





All about Pre-filled Syringe Systems Training Course

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October 18th – 19th, 2023 Gothenburg



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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			INTERNATIONAL STANDARD
ICS 11.040.25	Ersatz für DIN ISO 11040-4:2007-10		ISO 11040-7 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)


**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



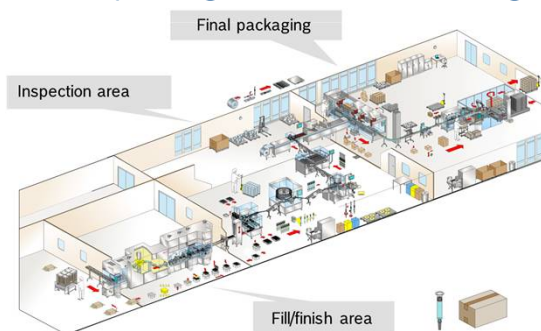
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Nested syringe processing

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Tub introduction into a RABS/Cleanroom

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Tub introduction into an Isolator

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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)

Inner bag

Outer bag

Tub

NOTE Reader bag bag windows are located on top of each bag to allow for sufficient permeability for sterilization gases and

Picture ISO 11040-7

SYNTEGON
PROCESSES & POLYMER

Change log for the document

Date	Issue	Revision	Description
20150220	SYNTEGON	1	Creation of the draft version
20150220	SYNTEGON	2	Inserting new images (chapter 2) and moving chapter 1

Table of Contents

- 1 Bag types 2
- 2 Construction of the bags 2
- 3 Construction of the bags for filling and processing of empty bag 2
- 4 Filling 2
- 5 Processing 2
- 6 Bag types 2

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Trend for (high speed) fill/finish lines

Folding of the inner bag is crucial

Size of the bag

Folding of the bag

Material of the bag

Source: Syntegon drawing number: 8-109-962-000



Source: Syntegon drawing number: 8-109-962-000

Source: Syntegon drawing number: 8-109-962-000

Source: Syntegon drawing number: 8-109-962-000

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Fill and Finish

Automatic Bag Opening

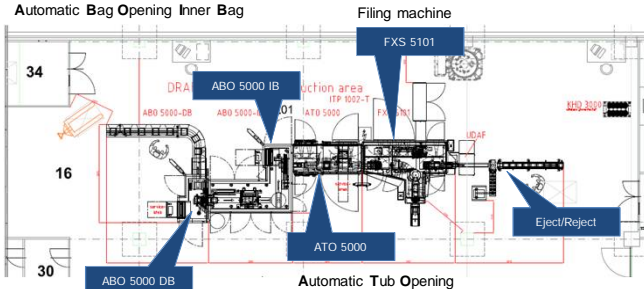
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Line Layout – high speed line



Automatic Bag Opening Inner Bag Filling machine

Automatic Bag Opening Double Bag = outer bag Automatic Tub Opening

Capacity:

1ml → 36.000 pc/h (w/o IPC)

1ml → 30.000 pc/h (1% IPC)

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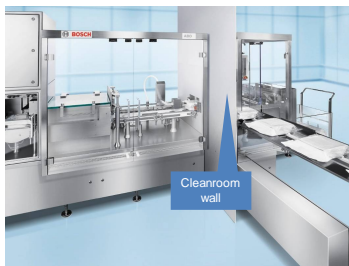
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Double bag opening



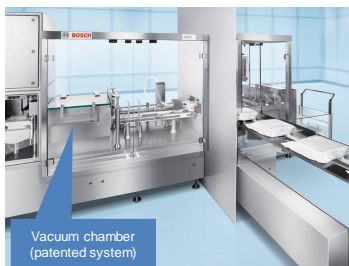
View from ABO Double Bag



Double bag opening

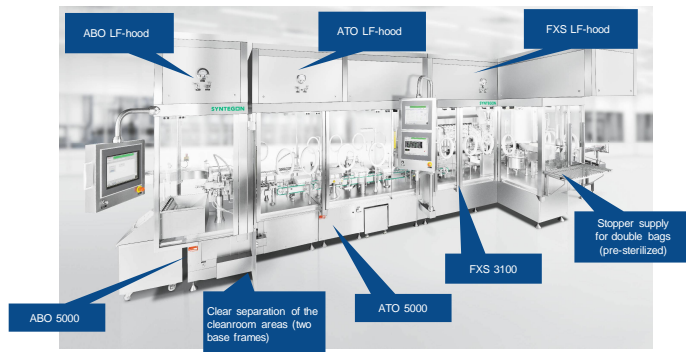


Arrangement / preparation for cutting the inner bag (patented system)





