

HOLOPACK

**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**



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bottelpack® History



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

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- **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

- **1990s**
 - **New bottelpack® machine generation (Types 321/321M - 360/360M)**
 - **Clean/Dirty 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

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bottelpack® model 3012/321

Capacities up to 9,000 vials per hour



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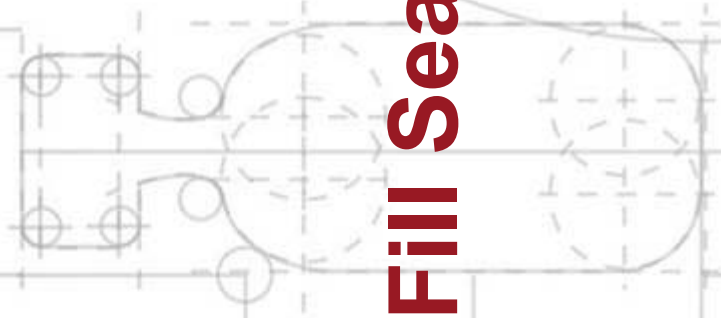
bottelpack® model 360

Higher capacities up to 18,000 vials per hour

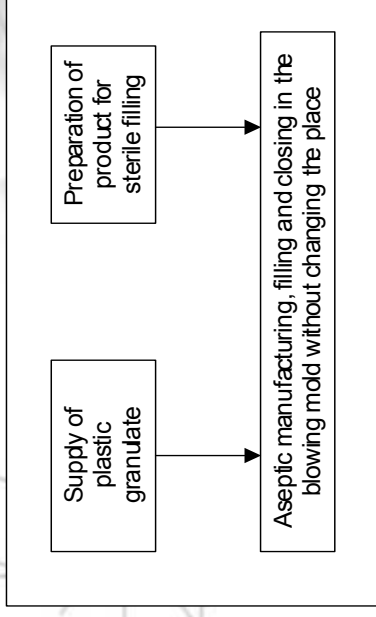
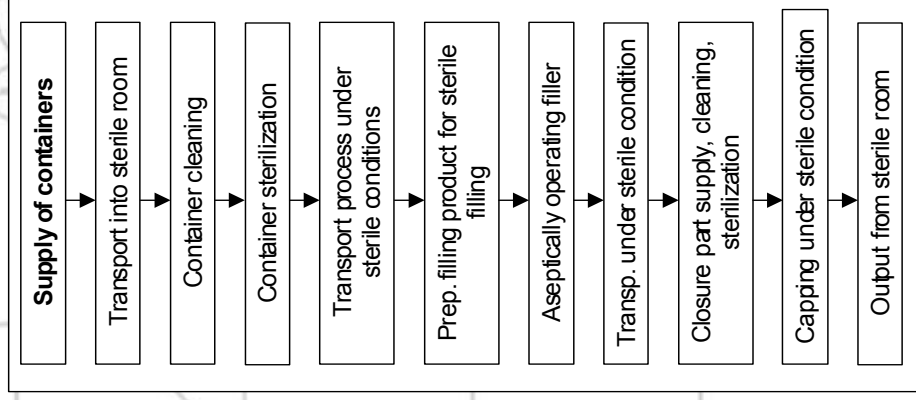


