PHARMACEUTICAL ELASTOMERIC CLOSURES

PHARM Connect – Budapest, 2015

Bruno Morchain - Technical Support Engineer

Delivering solutions, shaping the future.
AGENDA

- Aptar Stelmi Overview
- Elastomeric closures requirements
- Pure Formulations and PremiumCoat™
- From unwashed to Ready To Use components
- Take away
Headquarters in Crystal Lake, Illinois
Over 12,000 Employees
Operating in more than 19 countries
New York Stock Exchange **ATR**
2013 Net Sales: 2.52 billion USD
APTAR PHARMA - ORGANIZATION

Aerosol, spray and dispensing drug delivery technologies

Elastomeric closures

SVP stoppers
SERUM
LYO

LVP stoppers

Syringe components
Aptar Stelmi: Elastomeric Closures - Facts and Figures

- Solution Provider in the Elastomeric Closure Market - leader in production of Prefilled Syringes Components
- 600 associates and 2 mirrored manufacturing sites in France
- Partner with most of the global players in Pharma – 50 years of expertise
- Multiple FDA, Anvisa, EMA inspections – 700+ customers in 70 countries
- 100% production in ready to sterilize (RTS) or ready to use (RTU)
- State-of-the-art International Technical Center run by dedicated experts and equipped with the latest technologies
- Continuous upgrading of production processes
- Deep understanding of pharmaceutical processes incl. freeze-drying, sterilization, filling and finishing.
Application Fields

- Small molecules
- Vaccines
- Anti-thrombotics
- Biologics
- Animal Health
- Other

SVP stoppers  LVP stoppers  Syringe components
**PRODUCT LINE**

**PRE-FILLED SYRINGE AND AUTO-INJECTOR COMPONENTS**

- **PLUNGERS**
  0.5ml, 1ml long, 1-3ml, 5ml, 10ml, 20ml, by-pass 1-3ml

- **TIP CAPS**
  Ribbed Tip Caps (RTC) - Luer lock and Luer cone - Mushroom

- **SOFT & RIGID NEEDLE SHIELD**
  1/2 inch, 5/8 inch, 1 inch

- **PLUNGERS FOR CARTRIDGES**
  1.5ml, 3ml

**SToppers**

- **Large Volume Parenteral (INFUSION)**
  Stoppers for glass vials 28/29mm, 32mm, 34mm, DIN and ISO ; Injection sites for IV bags

- **Small Volume Parenteral (SERUM, ANTIBIO)**
  13 and 20mm, ISO and blow back

- **LYOPHILIZATION**
  13mm, 20mm, 28mm, 32mm

- **DIAGNOSTIC**
  DIN 14, DIN 18, DIN 22

**Other range**

- **DROPPER BULBS**
  0.2ml, 0.8ml, 1ml
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Elastomeric Closures requirements

Fundamental principle:
integrity guaranteed during packaging, storage and administration to the patient

- Avoid losses & leakages
- Avoid evaporation (water, solvent, active ingredients)
- Protect from water, light, ozone
- Avoid external contamination
- Compatible with sterilization methods (steam – gamma)

- Avoid active ingredient modification

- Avoid damaging needle
- Avoid fragmentation
- Enable multipiercing
- Good functional properties for syringes

- Compliance with the pharmacopoeias

Note that machinability on the filling lines is also key
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# HALOBUTYL: CHLOROBUTYL & BROMOBUTYL

## VERY LOW PERMEABILITY
- The most impermeable to gases and steam

## CHEMICAL INERTNESS
- Simpler vulcanization systems
- No need for antioxidants in the formulation
- Low level of extractable/leachables

## PHYSICAL AND CHEMICAL RESISTANCE
- Resistance to heat, oxidization, ozone and aging
- Self-sealing properties

## OTHER PROPERTIES
- Low moisture content (used for lyophilized product)
- Process performance

## APPLICATION
- Prolonged contact with the drug product (stoppers, plungers)
- Formulations in compliance with international compendia (USP, EP, JP)
- Bromobutyl preferred for lyophilized applications
# APTAR STELMI VERSATILE HALOBUTYL FORMULATIONS

<table>
<thead>
<tr>
<th>6422</th>
<th>6720</th>
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<tbody>
<tr>
<td><strong>CHLOROBUTYL FORMULATION</strong></td>
<td><strong>BROMOBUTYL FORMULATION</strong></td>
</tr>
<tr>
<td>- Lower hardness,(43) higher elasticity: Outstanding coring &amp; seal sealing properties</td>
<td>- Higher hardness (51): Outstanding machinability</td>
</tr>
<tr>
<td>- Main applications: small molecules, unbuffered NaCl solutions; vaccines</td>
<td>- Low moisture: preferred formulation for freeze dried products &amp; powders</td>
</tr>
<tr>
<td>- Main components: Liquid LVP &amp; SVP stoppers syringe plungers</td>
<td>- Zinc free</td>
</tr>
<tr>
<td>- Different base elastomers</td>
<td>- Different fillers</td>
</tr>
<tr>
<td>- Different curing system</td>
<td>- Different ionic profiles</td>
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</table>

- Versatility: range of compatibility, range of components
- Compliance with EP, USP, ISO, JP
- Compatibility with steam, EtO & gamma sterilization
Coated Materials and Assemblies

- Components could be delivered in a single material
  - Ex: plunger in formulation 6720 grey

- Components could be co-injected
  - Ex: elastomer + thermoplastic

- Components could be assembled
  - Ex: Needle Shields made of 4800 grey + a polypropylene shell to make a Rigid Needle Shield

