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All about Pre-filled Syringe Systems Training Course


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May 31st - June 1st, 2022 Basel


 


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Fill and Finish - Introduction -



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Important norms: ISO 11040-4/-7

DEUTSCHE NORM Juli 2017

	DIN ISO 11040-4	DIN	
ICS 11.040.25	Ersatz für DIN ISO 11040-4:2007-10		First edition 2015-04-01

**Vorgefüllte Spritzen –
Teil 4: Spritzenzylinder aus Glas für Injektionspräparate und sterilisierte
und vormontierte Spritzen zur Abfüllung (ISO 11040-4:2015)**

Prefilled syringes –
Part 4: Glass barrels for injectables and sterilized subassembled syringes ready for filling
(ISO 11040-4:2015)

Seringues préremplies –
Partie 4: Cylindres en verre pour produits injectables et seringues pré-assemblées stérilisées
préremplissables (ISO 11040-4:2015)


**INTERNATIONAL
STANDARD ISO
11040-7**

**Prefilled syringes –
Part 7:
Packaging systems for sterilized
subassembled syringes ready for filling**

Seringues préremplies –
Partie 7: Systèmes d'emballage pour les seringues stérilisées prêtes à
l'emploi préremplissables


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PDA Technical Report




Technical Report No. 73

Prefilled Syringe User Requirements for Biotechnology Applications

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Bulk Processing – some remarks

Challenges:

- Syringes not stable for transport
- Siliconization has to be adapted to each format
- Not flexible for new components (tip cap, LLA)
- Syringes with needle cannot be processed in the tunnel
- Can be done with autoclaves → high effort, batchwise process

Advantages:

- Proven sterilization process
- Proven transfer to the filling area
- Cheaper packaging material
- Full control of the manufacturing / siliconization process

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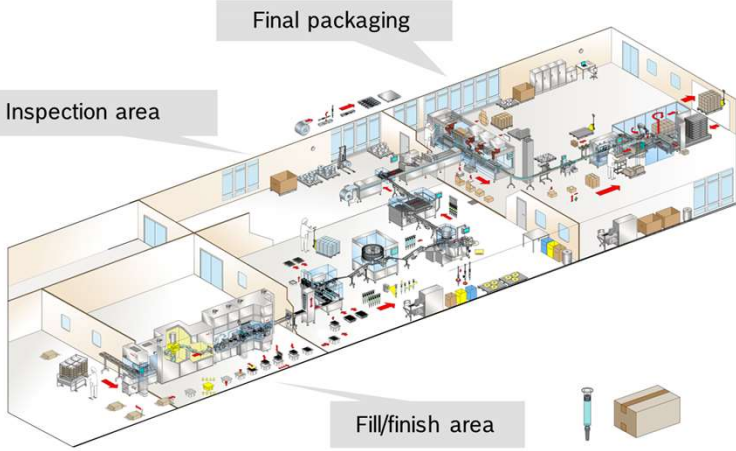
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Nested syringe processing



Final packaging

Inspection area

Fill/finish area


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










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Tub introduction into a RABS/Cleanroom


E/D	C	C	A		
					
					

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
















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Tub introduction into an Isolator


E/D	D/C		A		
					
					
					

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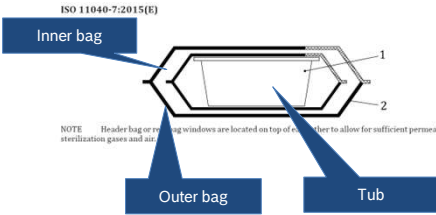
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Trend for (high speed) fill/finish lines

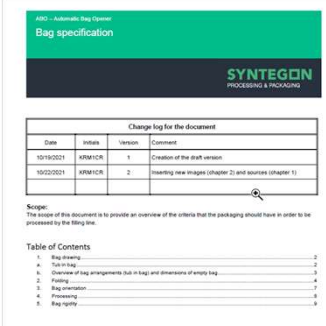
(Fully automatic) No touch-transfer (NTT) with double bags in order to avoid e-beam

ISO 11040-7:2015(E)



NOTE Header bag or resealing windows are located on top of inner bag to allow for sufficient permeability for sterilization gases and air.

