A joint approach to optimize resource and energy efficiency while ensuring patient safety

VALUE CHAIN PLAYERS

BOREALIS | Borouge

Paulo Cavacas
Business Development Manager

ROMMELAG

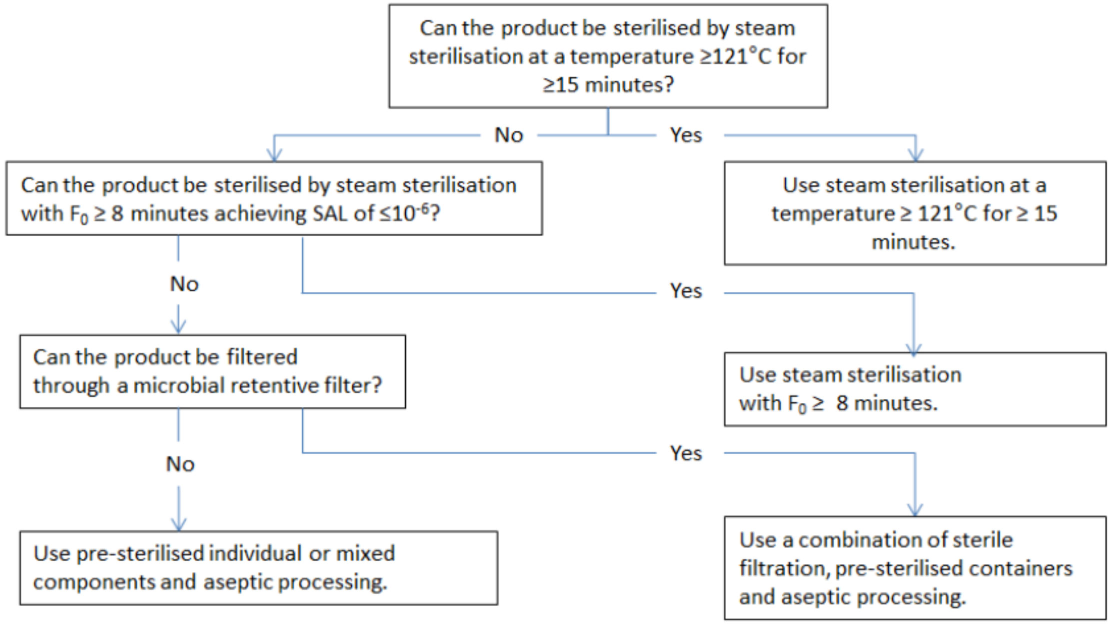
Christoph Bohn

SYNTEGON
PROCESSING & PACKAGING

Isa Alkan
Director of Sales

From regulatory standpoint, sterilisation at 121ºC is preferred. Can BFS bottles stand it still meeting end use requirements?

Figure 1 Decision tree for sterilisation choices for aqueous products



When moving down the decision trees, the methods generally show a decreasing assurance of sterility and therefore, the first feasible option should normally be chosen.*

* From 'Guideline on sterilisation of the medicinal product, active substance, excipient and primary container EMA/CHMP/CVMP/QWP/850374/2015

A multitude of needs to be studied require a collaborative approach

Easy to pierce

Easy empty

Drop resistance

Bottle self standing

Visual inspection

Regulatory compliance

BFS production efficiency

VALUE CHAIN NEEDS

Energy consumption

Sterilisation cycle time

Borealis innovative raw material solution: Bormed^{TM} SB815MO

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Borealis at a glance

Worldwide

Head Office in **Vienna**, Austria. Operating on **five continents** in **120 countries**

Market Position

#2 among polyolefin producers in **Europe**

Employees

More than **6,800 employees**

Line of Business

Production and distribution of **polyolefins**, **base chemicals** and **fertilizers**

Ownership Structure

64% Mubadala, United Arab Emirates / **36%** OMV, Austria

Financial figures

Net profit 2018 – **MEUR 906**
Net sales 2018 – MEUR 8,337

Joint Venture

Borouge – the world‘s largest integrated polyolefin complex in Ruwais, UAE

Joint Venture

Bayport Polymers – brings Borstar® technology to American polyethylene markets

Circularity

Two **polyolefin recycling operations** in Europe

Patents

117 priority patents filed in 2018

Borealis Polyolefins are indispensable in many segments of the economy


Automotive


Energy


Pipe and fittings


Consumer Products


Healthcare


Polymer Solutions

Circular Economy Solutions

Dedicated service for the Healthcare Industry: the Bormed™ concept

- Long-term supply
- Step change innovation
- Planning prioritisation
- Value chain partnerships

- Change control procedure
- Consistency
- Regulatory compliance
- Enhanced operating instructions

- Information management
- Proactive notifications
- Dedicated team of experienced specialists
- Global support