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Blow Fill Seal Process

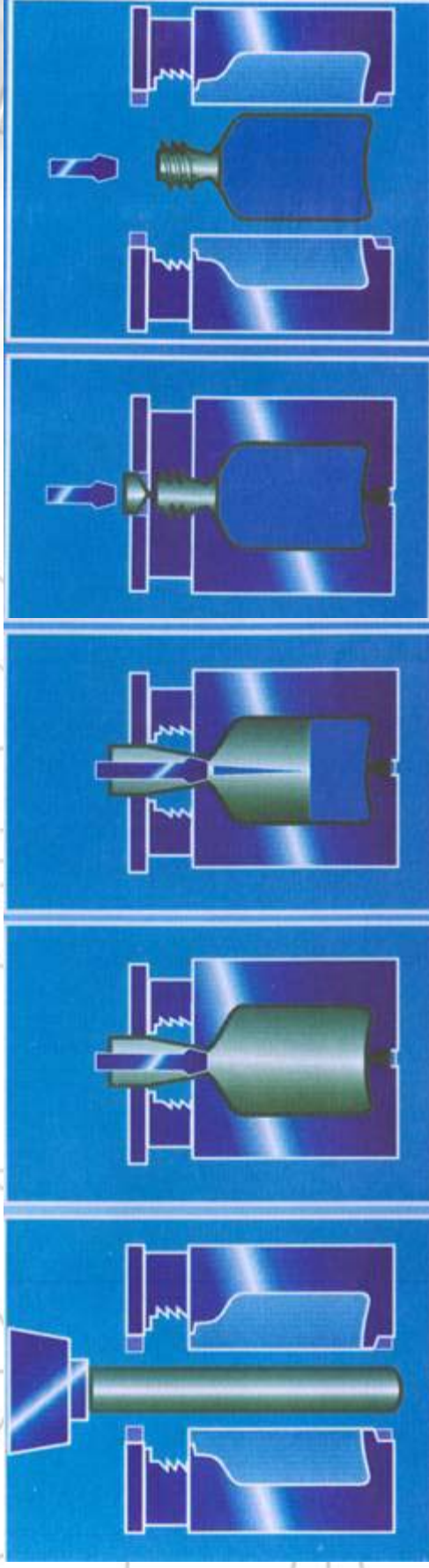


Conventional vs. BFS



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BFS Process Overview



**Parison
Extrusion**

**Molding by
blowing and
vacuum**

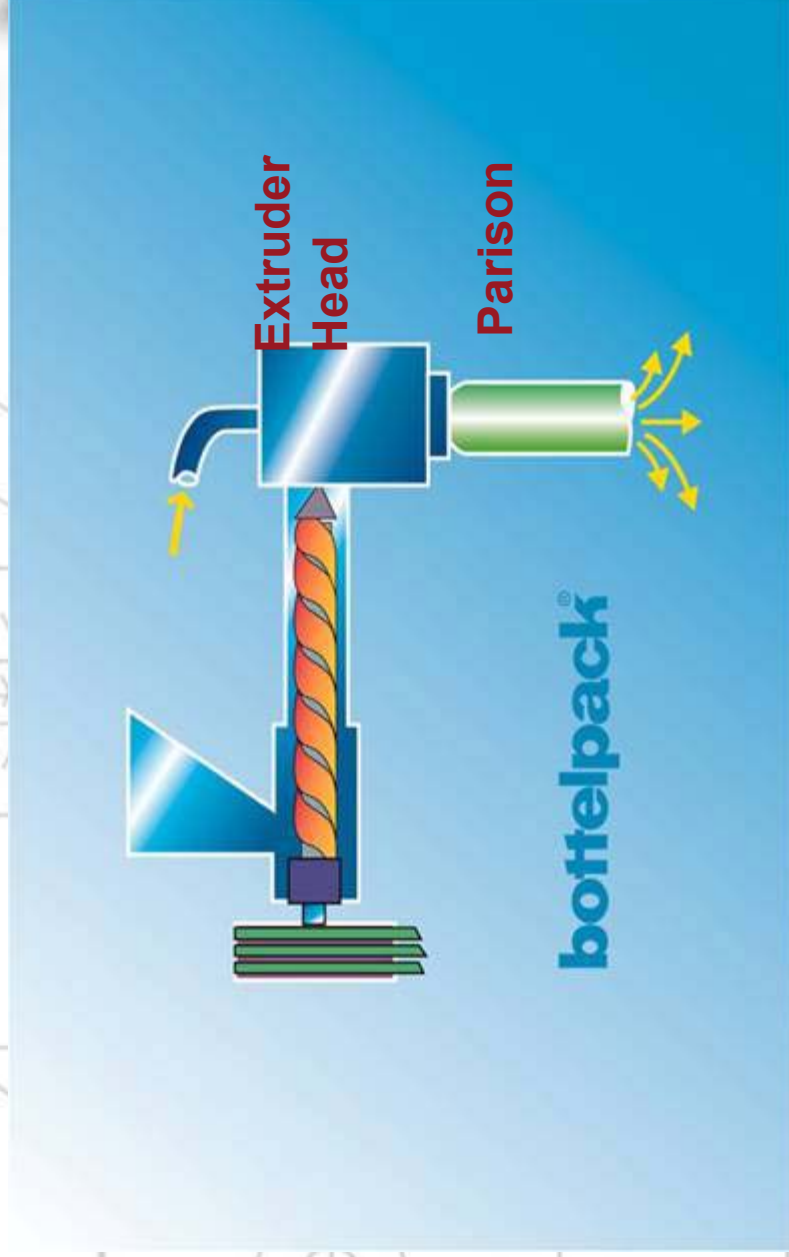
Filling

**Container
sealing**

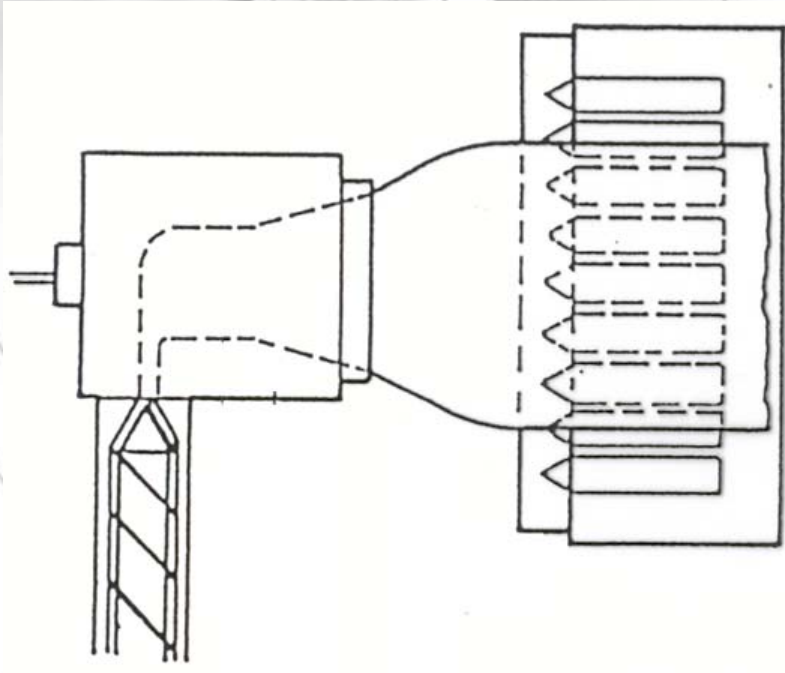
Product

Process step 1

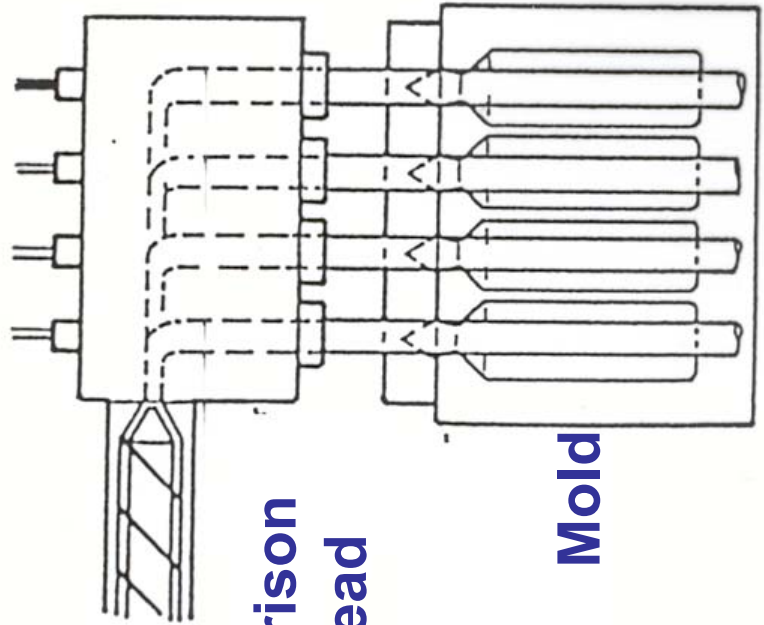
- Plastic melting and extrusion (170-230°C; up to 350 bar)
- Extrusion provides sterilization and depyrogenation



Single/Multiple parison extrusion



Single parison extrusion



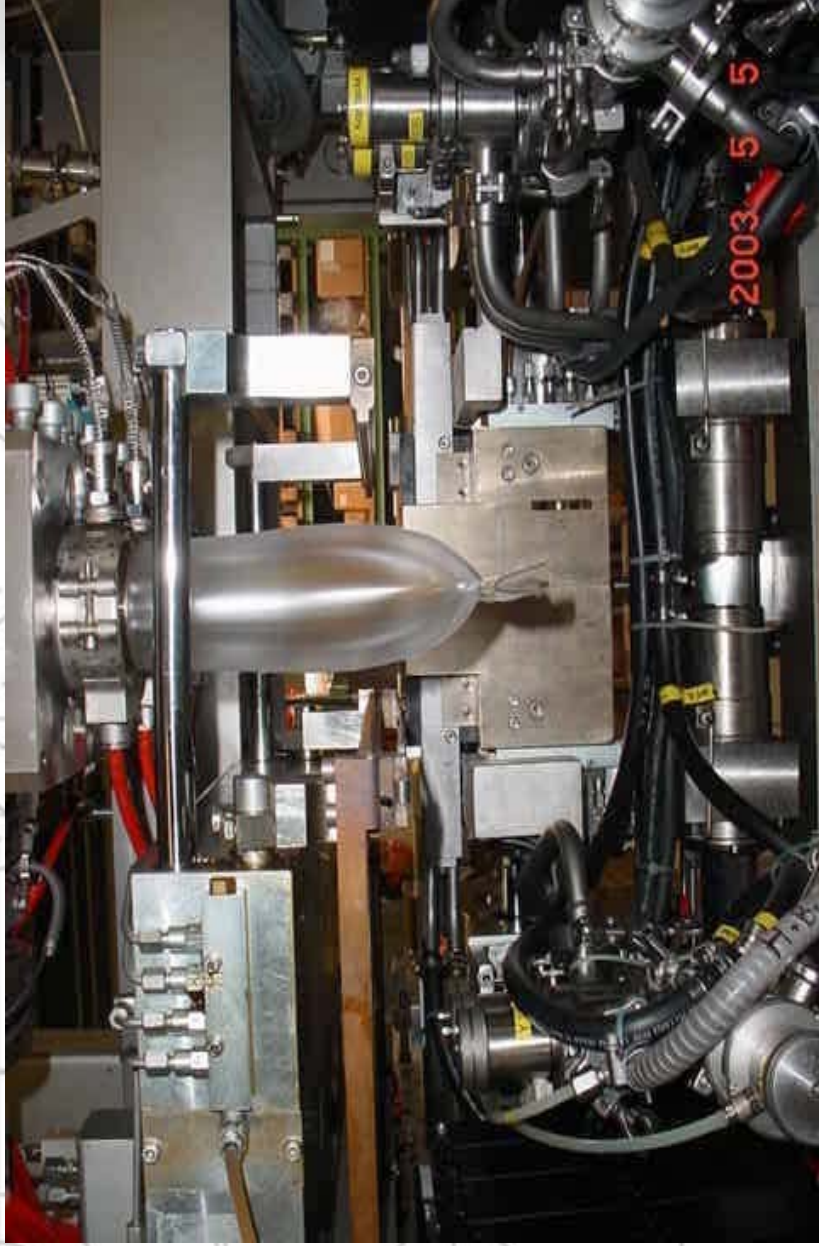
Parison head

Mold

Multiple parison extrusion

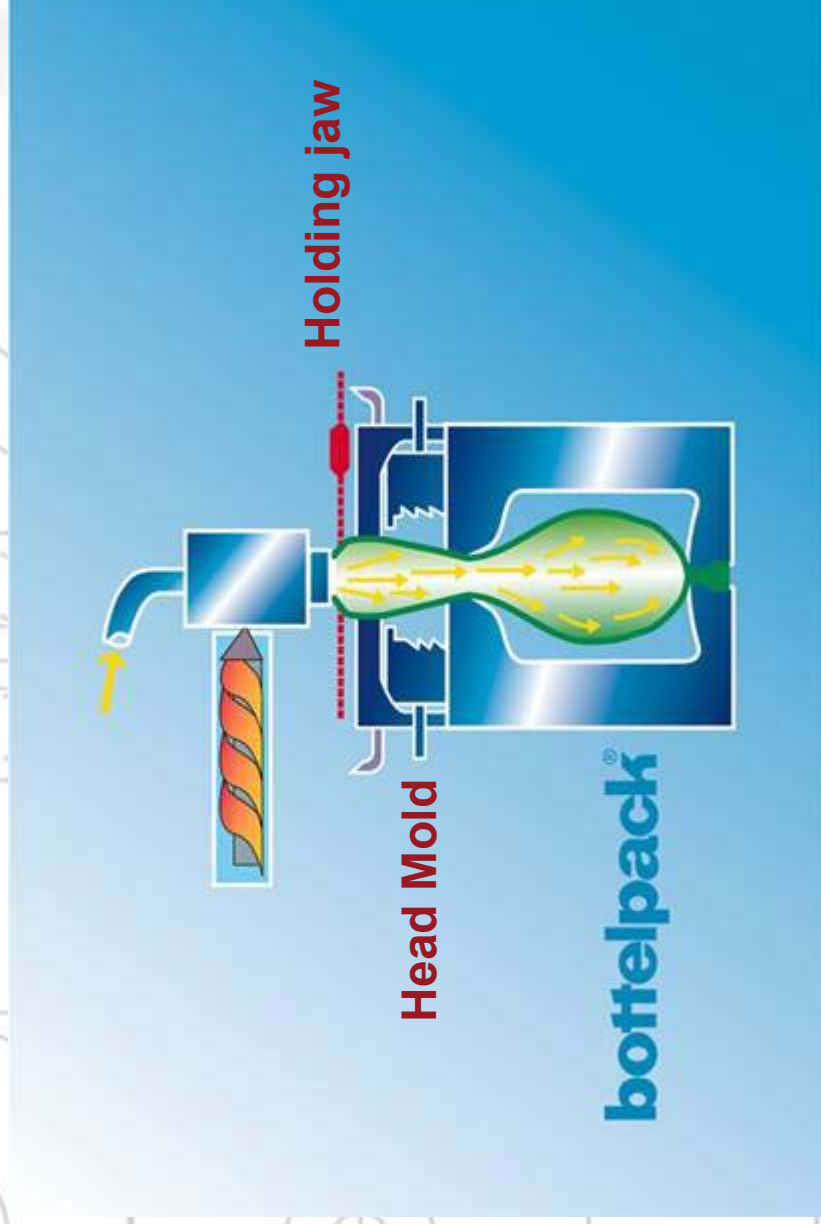
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Parison



