LVP Polyolefin solutions addressing different packaging and regulatory requirements

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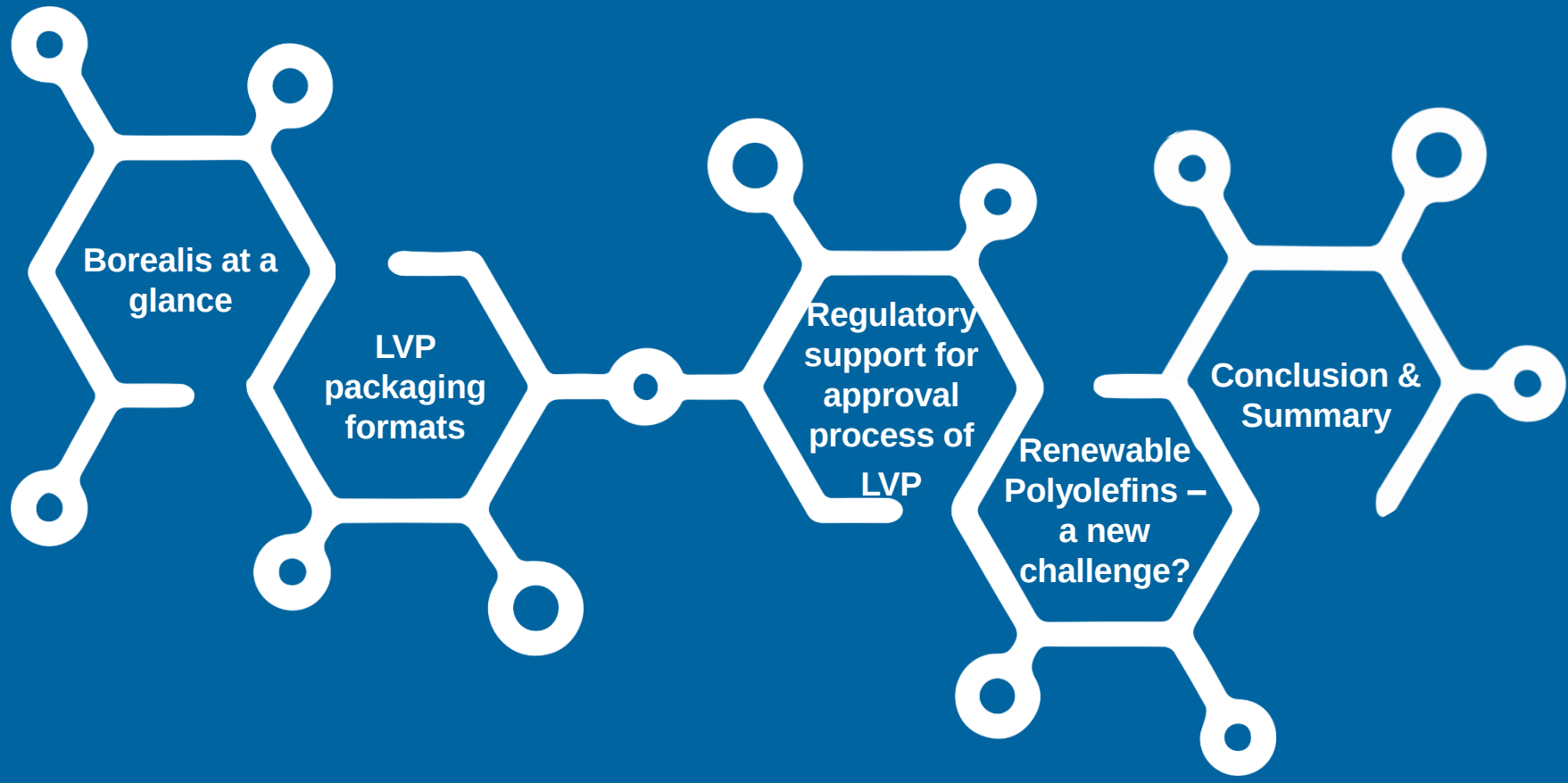
Large Volumes Parenteral Packaging Virtual Symposium
24 – 25 March 2021

BOREALIS

Borouge

Overview



Borealis at a glance

Borealis at a glance

Worldwide

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

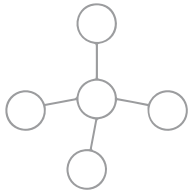
Market Position

#2 among polyolefin
producers in **Europe**

Employees

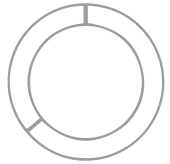
More than
6,900 employees

Line of Business



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

Ownership Structure



75% OMV, Austria /
25% Mubadala, United Arab
Emirates

Financial figures

Net profit 2019 – **MEUR 827**
Net sales 2019 – EUR 8.1 billion

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

120 priority patents
filed in 2019

Borealis at a glance

LVP packaging formats

Regulatory support for approval process of LVP

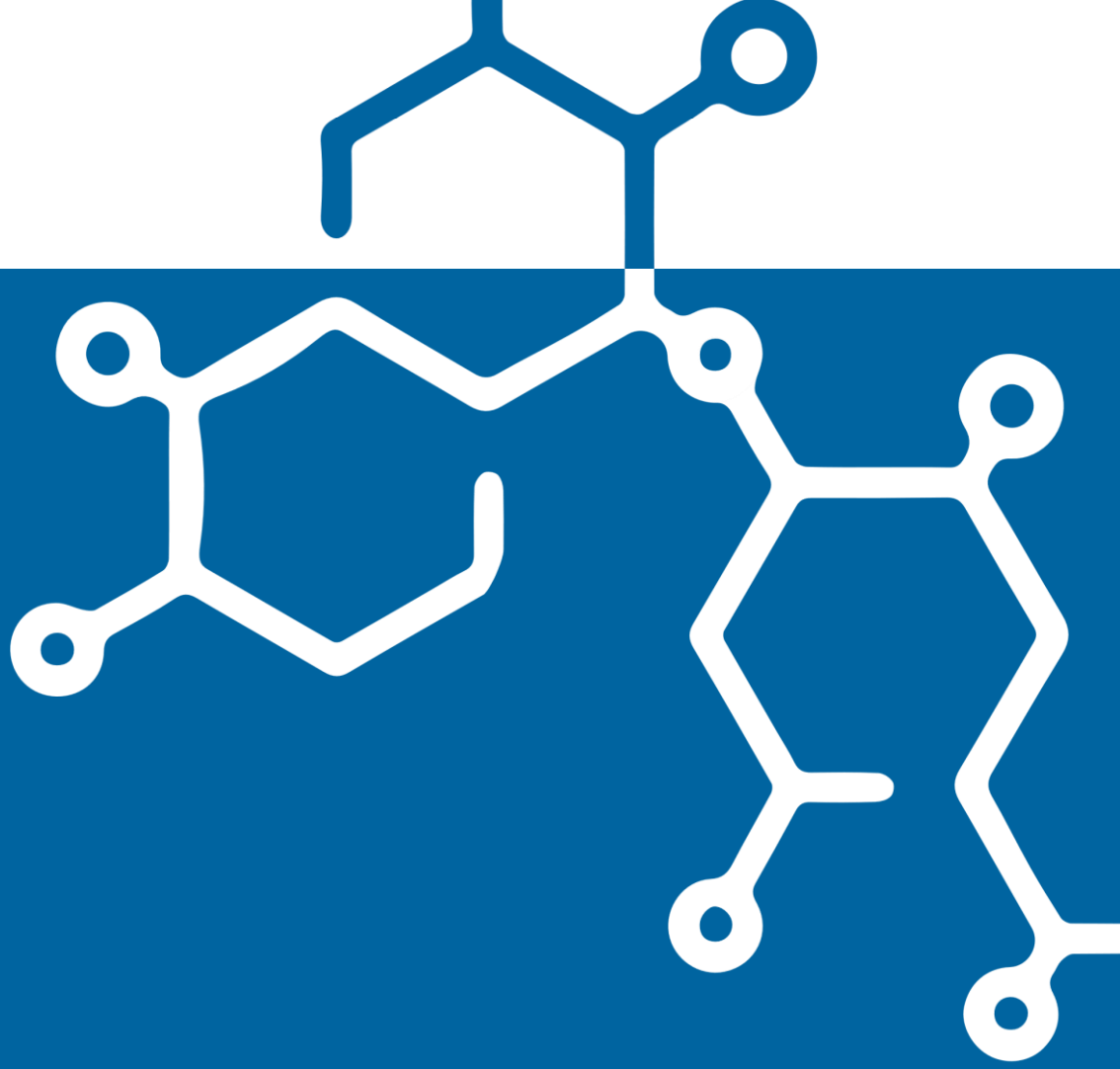
Renewable Polyolefins – a new challenge?

