FILLING YOUR NEEDS

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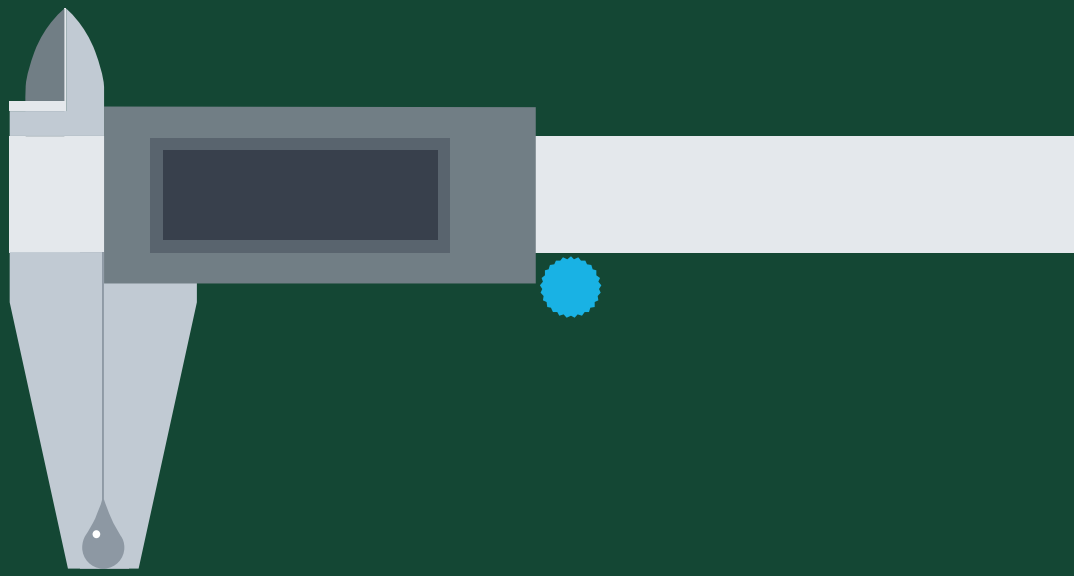
Blow-Fill-Seal technology in Large Volume Parenteral Packaging

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



Blow-Fill-Seal technology in Large Volume Parenteral Packaging

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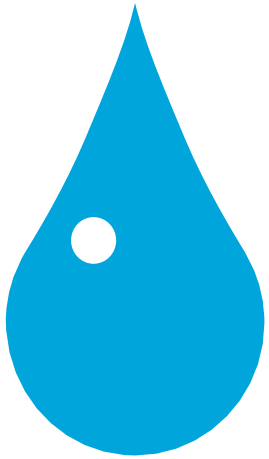
Overview



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.

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Kocher-Plastik

Maroplastic

ROMMELAG CMO

Holopack

Maropack

Blow-Fill-seal (BFS) technology is based on well known extrusion-blow molding.

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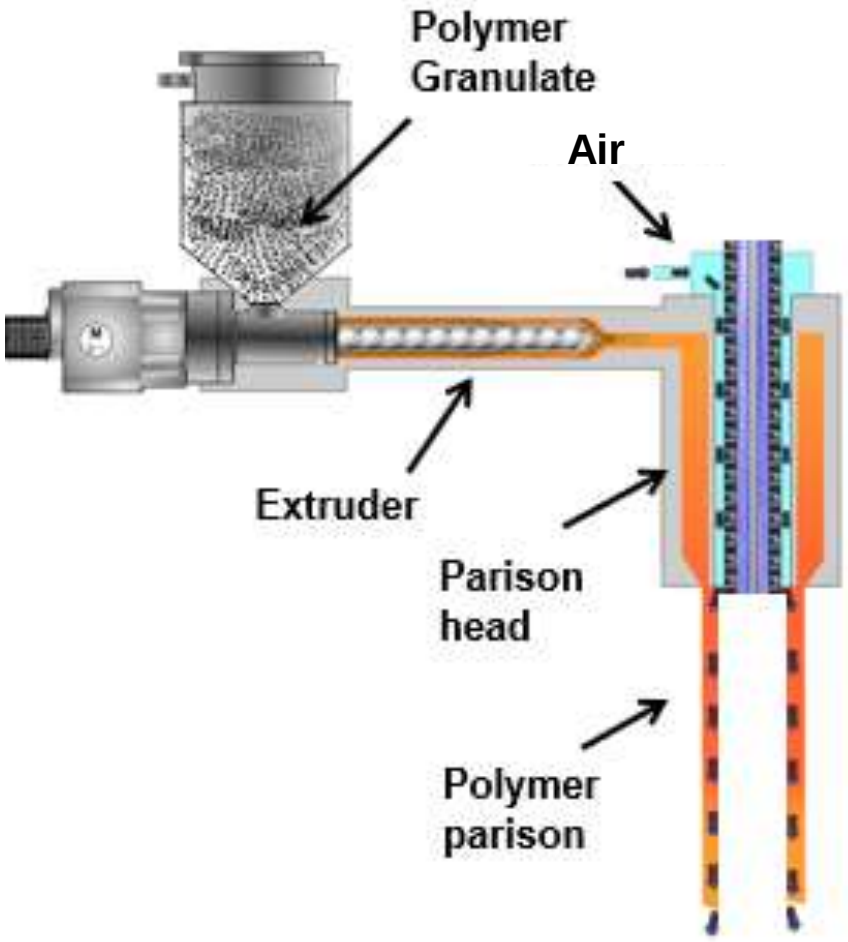
Extrusion blow molding principle



