Blow-Fill-Seal technology in Large Volume Parenteral Packaging

Nelson Symposium March 24th, 2021  Michael Spallek, Rommelag R&D
Overview

1. Rommelag and Principles of Blow-Fill-Seal
2. Containers & Material Selection
3. Recent Innovation in LVP-packaging
4. Summary
Rommelag engineering and Rommelag CMO: Synergy of machine & contract manufacturing in Blow-Fill-Seal.
Blow-Fill-seal (BFS) technology is based on well known extrusion-blow molding.
Within seconds Blow-Fill-seal (BFS) produces filled and closed LVP-containers from polymer granulate.

EXTRUSION
Polymer parison Extrusion

BLOWING
Bottles are blown into mould

FILLING*
Time-Pressure-Dosing system

SEALING
Head mould closes

DEMOULDING
• Moulds open
• Container removed

cycle time approx. 15 sec

/2/ The manufacture of sterile pharmaceuticals and liquid medical devices using blow-fill-seal technology, BFS International Operators Association, Editio Cantor Verlag, 2016
Blow-Fill-Seal in a detailed view on LVP-Bottles produced from an 8-fold mold.
BFS is highly integrated aseptic pharma packaging: Advanced aseptic technology overview.
BFS is Advanced aseptic technology well established in the pharma market.

BFS is a production process based on extrusion blow molding dedicated to pharma packaging.

Key features:

-1- Advanced Aseptic Processing*

-2- Hygienic design

-3- Ultra-Compact A-Zone 500 x 200 mm

-4- Production capacity (e.g. 250 ml, PP):
   from 2000 pcs /h (bp 321, 8 fold); 12 mio/a
   up to 8800 pcs /h (bp 364, 14 fold); 52 mio/a

*USP < 1116> "Advanced aseptic processing" EU-GMP Guide Annex 1 (Chapter 26-27)

Michael Spallek / Johannes Geser  BFS for LVP packaging  Nelson Symposium
BFS is used for primary packaging of liquid drug products from LVP to ophthalmics.

Typically 0.2 ml to 10 ml and 300 ml

Typically 1 ml to 20 ml

Typically 50 ml to 1000 ml

Typically 0.2 ml to 10 ml and 300 ml
BFS for LVP cover bottle-type & bag type containers.

LVP Container designs

BFS-Bags
Single drug contact materials for BFS packaging are medical grade polyolefins.

**LDPE or PP**
Medical grades from e.g.
Borealis (Bormed®)
LyondellBasell (Purell®),
INEOS, Total, Flint Hills, etc.

Autoclavable LDPE 106-115°C; 
**PP 121°C**

Extractables dossiers available for selected PE and PPs (by Toxikon)

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**E&L Summary by Piet Christiaens**

For aqueous Drug Products, the Extractable Results show a low risk of leaching of compounds to a relevant level.

Piet Christiaens & Michael Spallek
The Importance of a thorough material selection for Blow-Fill-Seal applications, an E/L-Perspective PDA Parenteral Packaging, Venice April 13, 2016
Coextrusion & cyclic polyolefins are options to fulfill specific requirements.

Principle of multi-layer containers and co-extrusion

COC / COP and compounds
Polyplastics or ZEON
- low sorption, good water barrier
- elastomeric grades available
The BFS test kit allows an easy pre-test / compatibility test with selected standard BFS materials.

- empty, closed BFS containers
- manufactured according GMP regulations
- inside sterile
- max. filling volume approx. 10 mL
- suitable for use in client’s lab
- low efforts to start first stability trials
- certain extractables dossiers available
BFS test kit handling is straightforward.

- Opening with scissors
- Warming with heat gun
- Closing with gripper
- Filling with syringe
- Finish
1. Rommelag and Principles of Blow-Fill-Seal
2. Containers & Material Selection
3. Recent Innovation: EasyEmpty-Bottles
4. Summary
The objectives for new high performance, self collapsing infusion bottles were challenging.

<table>
<thead>
<tr>
<th></th>
<th>Established LD-PE-bottle</th>
<th>Established PP-bottle</th>
<th>New bottle</th>
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<tbody>
<tr>
<td>Safety</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Particulate matter</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>Sterilization temperature</td>
<td>106°C</td>
<td>121°C</td>
<td>121°C</td>
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<tr>
<td>Sterilization time</td>
<td>≥ 85 min</td>
<td>≥ 20 min</td>
<td>≥ 20 min</td>
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<tr>
<td>Container size</td>
<td>Minimal headspace</td>
<td>Increased headspace</td>
<td>Minimal headspace</td>
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<tr>
<td>Unvented administration</td>
<td>Good</td>
<td>Good, if…</td>
<td>Good</td>
</tr>
</tbody>
</table>
The relevant parameters for the discharge behavior have been identified.

Ishikawa - Analysis

BFS-process
- Wall thickness

Material
- Terminal sterilization
- Young’s modulus
- Costs
- Cap size
- Headspace / fill ratio
- Shape

Medical requirements
- Flow rate
- Non-vented
- Pressure
- Needle size

Container design

Environment

Safe & efficient infusion

Various

PDA Parenteral Packaging

Christoph Kaschta / Rommelag Engineering
Analysis of various “standard bottle designs” indicated design improvements.

Input A: Design / shape

- Hinges
- Folding triangle
- Folding edges
First results show that the simulation reflects the folding process.

Simulation:
- huge dislocation
- no dislocation of the FEM volume element

folding works & use low Young’s modulus PP
The new EasyEmpty design bottles compare very well to established products on the market.
Summary: Blow-Fill-Seal technology in Large Volume Parenteral Packaging.

Take home Messages

1. Within seconds Blow-Fill-seal (BFS) produces filled and closed LVP-containers from polymer granulate.

2. Polyolefins are well established for BFS-primary packaging of LVPs using a single drug contact material.

3. Coextrusion & cyclic polyolefins are options to fulfill specific requirements e.g. low sorption with COP & COC.

4. The BFS test kit allows an easy pre-test for material selection.

5. The administration behavior of the new EasyEmpty design bottles compares very well to established products on the market.


4. EU Guidelines to Good Manufacturing Practice, Annex 1, Manufacture of Sterile Medicinal Products, Brussels, 2008

5. Michael Spallek et al., Heat effects on sensitive formulations during blow-fill-seal processing, PDA Parenteral Packaging, Brussels, 3-2014