LVP packaging formats

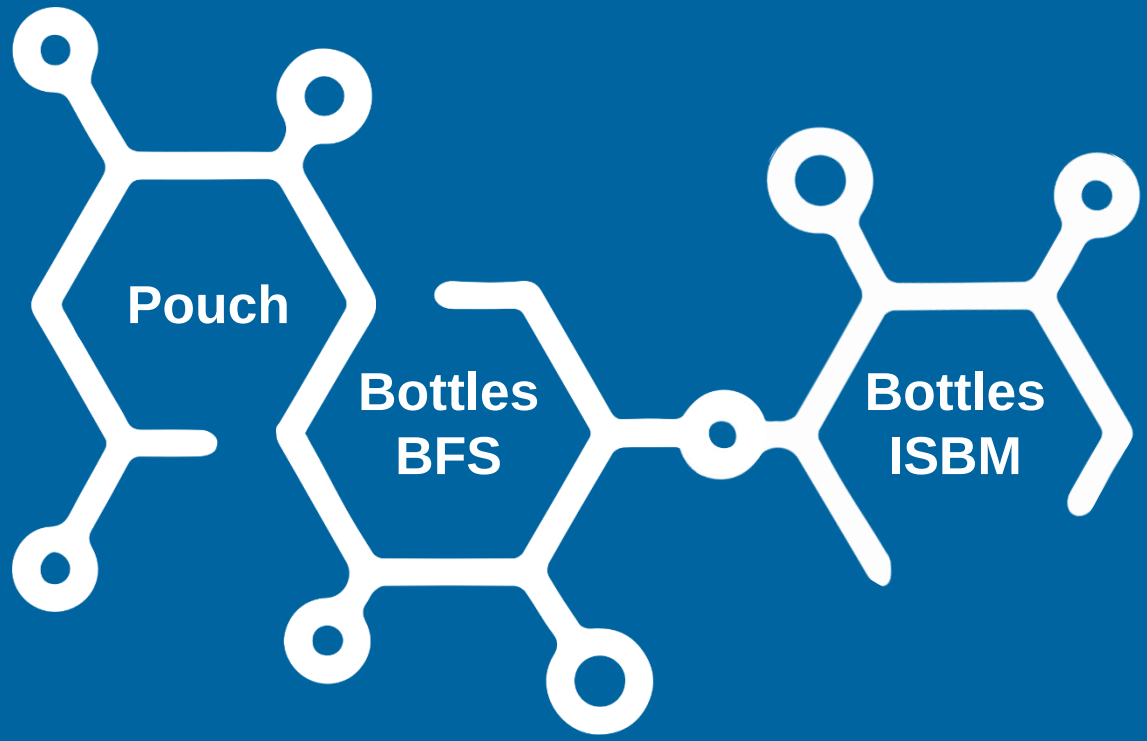
LVP can be packed in different packaging formats.

Different packaging options drive the need for:

– Different raw materials of construction (LDPE vs PP/Plastomer, monomaterial structures vs complex ones)
– Different key regulatory requirements

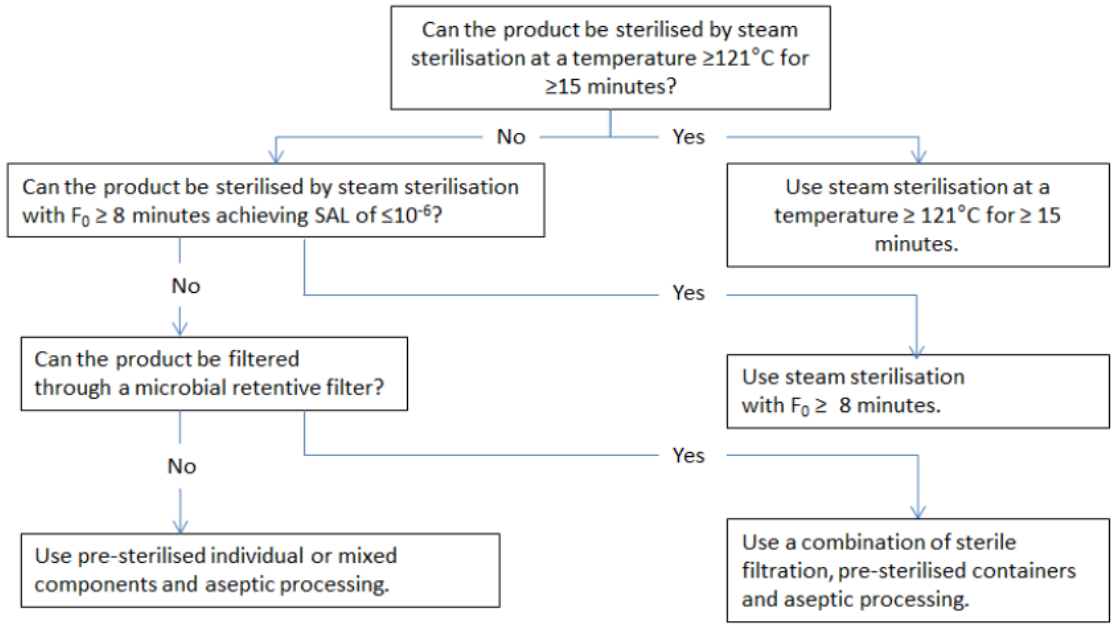


LVP packaging formats



From regulatory standpoint, sterilisation at 121ºC is preferred

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

Required data for quality dossiers depending on sterilisation temperature

Table 1 Cycles for steam sterilisation and post-aseptic processing terminal heat treatment and corresponding data required in the quality dossier

Cycle	Type of process	Information in dossier*	Bioburden level before steam sterilisation or terminal heat treatment	Bioburden Characterised	Process hold temperature
Ph. Eur. 5.1.1 Reference Cycle	Sterilisation	1, 6	100 CFU/100ml (non-routine)	No	≥ 121 °C for ≥15 minutes
Overkill cycle F_o >12 min	Sterilisation	1, 2, 3, 4, 7	100 CFU/100ml (non-routine)	No	≥ 121 °C
F_o > 8 min	Sterilisation	1, 2, 3, 4, 7	100 CFU/100ml (routine)	No	> 115 °C
F_o > 8 min	Sterilisation	1, 2, 3, 5, 7, 8	100 CFU/100ml (routine)	Yes**	> 115 °C
F_o > 8 min	Sterilisation	1, 2, 3, 4, 7	100 CFU/100ml (routine)	Yes	> 110 °C
F_o > 8 min	Sterilisation	1, 2, 3, 5, 7, 8	100 CFU/100ml (routine)	Yes**	> 110 °C
F_o <8 min	Post-aseptic processing terminal heat treatment	1, 2, 3, 4, 7, 8	0 CFU/100ml, aseptic filtration and processing prior to terminal heat treatment (routine)	Yes***	> 110 °C****
F_o <8 min	Post-aseptic processing terminal heat treatment	1 2, 3, 5, 7, 8	0 CFU/100ml, aseptic filtration and processing prior to terminal heat treatment (routine)	Yes***	> 110 °C****

* For clarification of the code numbers, see below

** In-process control demonstrating acceptable heat resistance of bioburden

*** The bioburden prior to the sterilisation step (i.e. filtration) should be characterised for heat resistance

**** Temperatures below 110 °C may be used if justified. The requirement for additional documentation for such cycles is evaluated on a case by case basis

Clarification of the information to be presented in the quality dossier

1: Sterilisation time, temperature profile

2: Sterilisation method (for instance saturated steam cycle, air/steam-overpressure cycle, vacuum phase) description including SAL

3: Validation of F_{0Phys} and F_{0Bio}

4: Biological indicator with a $D_{121} \geq 1.5$ minutes used in the validation

5: Biological indicator with a $D_{121} < 1.5$ minutes used in the validation

6: No validation data requested in the dossier, only a confirmation that validation has been performed.

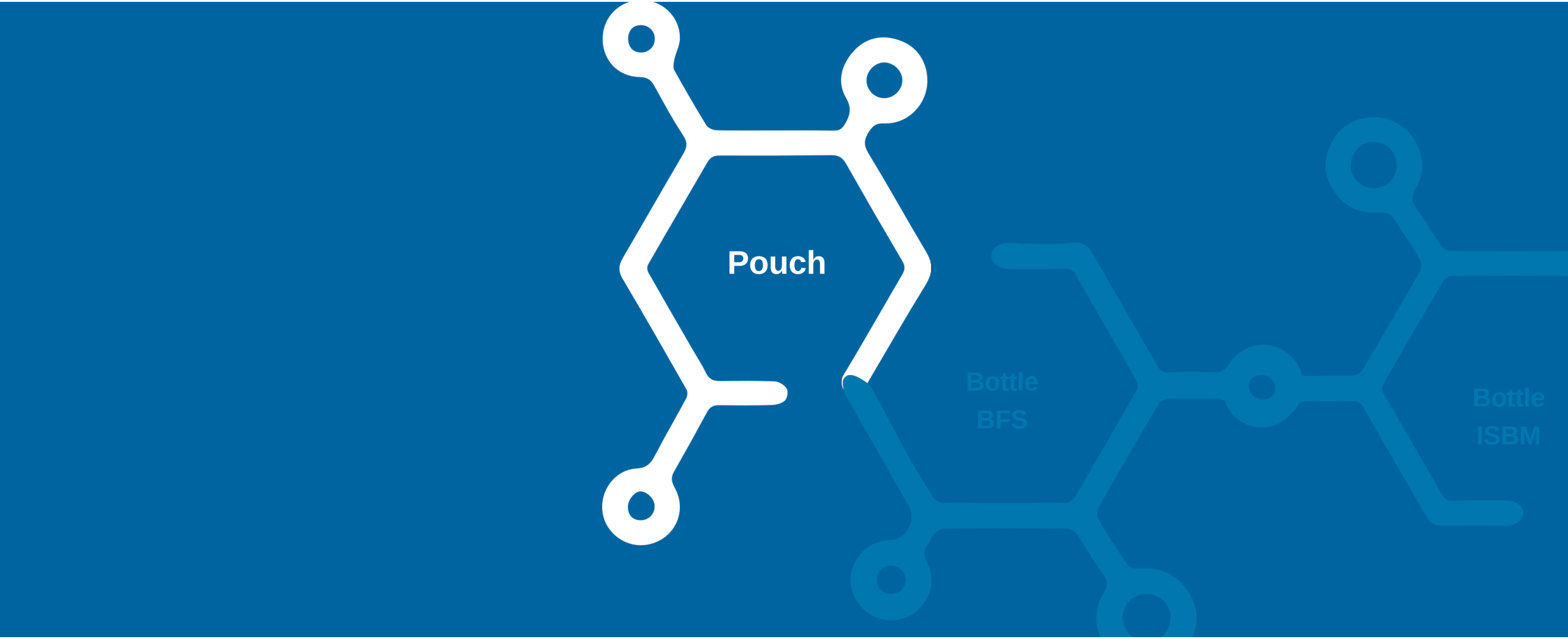
7: Validation data to be provided in the dossier is presented below