Picture ISO 11040-7




Change log for the document


Date	Initials	Version	Comment
10/18/2021	MFR/ICR	1	Creation of the draft version
10/22/2021	MFR/ICR	2	Inserting new images (chapter 2) and sources (chapter 1)

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Line Layout – high speed line


Capacity:

1ml → 36.000 pc/h (w/o IPC)
1ml → 30.000 pc/h (1% IPC)

Not for distribution, requests for handout can be discussed individually



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Fill and Finish

Automatic Bag Opening



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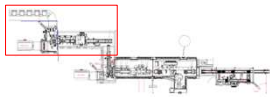
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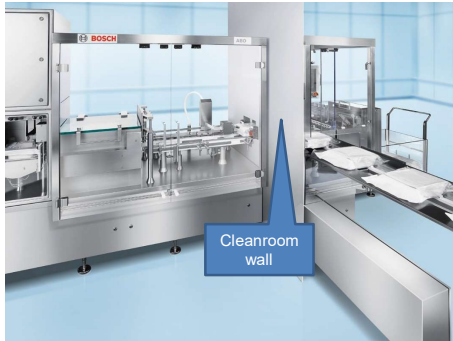
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Double bag opening



View from ABO Double Bag



Cleanroom wall

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Double bag opening



Arrangement / preparation for cutting the inner bag (patented system)



Vacuum chamber (patented system)

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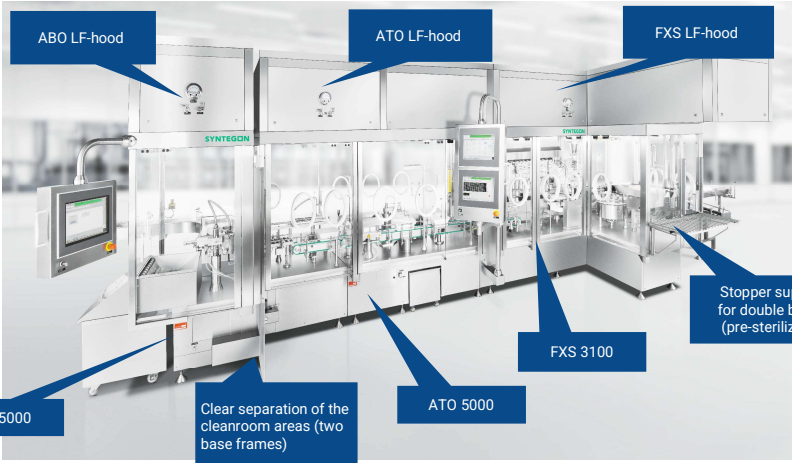
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Filling line in RABS with Automatic Bag and Tub Opening



ABO LF-hood

ATO LF-hood

FXS LF-hood

ABO 5000

Clear separation of the cleanroom areas (two base frames)

ATO 5000

FXS 3100

Stopper supply for double bags (pre-sterilized)

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Filling line under isolator with Automatic Bag and Tub Opening



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Automatic Bag Opening in detail

Requirements

- Up to 6 tubs/bags per minute
- Clear separation of clean room areas
- Protection of the tub (by the bag) as long as possible
- Safe separation of tub and bag
- No contact bag outside – tub outside
- Minimizing the risk of particles
- Only one piece of waste



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Automatic Bag Opening



Clear separation of the cleanroom areas (two base frames)



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Automatic Bag Opening – Basic Configuration



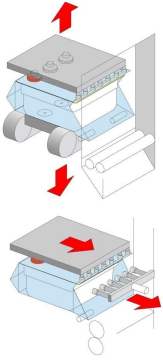
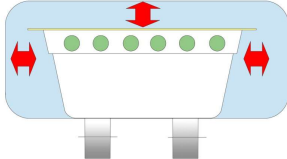
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Aseptic Tub Transfer – a Bundle of Measures

No contact bag outside – tub outside, especially at the top of the tub.

Protection of the tub (by the bag) as long as possible. Removal just before the transfer.




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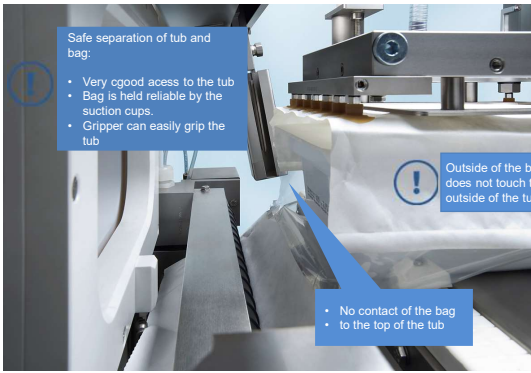
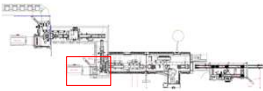
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Automatic Bag Opening