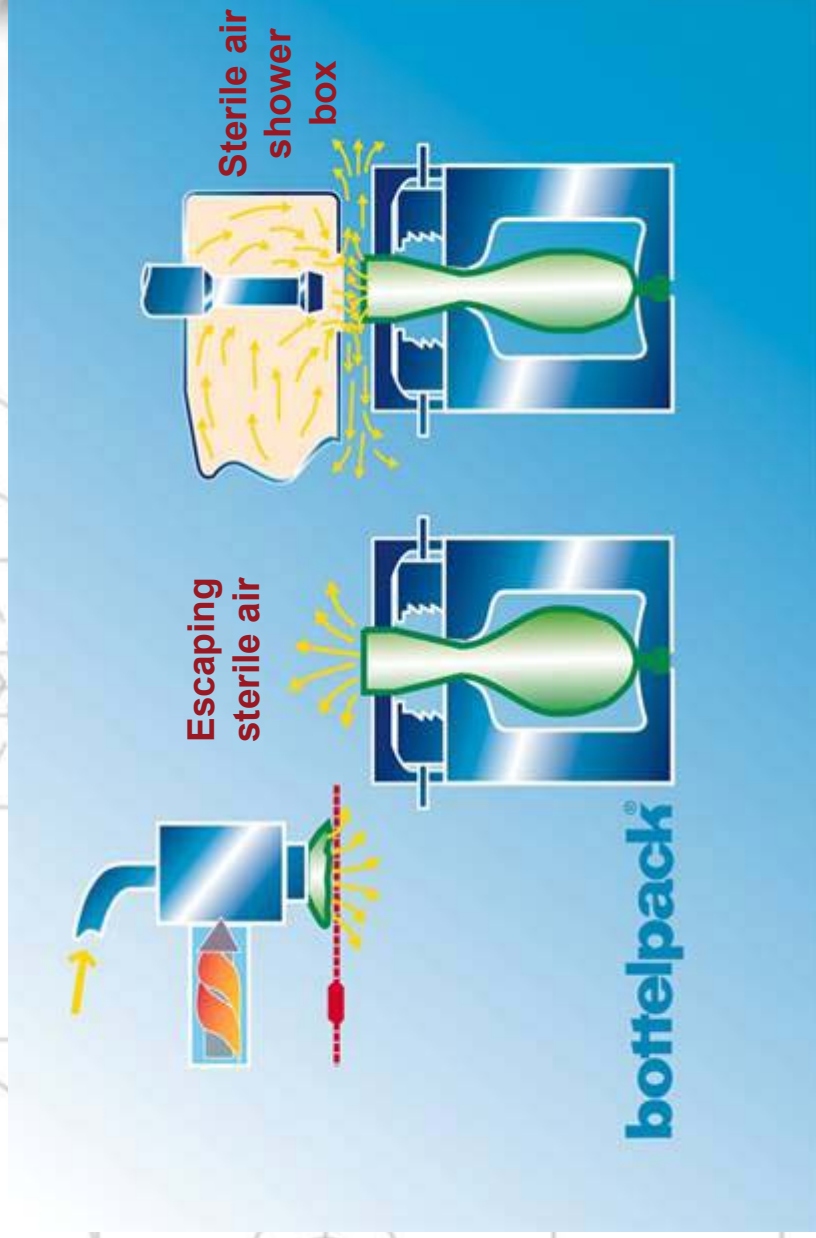
Process step 2

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

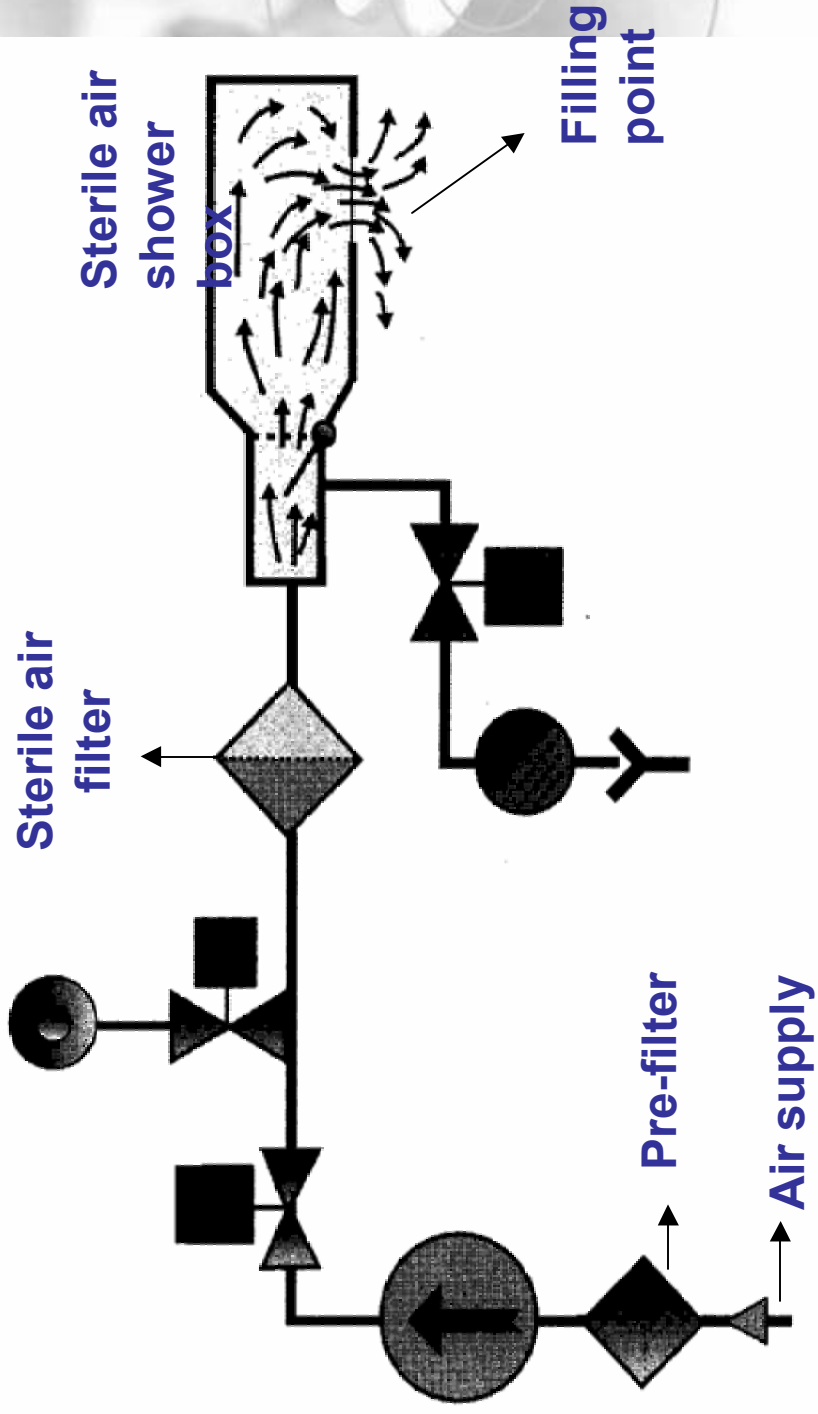


Process step 3

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

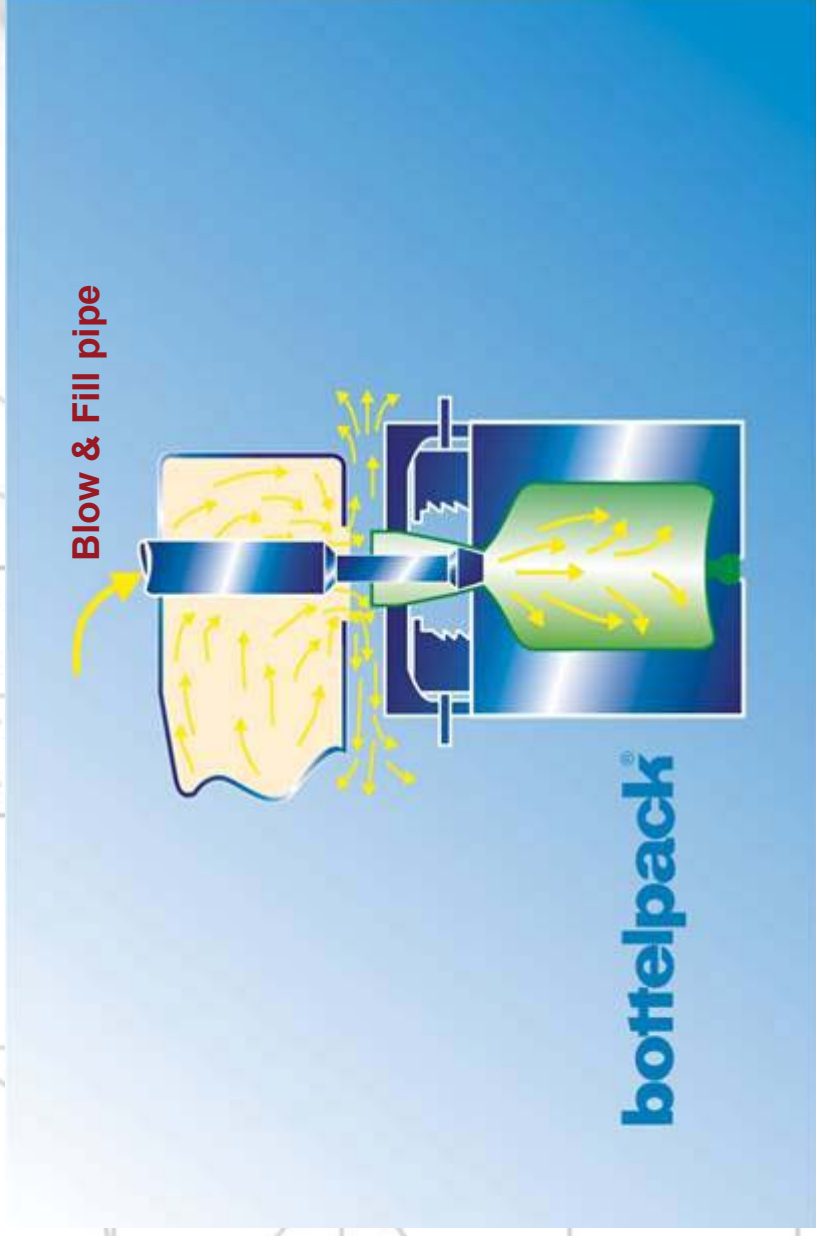


Sterile Filling Space



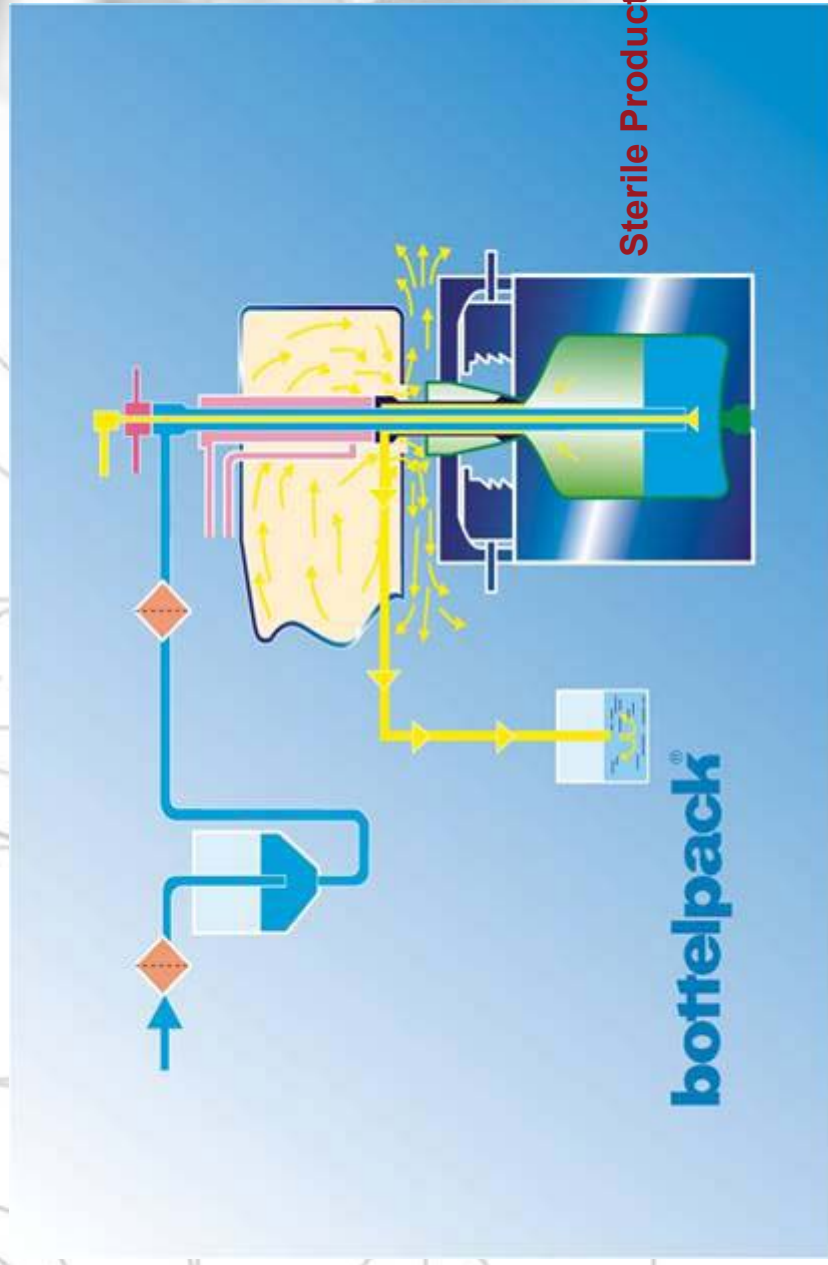
Process step 4a

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