8: Additional validation data to be provided in the dossier is presented below

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

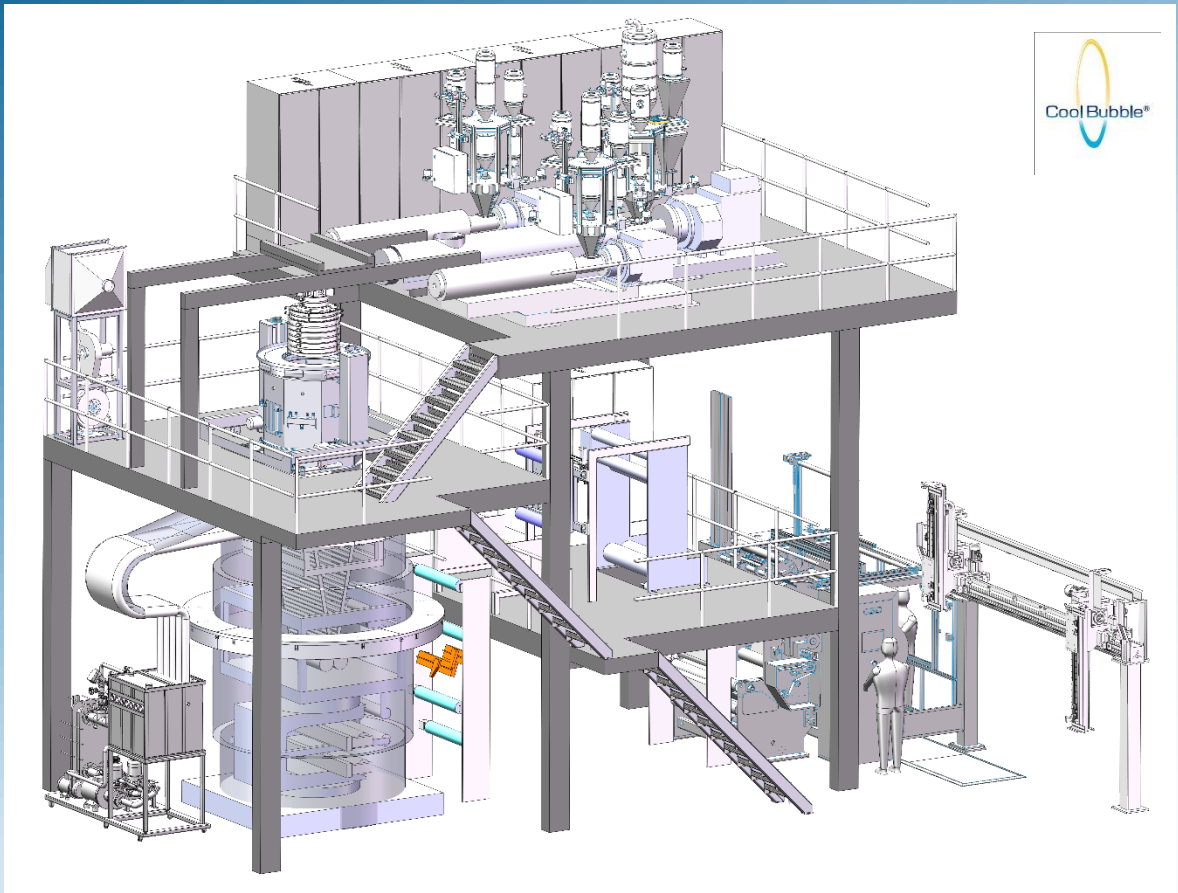
The lower the sterilisation temperature, the more testing and validation work needs to be performed for the quality dossier.

The choice of material for an LVP container is essential for the workload that needs to be performed.



Film extrusion process for LVP pouch

Water quenched blown film



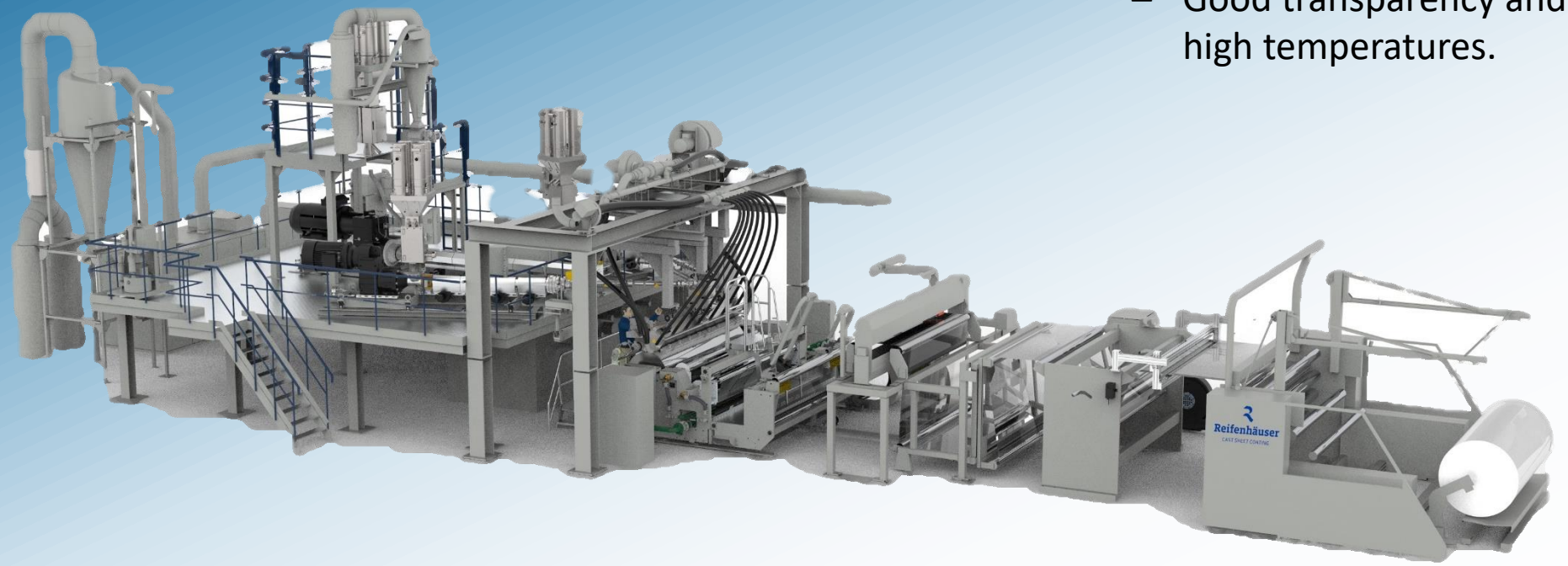
Film characteristics:

- Excellent optical properties like transparency and gloss
- Outstanding deep draw thermoformability due to the amorphous polymer structure
- Exceptional softness or suppleness

KUHNE GROUP CREATING VALUES BLOWN-FILM LINES

Film extrusion process for LVP pouch

Cast film



Film characteristics:

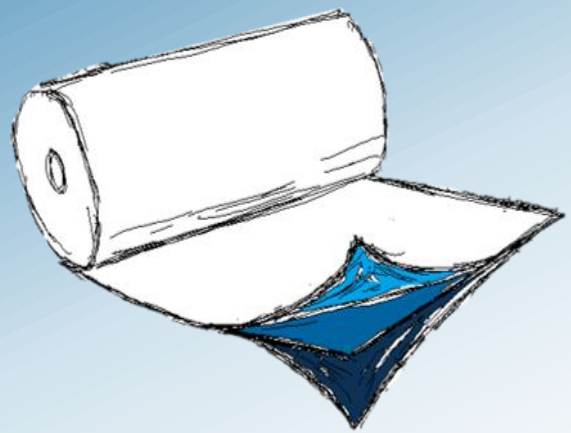
- Very good resistance to tears & puncture
- Good transparency and heat resistance at high temperatures.

Reifenhäuser
CAST SHEET COATING

Key performance criteria for LVP pouch film

Typical example for an LVP Pouch film

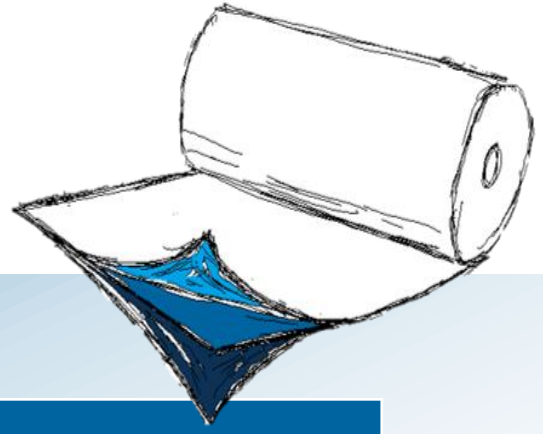
- 3-layer structure
- Complex film recipes
- Every layer offers important functionality



External layer	**Transparent heat resistant layer** − High melting temperature − Sterilisation resistance at 121°C − Transparency − Toughness
Core layer	**Very soft, very tough and transparent layer** − High toughness at low temperatures − Sterilisation resistance at 121°C and post sterilisation transparency − Softness for easy collapsibility of the bag
Internal layer	**Transparent and sealable layer** − Low S.I.T* / Seal ability − Sterilisation resistance (seal toughness, no sticking) at 121°C and post sterilisation transparency