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

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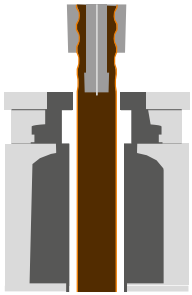	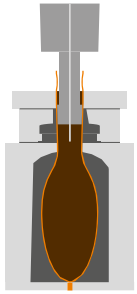	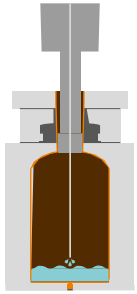		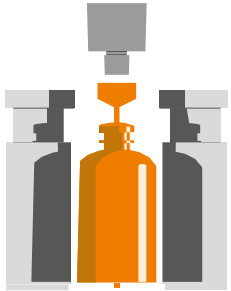
EXTRUSION	**BLOWING**	**FILLING***	**SEALING**	**DEMOULDING**
Polymer parison Extrusion	Bottles are blown into mould	Time-Pressure-Dosing system	Head mould closes	• Moulds open • Container removed

cycle time approx. 15 sec

/1/ R. Oschmann and O.E. Schubert, Eds., Blow-Fill-Seal Technology, CRC Press, Stuttgart, 1999
/2/ The manufacture of sterile pharmaceuticals and liquid medical devices using blow-fill-seal technology, BFS International Operators Association, Editio Cantor Verlag, 2016
/3/ The manufacture of sterile pharmaceutical products using Blow-Fill-Seal-Technology, PDA, Technical Report No. 77, 2017

Blow-Fill-Seal in a detailed view on LVP-Bottles produced from an 8-fold mold.

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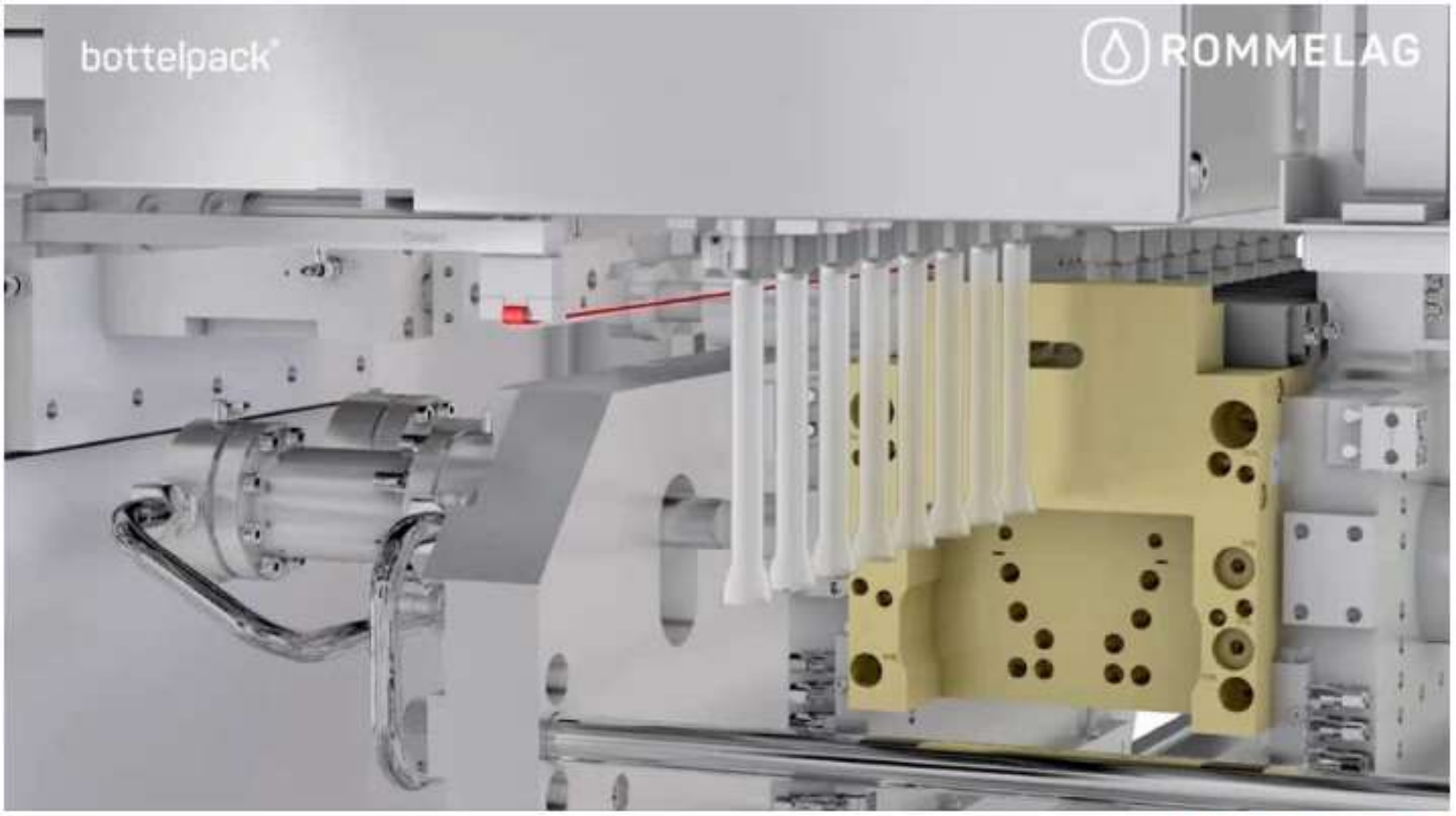

