Sterile packaging of liquid pharmaceuticals
Using rommelag bottelpack®
blow-fill-seal machines

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Contents

• bottlepack® History
• Blow Fill Seal process
• Manufacturing
• Container Design
bottelpack® BFS machine history

• 1960s
  - Invention of the BFS process
  - First bottelpack prototype 1963
  - Low capacity with one mold
  - Relay controlled
  - No aseptic systems
  - Bigger fill volume
  - Customers in Germany and Europe
• **1970s**

- Medium-high capacity machine with 2-10 molds
- Machine for small fill volumes (0.2 - 50 mL)
- Machine designs for aseptic filling (product filters, CIP, SIP)
- Piston dosing/tube dosing systems for big/small volumes
- relay-controlled machines
- Worldwide machine export; license production in USA
• 1980s
  - High capacity machine for small fill volumes with 15 molds (type 4010M)
  - Automatic machine program changes
  - Time pressure dosing as standard system
  - PLC controlled machines
  - Alarm message on display
  - Production documentation
- New bottelpack® machine generation (Types 321/321M - 360/360M)
- Clean/Dirt concept machine design
- Increased level of automation using PLCs
- Development of Co-extrusion and PET processing technique for BFS
- ISO 9001 Certificate
bottelpack® BFS machine types - today

• Single parison types for bottle manufacturing (50 - 2000ml). Machine Types:
  - 3012 (one mold)
  - 321 (one mold)
  - 360 (two molds)

Capacity range: ~ 250 - 4,000 bottles/h
• Multiple parison types for ampoule manufacturing (0.2 - 50 ml). Machine Types:
  - 3012 M (one mold)
  - 321 M (one mold)
  - 360 M (two molds)
  - 4010 M (fifteen molds)

Capacity range: ~ 2,500 - 30,000 ampoules/h
bottelpack® model 3012/321

Capacities up to 9,000 vials per hour
bottelpack® model 360

Higher capacities up to 18,000 vials per hour
Blow Fill Seal Process
Conventional vs. BFS

Supply of containers
- Transport into sterile room
- Container cleaning
- Container sterilization
- Transport process under sterile conditions
- Prep. filling product for sterile filling
- Aseptically operating filler
- Transp. under sterile condition
- Closure part supply, cleaning, sterilization
- Capping under sterile condition
- Output from sterile room

Supply of plastic granulate

Preparation of product for sterile filling

Aseptic manufacturing, filling and closing in the blowing mold without changing the place
BFS Process Overview

Parison Extrusion
Molding by blowing and vacuum
Filling
Container sealing
Product
Process step 1

- Plastic melting and extrusion (170-230°C; up to 350 bar)
- Extrusion provides sterilization and depyrogenation
Single/Multiple parison extrusion

Parison head

Mold

Multiple parison extrusion

Single parison extrusion
Parison
Process step 2

- Main mold seals the lower parison end
- The parison is separated by a knife
- Sterile air kept in the parison
Process step 3

- Rapid mold movement to filling position
- Sterile air shower box (100) protects filling point
- Blowing/filling unit at rest position
Sterile Filling Space

- Air supply
- Pre-filter
- Sterile air filter
- Sterile air shower box
- Filling point
- Sterile Filling Space
Process step 4a

- Lowered blowing/filling unit is placed tightly on top of main mold
- Blow molding by sterile air and/or vacuum
Process step 4b

- **Filling - Time pressure dosing**
Aseptic Piping and Sterile filtration

- **Product Filters** - 0.2 micron
- **Parison Air Filter**
- **Sterile space Air Filters**
Time Pressure Dosing

- Product supply
- Constant buffer air
- Product tank
- Dosing block, timer controlled
- Container
Process step 5

- Filling needles withdraw into the sterile space
- Head mold seals container hermetically
Manufacturing
Manufacturing Components

- Fill Suite
- Machine Qualification
- Bulk Solution
- Utilities
Fill Suite Environment

• Fill suites are designed to separate the BFS machine’s aseptic part from its utilities
Basic bottelpack® machine lay-out

- Mechanica l cabinet
- Plastic granulate hopper
- Electronic cabinet
- Filling system
- Buffer tank
- Main frame
- Positioning head
- Mold movement
Fill Suite Segregation

The "Dirty" Side

- Separating potential sources of contaminants from the filling environment

Stainless Steele Barrier Wall
Fill Suite Segregation
The “Dirty” Side

• Separating potential sources of contaminants from the filling environment.
Fill Suite Segregation
The “Clean” Side

- Houses the parison extrusion, and sterile filling space under a sterile laminar air hood
Sterile laminar air hood

- Room Class 100,000
- LUWA, Laminar Sterile Air Shower, Class 10,000
- Sterile Filling Space, Class 100
Main activities of Machine Qualification

• **Installation Qualification (IQ)**
  - Check of the main components for correctness according specification (material and type)

• **Operational Qualification (OQ)**
  - Check of main functions of the equipment

• **Performance Qualification (PQ)**
  - Check of processes functions and efficiencies, output, capabilities etc.
• Process Qualifications

- 3 x Media fills

- 3 x SIP-Validation (Sterilization in Place) with biological indicators (BI)

- 3 x CIP-Validation (Cleaning in Place)
Bulk Solution
Bulk Solution

• Solution is transferred into the Holding tank through a 0.2 micron Pall Filter

• Solution in the Holding tank is maintained under positive pressure with sterile air
Utilities
Stable supply and quality of utilities

- **Electric power:**
  - Connection: 35-100 kW, depending on machine type
  - Consumption: 25-60 kW, depending on machine type

- **Compressed air:** oil and moisture free quality, 8 bar min.