* S.I.T. Sealing Initiation Temperature

Example of 3 layer film for LVP pouch

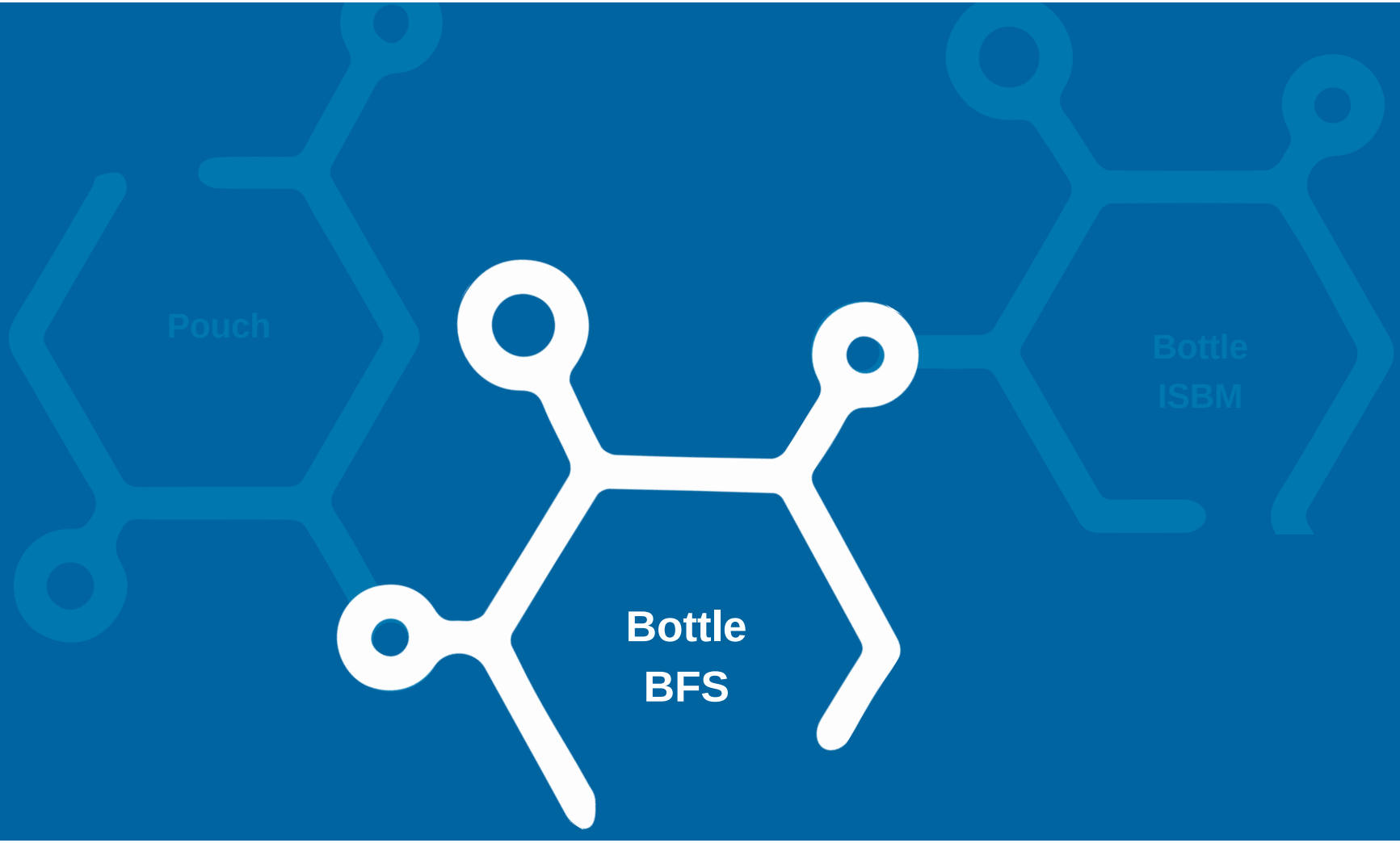


Example of 3 layer film construction (200µm)			
	Polymer type	**Layer**	**Functionality**
Outer layer	PP Homopolymer PP Random Copolymer + 0-10% impact modifier (Plastomer /other)	20µm	• Transparent • Heat resistant
Core layer	(Soft) PP Random Heterophasic Copolymer + 0-60% impact modifier (Plastomer /other)	130-160µm	• Very soft • very tough • Transparent
Inner layer	PP Random Copolymer PP Terpolymer + 0-20% impact modifier (Plastomer /other)	30-50µm	• Transparent • Sealable

Conversion film to pouch

Advantages and challenges of LVP pouches

- Multilayer (3 or more layers) construction with different materials
- Flexibility in design and establishing different performance criteria's
- Custom made solutions
- Multichamber systems possible
- Integration of the pouch machine into a filling line, transport of the film rolls to the conversion line
- Sterilisation at 121°C PP based pouches



What is a Blow-Fill-Seal process?

Blow-Fill-Seal (BFS) technology is a manufacturing technique used to produce small, (0.1mL) and large volume, (up to 1000ml) liquid-filled ampoules and containers.

Basic concept of BFS:

A container is formed, filled and sealed in a continuous process without human intervention, in a sterile enclosed area inside a machine.

The process is multi-stepped: first, medical grade plastic resin is vertically heat extruded through a circular die to form a parison. The parison is then enclosed within a two-part mould, and cut above the mould. The mould is transferred to the filling zone, where mandrels are lowered and used to blow the plastic to form the container within the mould. Following the formation of the container, the same mandrel is used to fill the container with liquid. Following filling the mandrels are retracted and a secondary top mould seals the container. All actions take place inside a sterile chamber inside the machine. The product is then discharged to a non-sterile area for labelling, packaging and distribution.

Materials used in BFS - LDPE

Historically LDPE is used in this monomaterial application.

Material performance:

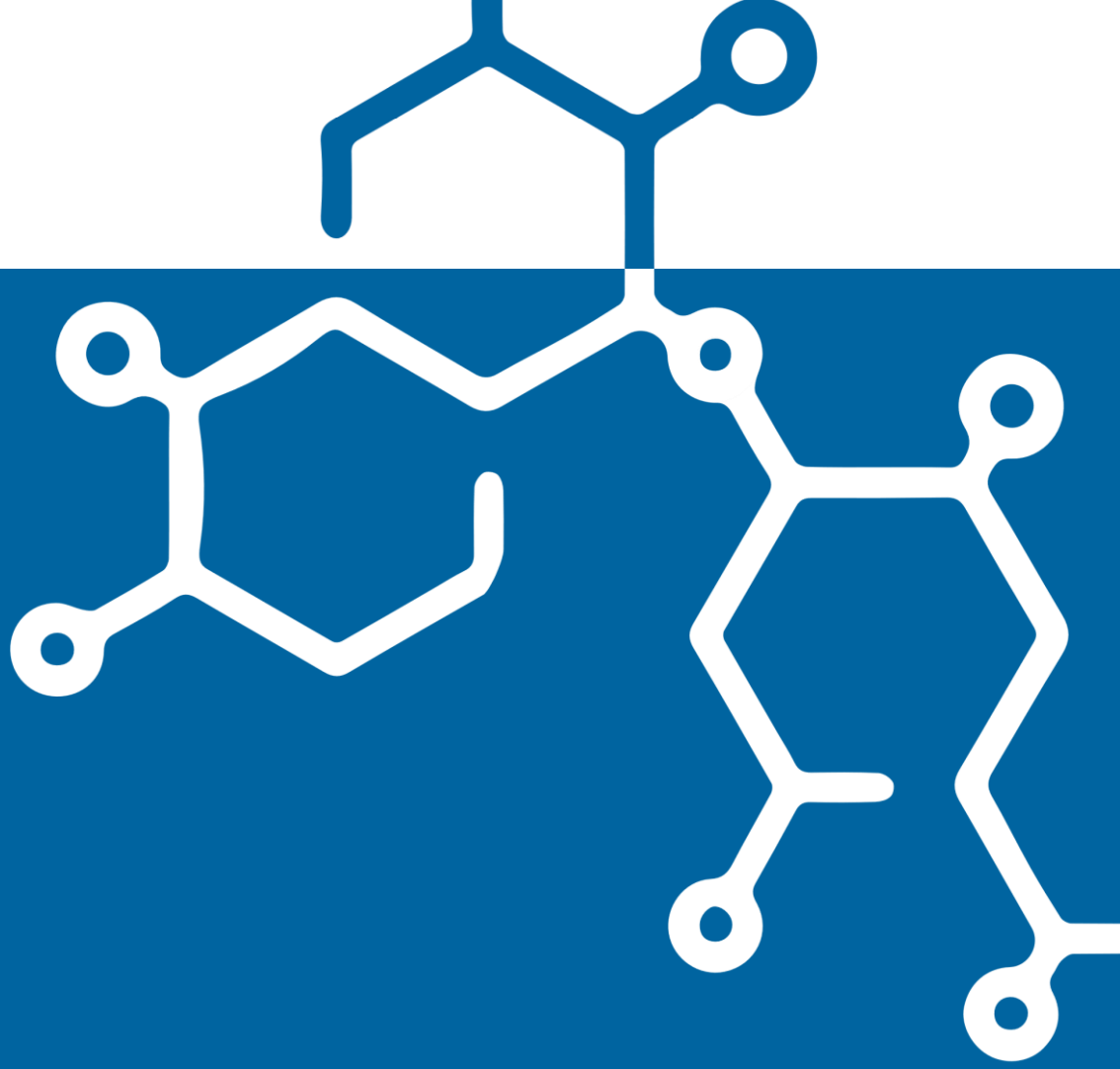
- Good combination of softness and transparency
- Easy processing
- Low extractables as LDPE normally comes without extra additvation
- Melting point far below 121°C
- With LDPE density above 927 kg/m3, sterilisation can be done up to 114ºC
- Depending on grade a sterilisation even at 110°C might not be possible

Materials used in BFS - PP

PP did not succeed in a first instance, as this material is usually not soft enough to ensure a good collapsibility of the bottles and showing not a good performance in the emptying tests. Today there are soft PP materials available, that show similar softness as an LDPE and therefor a similar behaviour.