Line video




NTT video



NTT animation





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Fill and Finish

Automatic Tub Opening



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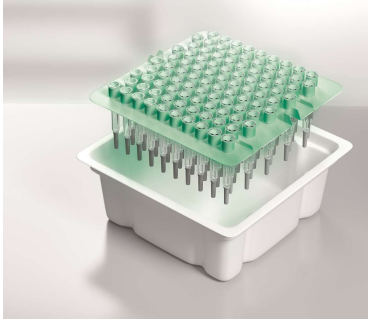
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Tub Opening

Requirements

- Up to 6 tubs/min
- Minimum particle generation
- Reliable gripping of the cover sheet
- Absolute reliable functionality



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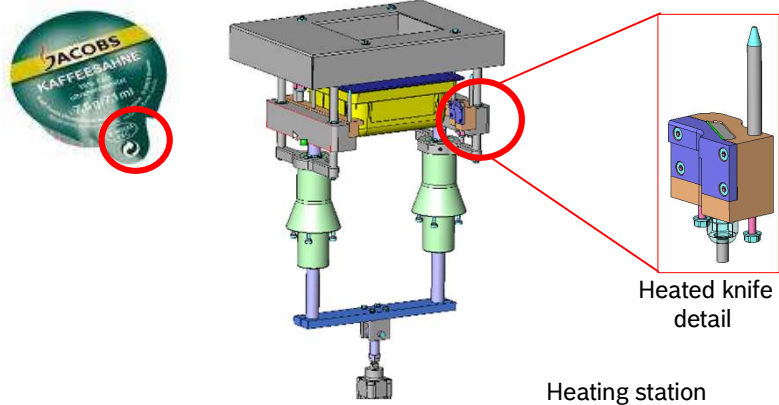
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Coffee Cream Concept – pre-Determined Breaking Line



The diagram shows a green coffee cream container with a yellow label that says 'JACOBS KAFFEEAHNE'. A red circle highlights a small circular feature on the bottom of the container. To the right, a 3D cutaway view of a mechanical assembly is shown, with a red circle highlighting a specific component. A red-bordered inset provides a detailed view of this component, labeled 'Heated knife - detail'. Below the main assembly is the label 'Heating station'.

Heating station

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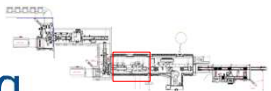
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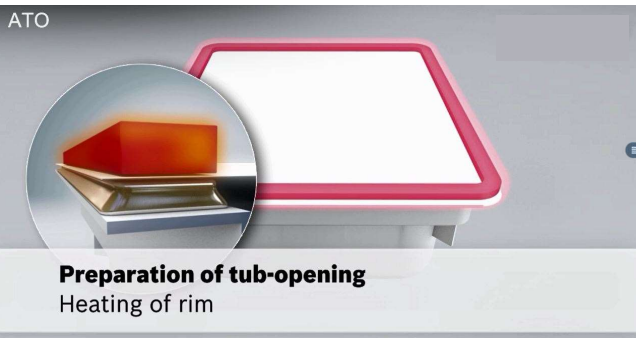
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Automatic Tub Opening – Pre-heating



Pre-heating of the tub rim. Temperatures adjustable at HMI for different qualities of packaging material (range from approx. 80°C to 120°C, typically around 100°C →

- Less particles
- Facilitates the opening process




Preparation of tub opening
Heating of rim

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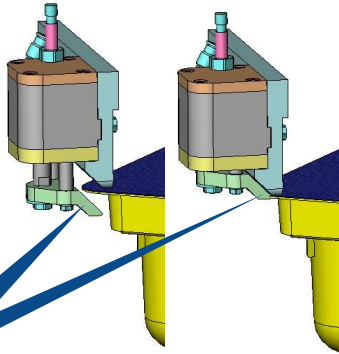
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Tub Opening – Detail

Coffee cream concept allows very safe gripping of the lid

gripper open
gripper closed




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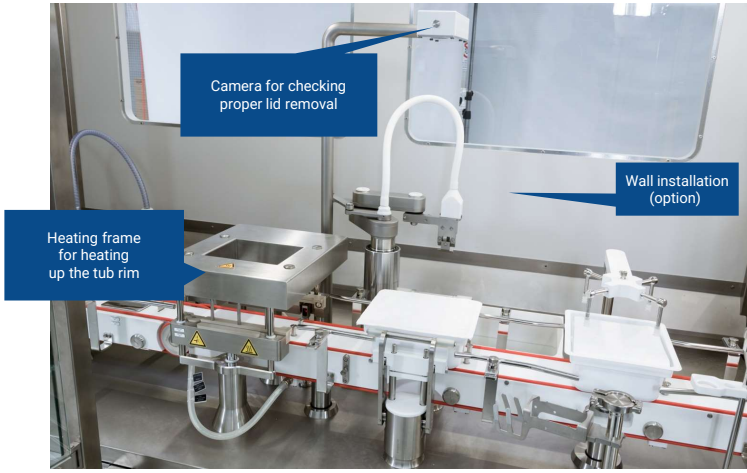
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Automatic Tub Opening



