td>
</tr>
<tr>
<td>Telstar</td>
<td>45</td>
<td>1.2</td>
<td>100%</td>
</tr>
</tbody>
</table>
Agenda

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5. Conclusion
Lyoseal® 20 mm

Lyoseal® is currently available in 13mm, 20mm, 28mm
LyoSeal® are supplied in Ready-to-Autoclave PE/Tyvek bags.
Process

Freeze dryer

Freeze Dry & Crimp-Seal

H₂O

H₂O

H₂O
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Case Study: Implementation of LyoSeal version 20mm

- Location: Big Pharma site, Europe
- Purpose: Clinical Production
- LyoSeal® version considered: 20mm
Drug product production process

Product (Warehouse) → Compounding Vessel → Holding Vessel

Unloading Lyo via Isolator → Transfer via Isolator

Lyophilisation Lyophiliser → Loading Lyo via Isolator → Transfer via Isolator

Immediate Container (Warehouse) → Rinsing Washing Machine → Depyrogenation Dry Heat Oven → Transfer Via Isolator

Sterile Filtration

Filling Filling Line
Modification of process equipment

List of equipment:

• Vial filling line and isolator
  – Pick and place system
  – Lyoseal bowl
  – Connection to transfer isolator
• New Transfer isolator
• New Interface isolator
• New standard freeze dryer
Modification of process equipment
Lyoseal deposition (movie)
Modification of process equipment

- Transfer to isolator
Modification of process equipment

- Transfer Isolator
- Interface Isolator (to FD “pizza-door”)
Modification of process equipment

- Freeze-Dryer
- Tray loading of vials into FD
• IOQ of vial filling line modifications
  – Incl smooth operation (incl Lyoseal placement without stopper displacement) for 30 minutes
• IOQ, CD, PQ of new isolators
• Commissioning, IOQ freeze dryer
  – Crimping force
  – Full load crimping \( \rightarrow \) All vials closed, no broken vials
Manufacturing process simulation

- Initially 3 consecutive runs
- 3 X 1500 vials with stopper and lyoseal
- No growth
- Growth promotion capability tests passed
- Particle measurement during capping: class A
- All vials closed in lyo
- No vials broken in lyo
- Semi-annual repetition with 1500 vials
Container closure integrity

- Validation strategy:
  - FMEA
  - Mold qualification
  - Dimensional check & influence of steam sterilisations
  - Helium leak tests at t0
  - Microbial ingress testing: P.diminuta + E.coli
  - Stability - after stress conditions: vacuum decay tests
Influence of steam sterilisations

- After 1 steam sterilisation & drying cycle: Changed dimensions after 1 cycle (within supplier specifications)
- Between 1st and 2nd steam sterilisation cycle: no changed dimension observed
- Similar tests at Biocorp: incl crimping force
Material:
- 10, 20 and 50 ml lyophilized vials containing placebo were manufactured (GMP conditions).

Method:
- Bottomless vials are placed into the chamber.
- Vacuum is set up into the chamber at approximately $10^{-3}$ mbars. Constant 0.2 bars Helium pressure is applied into the vials.
- Helium leak is measured at room temperature ($21^{\pm 3}C$) through a mass spectrophotometer.
Helium test: equipment
Helium test: Results:

- The leak rates results are similar to the leak rates observed for vials crimped with aluminium caps.

<table>
<thead>
<tr>
<th>Helium Test</th>
<th>Mean leak rate Atm.cm$^3$.s$^{-1}$</th>
<th>Standard deviation</th>
<th>Experimental Error Atm.cm$^3$.s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>10ml Lyoseal</td>
<td>$1.9 \times 10^{-10}$</td>
<td>$9.3 \times 10^{-11}$</td>
<td>$6.2 \times 10^{-11}$</td>
</tr>
<tr>
<td>10ml Flip-off</td>
<td>$1.2 \times 10^{-10}$</td>
<td>$2.4 \times 10^{-11}$</td>
<td>$3.5 \times 10^{-11}$</td>
</tr>
<tr>
<td>20 ml Lyoseal</td>
<td>$1.4 \times 10^{-10}$</td>
<td>$1.1 \times 10^{-10}$</td>
<td>$7.5 \times 10^{-11}$</td>
</tr>
<tr>
<td>20ml Flip-off</td>
<td>$5.9 \times 10^{-11}$</td>
<td>$1.8 \times 10^{-11}$</td>
<td>$2.6 \times 10^{-11}$</td>
</tr>
<tr>
<td>50ml Lyoseal</td>
<td>$3.0 \times 10^{-10}$</td>
<td>$1.4 \times 10^{-10}$</td>
<td>$9.3 \times 10^{-11}$</td>
</tr>
<tr>
<td>50ml Flip-off</td>
<td>$2.6 \times 10^{-10}$</td>
<td>$1.6 \times 10^{-11}$</td>
<td>$2.4 \times 10^{-11}$</td>
</tr>
</tbody>
</table>