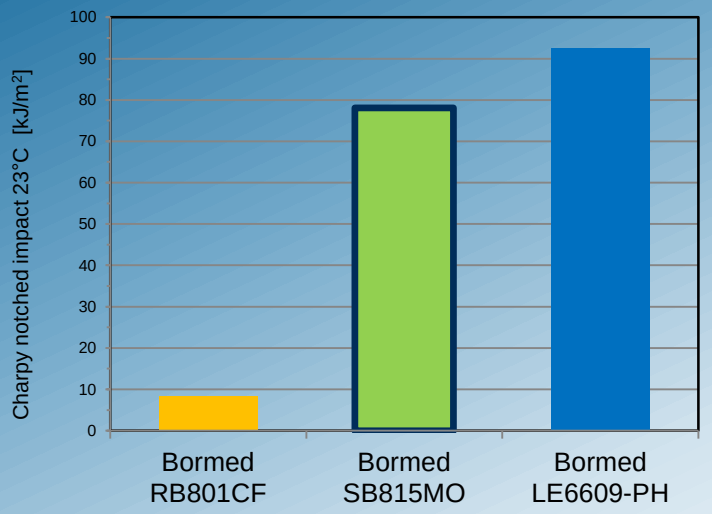
Material performance:

- Sterilisation at 121°C. Even a sterilisation at 132°C is possible, although usually not needed
- Depending on the grade similar softness and transparency as LDPE materials or highest transparency with stiffer grades
- BFS processing of soft PP needs special attention