Camera for checking proper lid removal

Heating frame for heating up the tub rim

Wall installation (option)



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Fill and Finish

Filling




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Fill/finish - Requirements

Syringe specific requirements:

- Up to 600 syringes / min ¹⁾
- Precise transport system
- No contact of the insertion tube with the syringe
- Suitable for all available filling systems
- Stoppering immediately after filling
- Transport of the tub



¹⁾ 16head up to 57.600/h


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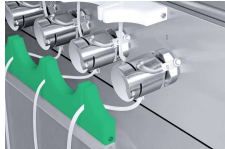


Overview of Filling Systems


- Rotary valve piston pumps
- Peristaltic pumps
- Time pressure filling system
- Mass flow filling system
- Rolling diaphragm pumps
- Combi filling station



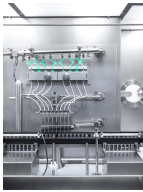
Rolling Diaphragm Pumps




Peristaltic Pumps



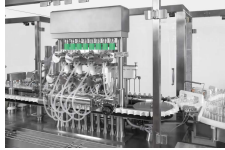
Piston Pumps




Time Pressure




Mass Flow



Combi Filling Station




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Filling System Comparison

		PRODUCT PROPERTIES							
		Similar to water	High viscosity	Protein / Biotech	Sus-pension	Warm / Cold filling	Crystallizing / Sugar containing	Minimum product loss	Repro-ducibility / Speed
FILLING SYSTEM	Piston Pump	++	++	0	0	0	0	0	++
	Peristaltic Pump	++	0	++	+	0	+	+	+
	Time Pressure	++	-	+(+)	++	0	++	++	+
	Mass Flow Metering	++	0	+	0	++	+	0	+
	Rolling Diaphragm Pump	++	0	+	0	0	+	0	+

- not possible / not reasonable
 0 possible with restrictions
 + possible solution
 ++ preferred solution



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Peristaltic Pumps Filling System

- Pump tubing (two parallel hoses) is compressed for product flow
- Pump tubing is a closed system from product supply up to the filling needle
- Accuracy is maintained between range of 0.5% to 1.5% of nominal fill volume, depending on tubing size and speed
- Two sizes available (up to 30ml, up to 500ml)
- Preferred solutions for single use applications



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Peristaltic Pumps Filling System

Benefits	Points to consider
<ul style="list-style-type: none"> • First choice for shear sensitive products (protein) • First choice for single-use-filling systems • Easy handling (one hand operation) • Tubing is the only size part • Closed system 	<ul style="list-style-type: none"> • Viscous products

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Peristaltic Pump with single-use filling system in a combi filling station



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Peristaltic Pump on syringe filler



Individual stopper
presence check
with sensors
to check rod position


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Rotary Valve Piston Pump Filling System

- Pumps available in either Stainless Steel or Ceramic
- Ceramic pumps fit in same pump stations as Stainless Steel



- Made of Al2O3 (99.7%) or ZrO2
- High wear resistance
- Chemical resistance in acid and alkaline range



- Made of 316 L stainless steel
- Parts are manufactured from one piece, no welded seams
- Electropolished


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Rotary Valve Piston Pump Filling System

Benefits	Points to consider
<ul style="list-style-type: none"> • Accurate, repeatable fill volumes, also at high speed • Most popular pump type, very well known • No seals • Simple assembly • Easy to clean and sterilize 	<ul style="list-style-type: none"> • Crystallising products • Longer CIP/SIP cycle time than TPF (more steel) • Not applicable for high temperature filling >35°C

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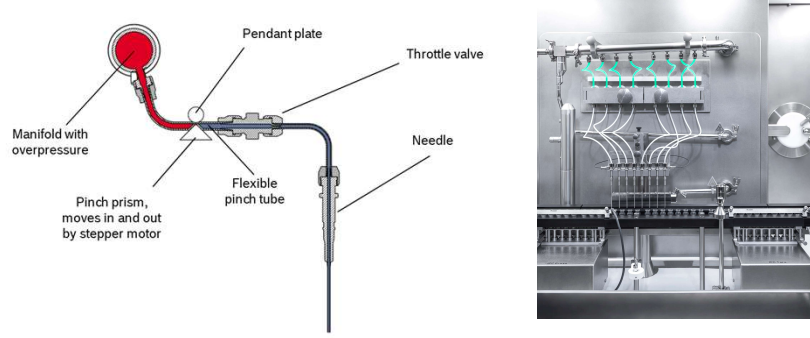
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Time Pressure Filling System