https://vimeo.com/224430468

BFS is highly integrated aseptic pharma packaging: Advanced aseptic technology overview.

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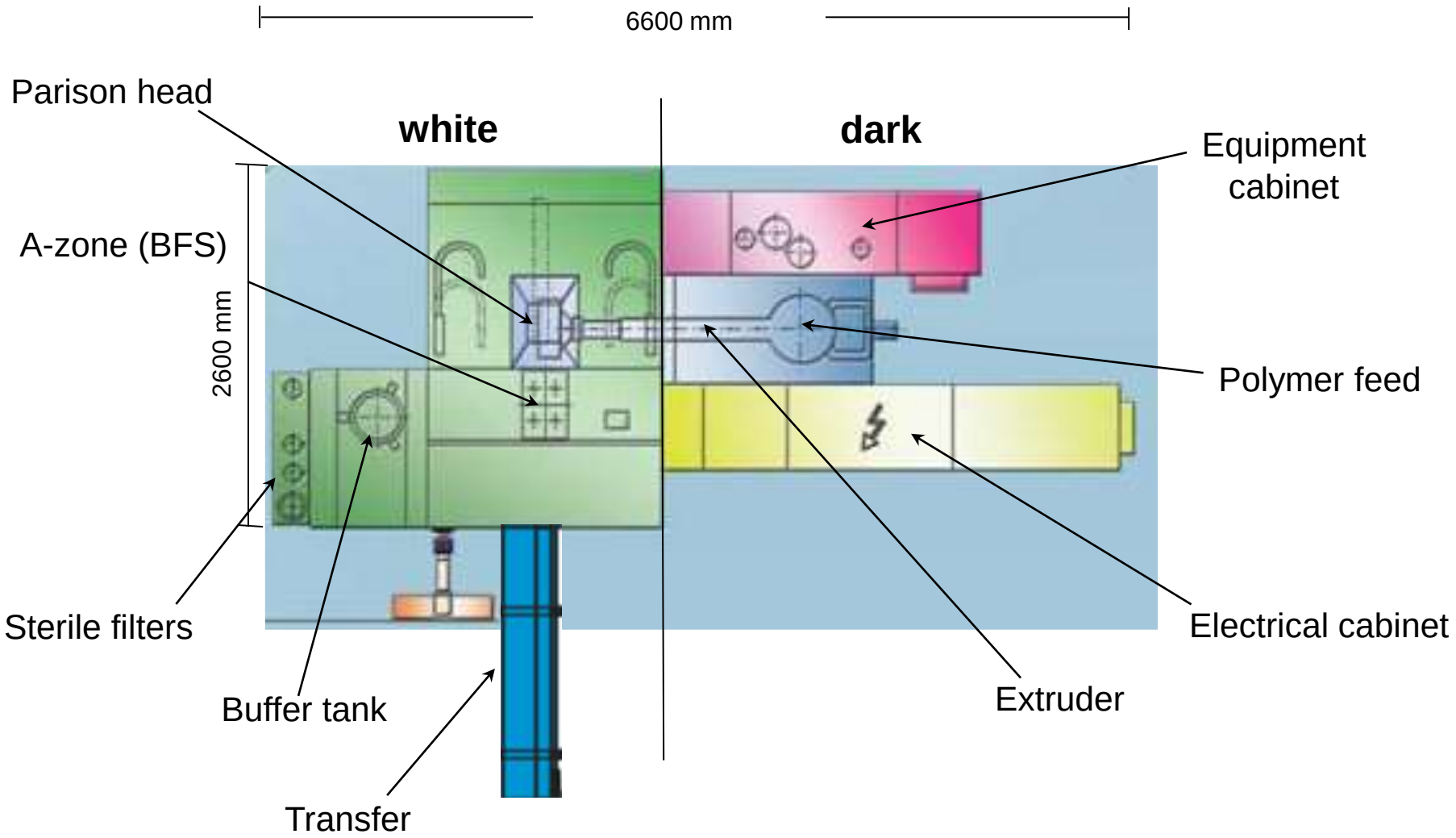