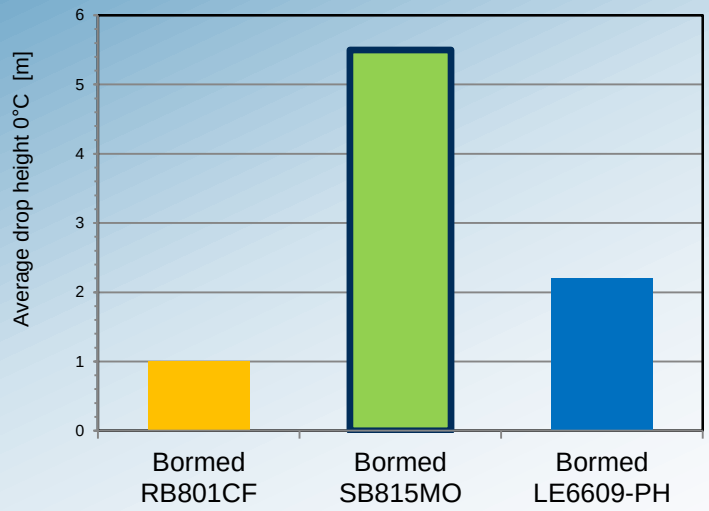


Bormed™ materials used in BFS – mechanical properties

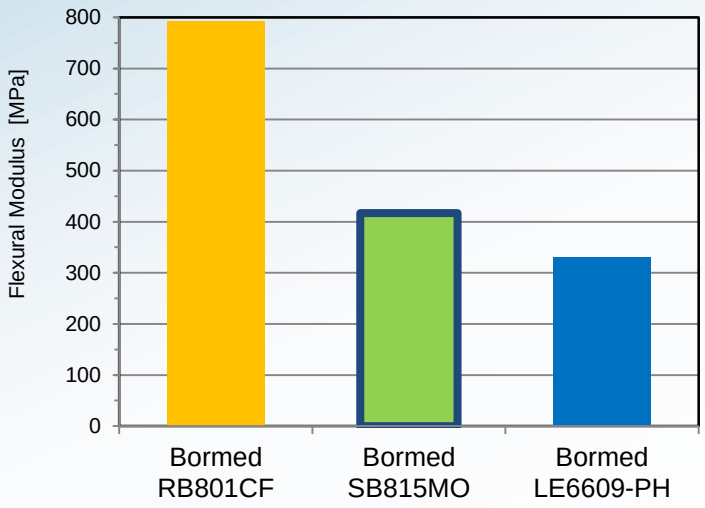
Impact strength



Average drop height at 0°C

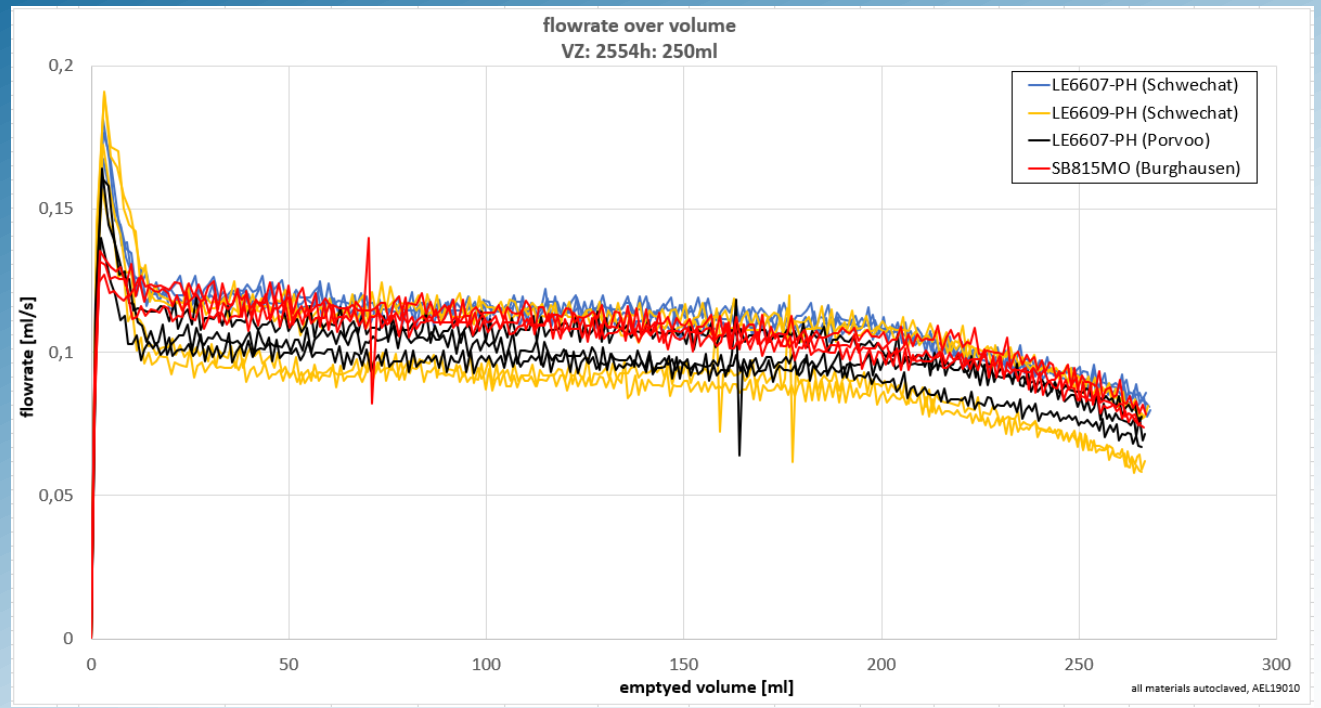


Stiffness comparison

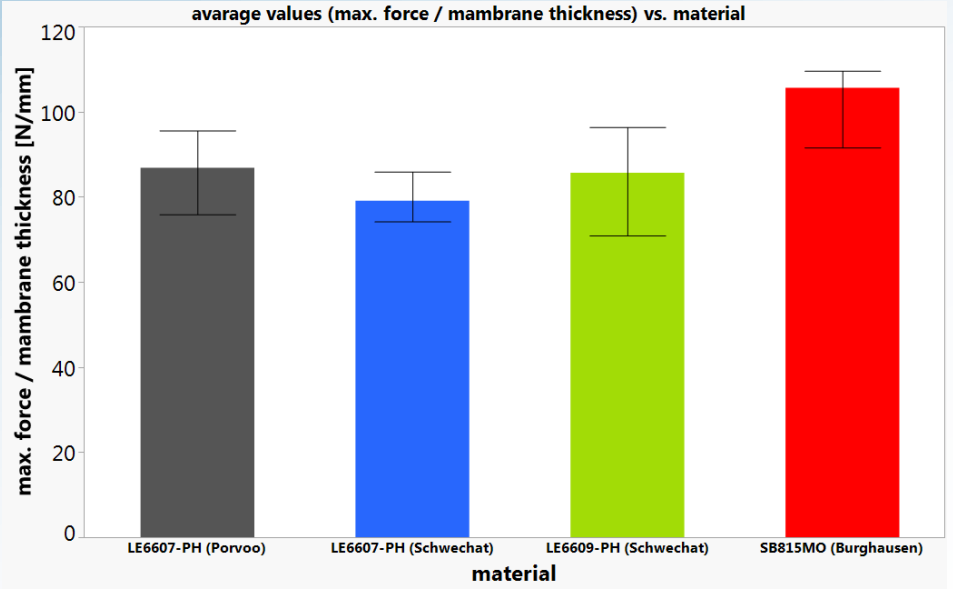


Bormed™materials used in BFS – emptying behaviour, piercing force

Emptying results



Piercing force



Bars: max/min

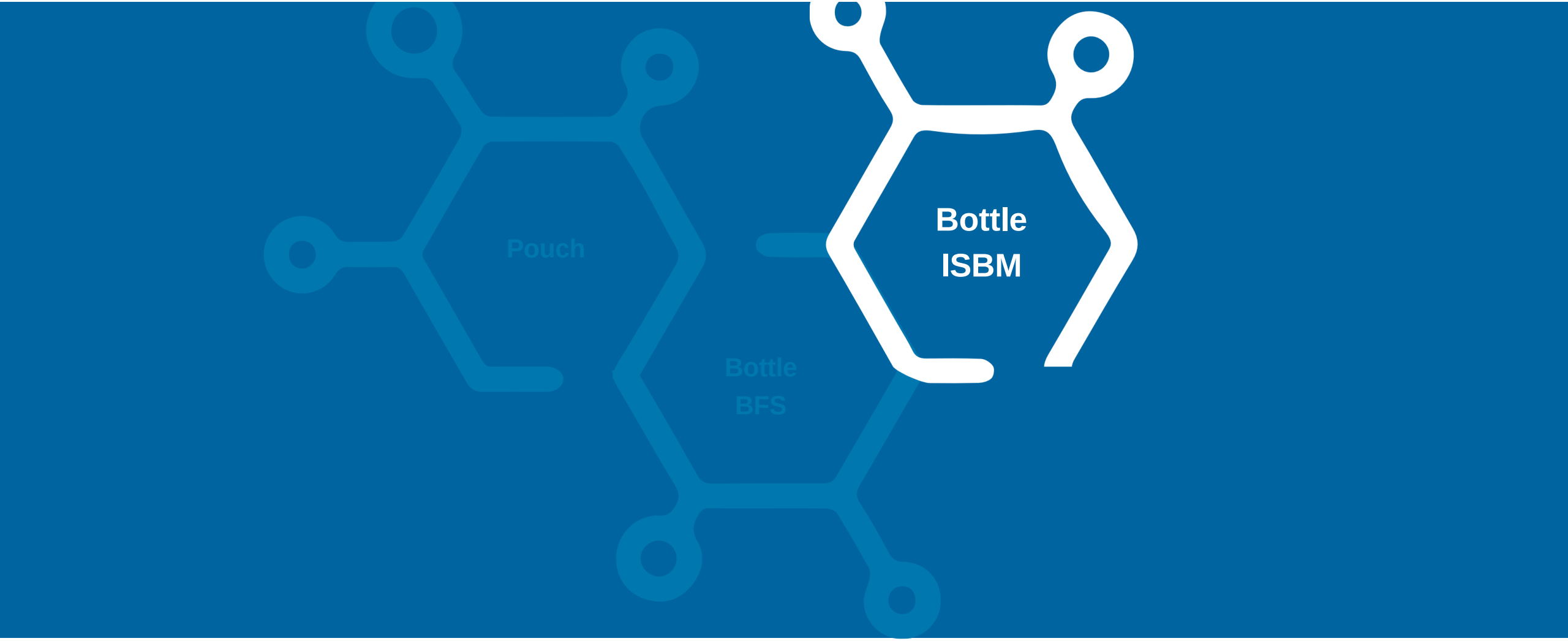
Source: Rommelag

Overview properties of materials used in BFS for LVP

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

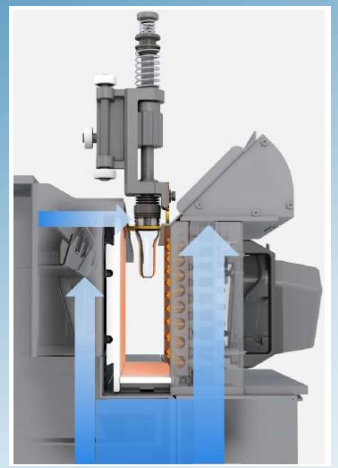
Advantages and challenges of BFS

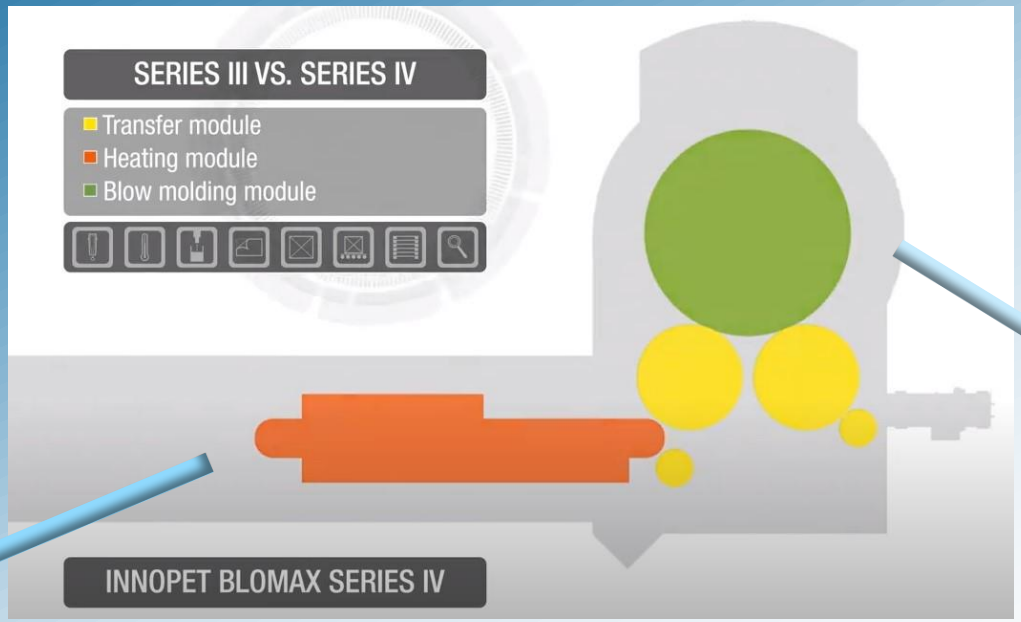
- LDPE and PP can be used in this process. Dedicated soft PP has been developed to provide best performance for LVP applications.
- Sterile and/or aseptic filling of bottles in one step, no transportation of empty bottles → low contamination risk
- Output is limited
- Depending on the choice of material, sterilisation at 121°C might not be possible, as for example with LDPE. The more testing and validation work needs to be performed for the quality dossier
- Monomaterial solution
- PP cannot necessarily be processed on a machine developed for LDPE without further adaption



How does Injection Stretch Blow Moulding (ISBM) work?

2 stage reheat process

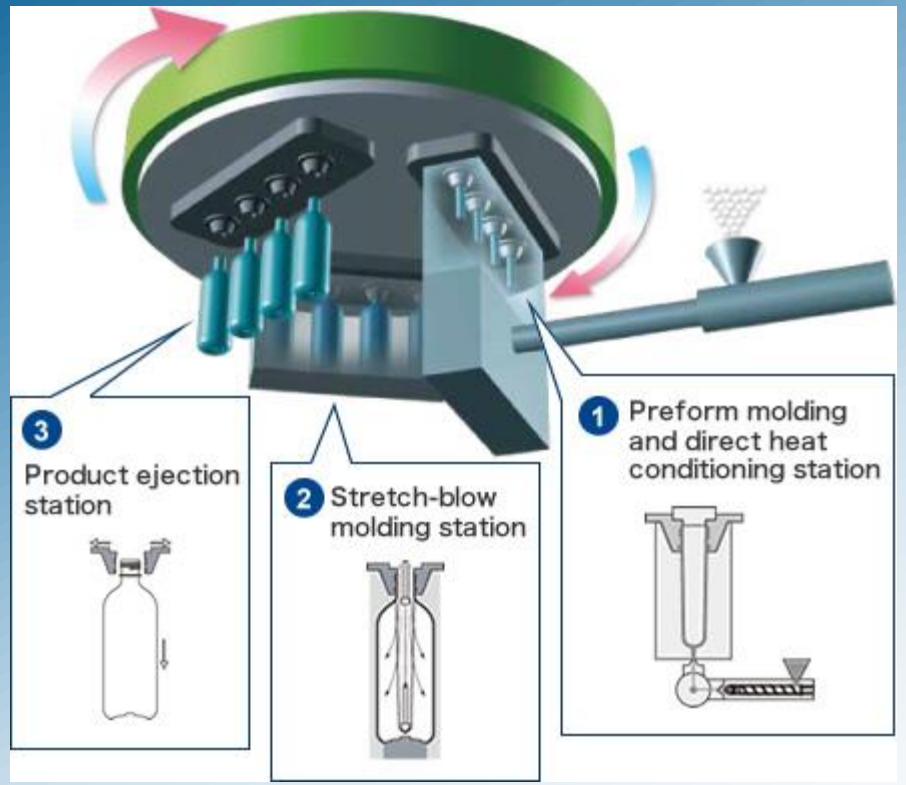


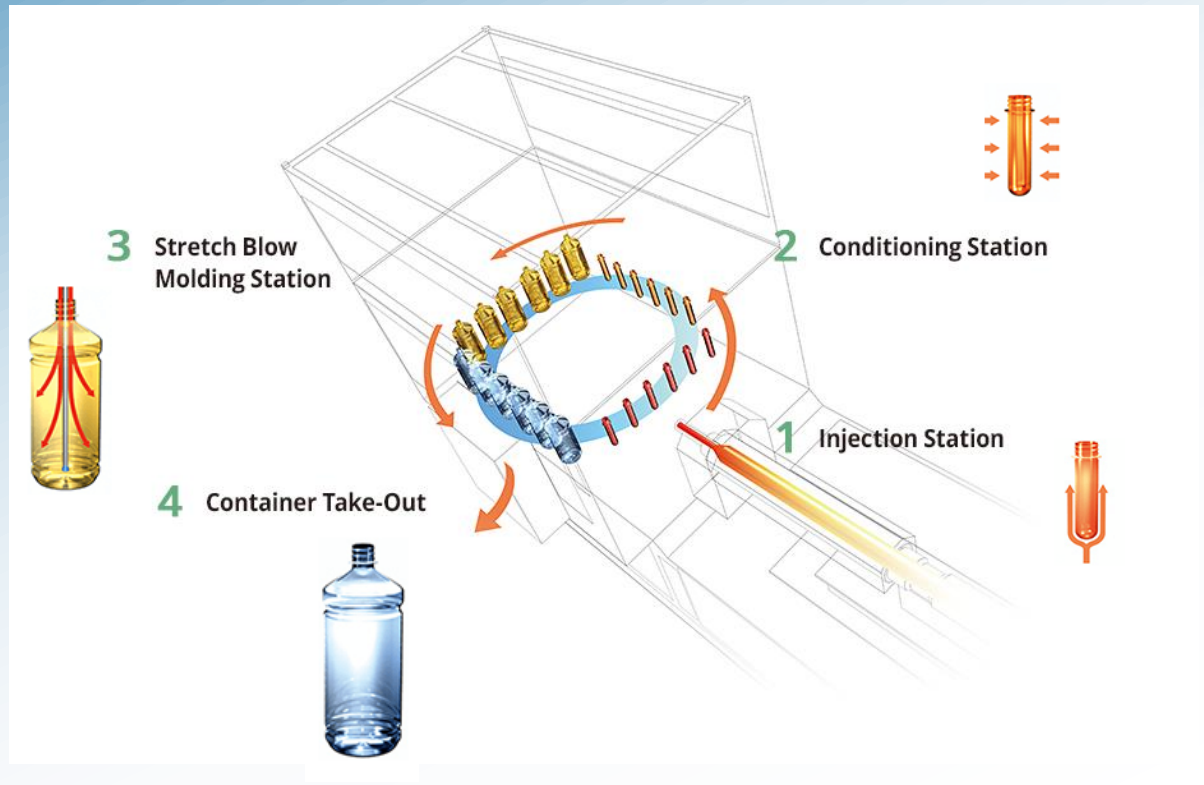


KHS InnoPET Blomax Serie IV:
StretchFlexx

How does Injection Stretch Blow Moulding (ISBM) work?