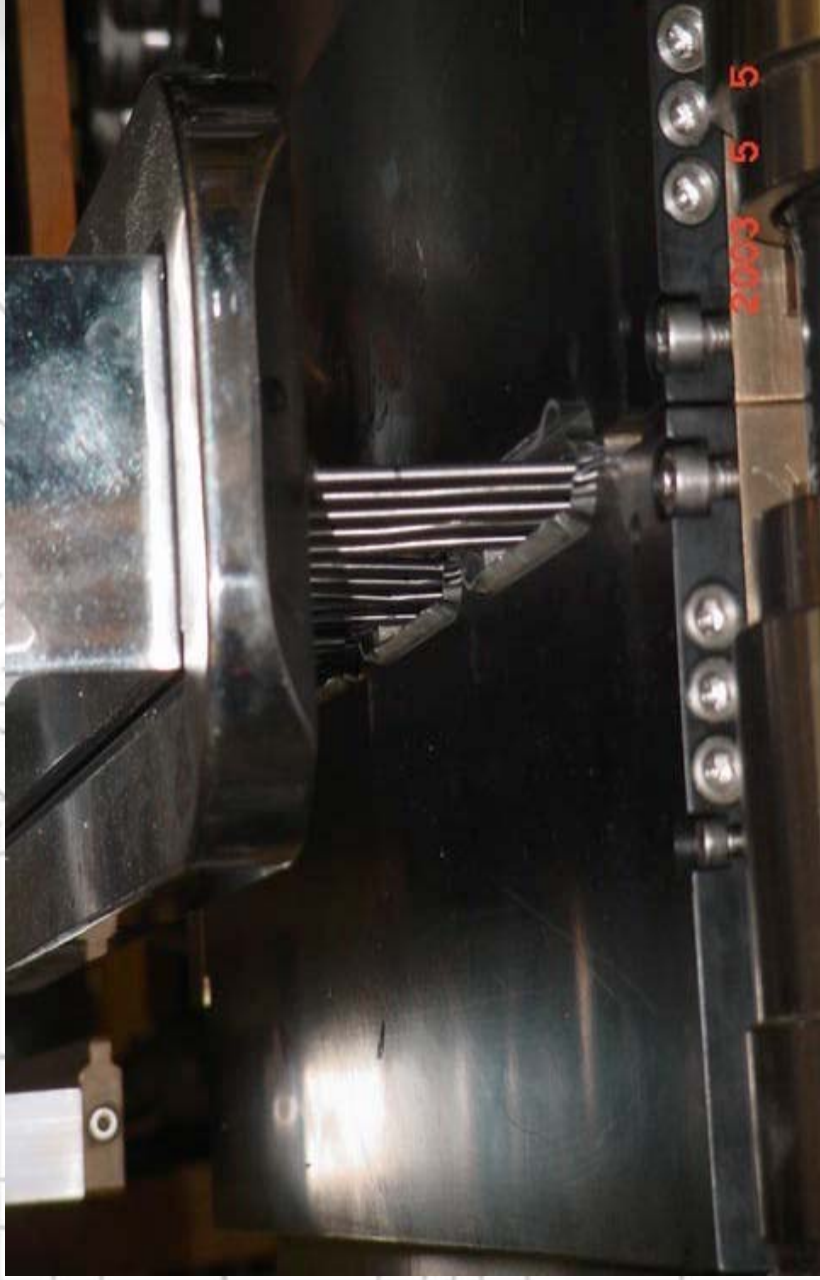
Process step 4b

- **Filling - Time pressure dosing**



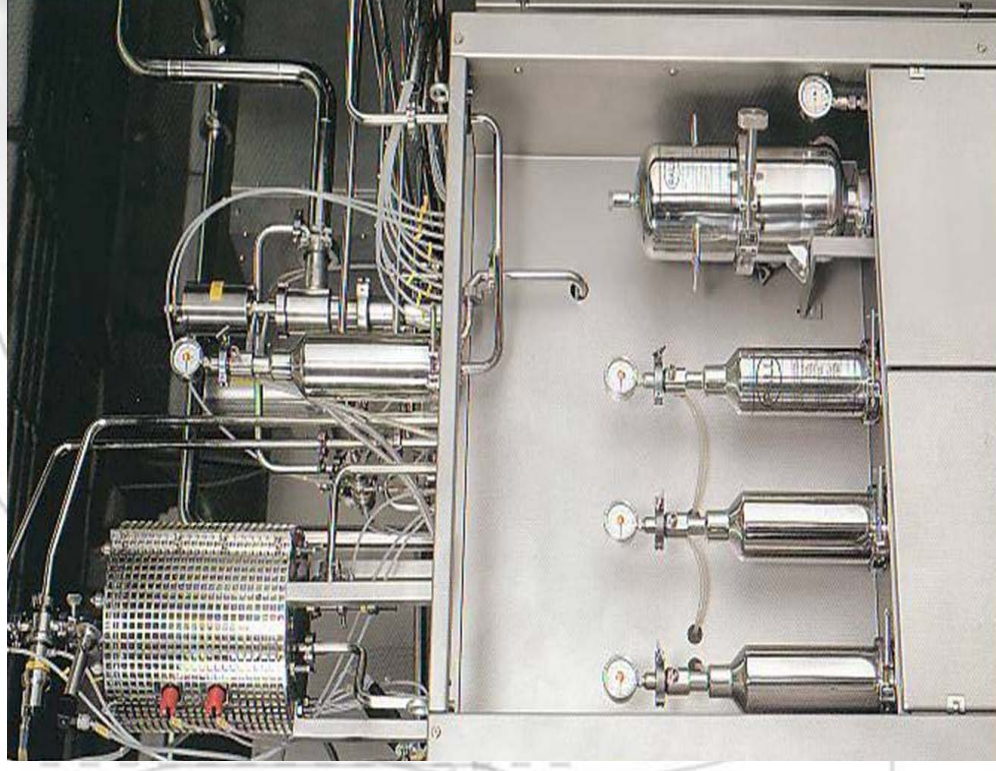
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Filling

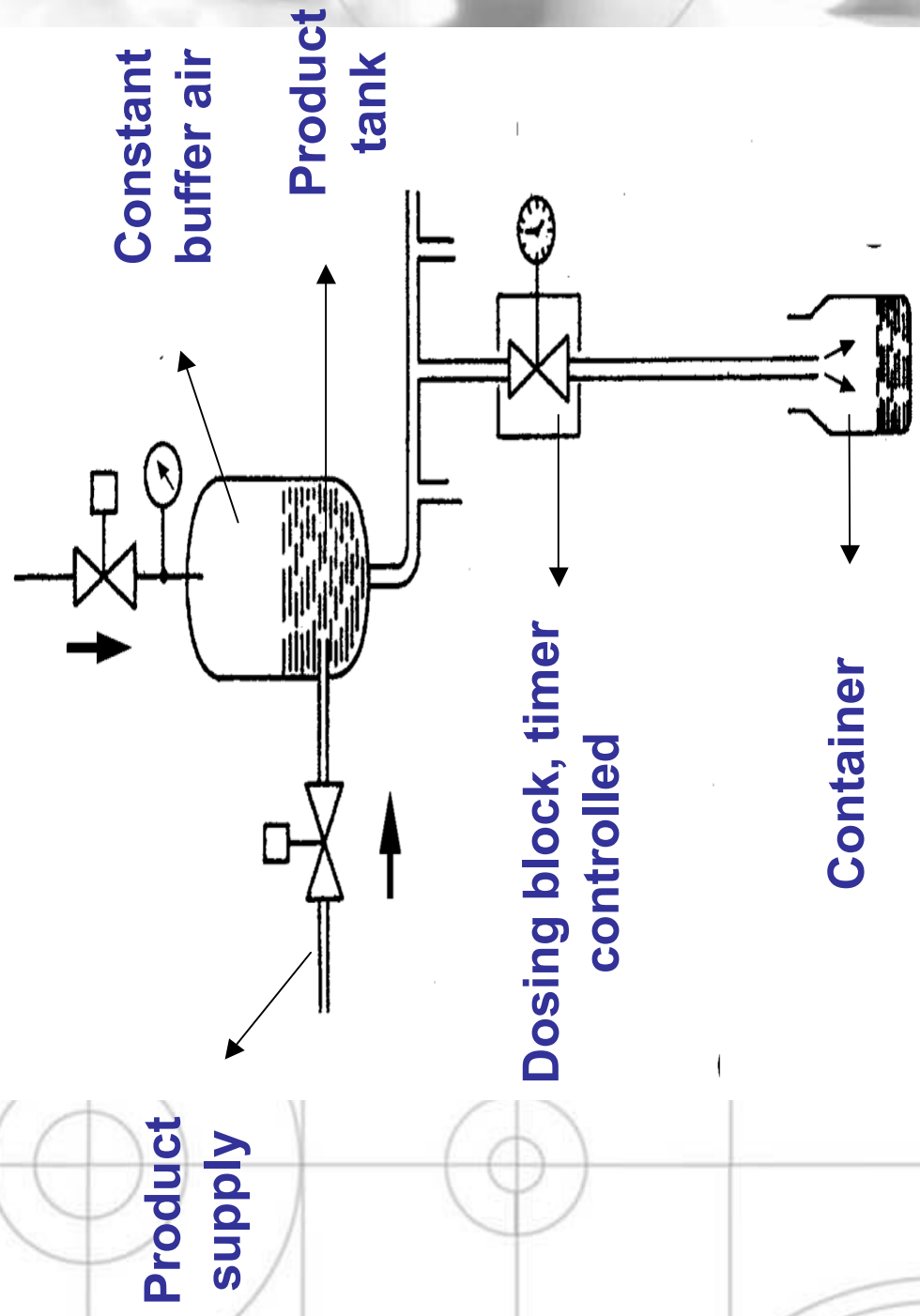


Aseptic Piping and Sterile filtration

- **Product Filters -
0.2 micron**
- **Parison Air Filter**
- **Sterile space Air
Filters**