BFS is Advanced aseptic technology well established in the pharma market.

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Bottelpack bp 321

Blow-Fill-Seal

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)
FDA 9-2004, Guidance for Industry, Sterile Products Produced by Aseptic Processing, Appendix 2: BFS

BFS is used for primary packaging of liquid drug products from LVP to ophthalmics.

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LVP

Typically 50 ml to 1000 ml

Inhalation & SVP

Typically 1ml to 20 ml

Eye care

Typically 0.2 ml to 10 ml and 300ml

BFS for LVP
cover bottle-type & bag type containers.

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LVP Container designs

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

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Standard Materials

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

Autoclavable LDPE 106-115ºC;
PP 121ºC

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

E&L Summary by Piet Christiaens

PDA Parenteral Drug Association

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.

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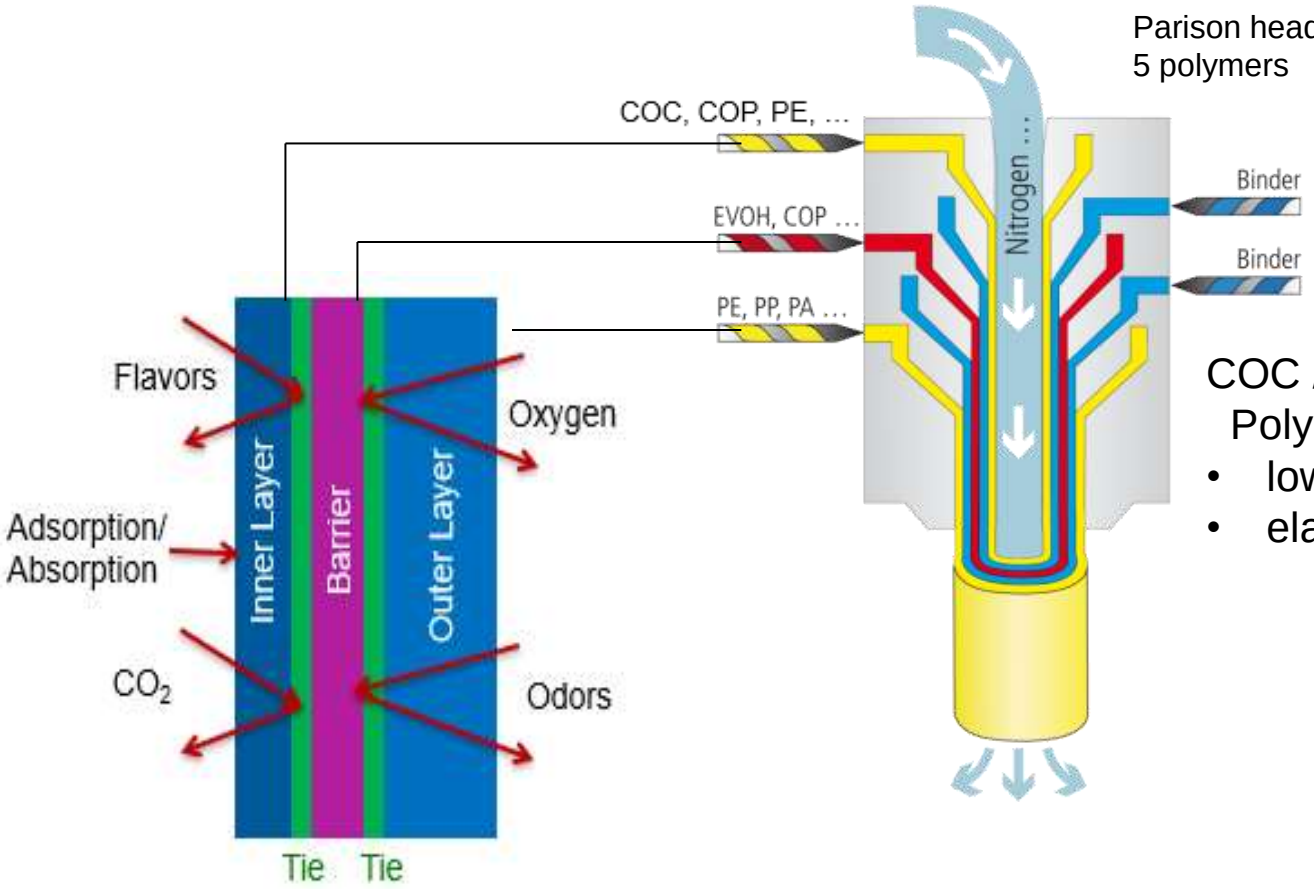
Principle of multi-layer containers and co-extrusion