1-step ISBM





AOKI

ASB Form Your Vision

Material performance

2-step process (reheat)

- Preform moulding can be done separately
- Reheating and stretch blow moulding can be implemented in a filling line to assure best cleanliness during filling procedure
- Special attention to the transport of preforms to the blowing machine to avoid contamination
- Lightweight containers possible
- No scrap
- Very high output possible
- Processing window narrow, but acceptable
- Injection moulding of preform at high quality necessary

1-step process

- Lightweight containers
- No scrap
- Process output is limited
- Process settings limited by the different processes that are performed in one go
- Low contamination risk, if the filling line is directly adapted to the blowing machine, no transport of preforms

Advantages and challenges of ISBM

- Random PP is used in this process. Special grades have been developed to give best processability in both injection moulding of preforms and stretch blow moulding of bottles.
- For the 2-step process usually a grade with a medium flowability is used, whilst in the 1-step process the extrusion grades also used for BFS give the best performance.
- Monolayer bottles can be lightweighted. Stiffness is increasing during stretching process. Wall thickness of 0.2-0.3mm possible. For optimal preform / bottle combinations and symmetric bottles also thinner might be possible.
- Challenges for PP ISBM in oval bottles. Special sequentiel heating is available for proper heating of the preform.
- Bottles are filled in a separate step. ISBM can be included in a filling line directly to avoid an additional transportation step.
- As PP is used, bottles can be sterilised at 121°C. Optimal design is necessary to avoid deformation.

Borealis at a glance

LVP packaging formats

Renewable Polyolefins – a new challenge?

Conclusion & Summary

Regulatory support for approval process of LVP

Medical Grade Plastic

The **guideline VDI 2017 „Medical Grade Plastics“** is defining a medical grade plastic:

Polymeric plastics […] are called **„Medical Grade Plastic“ (MGP)** when they are intended for use by a given manufacturer in the manufacture of finished products in the following application areas:

- medical devices […]
- in-vitro diagnostics […]
- primary pharmaceutical packaging […]

[…] A common characteristic of MGP´s is compliance with specific minimum requirements in relation to:

- rigorous change mangement […]
- specific quality management […]
- guarantees on security of supply and availabilty, as well as logistic requirements for MGPs
- support when fulfilling the manufacturer´s binding regulatory specifications, such as tests for contact with food or biocompatibility

Bormed™ Concept: Dedicated service for the Healthcare Industry

COMMITMENT

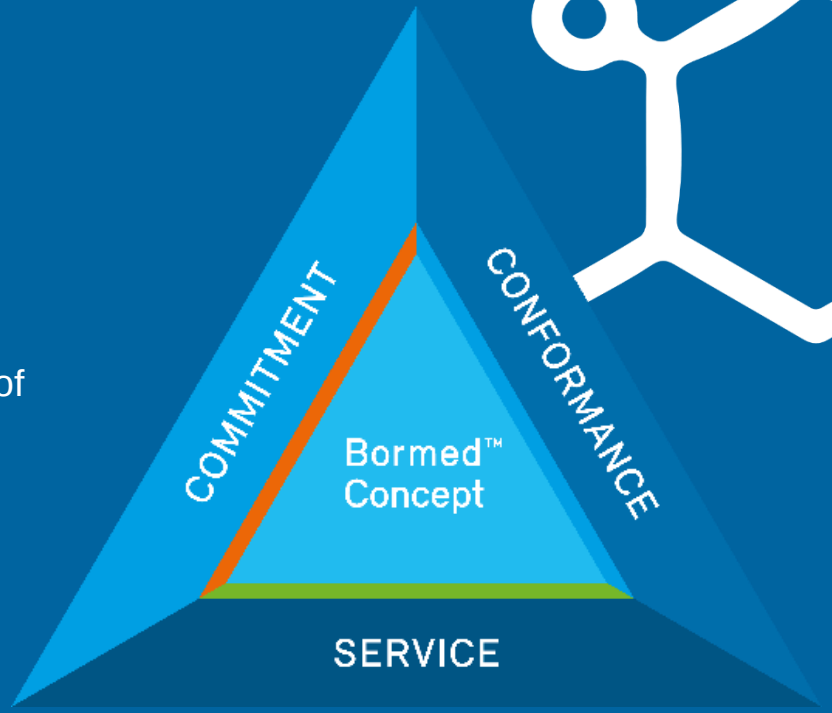
- Dedicated portfolio of branded PE & PP
- Continuity of supply regulated by Technical Delivery Specification
  - Product made available up to 5 years (2 years pre-notification and a last call volume combined with 3 year shelf life)
- Consistency of the product recipe via rigorous change control procedure
- The Bormed Directive (PO4047): operating instructions for the development, production, storage and delivery to the end customer of Bormed products

CONFORMANCE

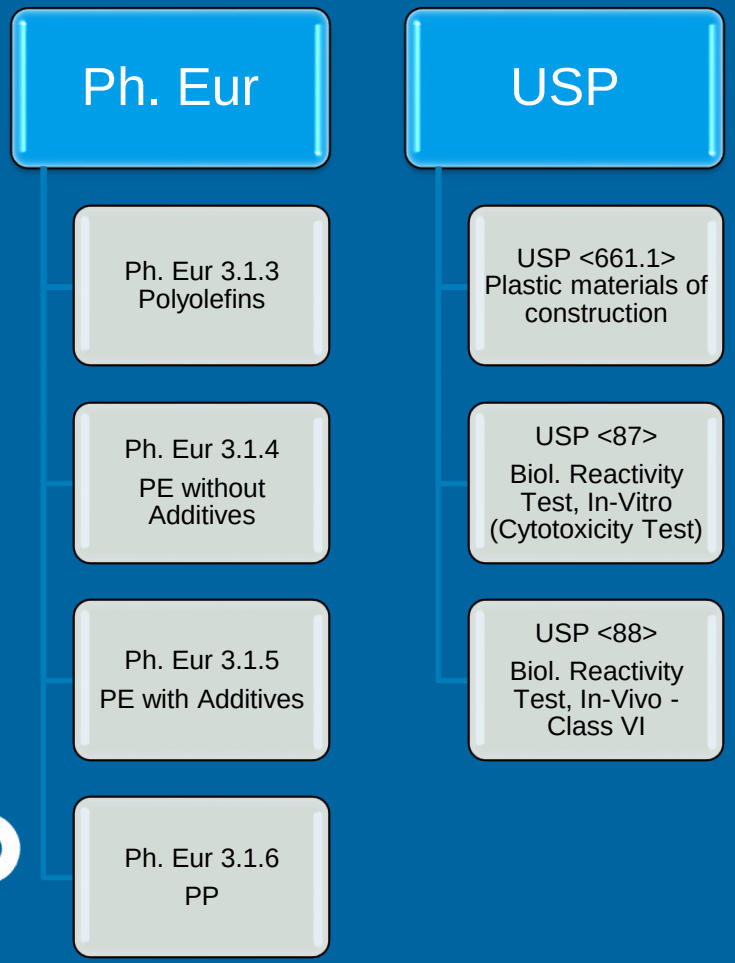
- Pharmacopeia compliance
  - External Ph. Eur., USP (incl. 661.1) and ISO 10993 testing: analysis reports can be shared on request; DMF listing; following VDI guidelines on MGP

SERVICE

- Extractable profiles that can be shared on request
- Globally available dedicated team of experienced technical and regulatory specialists
- Innovation in products and services relevant for Healthcare industry