The diversity of Healthcare applications Bormed™ serves

Diagnostic Devices

PP, PS

Pharma Packaging

IV Bags
PVC, PP. PE

IV Bottle
Glass, LDPE, PP

IV Ampoules
Glass, LDPE, PP, COC

Caps & Closures
LD, HD, PP

Insulin pens
PP, ABS, PC, POM…

Meter Dose Inhalers
ABS, PC, PP

Dialysis filter housings
PC, PP

Medical Devices

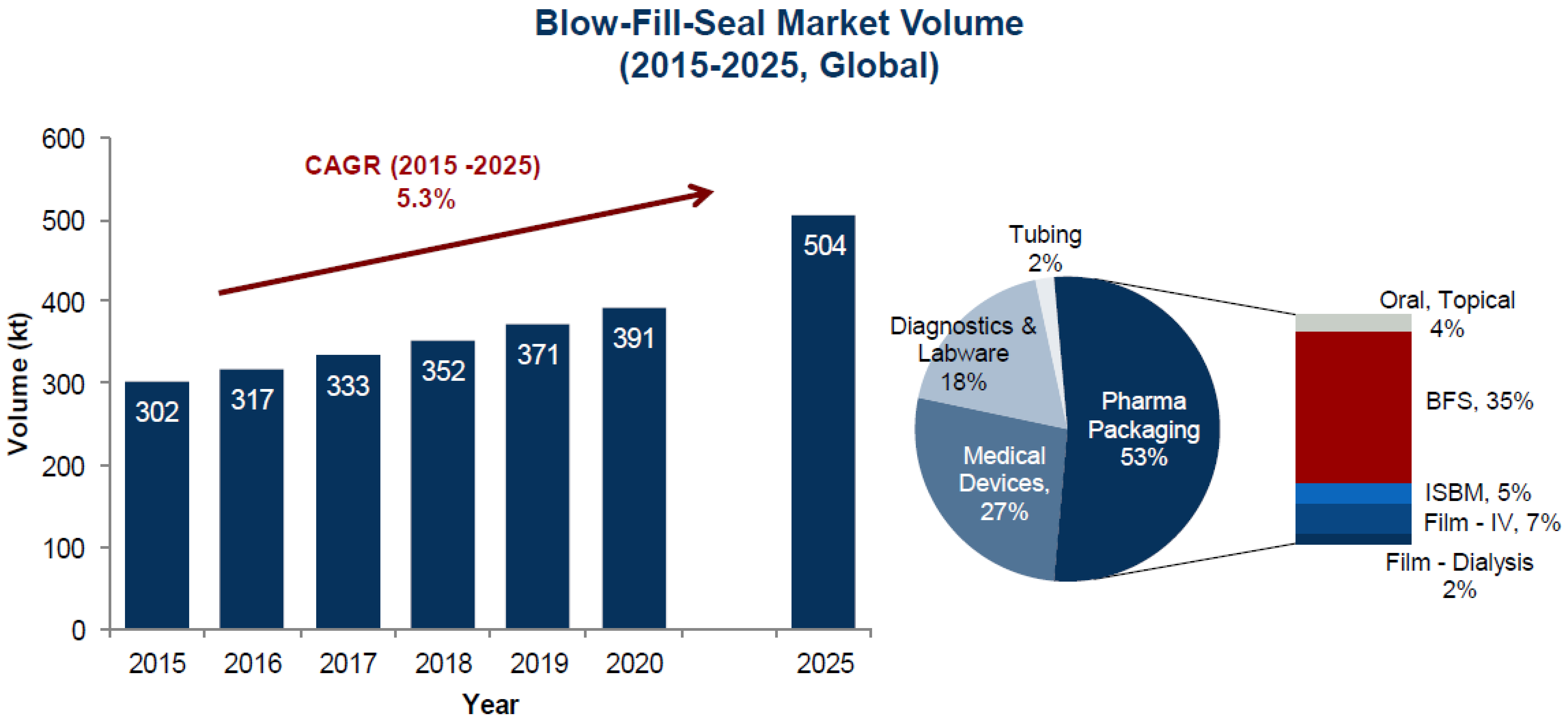
2,3p syringes
excl. gasket
PP & HDPE

Prefilled syringes
PP, COC, glass

Tubing

PVC, compounds, PP

BFS market volume*



*Regulated Polyolefins in Healthcare Applications – Frost&Sulivan 2016

Bormed™ for BFS Material Solutions

Regardless of what material you need, Borealis aims to be the supplier of choice through our complete portfolio offering

Bormed LDPE	Bormed HDPE	Bormed Semi-soft PP	Bormed Soft PP
LE6600-PH	HE2581-PH	RB801CF	SB815MO
LE6607-PH			
LE6609-PH			

	LDPE	HDPE	RB801CF	SB815MO
Processability	+	+	+	+
Ph.Eur compliance	+	+	+	+
Transparency	+	-	++	+
Sterilisation at 121°C	-	+	+	+
Low Stiffness (Flex) => Collapsibility	+	--	-	+

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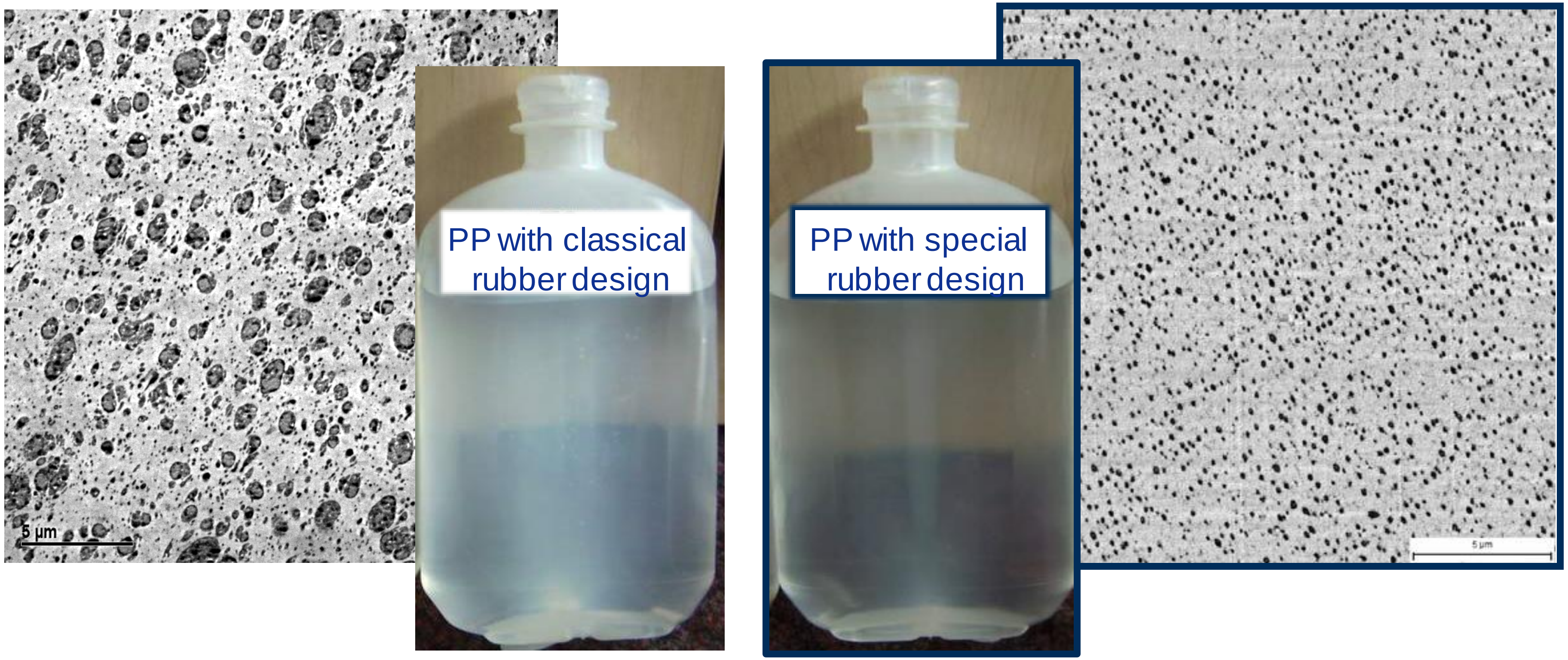
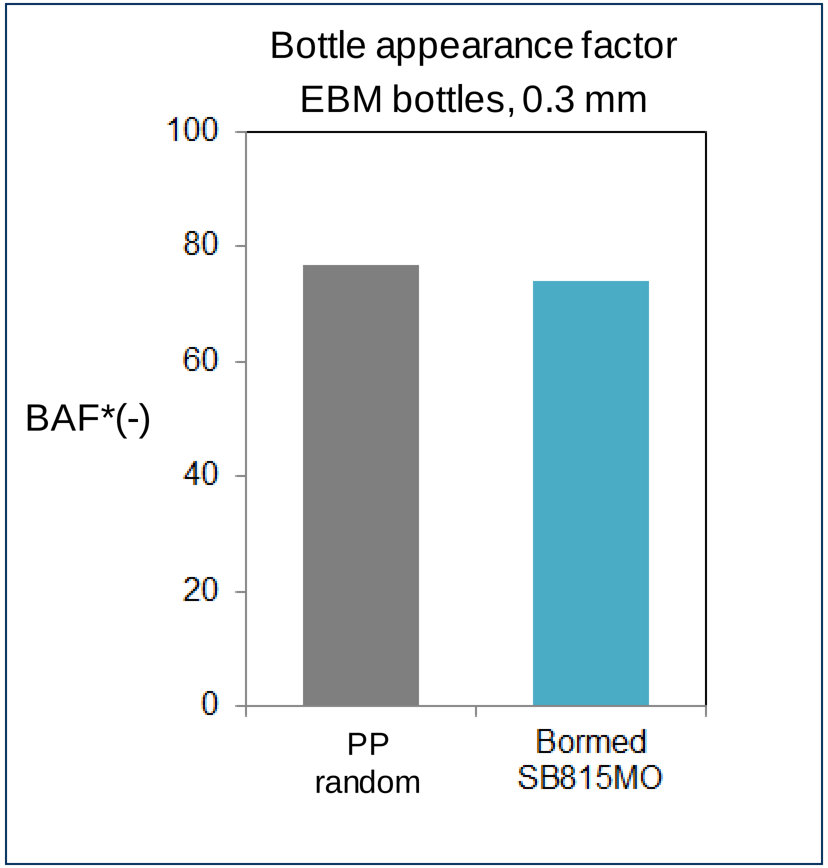
Bormed™ SB815MO for Blow-Fill-Seal (BFS) applications