Product path from manifold to container



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Time Pressure Filling System

Benefits	Points to consider
<ul style="list-style-type: none"> Easy size changeover Very simple mechanical set-up Easy cleaning Closed system No problems with crystallising products CIP/SIP handling, faster cycle 	<ul style="list-style-type: none"> Accuracy if product viscosity is highly dependent on temperature Oily products Control system needs educated staff

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Combi Filling Station



Rotary valve piston pump Peristaltic pump Rolling diaphragm pump Time-pressure-filling

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In Process Checkweigh under Isolator – Detail



Weighing cells

Gripper for syringes

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Filling Laboratory – Content of typical test protocol

- Customer name
- Product name
- Filling Volume
- Filling size parts (needle, tubing, ...)
- Output
- Design of filling system and product header
- Parameters of filling system (e.g. speed of peristaltic pump, acceleration)
- Parameters of filling needle movement



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Fill and Finish

Stopper Insertion Principles



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Reasons for different stopper setting methods

- Coated stoppers, sensitive to compression
- Residual oxygen when filling oxygen sensitive products
- Residual air bubble when using autoinjectors or pen systems
- Viscous filling products
- Sensitive polymer syringes



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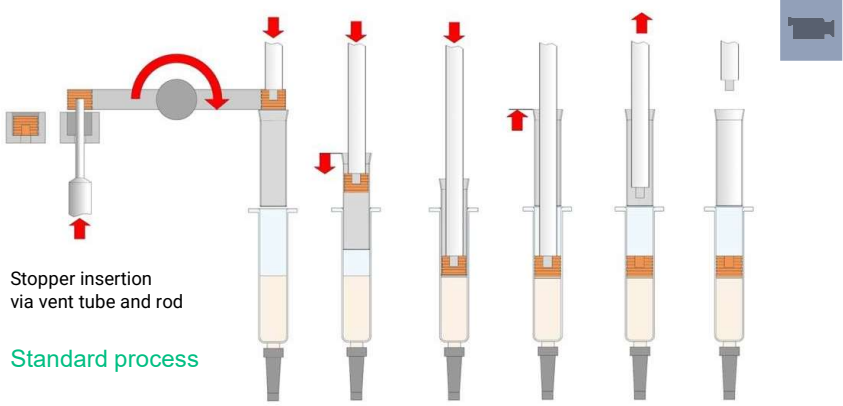
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Stopper insertion principles



Stopper insertion via vent tube and rod

Standard process

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Stopper insertion principles

Stopper insertion via vent tube and rod + gassing

For reducing residual oxygen

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Slides for hands on Training


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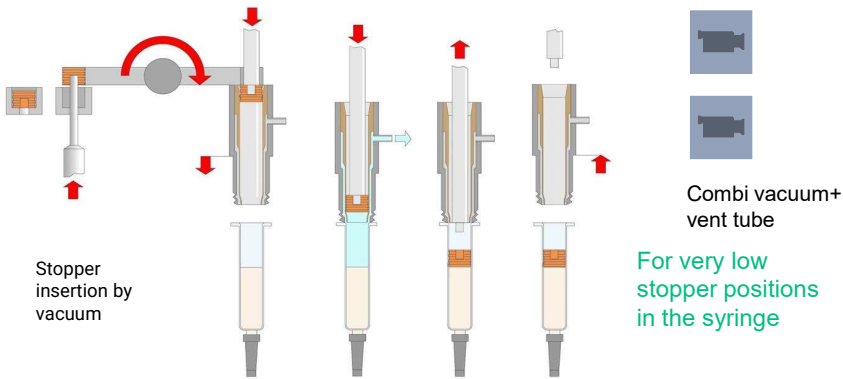
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Stopper insertion principles



Combi vacuum+ vent tube

For very low stopper positions in the syringe


For coated stoppers and/or to reduce air bubble

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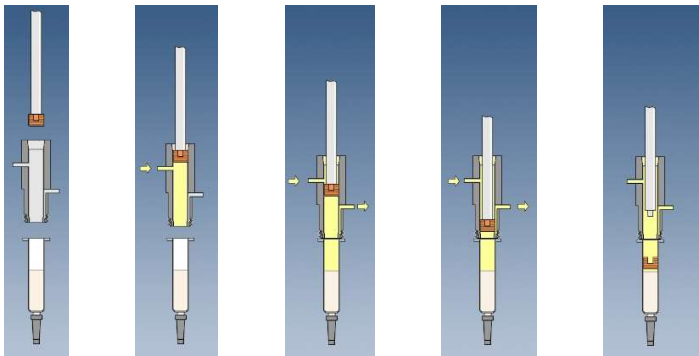
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Stopper insertion principles