Filling line in RABS with Automatic Bag and Tub Opening



Filling line under isolator with Automatic Bag and Tub Opening





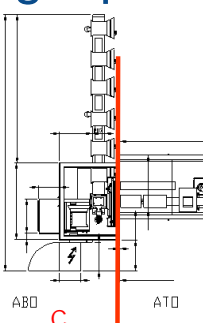
Automatic Bag Opening in detail

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



Automatic Bag Opening

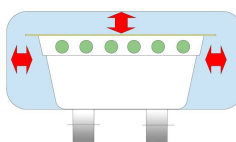
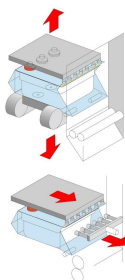




Automatic Bag Opening – Basic Configuration



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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Automatic Bag Opening



! Safe separation of tub and bag:

- Very good access to the tub
- Bag is held reliably by the suction cups
- Gripper can easily grip the tub

! Outside of the bag does not touch the outside of the tub

- No contact of the bag to the top of the tub

Line video

NTT video

NTT animation

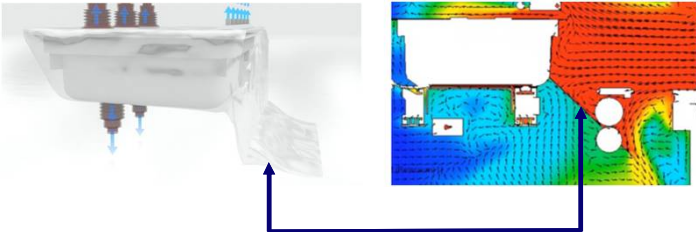
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Automatic Bag Opening – CFD Simulation




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Fill and Finish

Automatic Tub Opening

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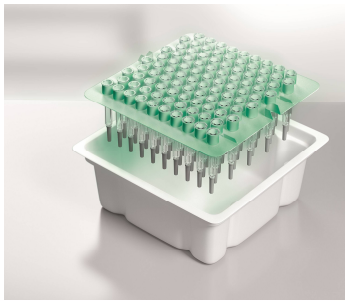
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Tub Opening

Requirements

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




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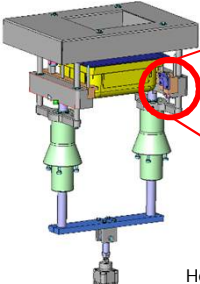
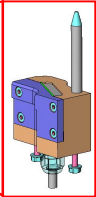
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Coffee Cream Concept – pre-Determined Breaking Line

Heating station


Heated knife detail

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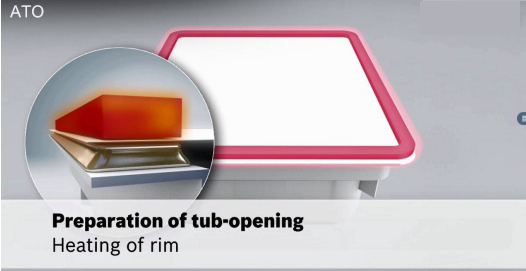
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Automatic Tub Opening – Pre-heating