Bormed™ SB815MO
Soft PP for BFS

Bormed™ SB815MO design offers best possible optical properties…

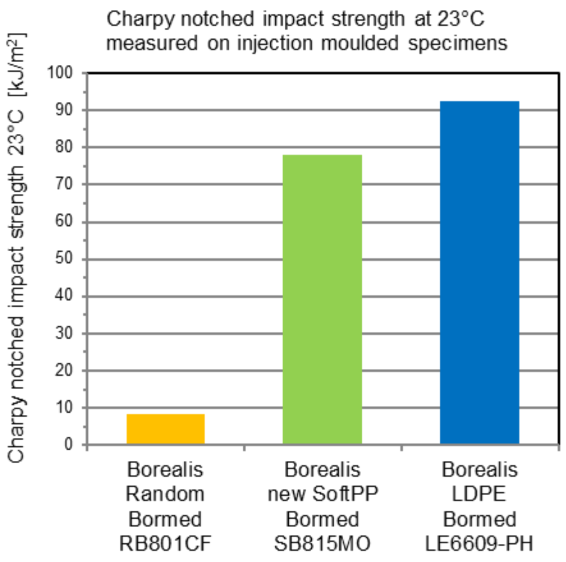


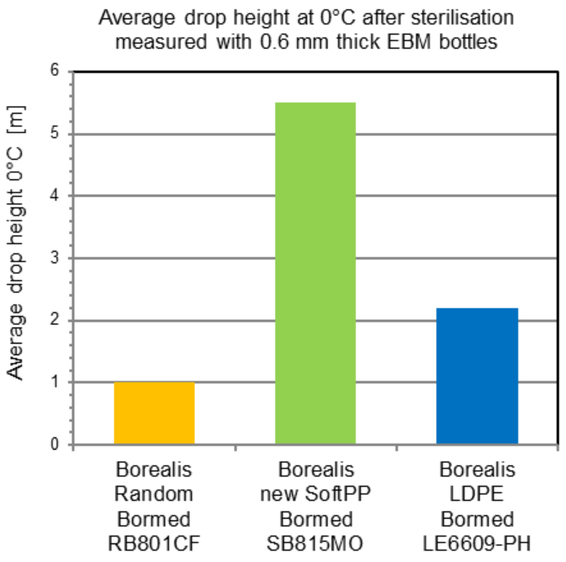
… which match the optics of a LDPE

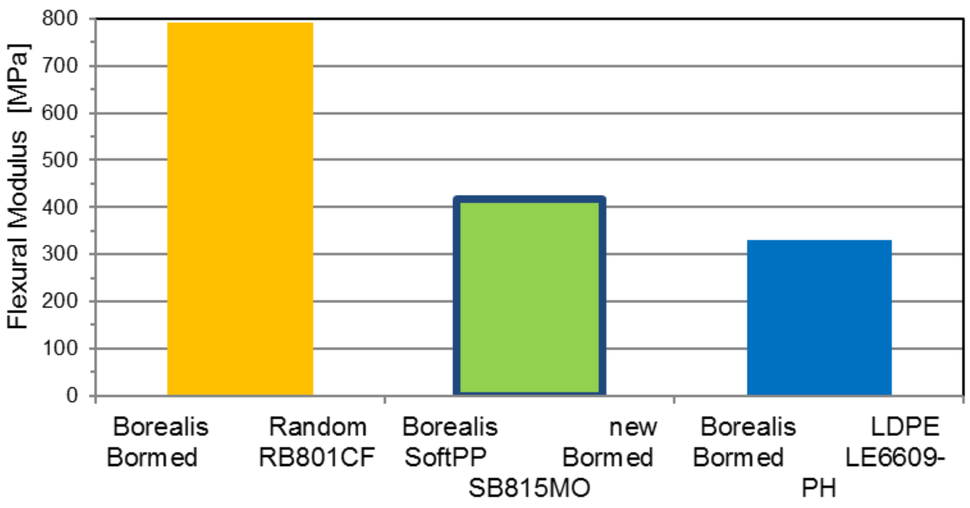


**BAF = (Clarity x Gloss) / Haze*

… complemented by softness and enhanced toughness!







Bormed™ has full Pharmacopeia compliance (EP, USP, ISO10993, DMF listing)

A multitude of needs to be studied require a collaborative approach

- Easy to pierce
- Easy empty
- Drop resistance ✓
- Bottle self standing
- Regulatory compliance ✓
- BFS production efficiency
- Sterilisation cycle time
- Visual inspection ✓

VALUE CHAIN NEEDS

Rommelag…

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Christoph Bohn

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Literature outlines weakness of PP bottle packaging

Literature

Pharmaceutical Development and Technology, 2010; 15(1): 6–34

Review of sterile packaging systems 23

Table 6. Comparative properties of major plastic polymers.[39,75,84]

Property	PVC (Polyvinyl chloride)	LDPE (Low density polyethylene)	HDPE (High density polyethylene)	PP (Polypropylene)	EVA (Ethylene vinyl acetate)
Compatibility with contained drug products	Poor	Good	Good	Good	Fair
Moisture permeation	Very poor	Good	Excellent	Good	Very poor
Heat sterilization	Fair	Poor	Good	Excellent	Very poor
Transparency characteristics	Good	Fair	Poor	Fair	Fair
Collapsibility characteristics	Excellent	Poor	Poor	Poor	Good
Disposability	Poor	Good	Good	Good	Fair

Research and Development, Baxter BioPharma Solutions, Bloomington, Indiana, USA

Gregory A. Sacha, Wendy Saffell-Clemmer, Karen Abram & Michael J. Akers
Journal Pharmaceutical Development and Technology Volume 15, 2010 - Issue 1 Practical fundamentals of glass, rubber, and plastic sterile packaging systems