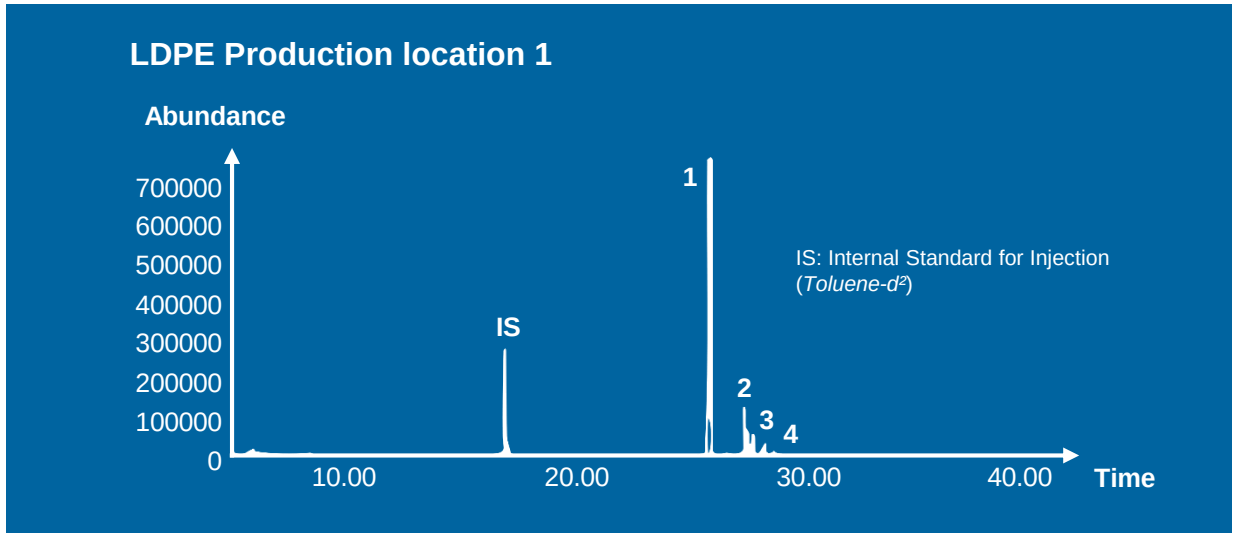


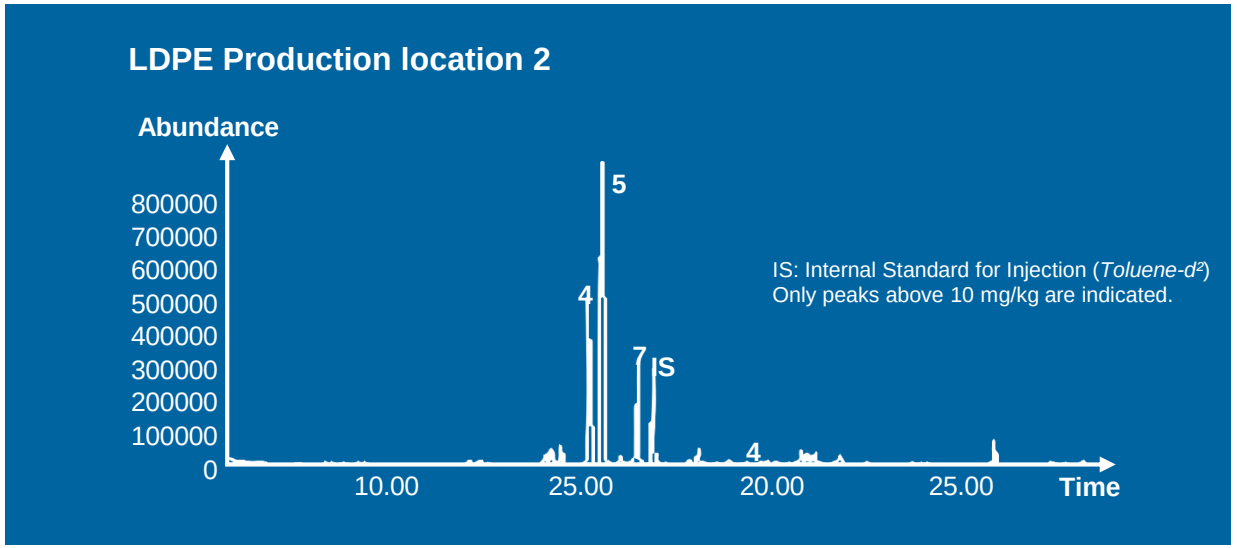
Externally conducted compendial testing available for Bormed



- For your Peace of Mind and even though change management is in place:
  - Yearly external testing of Ph. Eur
  - USP external testing every 5 years (as it involves animal testing)
- Analysis reports can be shared on request
- All Bormed grades are US DMF listed: LoA issued upon request

Going the extra mile: our extractable testing





- Extractives are generally LMW polymer, additives and species from processing e.g. degradation and side reaction products
- The profile of a few pellets will differ to a moulded and subsequently sterilised container. Adding colorant will change the profile further

Value for the customer

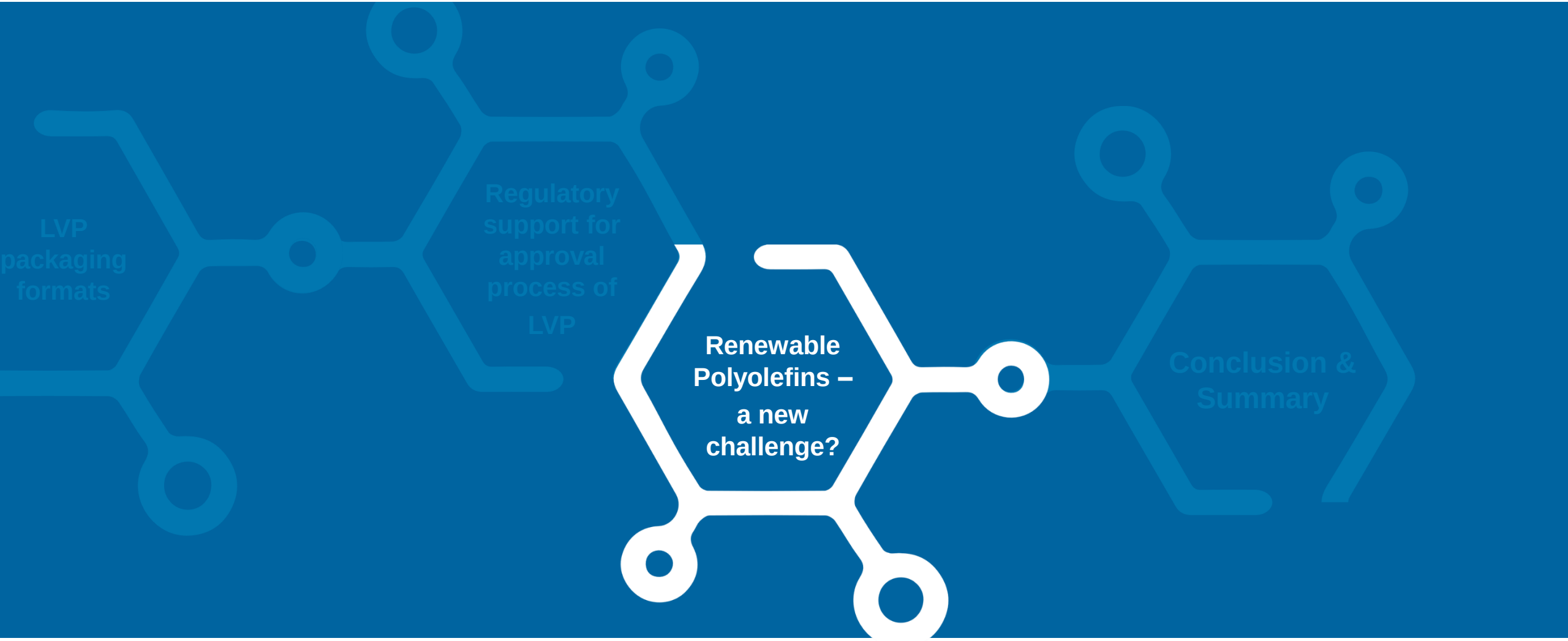
- Extractive data on resin can support informed decision making and validation at an early stage – time/money saving of customer's testing programme
- Analysis reports and product composition disclosure can be shared on request under NDA

Value for Borealis

- Being able to actually quantify on molecular level the effect changes could have

Extractable testing

- Testing programme determined in co-operation with Nelson Labs
- Programme consists of:
  - Headspace GC/MS on pellets: organic volatiles
  - Extraction with 3 solvents
    - GC/MS for semi-volatile organics
    - LC/MS for non-volatile organics
  - Identification of compounds present >5µg/ml
- Solvents are UPW, Ethanol and Hexane
  - Chosen to give the broadest possible dataset whilst still remaining relevant to majority of industry
- Extractable data can be shared under NDA along with composition disclosure (formulation) on request
- When change data provided, test side by side with control spike



Circular Economy: introducing the Bornewables and in the near future chemically recycled POs for Healthcare

Solutions for Healthcare

Recyclates	BORCYCLE™		Borcycle™ C	The Bornewables™
	Borcycle™ M	Borcycle™ S		
	 			
Mechanical Recycling	**Advanced Mechanical Recycling**	**Solvent based Recycling**	**Chemical Recycling**	**Renewable-based POs**
Granulates that deliver primarily dark colours with challenges in odour and impurities; not food approved	Recyclates and compounds that overcome challenges of state of the art recyclates: light colours; reduced odour impurities; not food approved	Purity levels close to virgin: transparent; improved processability; further odour improvements; not food approved	– Virgin equivalent – Food approved grade – Offered with the Bormed service package for medical grade plastics	– Virgin equivalent – Food approved grade – Offered with the Bormed service package for medical grade plastics
Not a viable option for most Healthcare applications as not a virgin equivalent and not food approved grades			**First generation demonstration**	**Commercially Available**

The Bornewables™ line of Bormed™ for more sustainable Healthcare solutions

- Wide range of Bormed PP homo, PP random, PP terpolymer and LDPE solutions for pharma packaging, medical and diagnostic devices
- Based on 2nd generation waste and residue renewable feedstock which helps to decouple production of plastics from fossil and offers lower environmental impact
- ISCC Plus certification provides authenticity and credibility to the new mass balance approach when followed by the entire value chain and allows for credible claims on final products

LVP packaging formats

Regulatory support for approval process of LVP

Renewable Polyolefins – a new challenge?

Conclusion & Summary

Summary of different packaging formats

	Pouches	BFS LDPE	BFS soft PP	ISBM 1-step	ISBM 2-step
Processability	++	++	+	-	+
Ph.Eur compliance	++	++	++	++	++
Transparency	++	-	-	++	++
Sterilisation at 121°C	++	-	++	++	++
Monomaterial / Multimaterial	**Mulitmaterial / Multilayer**	**Monomaterial**	**Monomaterial**	**Monomaterial**	**Monomaterial**
Output	+	-	-	-	++
Protection against Contamination	-	++	++	+	-
Lightweighting	++	-	-	++	++

Conclusion

Polyolefins can serve all different kinds of LVP packaging formats addressing different challenges in processing, sterilisation and regulatory requirements.

The choice of a Medical Grade Plastic can help to reduce risks and to gather the best support possible for LVP evaluation from raw material side.

New opportunities for renewable sourced materials can help in reaching your sustainability goals.

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Thank you