To minimize air bubble and the residual oxygen



Stopper insertion by vacuum + gassing

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Stopper insertion principles

Stopper insertion by vacuum + fractional gassing

For lowest residual oxygen values

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Stoppering station

Short tracks and no additional vibration lanes

Optimized size of Sorting bowl - Diameter 400 mm

Sorting bowl in front of the machine – operator side

LAF friendly and clear design

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Basic Configuration Stopper Supply



Detection of stopper presence perrow (not individual):
When one or more stopper(s) is (are) not present in vent tube
→ rod is not lifted
→ sensor is blocked

Stopper re-supply, made of stainless steel


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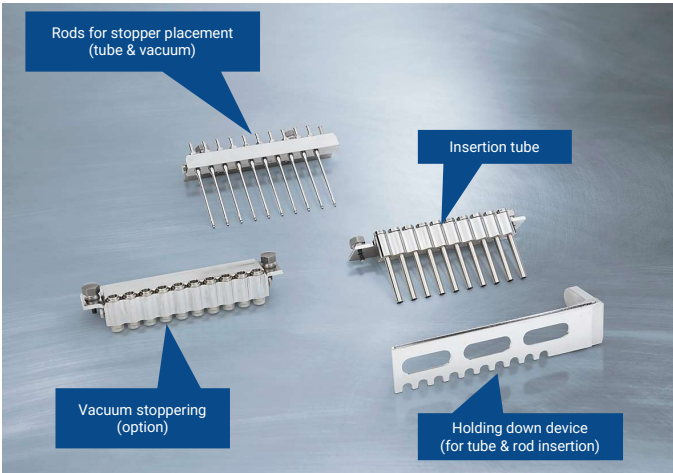
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Size Parts Stopper Placement



Rods for stopper placement (tube & vacuum)

Insertion tube

Vacuum stoppering (option)

Holding down device (for tube & rod insertion)

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Fill and Finish



Special topic: Vacuum filling

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Vacuum filling / stoppering

Animation  Video 



Pump station, reinforced for vacuum filling

Rods for stoppering

Filling needles


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Vacuum filling / stoppering



- Teflon hoses for filling hyaluron acid
- Suction cups (silicone) for sealing the syringes, combined for filling and stoppering
- Transport carriers


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Vacuum filling / stoppering



- Vacuum for product supply from onsite tank
Vacuum for degassing of product
Pressure for product supply towards filling pumps / filling station
- Special Intermediate tank for product supply for minimizing air bubbles
- All outlets at the bottom for minimizing air bubbles
- Product supply from below for minimizing air bubbles
- Level control intermediate tank by gravity
→ more safety, more reliable
- Filter units for:
 - ▶ vacuum filling
 - ▶ vacuum stoppering
 - ▶ intermediate tank

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Manufacturing Aspects

Regarding Filling, Finishing and Assembly

RABS/Isolator/Stopper Supply/End of filling line

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RABS Stopper Supply Including Sliding Pane



Stopper loading from operation side

Easy logistics / no crossing of the line

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Nested Syringe Filling Machine with Isolator



Stopper supply with exchangeable Port

Wash down air ducts

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Isolator Stopper Supply



Exchangeable port for stopper supply

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Exchangeable Port for Stopper Supply

Port Getinge



Outside view



Inside view

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Exchangeable Port for Stopper Supply

Port from Sartorius stedim for BD TSCF stoppers (former IDC)



Outside view



Inside view


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Topics for Mock-Up (Selection)



- Positioning and number of gloves
- Media connections
- Stopper supply
- Position of particle and microbiological monitoring
- Handling inside the barrier system: Start up of line, line clearance and trouble shooting

Conclusion: After the mock-up major adaptations of the machine design can be necessary for optimized barrier system use.