- The leak rates correspond approximately to a capillary channel of 0.075 μm
**Method:**

221 vials were filled with 10 ml trypticase soya broth (TSB) under media fill conditions, then immersed for 24 hours at 35°C ±2°C in a contaminated media containing at least 15.10^{10} Pseudomonas diminuta and 32.10^{10} Escherichia coli. The vials were incubated for 14 days at 35°C ±2°C and checked for microbial ingress. Growth promoting properties were tested to validate the test conditions.

**Results:**

No growth was observed in the vials from microbial ingress test. Growth promoting capability tests passed.
Stability study

• Vacuum decay test to demonstrate that the LyoSeal® cap is able to maintain the integrity of finished vials product under accelerated and over the shelf life ICH storage conditions

• Test conditions:
  +5°C ±3
  +25°C ±2 - 60% RH ±5%
  -20°C ±5
  +40°C ±2 - 75% RH ±5%

• Equipment:
  – Wilco (W07MC/V n° 0800 52)
  – Tester calibrated for a 20μm leak detection
### ICH studies: Products stored at + 5°C ±3

<table>
<thead>
<tr>
<th></th>
<th>T0</th>
<th>T3</th>
<th>T6</th>
<th>T12</th>
<th>T24</th>
<th>T37</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 ml Lyoseal</td>
<td>-</td>
<td>23/24 accepted</td>
<td>24/24 accepted</td>
<td>23/24 accepted</td>
<td>23/24 accepted</td>
<td>23/24 accepted</td>
</tr>
<tr>
<td>10 ml Flip-off</td>
<td>-</td>
<td>24/24 accepted</td>
<td>24/24 accepted</td>
<td>24/24 accepted</td>
<td>24/24 accepted</td>
<td>24/24 accepted</td>
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<tr>
<td>20 ml Lyoseal</td>
<td>-</td>
<td>24/24 accepted</td>
<td>24/24 accepted</td>
<td>24/24 accepted</td>
<td>24/24 accepted</td>
<td>24/24 accepted</td>
</tr>
<tr>
<td>20 ml Flip-off</td>
<td>-</td>
<td>24/24 accepted</td>
<td>24/24 accepted</td>
<td>24/24 accepted</td>
<td>24/24 accepted</td>
<td>24/24 accepted</td>
</tr>
<tr>
<td>50 ml Lyoseal</td>
<td>-</td>
<td>24/24 accepted</td>
<td>24/24 accepted</td>
<td>24/24 accepted</td>
<td>24/24 accepted</td>
<td>24/24 accepted</td>
</tr>
<tr>
<td>50 ml Flip off</td>
<td>-</td>
<td>24/24 accepted</td>
<td>23/24 accepted</td>
<td>24/24 accepted</td>
<td>24/24 accepted</td>
<td>24/24 accepted</td>
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</table>

(1): 1 broken vial not tested
<table>
<thead>
<tr>
<th></th>
<th>T0</th>
<th>T3</th>
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<th>T37</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICH studies</strong></td>
<td><strong>Products stored at + 25°C ±2 – 60% RH ±5%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 ml Lyoseal</td>
<td>30/30 Accepted</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10 ml Flip-off</td>
<td>29/30 accepted (2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20 ml Lyoseal</td>
<td>30/30 Accepted</td>
<td>24/24 Accepted</td>
<td>24/24 Accepted</td>
<td>24/24 Accepted</td>
<td>24/24 Accepted</td>
<td>24/24 Accepted</td>
</tr>
<tr>
<td>20 ml Flip-off</td>
<td>30/30 Accepted</td>
<td>24/24 Accepted</td>
<td>24/24 Accepted</td>
<td>24/24 Accepted</td>
<td>24/24 Accepted</td>
<td>24/24 Accepted</td>
</tr>
<tr>
<td>50 ml Lyoseal</td>
<td>40/40 Accepted</td>
<td>24/24 Accepted</td>
<td>24/24 Accepted</td>
<td>24/24 Accepted</td>
<td>24/24 Accepted</td>
<td>24/24 Accepted</td>
</tr>
<tr>
<td>50 ml Flip off</td>
<td>40/40 Accepted</td>
<td>24/24 Accepted</td>
<td>25/25 Accepted</td>
<td>23/24 Accepted</td>
<td>24/24 Accepted</td>
<td>24/24 Accepted</td>
</tr>
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</table>