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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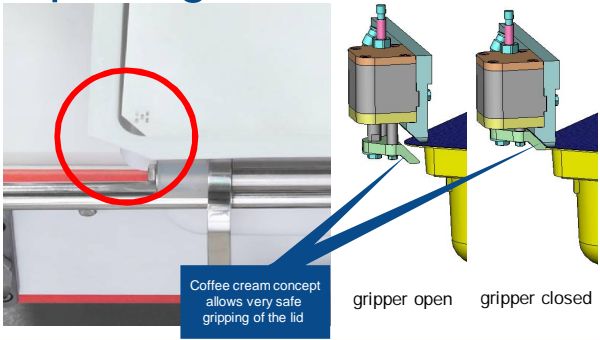
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Tub Opening – Detail



Coffee cream concept
allows very safe
gripping of the lid

gripper open

gripper closed

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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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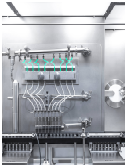
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Overview of Filling Systems


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



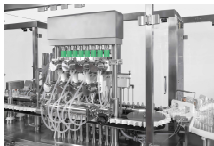
Piston Pumps




Time Pressure



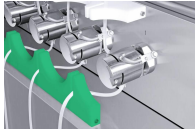
Mass Flow



Combi Filling Station



Rolling Diaphragm Pumps



Peristaltic Pumps

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Filling System Comparison

		PRODUCT PROPERTIES							
		Similar to water	High viscosity	Protein / Biotech	Suspension	Warm / Cold filling	Crystallizing / Sugar containing	Minimum product loss	Reproducibility / 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

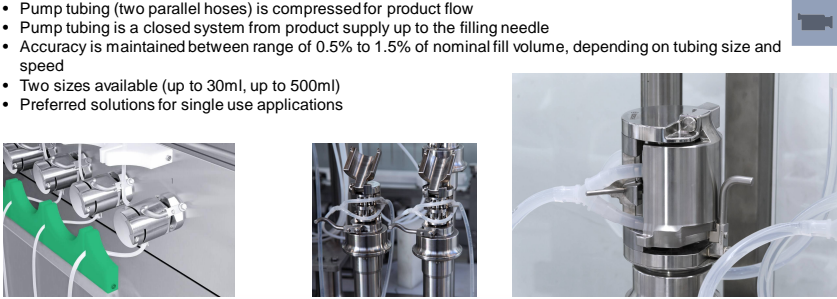
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Peristaltic Pumps Filling System

- 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



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

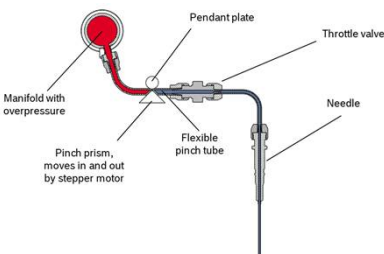
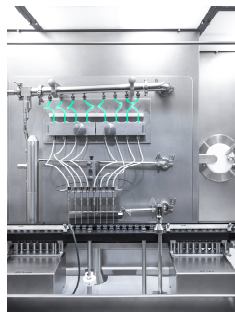
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Time Pressure Filling System

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



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

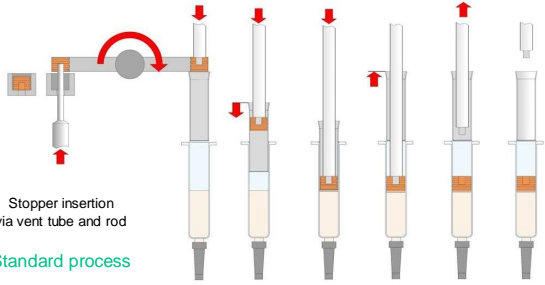


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Stopper insertion principles



Stopper insertion
via vent tube and rod

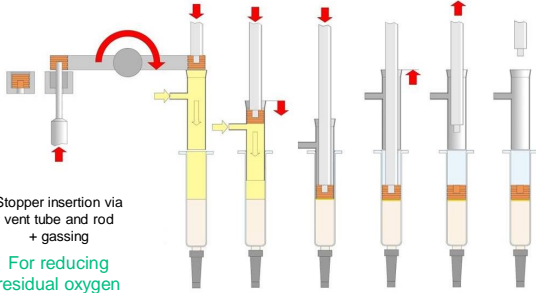
Standard process

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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