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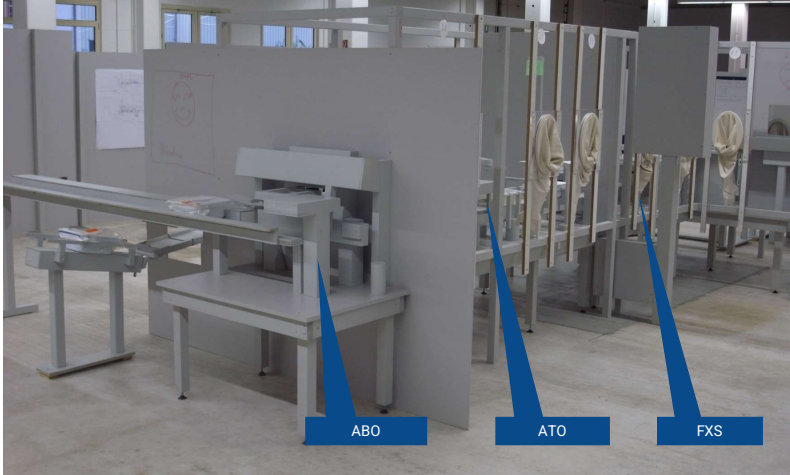
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Mock Up for Isolator & RABS



ABO ATO FXS

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Tub Reject

Nest Matrix showing good/bad syringes

Seperate discharge conveyer with pneumatically operated turn switch

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Manufacturing Aspects

Regarding Filling, Finishing and Assembly

Combi Filling – Robotic Filling

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New Trends – Packaging Material – Pre-Sterilized (Selection)

Tub & nest approach (syringes, vials and cartridges)



Packaging material pictures by Gerresheimer

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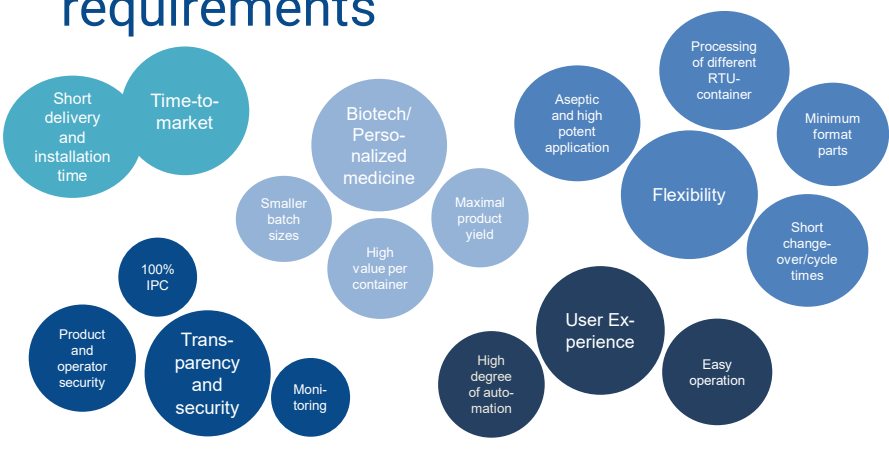
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Market trends and requirements



- Short delivery and installation time
- Time-to-market
- Biotech/ Personalized medicine
- Smaller batch sizes
- High value per container
- Maximal product yield
- Aseptic and high potent application
- Processing of different RTU-container
- Minimum format parts
- Flexibility
- Short change-over/cycle times
- 100% IPC
- Product and operator security
- Transparency and security
- Monitoring
- High degree of automation
- User Experience
- Easy operation

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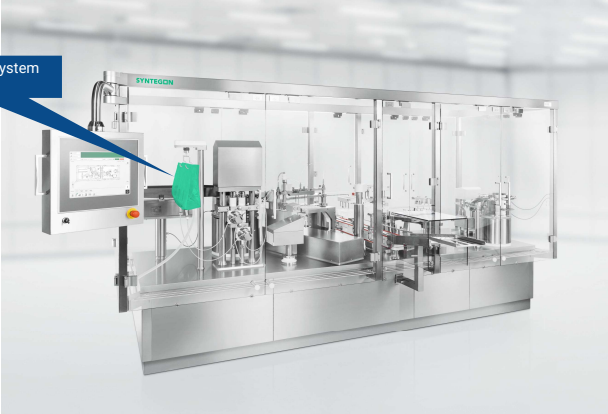
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Combi nest filler for syringes, vials, cartridges

Single use filling system
PreVAS



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Combi Nest filler Line

Not for distribution, requests for handout can be discussed individually

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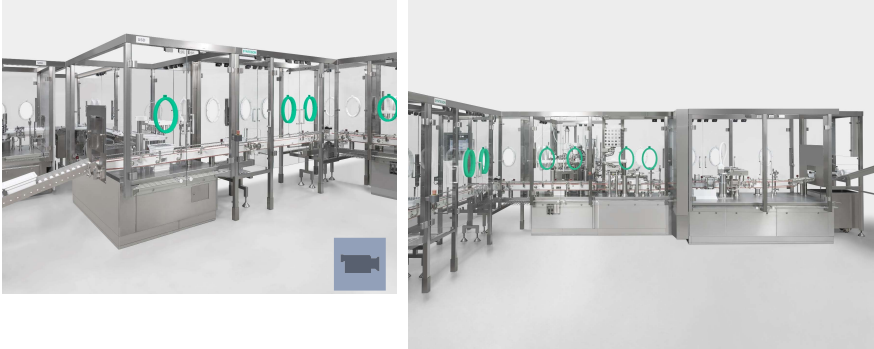
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Combi nest filler for syringes, vials, cartridges



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Combi Nestfiller Line

Not for distribution, requests for handout can be discussed individually

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Longterm vision

Shifting drug production from a human-centered...