Three LDPE and the new soft PP have been tested

Overview

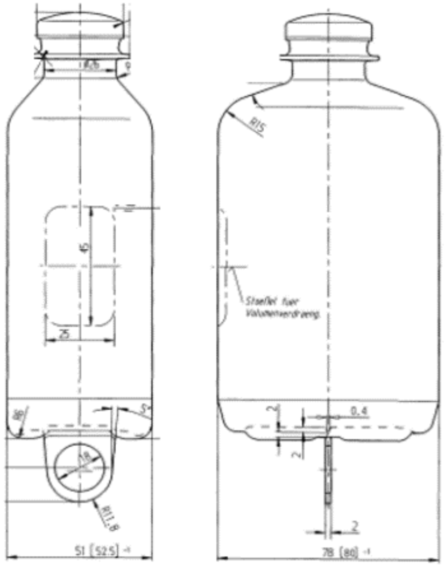
No		Trial no.	Material	Manufactu-ring process	Density [g/cm³]	MFI [g/10min] (2,16kg/190°C LDPE) (2,16kg/230°C PP)	Tensile Modulus [MPa]
1	LDPE	PE07-S-275	LE6607-PH (Schwechat)	tubular	0,927	0,3	300
3	LDPE	PE07-P-275	LE6607-PH (Porvoo)	autoclave	0,927	0,3	300
2	LDPE	PE09-S-275	LE6609-PH (Schwechat)	tubular	0,930	0,3	350
4	PP	PP815-B-275	SB815MO (Burghausen)	-	0,9	0,3	**475**

BFS Processing shows only minimal differences between the LDPEs; PP needs special attention

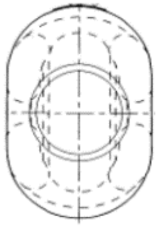
Comparison

No	Polymer	Polymer Type	Extrusion	Process window	Cooling time	Punching system	Pins for transport	Power of extruder motor	Cutting edge	Vacuum slits
1	LDPE	**LE6607-PH tubular** (Schwechat)	+	+	+	Internal	Standard	medium	wide	Large
2	LDPE	**LE6607-PH autoclave** (Porvoo)	Additional shear part recommended	+	+	Internal	Standard	medium	wide	Large
3	LDPE	**LE6609-PH tubular** (Schwechat)	+	+	+	Internal	Standard	medium	wide	Large
4	PP	**SB815MO** (Burghausen)	0	-	**longer**	External	PP specific	high	small	small

Typical oval standard bottles were tested for administration performance



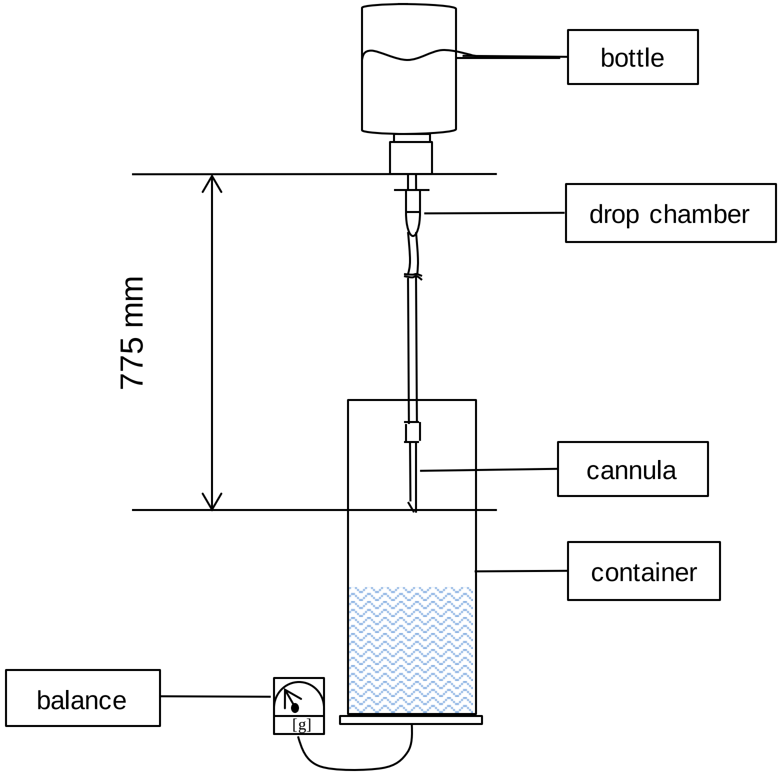
- Nominal volume: 250 ml
- Filling volume: 275 ml
- Filled product: demineralized water
- Bottle weight empty: 18.5 g
- Condition: autoclaved
- Production date: May 2017



VZ: 2554h

Rommelag's standard test protocols was applied for performance tests

-1- Emptying



- Caps: West Insocap
- Determine bottle weight before and after testing → residual weight
- Pre-filled infusion tube
- H = 775 mm
- data recording with balance (1 value / s)
- 1 g = 1 ml (ρ_{water} = 1 g/cm^3)
- Flowrate [ml/s] = $\frac{\Delta V\ [ml]}{\Delta t\ [s]}$

The soft PP bottles emptying performance is very similar to the LDPE

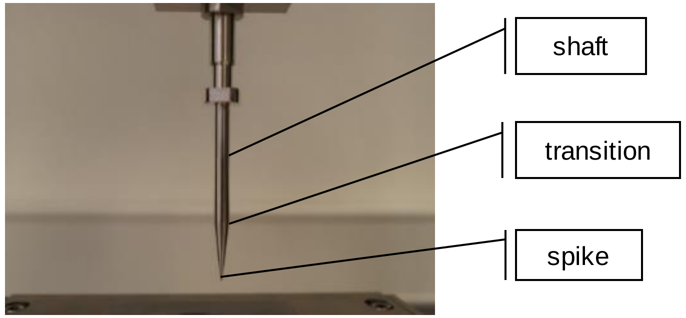
Emptying Results

No	material	bottle weight, filled with cap [g]	residual weight [g]	empty weight with cap [g]	empty weight, without cap [g]	filling volume [ml]	emptyed volume [ml]	emptyed volume [%]	residual volume [ml]
1	LE6607-PH (Schwechat)	297,4	29,2	22,5	18,5	274,9	268,3	97,6%	6,6
2	LE 6607-PH (Porvoo)	296,3	29,4	22,6	18,5	273,8	267,0	97,5%	6,8
3	LE6609-PH (Schwechat)	296,3	28,7	22,4	18,4	273,9	267,7	97,7%	6,2
4	SB815MO	295,9	28,8	22,4	18,6	273,5	267,1	97,7%	6,4