(2): Important leak detected (crimping failure)
ICH accelerated studies: Products stored at -20°C ±5°C

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<th>T37</th>
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<tbody>
<tr>
<td>10 ml Lyoseal</td>
<td>-</td>
<td>30/30 accepted</td>
<td>30/30 accepted</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>10 ml Flip-off</td>
<td>-</td>
<td>30/30 accepted</td>
<td>30/30 accepted</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>50 ml Lyoseal</td>
<td>-</td>
<td></td>
<td>30/30 accepted</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>50 ml Flip-off</td>
<td>-</td>
<td></td>
<td></td>
<td>30/30 accepted</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

ICH accelerated studies: Products stored at 40°C ±2 -75% RH ±5%

<table>
<thead>
<tr>
<th></th>
<th>T0</th>
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<th>T12</th>
<th>T24</th>
<th>T37</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 ml Lyoseal</td>
<td>-</td>
<td>30/30 accepted</td>
<td>29/30 accepted</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>10 ml Flip-off</td>
<td>-</td>
<td>30/30 accepted</td>
<td>30/30 accepted</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>20 ml Lyoseal</td>
<td>-</td>
<td>30/30 accepted</td>
<td>30/30 accepted</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>20 ml Flip-off</td>
<td>-</td>
<td>30/30 accepted</td>
<td>30/30 accepted</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
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5. Conclusion
5: Conclusion

- Benefits by using Lyoseal®:
  - Class A crimping
  - Vials sealed in freeze-dryer without extra aseptic manipulation or aseptic transfer
    - increased assurance of sterility maintenance
    - Containment ↑
  - Less breakage of vials
    - No stoppers sticking to shelves
    - Overseal buffers closing force
  - Elimination of crimping issues
  - Elimination of metal components and potential metal particles

- Lyoseal® delivers Quality by Design
Outlook 2011-2012

• Lyoseal® distribution:
  – IP owned by Biocorp
  – Exclusive and worldwide Sales & Marketing licensee: West Pharmaceutical Services

• New production equipment using LyoSeal to be implemented in 2011 at a pharmaceutical company:
  – Intended for Commercial production
  – Hi-speed filling & capping

• Open-door day & workshop around technology being organized:
  – Location: Europe
  – Focus: Hi-speed filling & stoppering machine using LyoSeal® in operation
  – When: Q4/2011
    • If you are interested and would like to participate, please contact +33 47355 7050 or info@lyoseal.com, mentioning „Lyoseal Workshop“
March 22, 2011

Dear Customer:

We are pleased to announce that West Pharmaceutical Services, Inc. and Biocorp Production S.A. France have concluded an agreement under which Biocorp grants West an exclusive and worldwide license for sales and marketing of the LyoSeal™ lyophilization closure.

Biocorp Production S.A., based in Beaune, France, is a highly regarded company in the development and manufacture of pharmaceutical closures and application systems.

The LyoSeal™ closure is an innovative, patented, plastic cap used to seal vials containing lyophilized drugs or liquid fills. It is compatible with standard vials and lyophilization closures and requires no extra equipment in the lyophilization manufacturing area for freeze-dried products or immediately after stoppering for liquid fills. The LyoSeal closure provides a high level of assurance of product integrity, identity, and quality, while also ensuring a high efficient process flow during filling and stoppering operations. It is currently available in 15mm and 20mm sizes, and additional sizes are under development.

With the LyoSeal closure, West is strengthening its product portfolio of stoppering solutions for lyophilized drugs. West’s leading leading products include auto and manual stoppers for vials and injection vials and corresponding stopper-seals under brands such as West AutoStop®, West FlipCap®, West Envirotect™, West FlipOff® CS, and West Speedy®.

The LyoSeal lyophilization closure expands West’s range of components that support developing, manufacturing, and marketing of pharmaceutical and biopharmaceutical drug products.

For further information, please contact your West Account Manager or our LyoSeal® Manager, Tony Broussard @ extension ±33 692 673 293 or email broussard@lyoseal.com

Yours faithfully,

Dr. Niels Schöllers
WestPharma Consulting, Europe

Laurent Fremin
WestPharma Europe

LyoSeal™ is the trademark of Biocorp Rostand & Co., a Development Company.
• Thank you for your attention.
• Questions are welcome

• To get in further contact regarding Lyoseal®:
  – info@lyoseal.com
  – +33 473 55 7050
  – Or your usual West Pharmaceutical Services sales contact