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.

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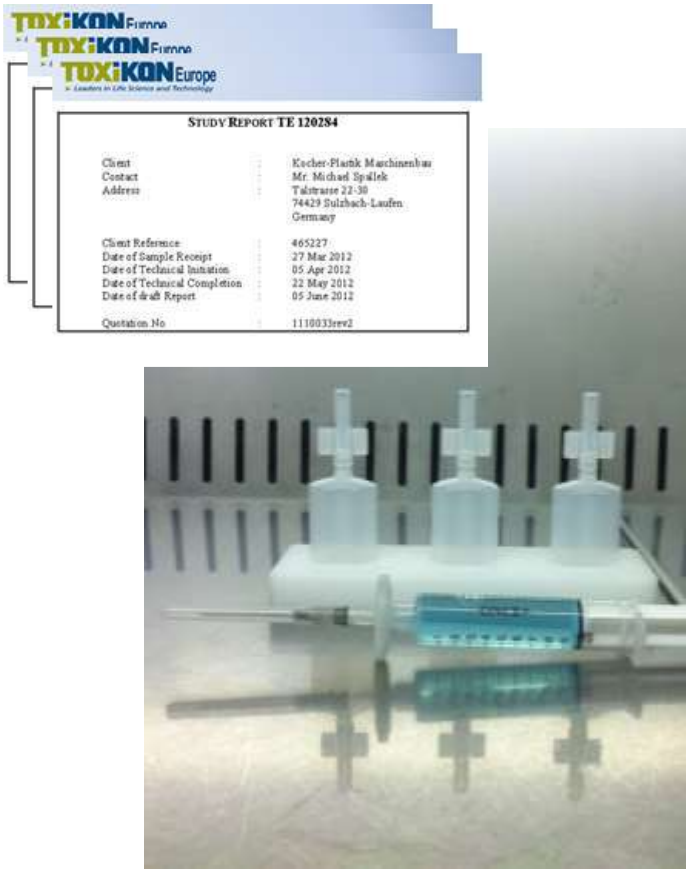
BFS-Test kits



- 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 straight forward.

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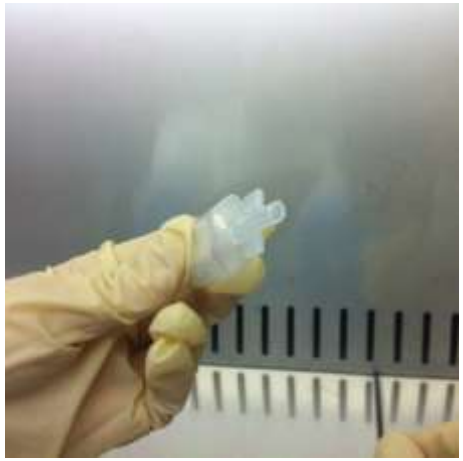
opening with scissors



filling with syringe

warming with heat gun

closing with gripper

finish

Blow-Fill-Seal technology in Large Volume Parenteral Packaging

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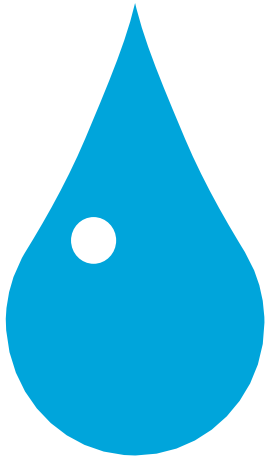
Overview