Rommelag's standard test protocols was applied for piercing tests

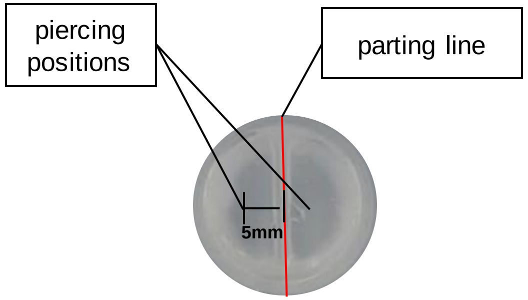
-2- Piercing

ISO Piercing pin



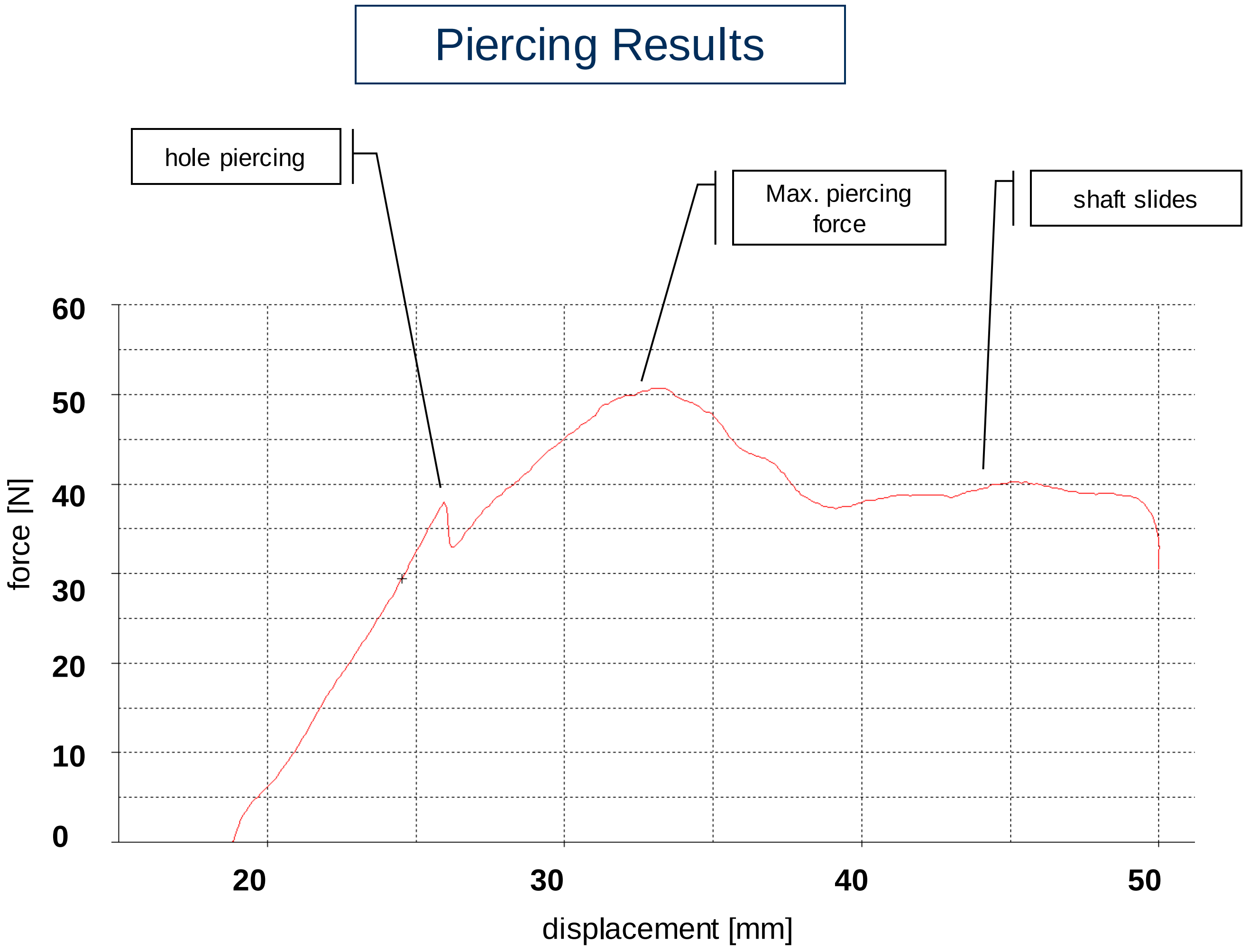
- Force gauge: Mecmesin MultiTest 10-i
- Norm: DIN EN ISO 15747:2017-08
- Material: stainless steel (1.4301)
- Test conditions: speed = 500 mm/min
  cleaning with acetone

Piercing position



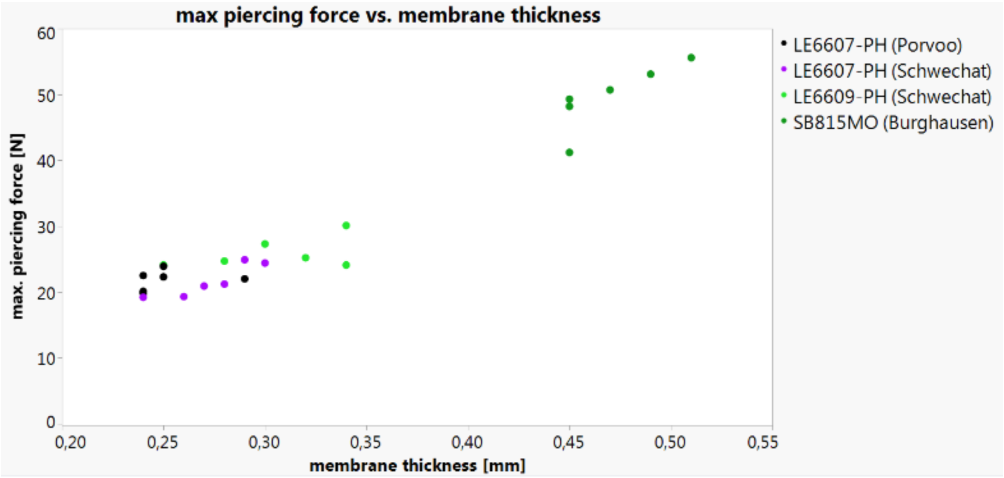
- No cap using
- Measuring the membrane thickness at the piercing positions