Time Pressure Dosing



Product supply

Constant buffer air

Product tank

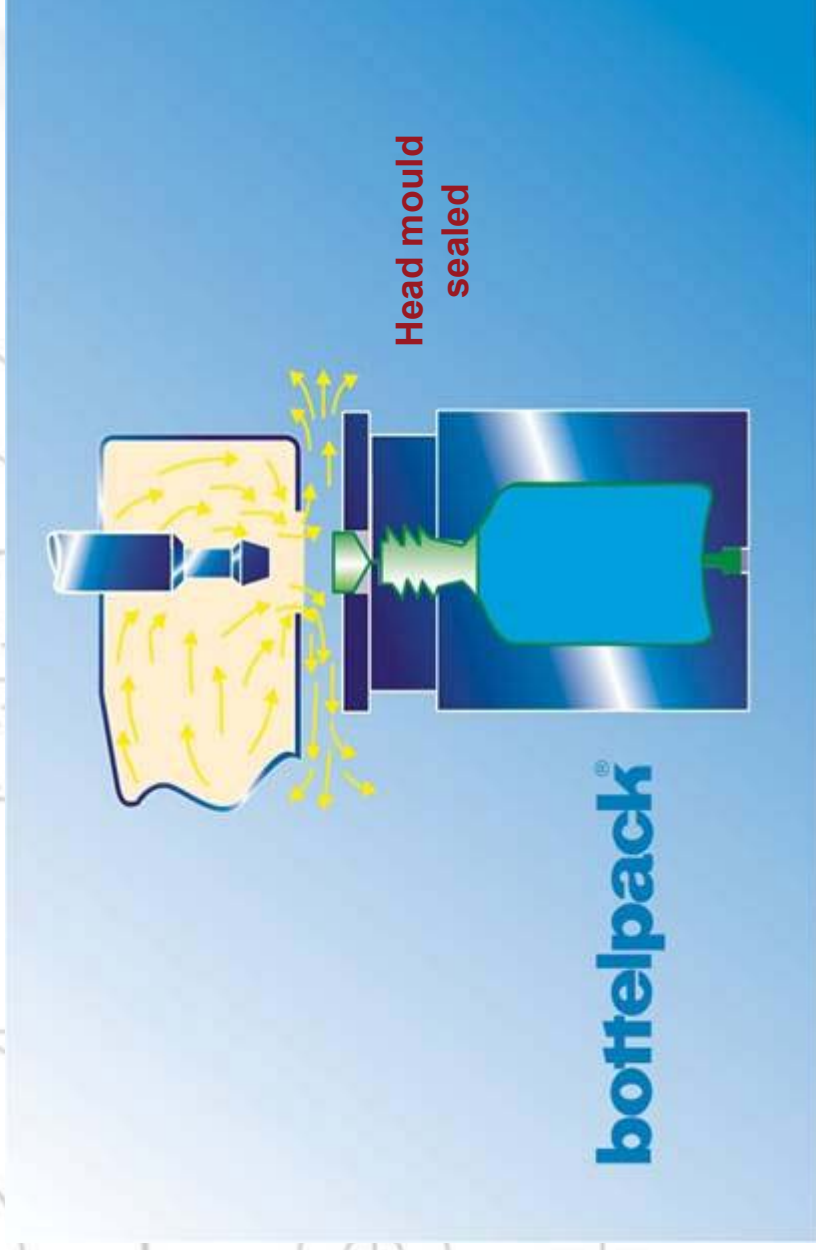
Dosing block, timer controlled

Container



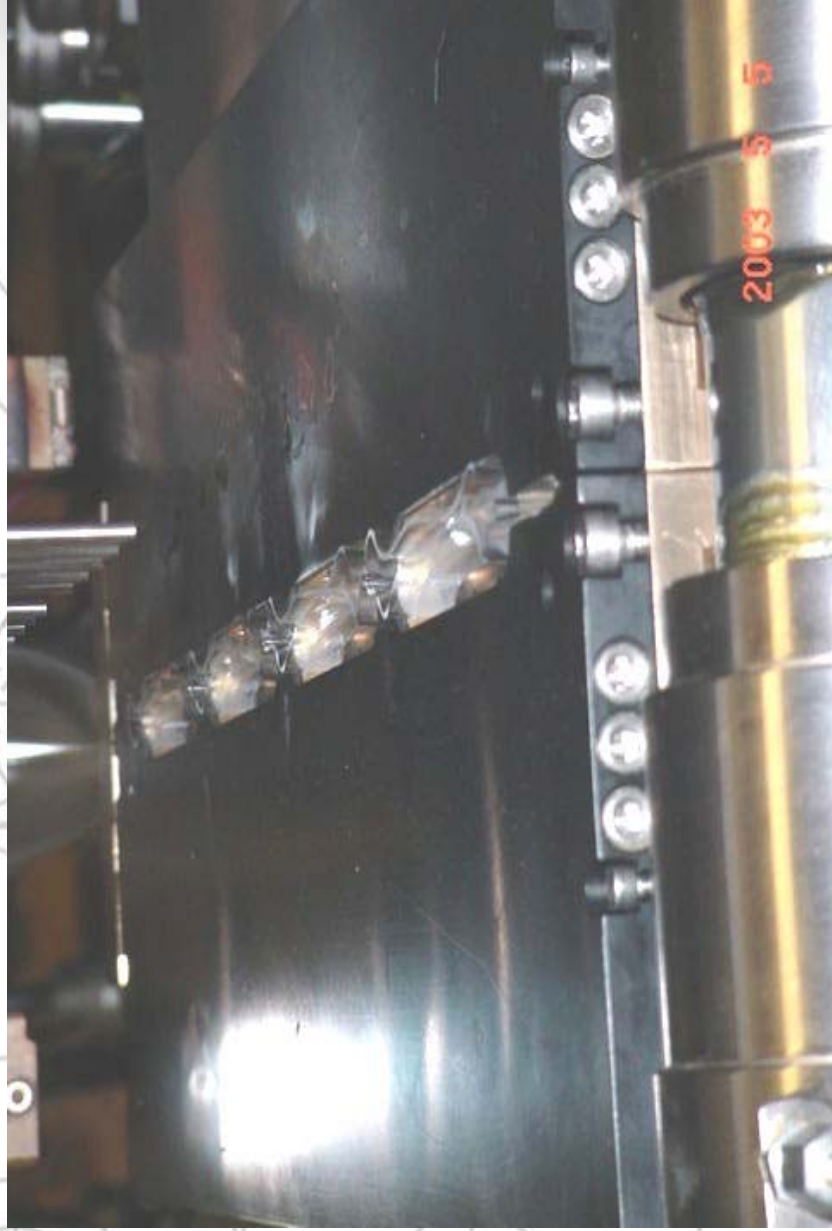
Process step 5

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



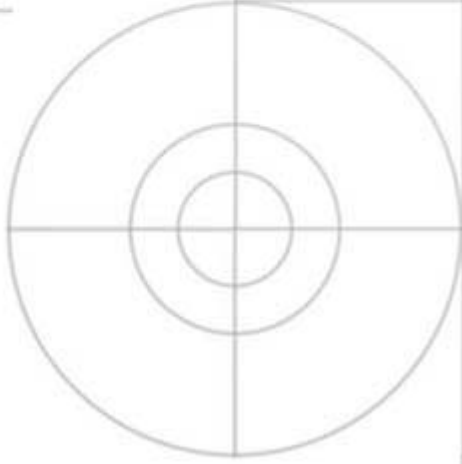
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Sealing



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Manufacturing



Overview

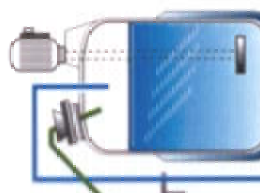


The **bottelpack**[®] is a complete and fully integrated system that extrudes and blow-moulds consumer- and environmental-friendly bottles or ampoules, fills them under aseptic conditions and seals them on one single compact machine.

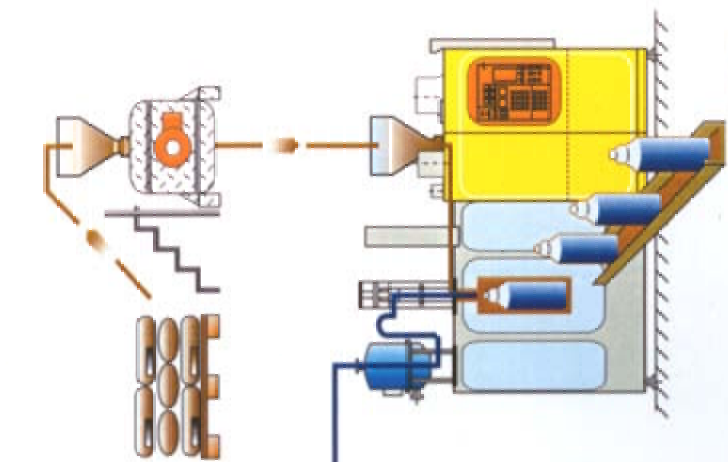
Material storage and control



Mixing tank



Storage and feeding of plastic granules



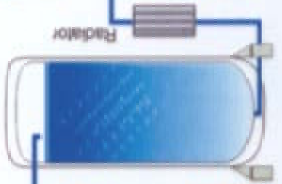
Demineralisation



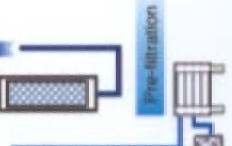
Boilification



Thermostatic water



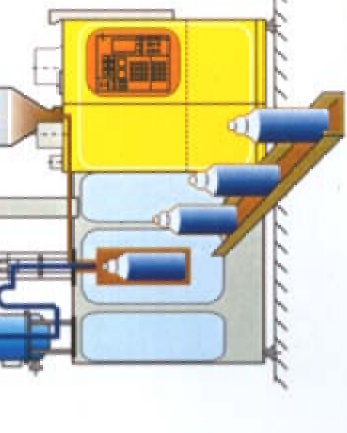
Fine-filtration



Pre-filtration



Control



bottelpack system flows, fills and seals in one operation

Water preparation

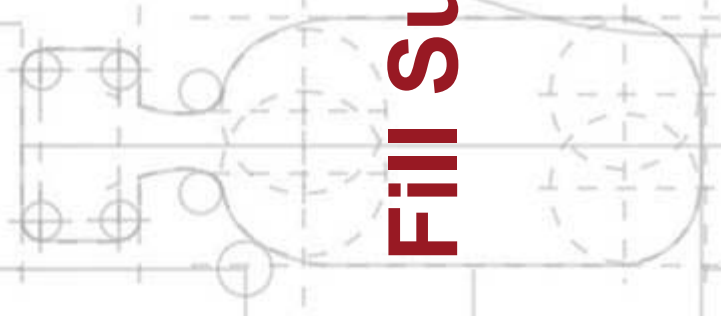
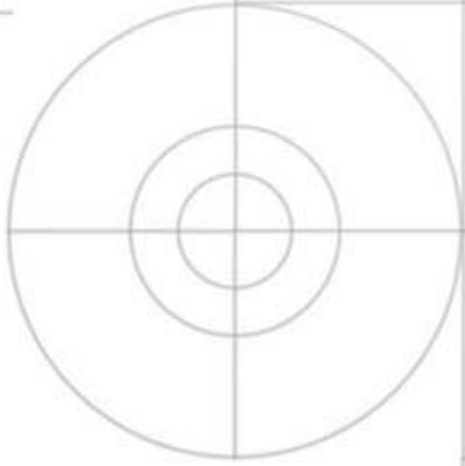
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Manufacturing Components