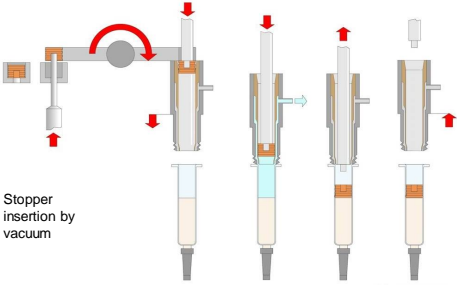
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Stopper insertion principles



Stopper insertion by vacuum


For coated stoppers and/or to reduce air bubble

Combi vacuum+ vent tube


For very low stopper positions in the syringe

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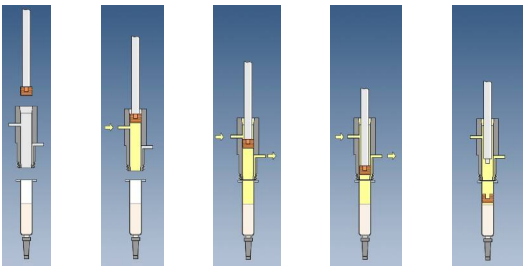


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Stopper insertion principles


To minimize air bubble and the residual oxygen



Stopper insertion by vacuum + gassing

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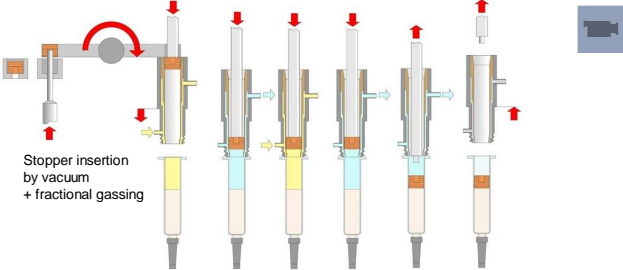
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Stopper insertion principles



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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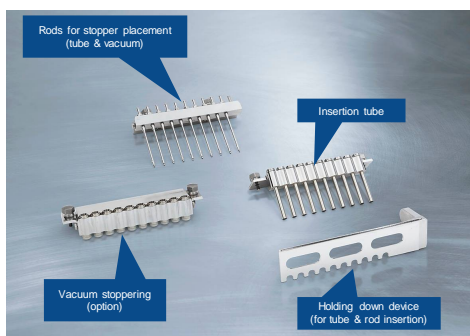
New Annex 1 - Stopper Supply via port operation from the outside



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Size Parts Stopper Placement




Fill and Finish

Special topic: Vacuum filling



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Vacuum filling / stoppering




Pump station, reinforced for vacuum filling

Rods for stoppering


Filling needles

Animation 


Video 

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Vacuum filling / stoppering



Transport carriers


Teflon hoses for filling hyaluron acid

Suction cups (silicone) for sealing the syringes, combined for filling and stoppering

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Vacuum filling / stoppering

Level control intermediate tank by gravity
→ more safety, more reliable

Filter units for:

- ▶ vacuum filling
- ▶ vacuum stoppering
- ▶ intermediate tank



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

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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



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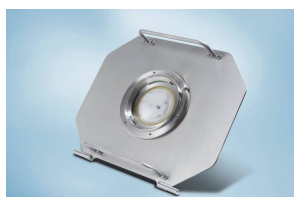
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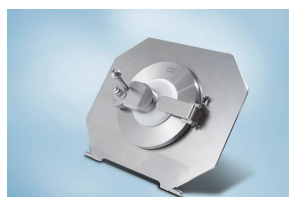
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Exchangeable Port for Stopper Supply

Port Getinge



Outside view



Inside view

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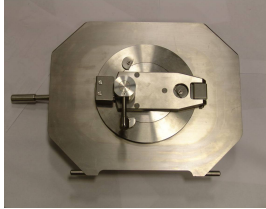
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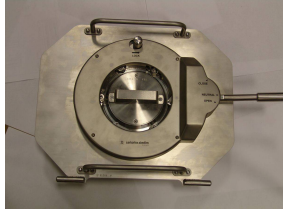
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Exchangeable Port for Stopper Supply

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.