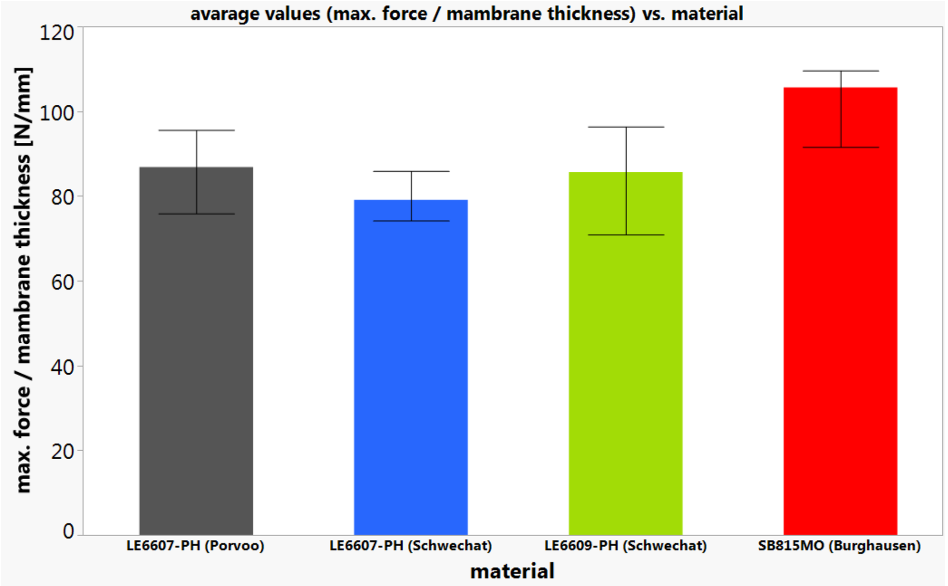
The force-displacement diagram shows the typical effects during pin insertion



2019-

The maximum piercing forces correlate to the membrane thickness





Bars: max/min

2019-

Summary

1. The different LDPE polymers behave almost similar.
2. BFS processing of soft PP needs special attention.
3. Bottle performance data (emptying & piercing) are within a similar range.

A multitude of needs to be studied require a collaborative approach

Easy to pierce ✓

Easy empty ✓

Drop resistance ✓

Bottle self standing

Regulatory compliance ✓

BFS production efficiency ✓

VALUE CHAIN NEEDS

Sterilisation cycle time

Visual inspection ✓

Syntegon SBM…

VALUE CHAIN PLAYER

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PROCESSING & PACKAGING

Isa Alkan

Director of Sales

SBM Schoeller-Bleckmann Medizintechnik GmbH
a Syntegon company

Process technology

Liquid dosage forms

Solid dosage forms

Inspection technology

Secondary packaging

- Freeze drying
- Production of small batches for clinical trials, as well as for medium production batches
- Harmonized interfaces for upstream and downstream line components

- Sterilization processes
- Highly sophisticated tailor made sterilizers
- Machinery for terminal product sterilization
- Machinery for equipment sterilization

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SBM Study 1000ml BFS containers
→ Joint contribution SBM – Rommelag - Borealis

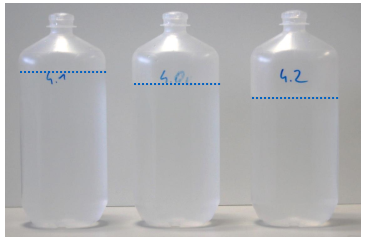
Borealis – different standard resins

Standard Resin	Production site	PE / PP	Melting Point
LE6607-PH	1130021150 Schwechat	PE	114°C
LE6607-PH	186948 Porvoo	PE	114°C
LE6609-PH	1130019750 Schwechat	PE	117°C
SB815MO	3220003139 Burghausen	PP	145°C

Bormed LDPE	Bormed HDPE	Bormed Semi-soft PP	Bormed Soft PP
LE6600-PH	HE2581-PH	RB801CF	SB815MO
LE6607-PH			
LE6609-PH			

Rommelag – bottles with different fill grades

- 900 ml
- 1000 ml
- 1100 ml



SBM – sterilization test runs @ test lab AUSTRIA

- Different **temperatures** as **close** as possible **to melting point**
- Different **loading pattern**
- Different **positions** in 3 layers to evaluate influences
- Cycle control via **reference sensors** / **BFS Bottle**

Source: Syntegon project team

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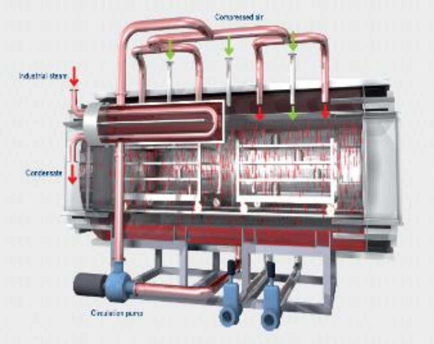
SBM Study 1000ml BFS containers
→ Test setup for the sterilization

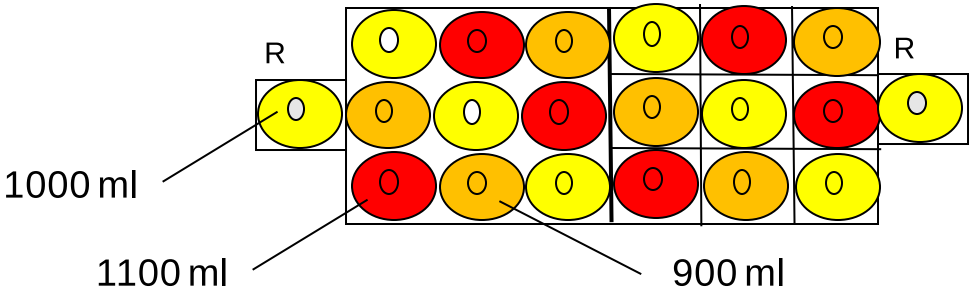
- **Sterilization method**: Hot water spray process / DIN 58959-1
- Water distribution by **distribution plates** on top of the chamber
- **Loading capacity**: 3 trays, 18 bottles each
- **Loading pattern**: 2 different industry standards

  Bottles with direct contact / Separation boxes
- **Loading distribution** – trays: Each color of the bottle reflects

  one fill grade with the same type and plastic
- **Cycle control**: Two separate boxes in lowest layer with