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

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Fill Suite



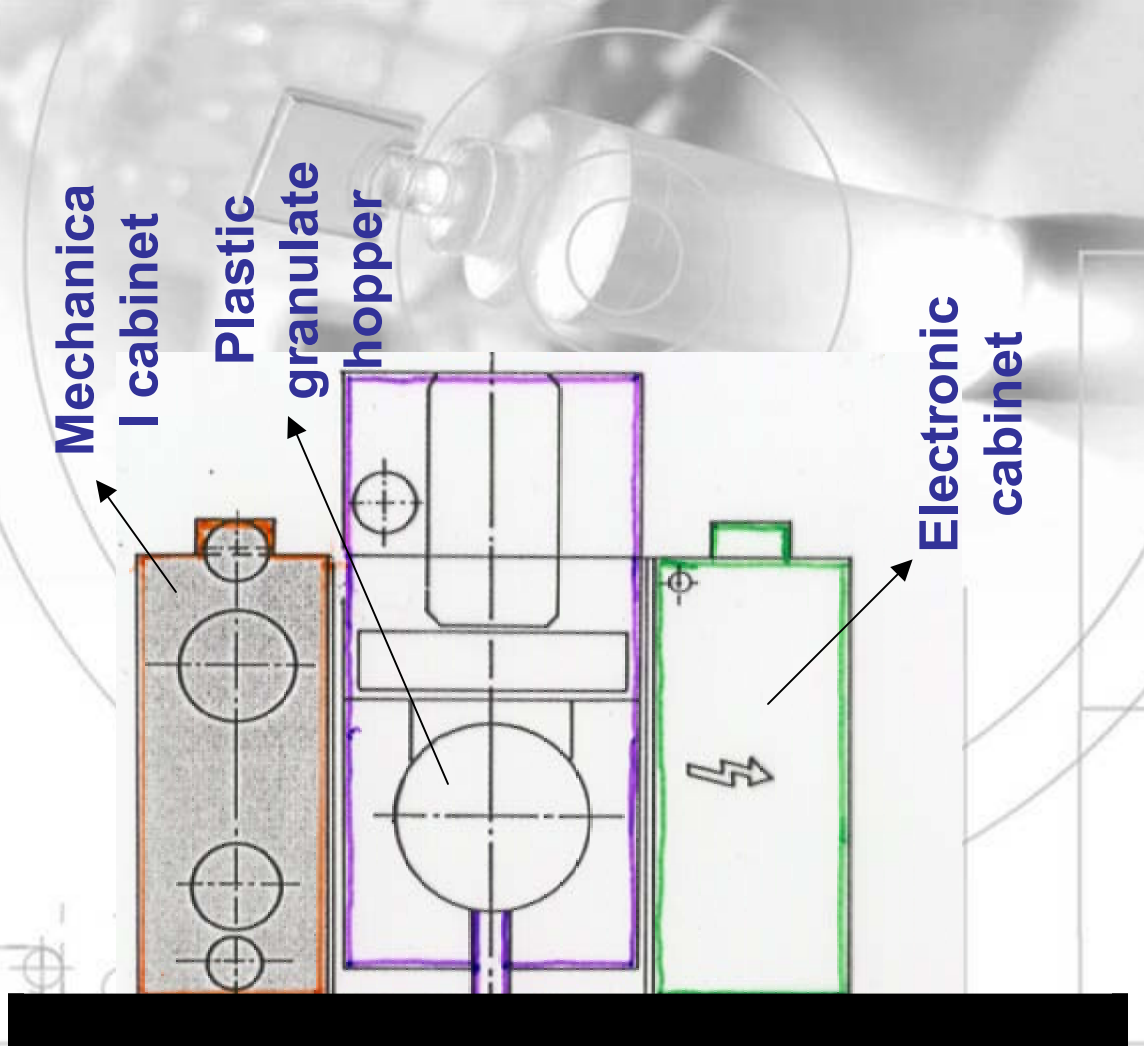
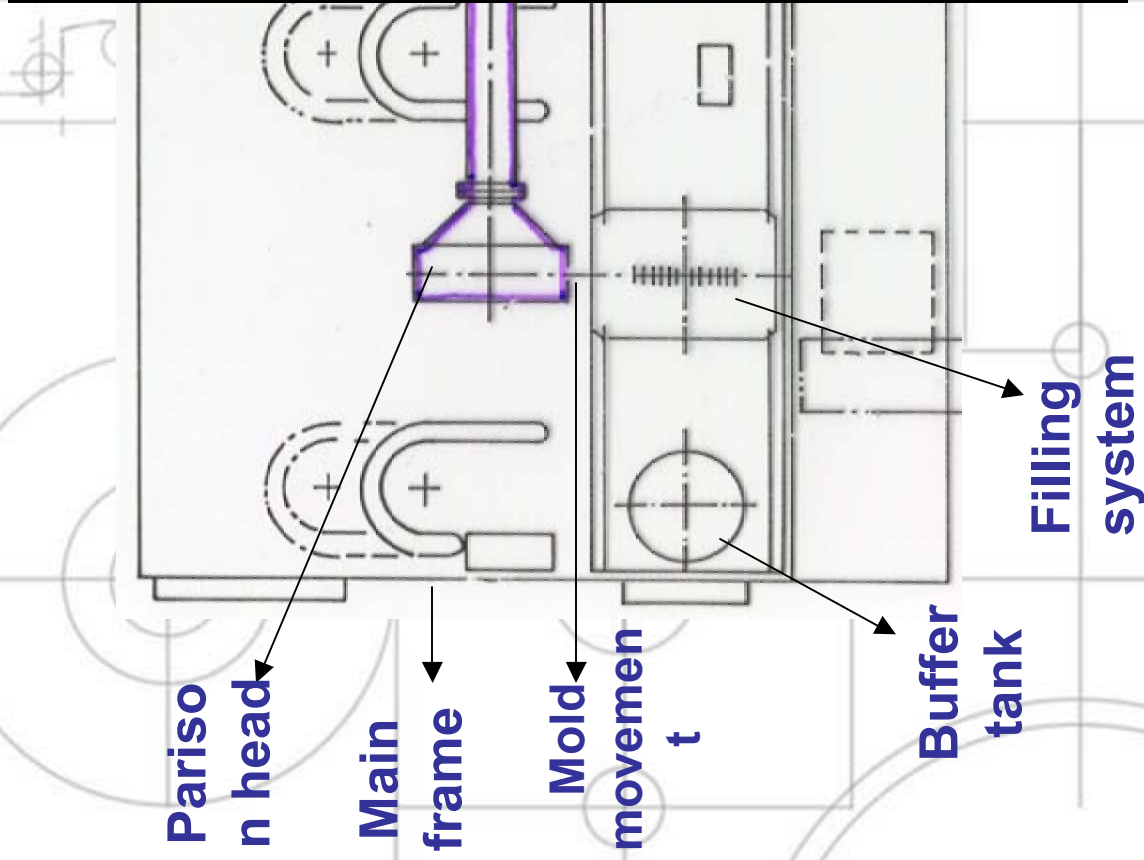
Fill Suite Environment

- Fill suites are designed to separate the BFS machine's aseptic part from its utilities



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Basic bottelpack® machine lay-out



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

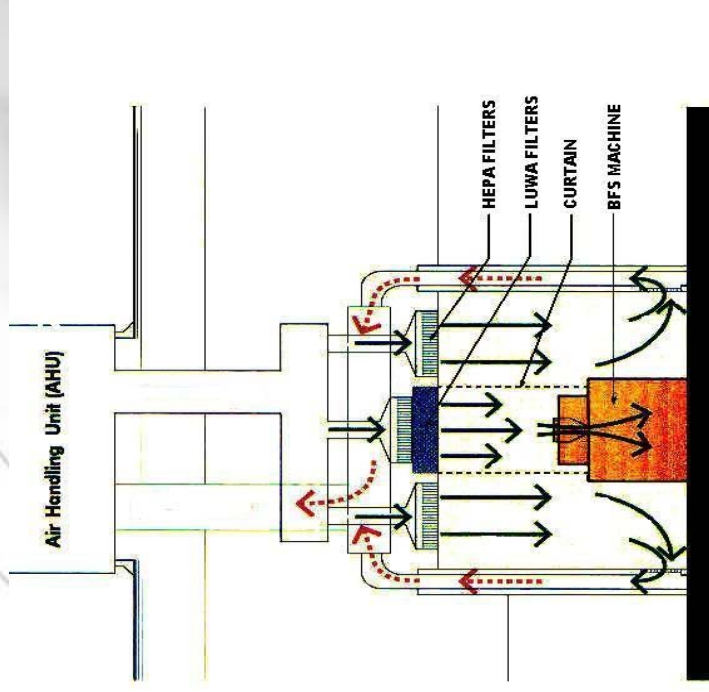
- Houses the parison extrusion, and sterile filling space under a sterile laminar air hood