- A film could be added to minimize the contact between the elastomer and the drug
  - Ex: ETFE film on stopper
Purposes of coatings

- Enhances compatibility - filters extractables coming from the elastomer
- For sensitive products - Minimizes absorption and adsorption phenomena
- Minimizes particles
- Increases lubricity
Focus on the ETFE film

- Inert material
- Chemical resistance to various solvents
- Compatible with rubber molding process
- No use of additives for a proper adhesion
- Sustains Gamma-irradiation

Ethylene tetrafluoroethylene
A combination of container closure integrity and improved compatibility

**PremiumCoat™**

ETF Film area for an improved compatibility with the drug product
A combination of container closure integrity and improved compatibility

**PremiumCoat™**

ETFEl Film area for an improved compatibility with the drug product

Non coated (with film) area for an improved sealing
Container Closure Integrity: similar behavior of non-coated stopper and PremiumCoat™

In severe conditions, after 6 months, we observed, no differences between a coated and a non-coated stopper (with non blow black vials*)
Combination of a state-of-the-art formulation with a ETFE inert Film

Significantly reduces leachable level

Proven Technology

Facilitates project development

Available and supported worldwide
:: Shape: Small Volume Parenteral stopper

:: Nature of the coating: Fluoropolymer Film (ETFE)

:: Coated area: surface of contact with drug

:: Rubber formulation: Bromobutyl

:: Finishing: UC6 Evolution (Ready to Sterilize with final rinse with WFI)
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:: Take away
Logical evolution from unwashed to “Ready To Use”

<table>
<thead>
<tr>
<th>Event</th>
<th>Year</th>
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<tbody>
<tr>
<td>Introduction of the first “Ready-to-Sterilize” components</td>
<td>1974</td>
</tr>
<tr>
<td>UltraClean 6 finishing introduction (last rinse in WFI)</td>
<td>1990</td>
</tr>
<tr>
<td>First approval of the UltraClean 6 finishing (RTS) in the USA</td>
<td>1992</td>
</tr>
<tr>
<td>DMF type V for the finishing UltraClean 6</td>
<td>1997</td>
</tr>
<tr>
<td>Sterile plungers for prefilled syringes</td>
<td>2003</td>
</tr>
<tr>
<td>Introduction of the finishing UltraClean 6 evolution</td>
<td>2005</td>
</tr>
<tr>
<td>Sterile stoppers</td>
<td>2008</td>
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Production Process of elastomeric closures

- REceiving
- Weighing
- Mixing
- Molding
- Trimming
- Finishing
- Packaging
- Quality controls
- Release

Formulation

Design

Washing / Siliconizing

Drying / Packaging
Washing and first rinsing operations in highly purified water (EP), in compliance with the FDA guidance

Final rinsing: WFI - Aptar Stelmi custom overflow rinsing

DMF Type V (covering all Aptar Stelmi facilities)
:: Validated Process
Reduction in bacterial endotoxins
Bacterial decontamination
Particulate decontamination
Consistent siliconization level
Absence of residual detergent

:: Comprehensive CoA, including
Physico-chemical results
Bioburden, endotoxins and PCI (results and specifications)
Visual check
Dimensional check
# Sterile Process of elastomeric closures

<table>
<thead>
<tr>
<th>PRODUCTION PROCESS &amp; MICROBIOLOGICAL CONTAMINATION</th>
<th>VALIDATION &amp; RE-VALIDATION</th>
<th>IRRADIATION</th>
<th>DOCUMENTATION &amp; REGULATORY FIELD</th>
</tr>
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<tr>
<td>&gt;Specific organisation &lt;br&gt; &gt;More frequent controls &lt;br&gt; &gt;Specific primary packaging &lt;br&gt; &gt;Specific configuration of palletisation for gamma irradiation</td>
<td>&gt;Comprehensive validation and re-validation (including bag seals and transport) &lt;br&gt; &gt;Dose Audit &lt;br&gt; &gt;Ageing study</td>
<td>&gt;Validated range 18 – 32 kGY</td>
<td>&gt;Certificate of sterility &lt;br&gt; &gt;DMF type V &lt;br&gt; &gt;Validation file &lt;br&gt; &gt;Certificate of irradiation</td>
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<tr>
<td>STERILITY GUARANTEED</td>
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- Centre de photocopie
- Sterile Process of elastomeric closures
- PHARM Connect 2015 – Aptar Stelmi
**From Ready to Sterilize to Ready to Use**

Transferring the washing and sterilization operations to the supplier

<table>
<thead>
<tr>
<th>Investment</th>
<th>Development</th>
<th>Validation</th>
<th>Re-validation</th>
<th>IPC Monitoring</th>
<th>Regulatory</th>
<th>Audits</th>
<th>Reception controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RTS</strong>*</td>
<td><strong>Equipment Area</strong></td>
<td><strong>Steam Sterilization</strong></td>
<td><strong>Sterility Monitoring</strong></td>
<td><strong>Filing</strong></td>
<td><strong>Supplier In-house</strong></td>
<td></td>
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<tr>
<td><strong>RTU STERILE</strong></td>
<td>* + steam sterilization in-house</td>
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*PHARM Connect 2015 – Aptar Stelmi*
TAKE AWAY

- Global leader and preferred partner, specialized in elastomeric closure solutions (stoppers and Pre-Filled Syringes components) for injectable drug delivery systems.

- Solution Provider: high purity formulations, *PremiumCoat™*, RTS, RTU.

- State-of-the-art manufacturing processes.

- Premium Quality and Technical Expertise based on more than 50 years of success on the regulated markets.
Thank you for your attention!