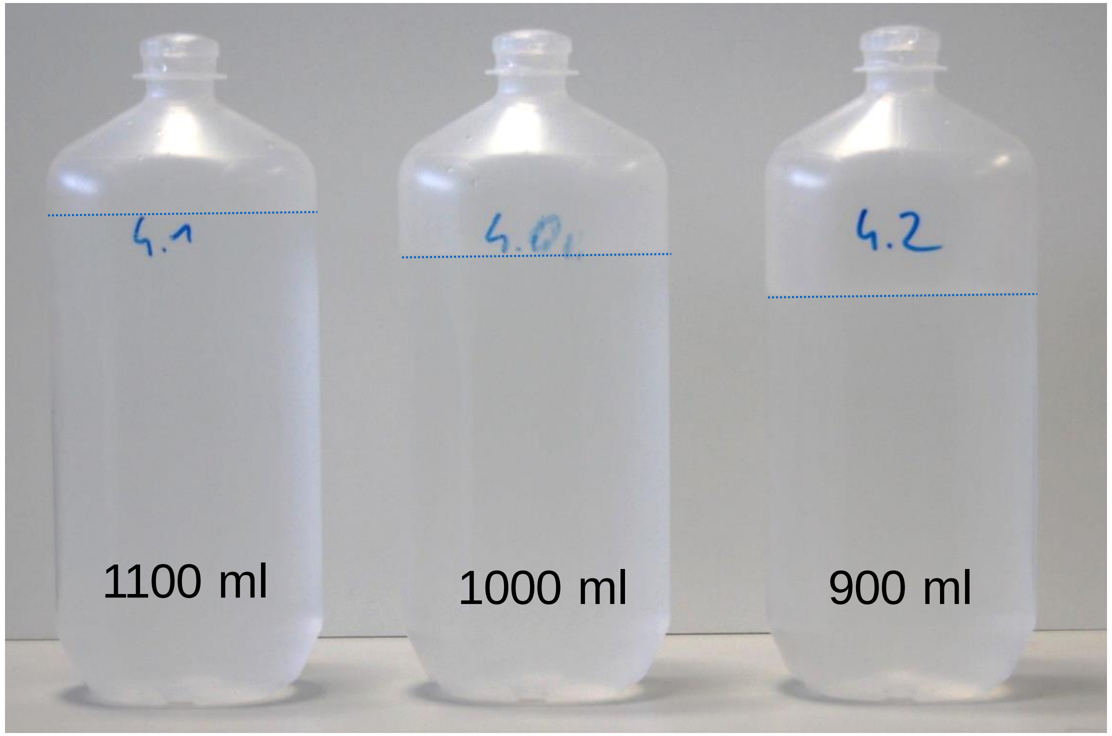
  reference temperature probes





SBM Study 1000ml BFS containers
→ Test setup for the sterilization

- Different filling grades before sterilization – reference bottle 1000 ml



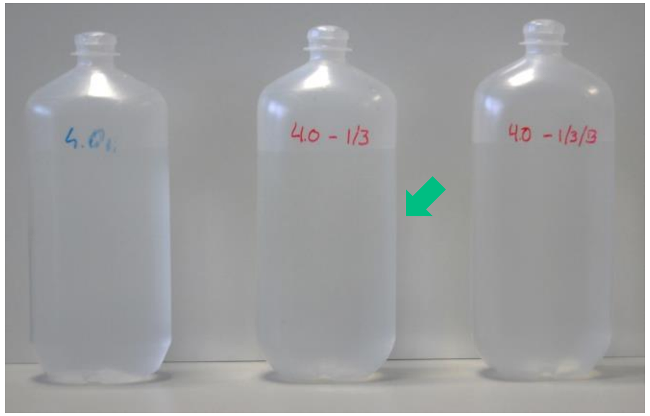
- Reference bottle (4.0) - not sterilized
  4.0 – 1/2 and 4.0 – 1/2/B - sterilized

Source: Syntegon project team

SBM Study 1000ml BFS containers
→ Results PP SB815MO with 121°C and 130°C (MP 145°C)

Sterilization @ 121°C (20 minutes fixed to stress the material):

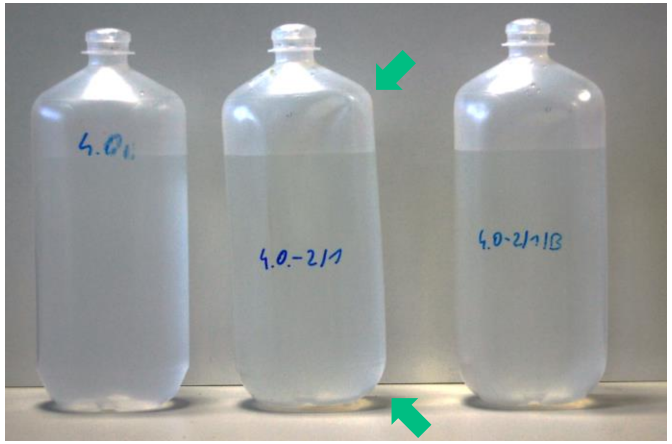
- **1000 ml** and **1100 ml** shape **OK**, little dents on the wider sides
- **900 ml** with **stronger denting** on wider sides,
- No difference in layer / no difference to single box position
- Bottles shrinked ~ 2-3mm
- **PP SB815MO less sensitive vs. PE**
  from sterilization point of view



121°C / 20 min.

Sterilization @ 130°C (20 minutes fixed):

- All bottles show deformations, single box looks better
- Bottles shrinked ~2-3mm
- For test purpose only, 130 for 20 min. / (F_0 = 200)



130°C / 20 min.

General recommendation based on F0=15: 121°C for 10-12 min.

Source: Syntegon project team

SBM Study 1000ml BFS containers
→ Results for PE LE6607-PH (SW) with 109/110,5/112 and 113,5°C

Sterilization @ 109°C (MP 114°C, target F0=8)

- No significant difference in layer, no difference direct vs. single box

Sterilization @ 110,5°C (MP 114°C, target F0=8)

- No significant difference in layer, **better shape/standing in single box**
  All bottles show **slight distortion**

Sterilization @ 112°C (MP 114°C, target F0=8)

- All sizes more **blown up on bottom**, first **dents in shoulder** area
- No significant difference in layer, **much better shape in single box**

With optimized cycle parameters and single boxes difficult but feasible!

Sterilization @ 113,5°C (MP 114°C, target F0=8)

- All bottles show **strong deformations** and dents
- No significant difference in layer, better shape in single box,
  outside box **bottles partly stuck/melted** together

109°C

112°C.

SBM Study 1000ml BFS containers
→ Results for PE LE6607-PH (PO) – 109 / 110,5 / 112 and 113,5°C

Sterilization @ 109°C (MP 114°C, target F0=8)

- No significant difference in layer, 900ml shape improved in single box

Sterilization @ 110,5°C (MP 114°C, target F0=8)

- No significant difference in layer, improvement in shape and standing in single box, 900ml again worst shape.

Sterilization @ 112°C (MP 114°C, target F0=8)

109°C

- All sizes show **more dents** and **900ml first deformations**
- No significant difference in layer, **much better shape in single box**

More sensitive than SW production but with optimized cycle parameters and single boxes feasible!

Sterilization @ 113,5°C (MP 114°C, target F0=8)

112°C

- All bottles show **strong deformations and dents**, partly stuck/melted together – **not recommended**

109°C

112°C.

Source: Syntegon project team

SBM Study 1000ml BFS containers
→ Results for PE LE6609-PH (SW) with 112 and 113,5°C

Sterilization @ 112°C (MP 117°C, target F0=8)

- Bottle **shape very nice**, tends to blow up (less in 900ml)
- No significant difference in layer and single box

Sterilization @ 113,5°C (MP 117°C, target F0=8)

- All with **very nice shape**, few **small dents** on the shoulders more with 900ml
- No significant difference in layer, shape better in single box
- With **optimized cycle parameters** and **single boxes** difficult but **feasible**!

115°C dismissed, strong deformations and dents not recommendable

112°C

113,5°C.