LUWA Curtain

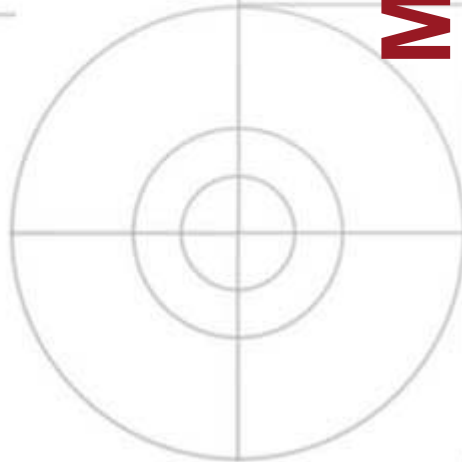
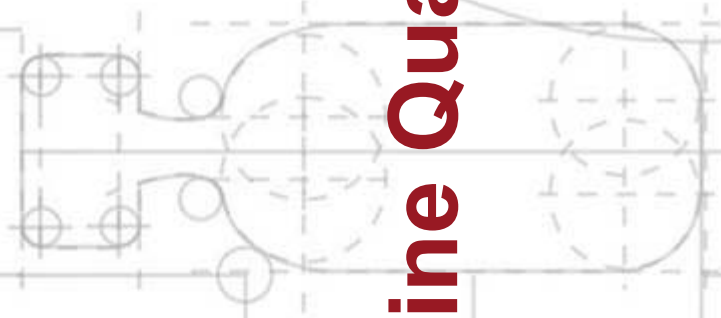
Sterile laminar air hood

- Room Class 100,000
- LUWA, Laminar Sterile Air Shower, Class 10,000
- Sterile Filling Space, Class 100



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Machine Qualification



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

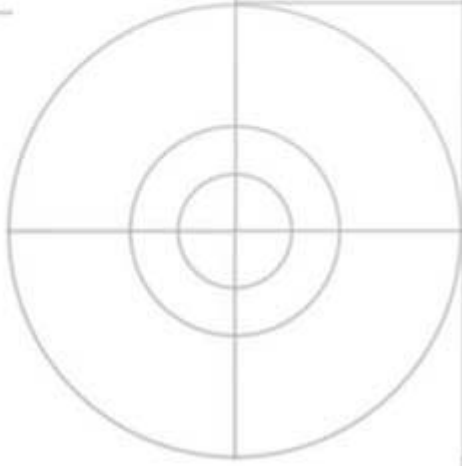
- 3 x Media fills

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

- 3 x CIP-Validation (Cleaning in Place)

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Bulk Solution



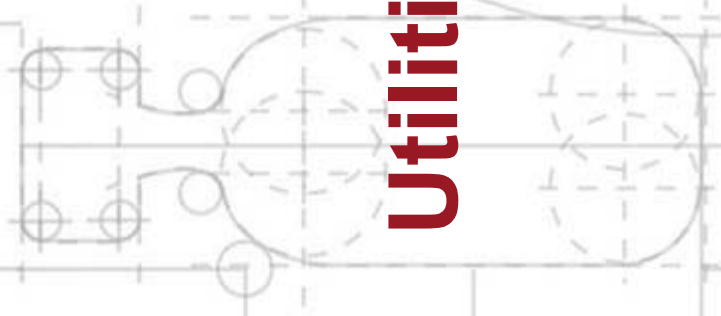
Bulk Solution

- 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



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Utilities

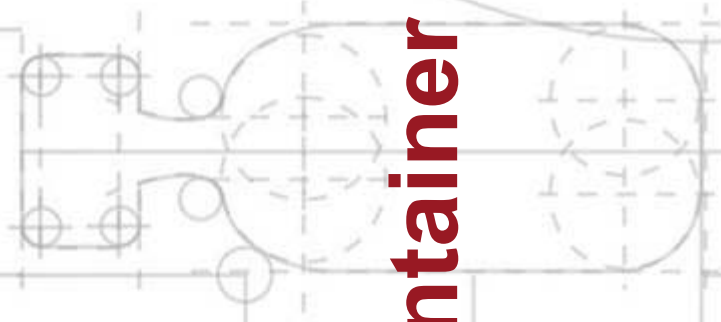
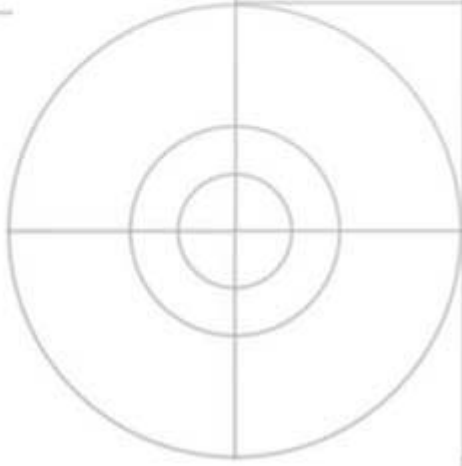


Stable supply and quality of utilities

- **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

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Container Design



Points to consider for container design:

- **Resin type for BFS**
- **Need for autoclaving**
- **Oxygen / Vapor permeation**
- **Light sensitivity**
- **Fill volume - dosage volume**
- **Closure designs**
- **Labeling Options**

Resin for BFS technology

	Low density polyethylene (LDPE) 0,915-0,93	High density polyethylene (HDPE) 0,94-0,95	Polypropylene (PP) 0,895-0,905
Density (g/cm ³)			
Melting index (g/10 min)	0,2-2	~2	~2
Clarity	good	poor	good
Gas permeation	medium	medium	medium
Vapor permeation	good	excellent	excellent
Drop resistance	excellent	good	satisfactory
Squeezability	excellent	satisfactory	poor
Regulatory conformity	EP III, Ed 1997 3.1.4 USP, class VI FDA, CFR 177-1520 (c) 2.2	EP III, Ed 1997 3.1.5 USP class VI	EP III, Ed 1997 3.1.6 USP, class VI FDA, CFR 177-1520 (c) 3.2
Application examples	eye drops inhalations ointments/cremes LVP/SVP	irrigation solutions oral solutions topical solutions	irrigation solutions LVP SVP eye drops

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

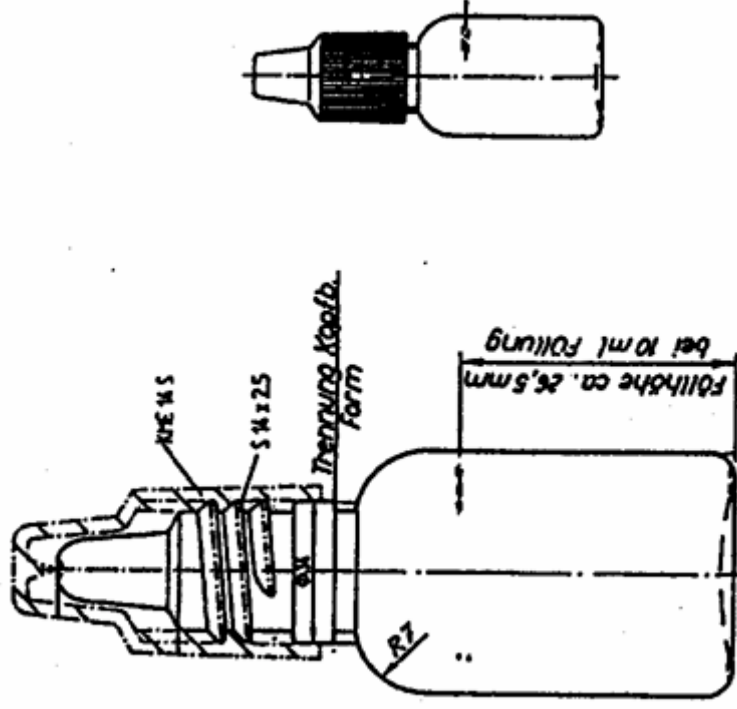
- PE, PP limited barrier properties for oxygen and CO₂
- Machine operation with nitrogen instead of sterile air
- Secondary packaging by pouching/over wrapping
 - supported by nitrogen
 - use of oxygen absorber

Light sensitivity

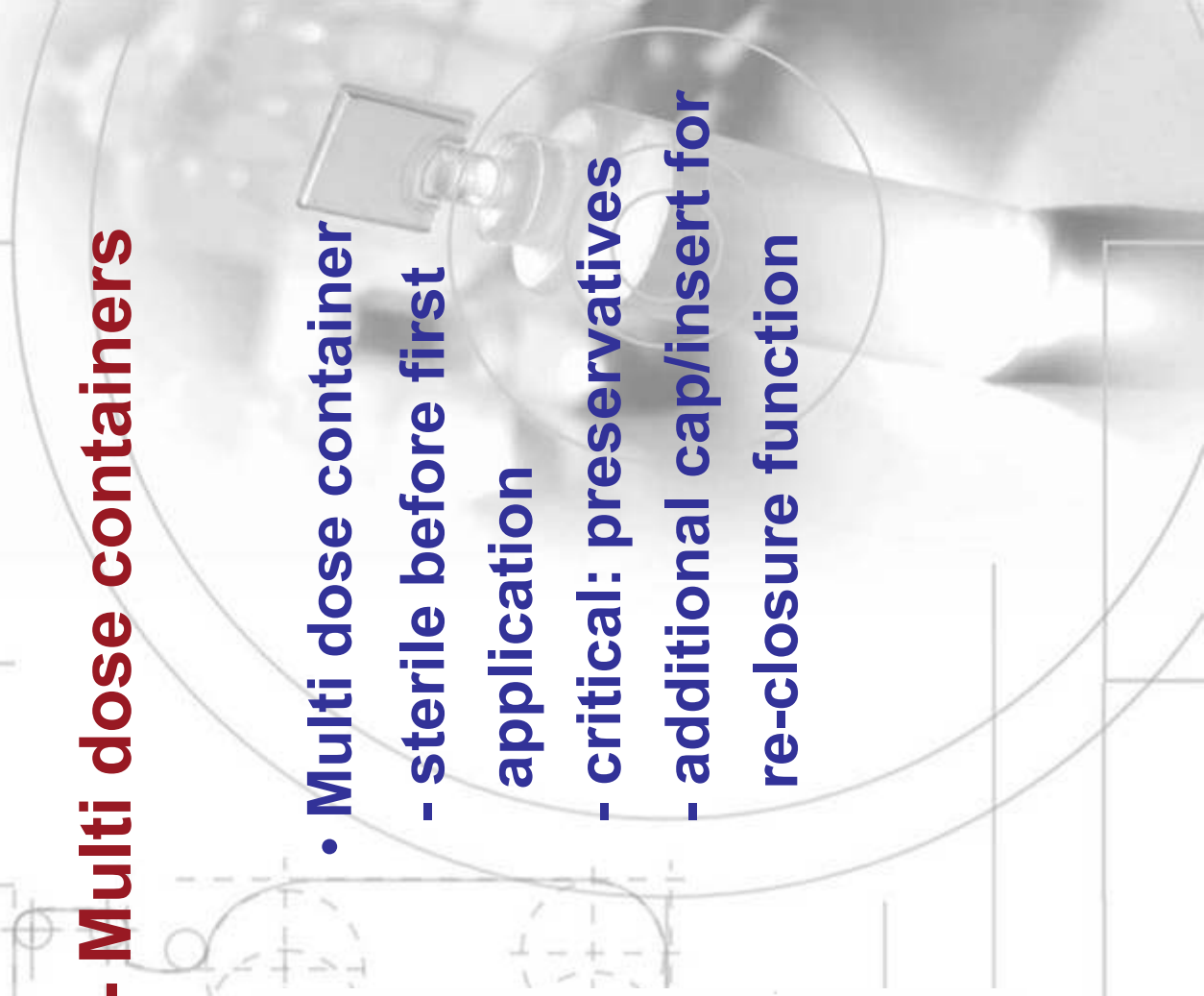
- **Secondary packaging into light-protective pouches/cartons**
- **Extrusion of colored parison**