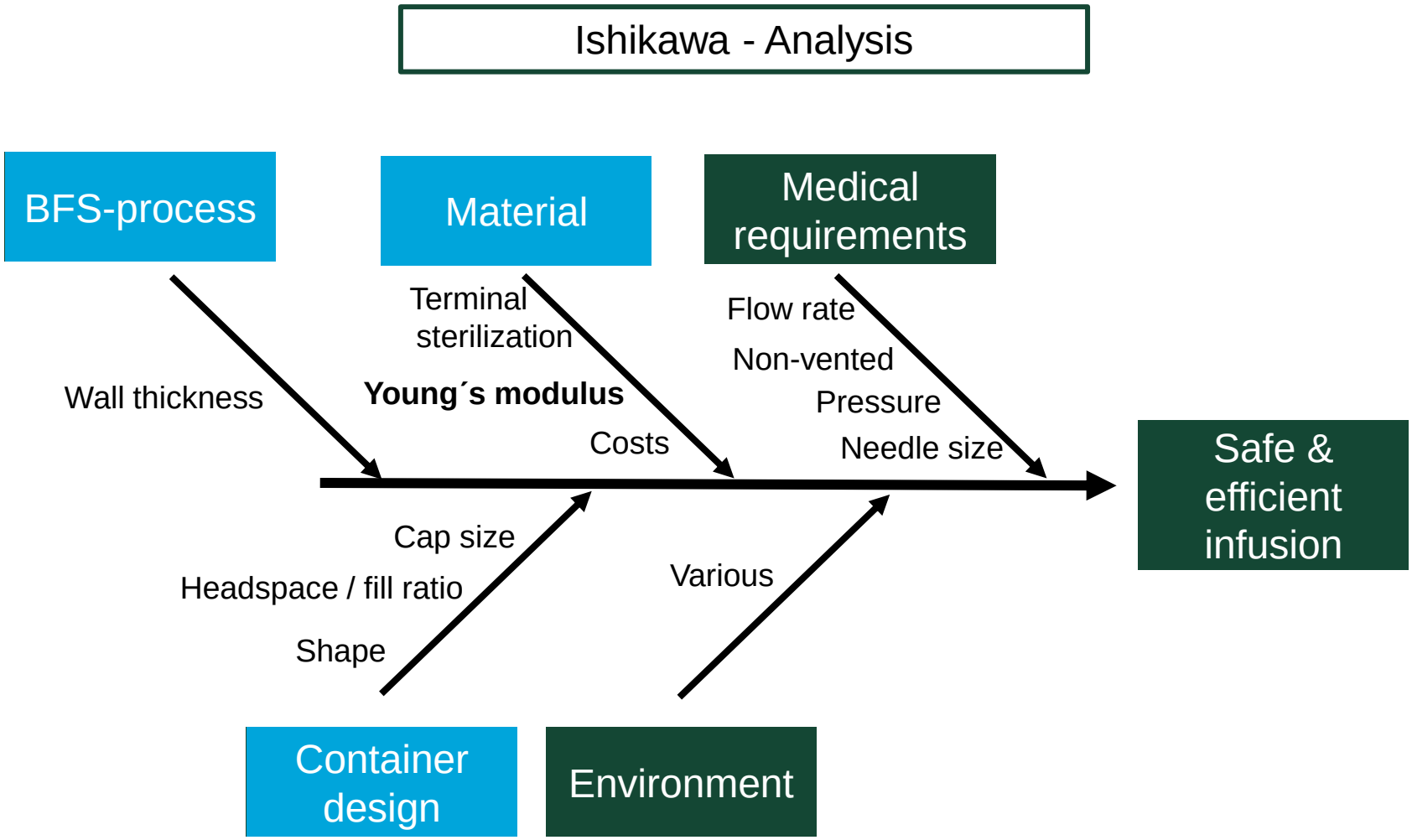
1. Rommelag and Principles of Blow-Fill-Seal
2. Containers & Material Selection
3. **Recent Innovation: EasyEmpty-Bottles**
4. Summary

The objectives for new high performance, self collapsing infusion bottles were challenging.