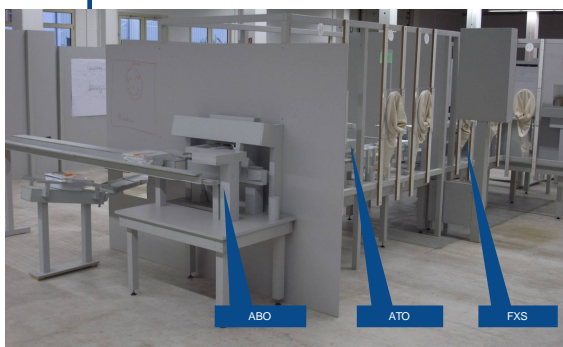
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Mock Up for Isolator & RABS



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Mock Up for Isolator & RABS



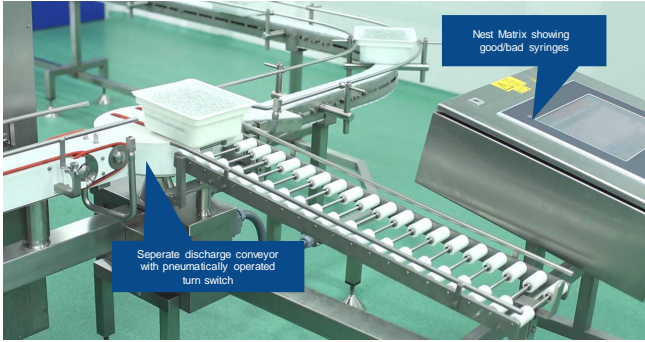
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Tub Reject




Nest Matrix showing good/bad syringes

Separate discharge conveyor 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)

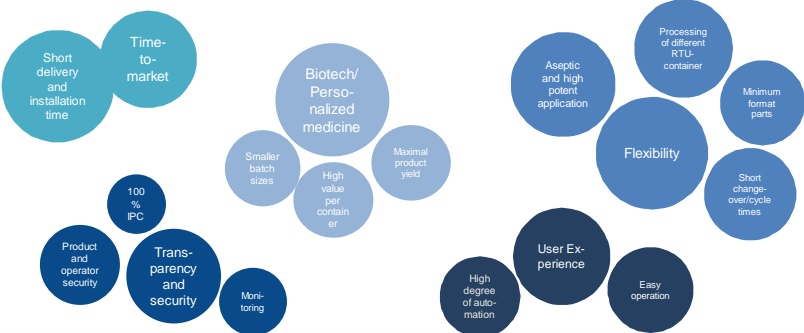


Packaging material pictures by Gerresheimer

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Market trends and requirements



Short delivery and installation time

Time-to-market

100% IPC

Product and operator security

Transparency and security

Monitoring

Smaller batch sizes

Biotech/ Personalized medicine

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

User Experience

High degree of automation

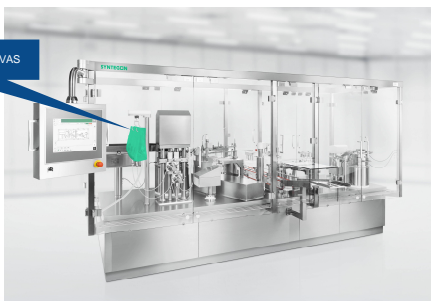
Easy operation

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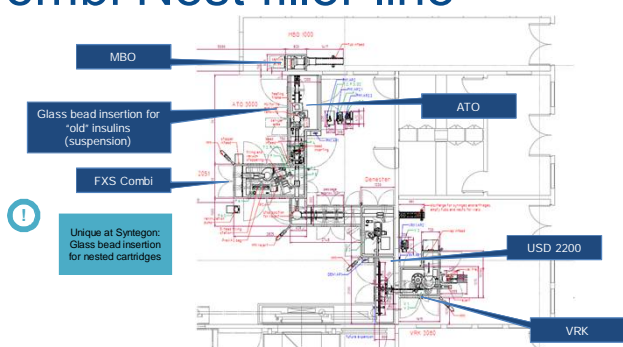