- **Cooling water:** ~ 1.3 - 2.0 m³/h at 12°C and 4 bar; dirt filtered at 55 micron

- **Pure steam (SIP):** ~ 25-40 kg/h particle filtered
Container Design
Points to consider for container design:

- Resin type for BFS
- Closure designs
- Fill volume vs. dosage volume
- Light sensitivity
- Oxygen / Vapor permeation
- Need for autoclaving
- Labeling options
## Resin for BFS technology

<table>
<thead>
<tr>
<th></th>
<th>Low density polyethylene (LDPE)</th>
<th>High density polyethylene (HDPE)</th>
<th>Polypropylene (PP)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Density (g/cm³)</strong></td>
<td>0.915-0.93</td>
<td>0.94-0.95</td>
<td>0.895-0.905</td>
</tr>
<tr>
<td><strong>Melting index</strong></td>
<td>0.2-2</td>
<td>~2</td>
<td>~2</td>
</tr>
<tr>
<td><strong>Clarity</strong></td>
<td>good</td>
<td>poor</td>
<td>good</td>
</tr>
<tr>
<td><strong>Gas permeation</strong></td>
<td>medium</td>
<td>medium</td>
<td>medium</td>
</tr>
<tr>
<td><strong>Vapor permeation</strong></td>
<td>good</td>
<td>excellent</td>
<td>excellent</td>
</tr>
<tr>
<td><strong>Drop resistance</strong></td>
<td>excellent</td>
<td>good</td>
<td>satisfactory</td>
</tr>
<tr>
<td><strong>Squeezability</strong></td>
<td>excellent</td>
<td>satisfactory</td>
<td>poor</td>
</tr>
<tr>
<td><strong>Regulatory conformity</strong></td>
<td>EP III, Ed 1997 3.1.4 USP, class VI FDA, CFR 177-1520 (c) 2.2</td>
<td>EP III, Ed 1997 3.1.5 USP class VI</td>
<td>EP III, Ed 1997 3.1.6 USP, class VI FDA, CFR 177-1520 (c) 3.2</td>
</tr>
<tr>
<td><strong>Application examples</strong></td>
<td>eye drops inhalations ointments/cremes LVP/SVP</td>
<td>irrigation solutions oral solutions topical solutions</td>
<td>irrigation solutions LVP SVP eye drops</td>
</tr>
</tbody>
</table>
Autoclaving

- PP, autoclaving possible at 121°C, 15 min
- PE, medium density (0.928 - 0.93), autoclaving at 106 -110°C, prolonged cycle time
- PE, low density (0.915-0.928): aseptic fill for heat sensitive products
Oxygen/ Vapor permeation

- PE, PP limited barrier properties for oxygen and CO₂
- Machine operation with nitrogen instead of sterile air
- Secondary packaging by pouching/over wrapping
  - supported by nitrogen
  - use of oxygen absorber
Light sensitivity

• Secondary packaging into light-protective pouches/cartons

• Extrusion of colored parison
Fill volume - Multi dose containers

- Multi dose container
  - sterile before first application
  - critical: preservatives
  - additional cap/insert for re-closure function
Multi-dose eye drop & ear drop bottles

Reclosable bottle for contact lens cleaning
Fill volume - Unit dose container

- Unit dose container
- no preservatives
- no capping part
- defined dose volume
- easy to apply
Unit-dose packages for contact lens care

Unit-dose eye, ear & nose drops

Ointments & creams
Specialty designs

Below containers for rectal & vaginal applications

Enemas with cannula or threads
Specialty Designs

[Image of various plastic containers and bottles]
Closure Designs

a) Standard twist-off
b) Thread for bigger caps/wider opening
c) Thread for pin caps
d) Membrane closure

Insertion of stoppers, nozzles, etc.
Closure Designs
Labeling Options

a) Embossing

b) Paper label on tabs

c) Direct printing on tabs

d) Conventional Labels
a) Embossing - Engraved Molds

- A mirror image of information is engraved on the surface of a mold’s cavity.
- Small vacuum ports on the mold surface pull in the soft plastic embossing the container.
Engraved Mold
Embossed Labeling
# Embossing

<table>
<thead>
<tr>
<th><strong>Pros</strong></th>
<th><strong>Cons</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>No maintenance of label inventories</td>
<td>Difficult to read on clear containers</td>
</tr>
<tr>
<td>Ensures 100% labeling of containers</td>
<td></td>
</tr>
<tr>
<td>Labels can not be removed</td>
<td></td>
</tr>
<tr>
<td>Ensure each unit is traceable</td>
<td></td>
</tr>
<tr>
<td>No leachables</td>
<td></td>
</tr>
</tbody>
</table>
b) Paper Labels on Tabs

- The mold is designed with a tab, or flag on the tail or the cap.

- Tab is a solid surface providing space for paper labels
Paper Label on Tab
<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearer to read</td>
<td>Potential leaching of label adhesive into solution</td>
</tr>
<tr>
<td></td>
<td>Greatly reduces potential leaching into the solution</td>
</tr>
</tbody>
</table>
c) Direct Printing on Tabs

- Ink Jet printing on tabs
- Product Information with barcodes, and
Direct Printing on Tab
## Direct printing on the Tab

<table>
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<th>Cons</th>
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</thead>
<tbody>
<tr>
<td>Clearer to read</td>
<td>Potential leaching into solution</td>
</tr>
<tr>
<td>Eliminates potential leaching from paper labels</td>
<td></td>
</tr>
<tr>
<td>Greatly reduces potential leaching into the solution</td>
<td></td>
</tr>
<tr>
<td>Allows for barcode printing on line</td>
<td></td>
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</table>
d) Conventional Labeling
Thank You
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