From Market to innovation

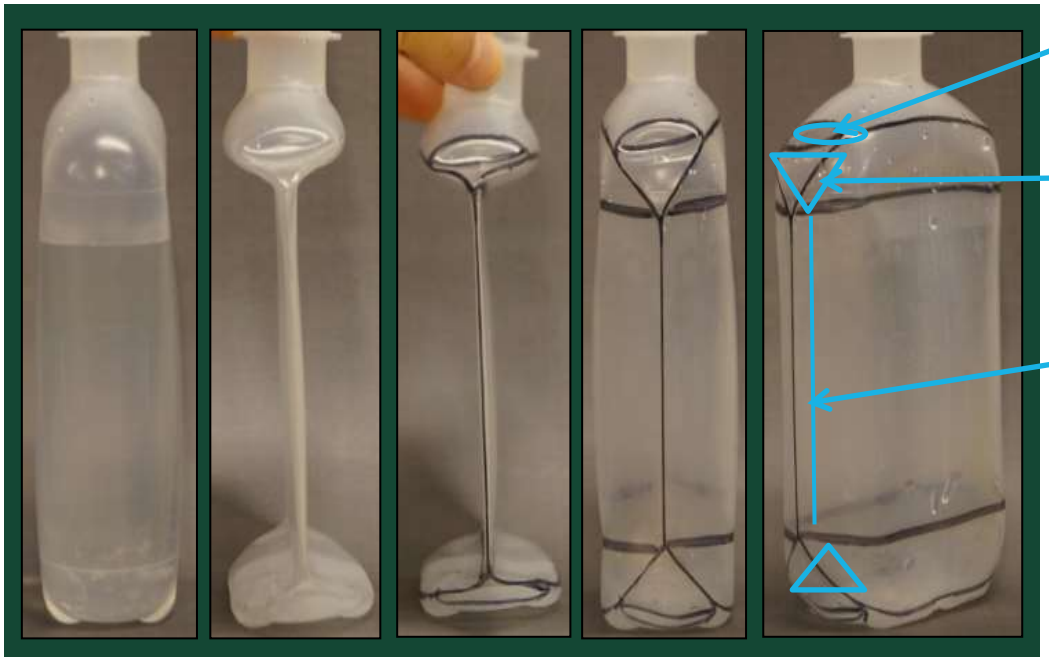
	Established LD-PE-bottle	Established PP-bottle	New bottle
Safety	+	+	+
Particulate matter	+	+	+
Sterilization temperature	106°C	121°C	121°C
Sterilization time	≥ 85 min	≥ 20 min	≥ 20 min
Container size	Minimal headspace	Increased headspace	Minimal headspace
Unvented administration	Good	Good, if…	Good

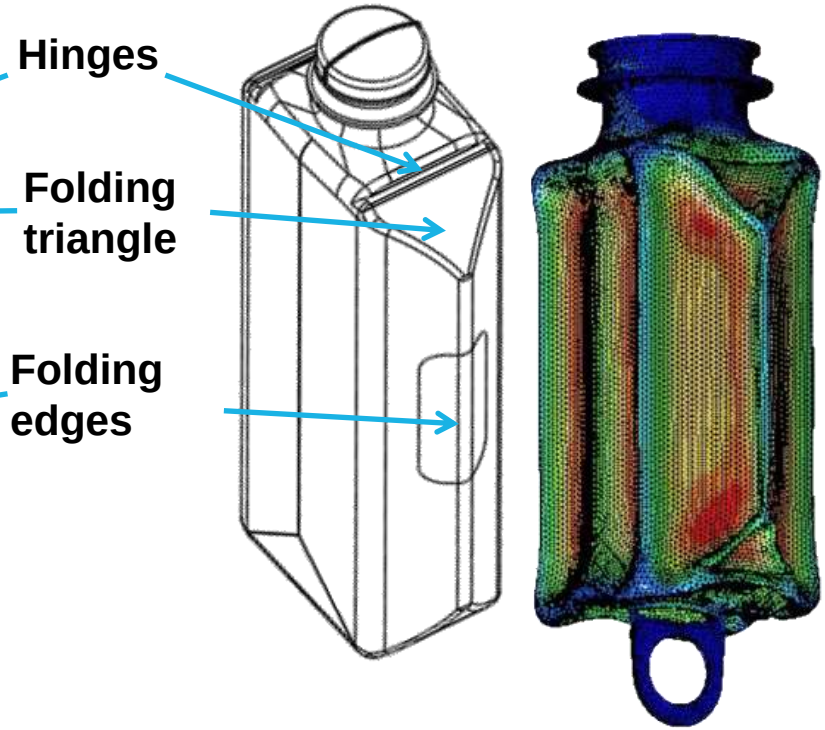
The relevant parameters for the discharge behavior have been identified.



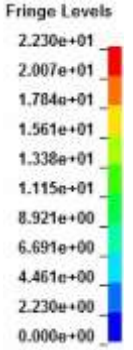
Analysis of various “standard bottle designs” indicated design improvements.