Source: Syntegon project team

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SBM Study 1000ml BFS containers
→ Summary – Main Parameters

- **Sterilization temperature**
- **Control of counter pressure** especially during heating and cooling phase
- **Fill grade of the bottle** (air to liquid ratio)
- **Shape of the bottle** after BFS machine
- **Wall thickness** of the bottles
- **Loading configuration** – direct contact vs. separation boxes
- Physical **characteristics of the plastic**, esp. MP

Source: Syntegon project team

SBM Study 1000ml BFS containers
→ Summary – Sterilization Temperature

Sterilization Temperature

- **Sterilization @ 5°C below melting point** of the plastic

  ⇨ **Safe operation**, no significant difference in shape of all bottles

- **Sterilization @ temperature closer to the MP**

  The closer the temperature to the MP – the higher the relevance of other parameters

  ⇨ Loading in **single boxes improves the shape** of the bottle

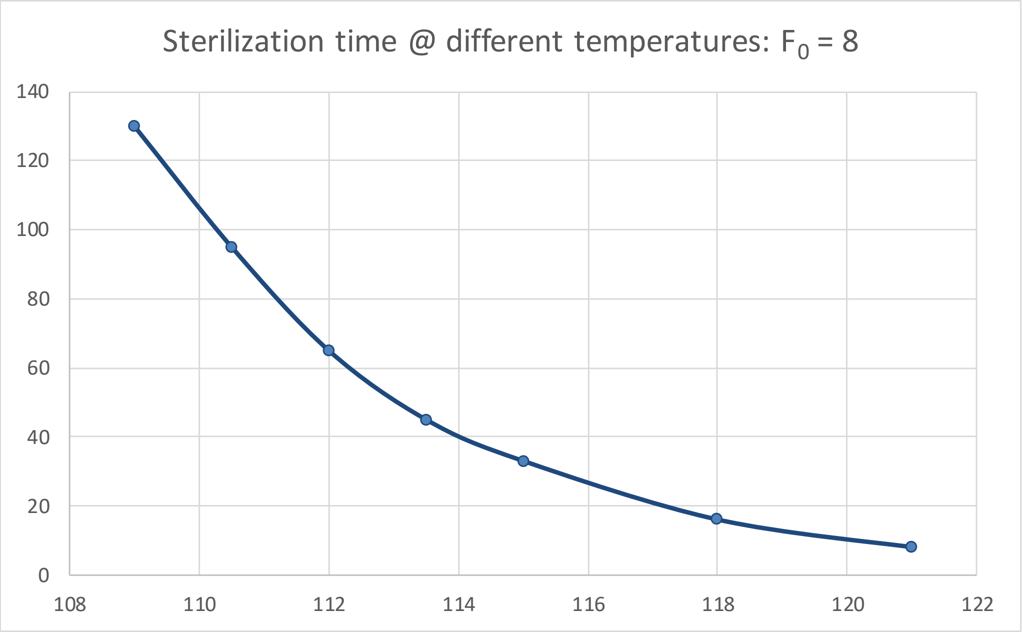
  - **Less air** in the bottle (e.g. 1100ml) **reduces dents** in shoulder area but requires higher counter pressure
  - **Higher requirement** for tray loading (manual or automatic loading) to assure straight standing on the trays.
  - **Higher requirements** on sterilization **process control** and **process development**

Sterilization temperature 3°C below melting point achievable with optimized setting of BFS machine and Sterilizer (with PP max. 123°C is sufficient for very short cycle)

Source: Syntegon project team

SBM Study 1000ml BFS containers
→ Summary: Capacity Example

Sterilization temperature		109 °C	112 °C	121 °C
Loading / Unloading	[min]	15	15	15
Heating / Cooling	[min]	55	55	65
Sterilization	[min]	130	65	20
TOTAL Cycle time		**200**	**135**	**100**
Bottles per batch	[pcs]	8 500	8 500	8 500
Cycles per day *)		6	9	12
Cycles per year **)		2 040	3 060	4 080
TOTAL OUTPUT p.a.	**[pcs]**	**17.300.000**	**26.000.000**	**34.700.000**
			50%	100%



Higher sterilization temperature

⇨ shorter cycle time

⇨ higher output or

⇨ smaller autoclaves

Source: Syntegon project team

A multitude of needs to be studied require a collaborative approach

Easy to pierce

Easy empty

Drop resistance

Bottle self standing

Regulatory compliance

BFS production efficiency

VALUE CHAIN NEEDS

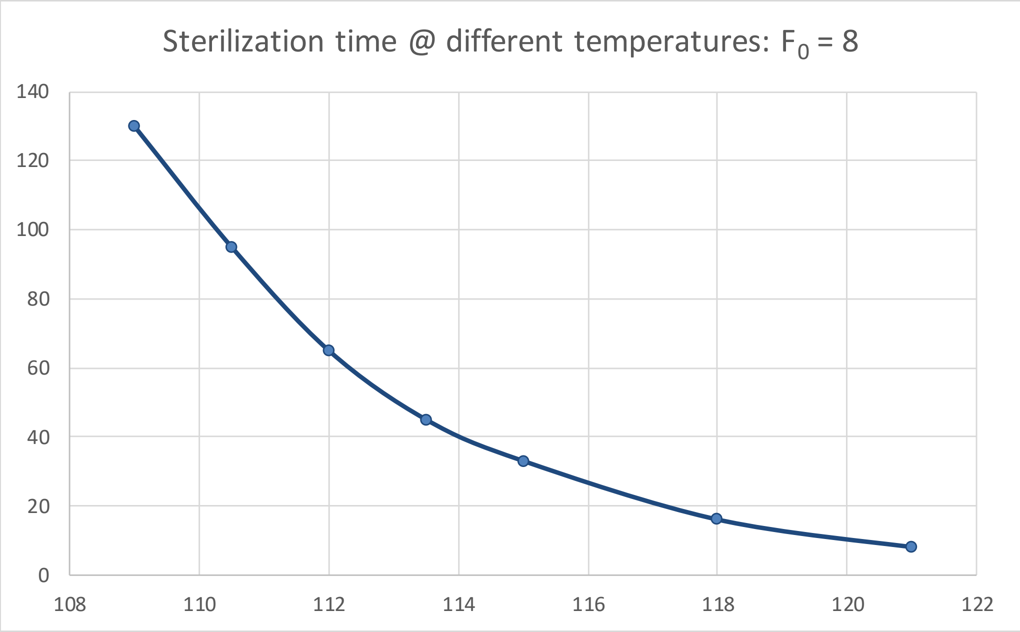
Sterilisation cycle time

Visual inspection

Backup slides

SBM Study 1000ml BFS containers
→ Summary: media consumption effect / batch

Sterilization temperature		109 °C	112 °C	121 °C
Loading / Unloading	[min]	15	15	15
Heating / Cooling	[min]	55	55	65
Sterilization	[min]	130	65	20
TOTAL Cycle time		**200**	**135**	**100**
Bottles per batch	[pcs]	8 500	8 500	8 500
Cycles per day *)		6	9	12
Cycles per year **)		2 040	3 060	4 080
TOTAL OUTPUT p.a.	**[pcs]**	**17.300.000**	**26.000.000**	**34.700.000**



Media consumption 109°C vs 121°C: (driven by longer heating and cooling phase but shorter total time)

⇨ steam for heating +12% ↑

⇨ cooling water + 14% ↑

⇨ electricity -30% ↓

From TCO point of view, cost/bottle will be less!

Source: Syntegon project team

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