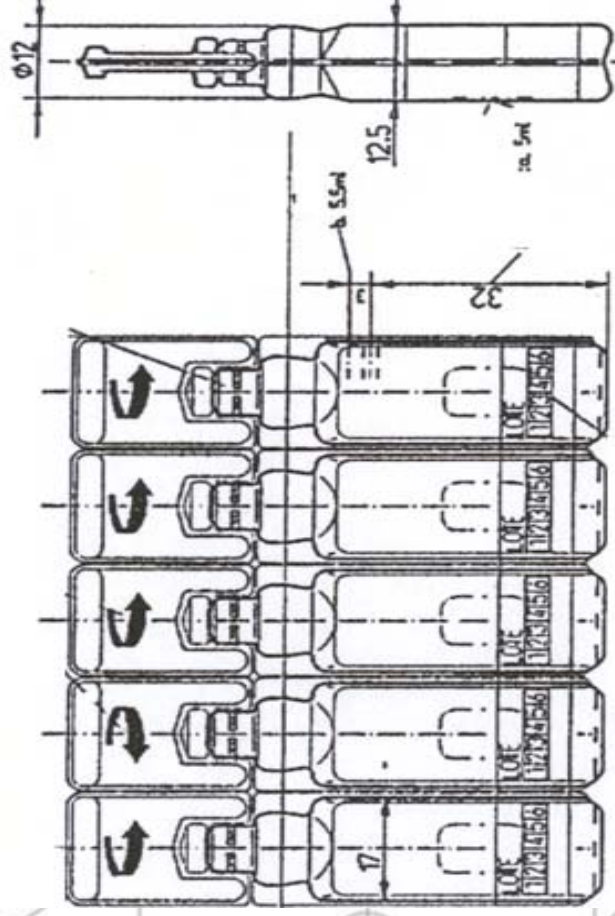
Fill volume - Multi dose containers



- Multi dose container
 - sterile before first application
 - critical: preservatives
 - additional cap/insert for re-closure function



Fill volume - Unit dose container



- Unit dose container
 - no preservatives
 - no capping part
 - defined dose volume
 - easy to apply

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Unit-dose packages for contact lens care



Unit-dose eye, ear & nose drops



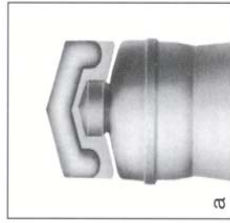
Ointments & creams

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Specialty Designs



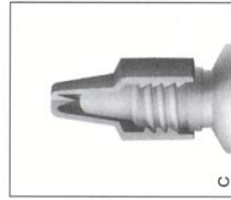
Closure Designs



a) Standard twist-off



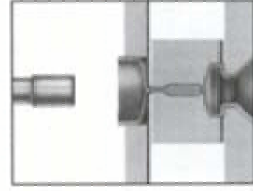
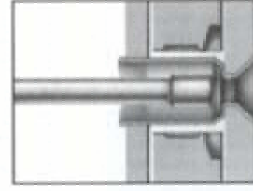
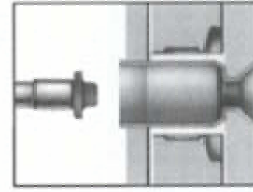
b) Thread for bigger caps/
wider opening



c) Thread for pin caps



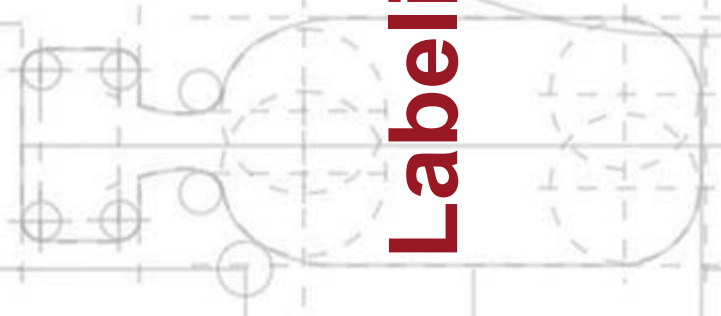
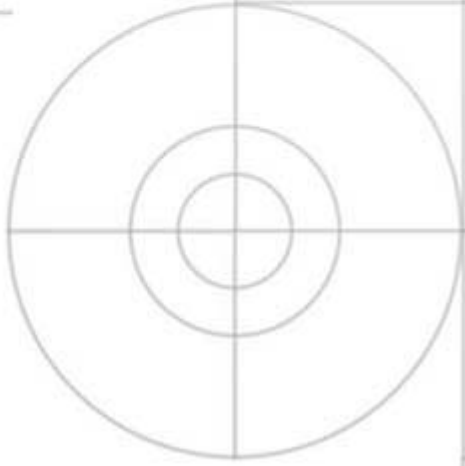
d) Membrane closure



Insertion of stoppers,
nozzles, etc.

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Labeling



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



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Embossed Labeling

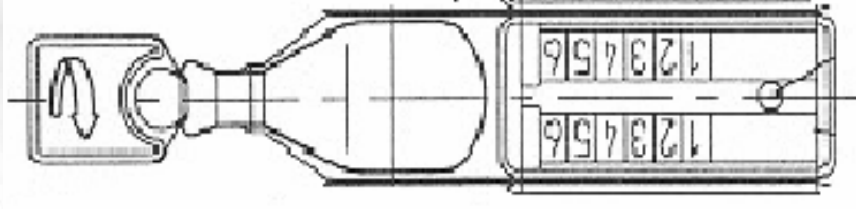


Embossing

Pros	Cons
No maintenance of label inventories	Difficult to read on clear containers
Ensures 100% labeling of containers	
Labels can not be removed	
Ensure each unit is traceable	
No leachables	

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**



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Paper Label on Tab

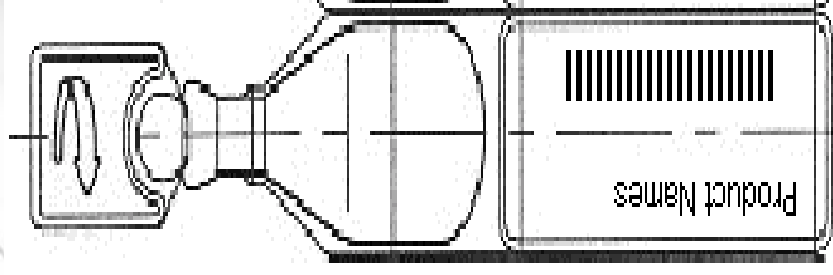


Paper label on Tab

Pros	Cons
Clearer to read	Potential leaching of label adhesive into solution
Greatly reduces potential leaching into the solution	

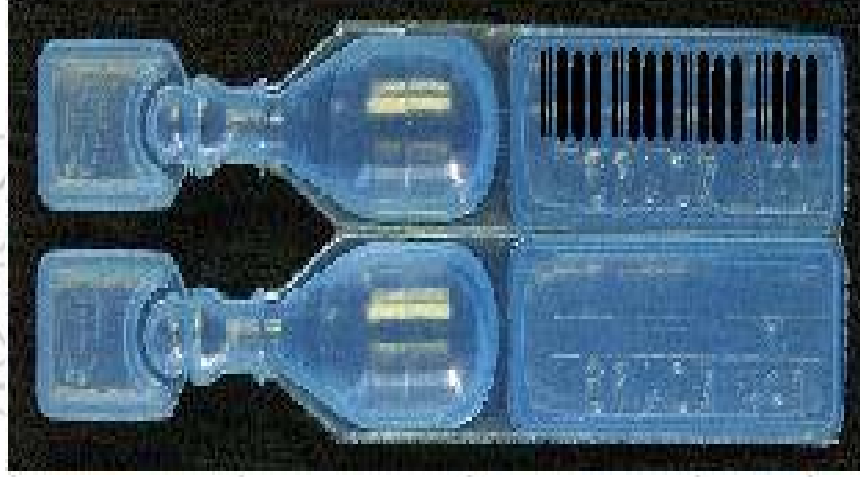
c) Direct Printing on Tabs

- Ink jet printing on tabs with barcodes, and product information



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Direct Printing on Tab



Direct printing on the Tab

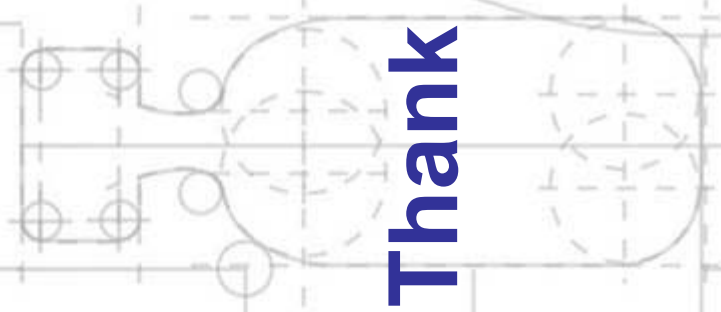
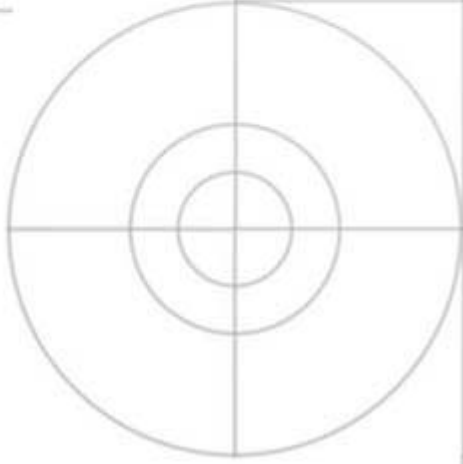
Pros	Cons
Clearer to read	Potential leaching into solution
Eliminates potential leaching from paper labels	
Greatly reduces potential leaching into the solution	
Allows for barcode printing on line	

d) Conventional Labeling



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Thank You



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

**Mohammad Sadeghi
V.P. R&D**

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