Input A : Design / shape





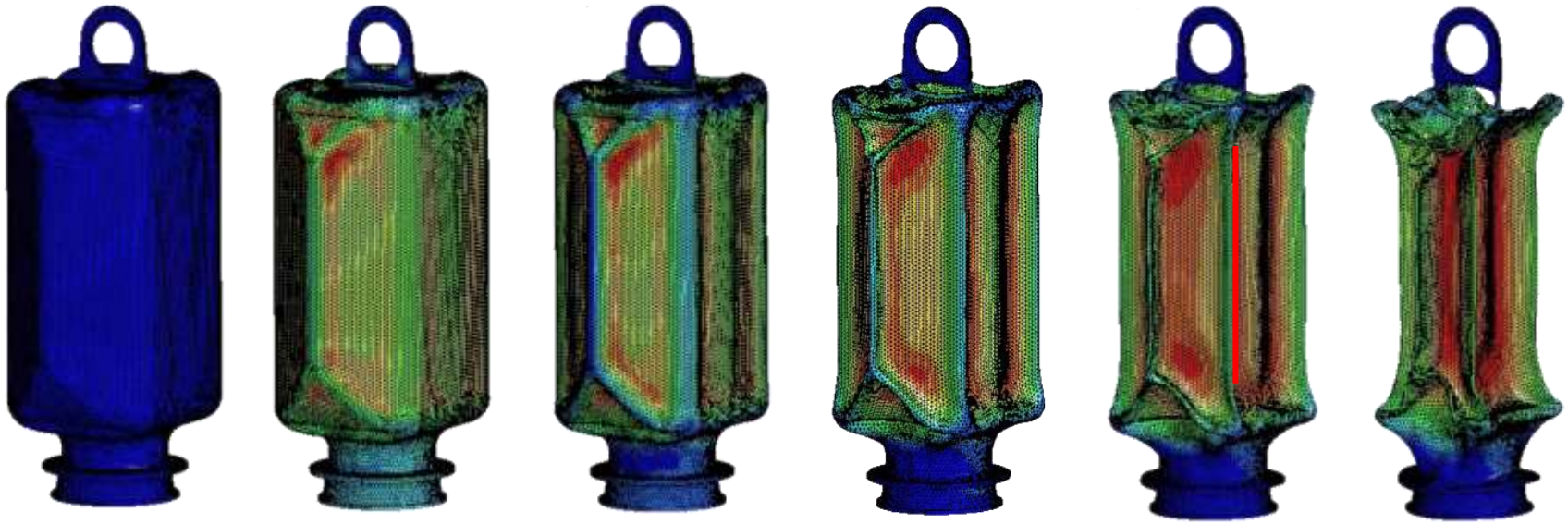
First results show that the simulation reflects the folding process.



huge dislocation

no dislocation
of the FEM volume element

Simulation:
folding works & use low Young's modulus PP



t_0 Discharge time t_{end}

The new EasyEmpty design bottles compare very well to established products on the market.

Market100 ml PP

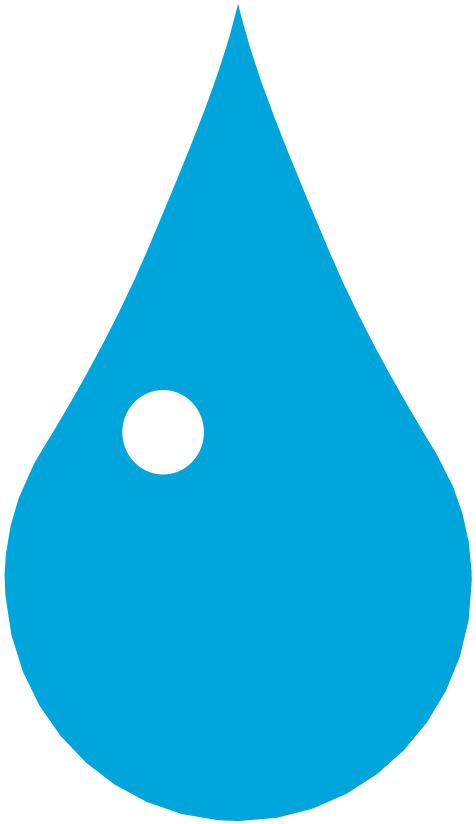
Fast motion; total time for EE (SB815MO) 18 min

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.

Literature



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3. The manufacture of sterile pharmaceutical products using Blow-Fill-Seal-Technology, PDA, Technical Report No. 77, 2017
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