Combi nest filler for syringes, vials, cartridges

Single use filling system PreVAS



Combi Nest filler line





Combi nest filler for syringes, vials, cartridges

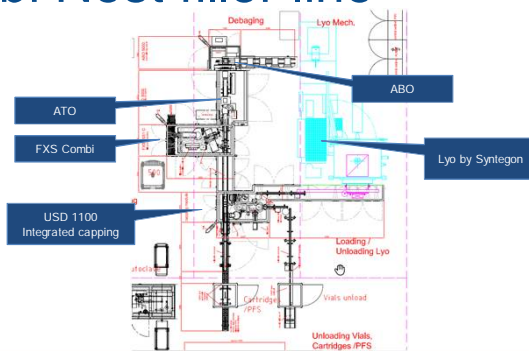


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Combi Nest filler line




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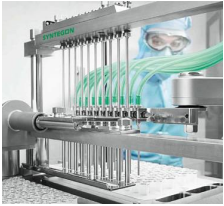
Longterm vision

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



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

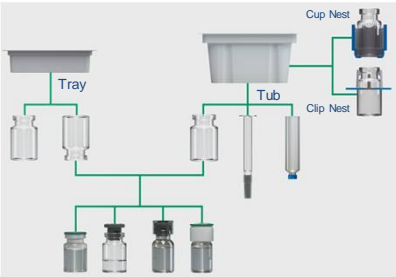
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Gloveless isolator

Versynta microBatch



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Requirements & Expectations

Regulatory expectations.

FDA Guidance

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.

R. Friedman: "Use of robotics in aseptic processing has the potential to profoundly reduce contamination risks"
Source: FDA Guidance for Industry: Sterile Drug Products, produced by aseptic processing (CDER, Sept 2004)

- No aseptic interventions by personnel - even no set-up.
- Instead, robotics will take over all main activities.

Presentation Ute Schleyer, Vetter and Klaus Ullherr Syntegon at ISPE Annual Meeting in Boston, Nov 1st 2021

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Requirements & Expectations

Regulatory expectations

Annex 1

So, what are we expecting?

Our expectation is that the contact parts (direct and indirect) are sterilized using a robust sterilization method that meets the current requirements of annex 1. This means that:

- the sterilizing agent reaches all of the critical surfaces in a consistent and repeatable manner, typically requiring processes such as moist or dry heat sterilization.
- the item is unloaded from the sterilization process either wrapped in integral covering or container, or is transferred under grade A conditions, such as a transfer isolator into the manufacturing isolator.
- We also expect that the parts are not exposed to the isolator environment until the isolator has been closed and after completion of the work zone decontamination VHP cycle.

Source: Andrew Hopkins, MIRA representative (Pig), commenting on EU Annex 1 (2011)

- The steam sterilized equipment is unloaded into a H₂O₂ decontaminated grade A.
- Unloading into a grade A environment, no VHP cycle after set-up!

Presentation Ute Schleyer, Vetter and Klaus Ullherr Syntegon at ISPE Annual Meeting in Boston, Nov 1st 2021

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Manufacturing Aspects

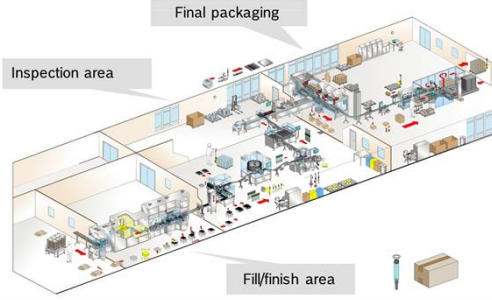
Regarding Filling, Finishing and Assembly

Rod insertion and labelling

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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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Glossary



- ISO 11040-4 syringe bodies
- ISO 11040-7 outer packaging
- PDA Technical Report No. 73, user requirements syringe
- Bag specification, Syntegon
- EU GMP Guideline, Annex 1

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Questions?

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