→


Elimination of all manual operations


...to a fully automatic production by implementing robotic technology.



*"The design of equipment used in aseptic processing should **limit** the number and complexity of aseptic interventions by personnel. (...) Automation of other process steps, including the use of technologies such as **robotics**, can further **reduce risk to the product.**"*

FDA Guidance for Industry Sterile Drug Products, produced by aseptic processing cGMP, Sept. 2004





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Flexible Filler customized





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Machine and Isolator = one unit

Versynta FFP – Flexible Filling Platform



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Machine and Isolator = one unit

Versynta FFP – Flexible Filling Platform



Animation

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FFP - Detail filling station



-  Video syringe
-  Video vial
-  Dose in 00:00 - 38

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Gloveless isolator

Versynta microBatch



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Development project Versynta - microBatch: Robotic competence on the smallest scale

- Creating a new industry standard for fill/finish of small batches by using a development partnership
- Clear trend to smaller batches for different types of ready-to-use containers and high value drugs
- Highly flexible and automated production cell
- **Gloveless Isolator, fully integrated, integrated air handling (work cell approach)**
- Processing of aseptic and high-potent micro batches
- Minimizing product loss (especially during start and end of production)
- Fast batch changes
- Complete batch-to-batch changeover within less than two hours

Joint development with





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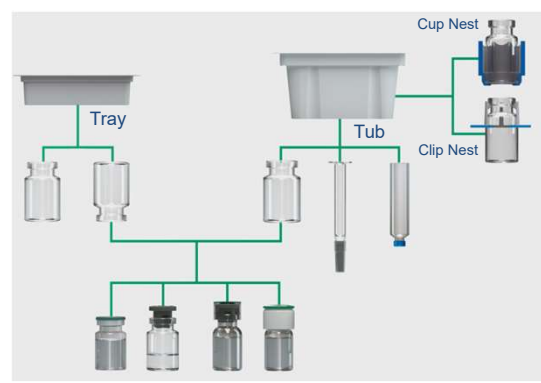
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Gloveless isolator

Versynta microBatch



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Manufacturing Aspects

Regarding Filling, Finishing and Assembly

Rod insertion and labelling

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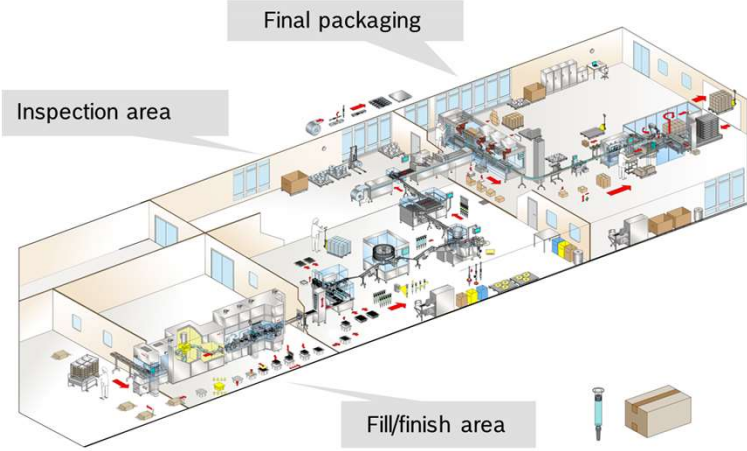
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Nested syringe processing



Final packaging

Inspection area

Fill/finish area

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Rod Insertion and Labeling





Video



Animation

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Summary



- There is a huge variety in filling and stoppering of syringes compared to e.g. vials
- The specific set-up is depending on the fill product and the syringe components
- Adapting the specific process of filling and stoppering on a production machine is quite challenging
- Interaction of containers/outer packaging and machine is crucial → collaboration between the manufacturers of syringes, plunger stoppers and machine builders is the key
- Bulk syringe processing is and will be an exception
- Processing nested syringes is state of the art
- More combi filling lines for small/medium batches (syringe, vial, cartridge)

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Questions?



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