


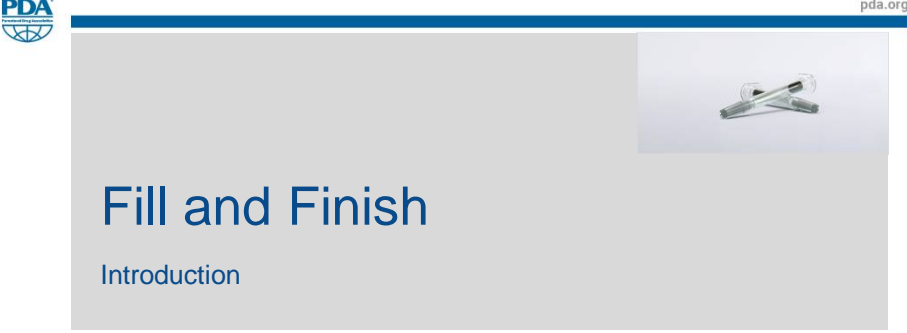
All about Pre-filled Syringe Systems Training Course


Klaus Ullherr
Senior Product Manager
Syntegon Technology

April 25th – 26th, 2024 Copenhagen

 PDA TRAINING

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Fill and Finish

Introduction

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New EU GMP guideline

The Rules Governing Medicinal Products in the European Union
Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for
Human and Veterinary Use


Annex 1
Manufacture of Sterile Medicinal Products


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Important norms: ISO 11040-4/-7

	DEUTSCHE NORM DIN ISO 11040-4	Juli 2017 	INTERNATIONAL STANDARD		ISO 11040-7 First edition 2015-04-01
	ICS 11.040.25	Ersetzt für DIN ISO 11040-4:2007-10			
Vorgefüllte Spritzen - Teil 4: Spritzenzylinder aus Glas für Injektionspräparate und sterilisierte und vormontierte Spritzen zur Abfüllung (ISO 11040-4:2015)			Prefilled syringes — Part 7: Packaging systems for sterilized subassembled syringes ready for filling		
Prefilled syringes — Part 4: Glass barrels for injectables and sterilized subassembled syringes ready for filling (ISO 11040-4:2015)			Prefilled syringes — Part 7: Systems of packaging for the syringes sterilized ready to be filled (ISO 11040-4:2015)		
Seringues préremplies — Partie 4: Cylindres en verre pour produits injectables et seringues pré-assemblées stérilisées préremplissables (ISO 11040-4:2015)			Seringues préremplies — Partie 7: Systèmes d'emballage pour les seringues stérilisées prêtes à l'emploi préremplissables		

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PDA Technical Report

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Technical Report No. 73
Prefilled Syringe User Requirements for
Biotechnology Applications

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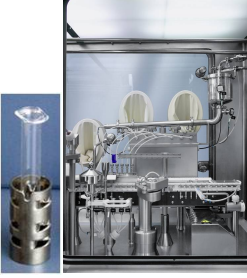
Bulk Processing – some remarks

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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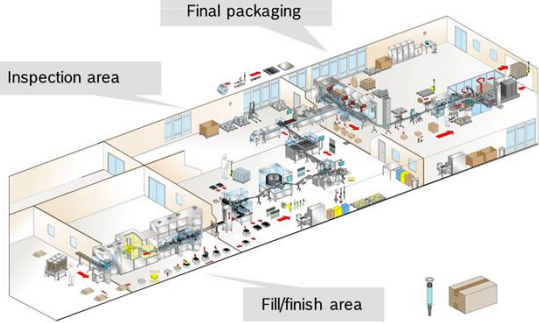
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Nested syringe processing




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
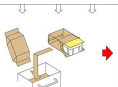
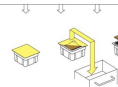
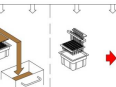
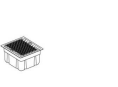


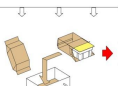
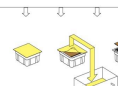
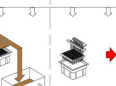
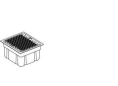
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Tub introduction into a RABS/Cleanroom

E/D	C	C	A		
					
					

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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)

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

Picture ISO 11040-7

Change log for the document			
Date	Issue	Revision	Comments
20150528	01/0001	1	Creation of the draft version
20150622	01/0001	2	Header bag on pages (chapter 2) and machine (chapter 1)

Table of Contents

- 1 Bag design 2
- 2 Bag filling 2
- 3 Machine filling (single-bag fill bags and automatic filling bags) 2
- 4 Header bag 2
- 5 Packaging 2
- 6 Programs 2

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Trend for (high speed) fill/finish lines

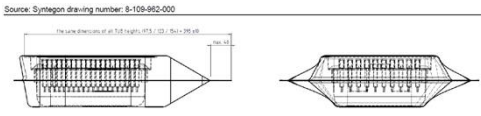
Folding of the inner bag is crucial

Size of the bag

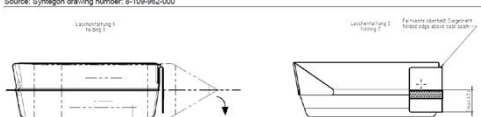
Folding of the bag

Material of the bag


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



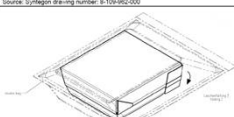
Source: Syntegon drawing number: 8-109-962-000



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



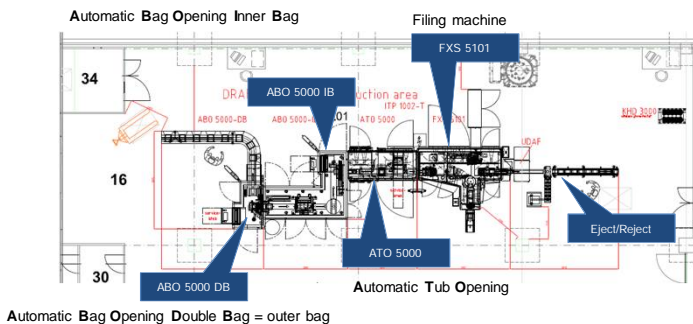
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Line Layout – high speed line

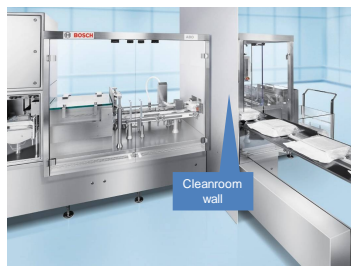
Capacity:
1ml → 36.000 pc/h (w/o IPC)
1ml → 30.000 pc/h (1% IPC)



Double bag opening

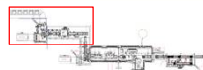


View from ABO Double Bag





Double bag opening



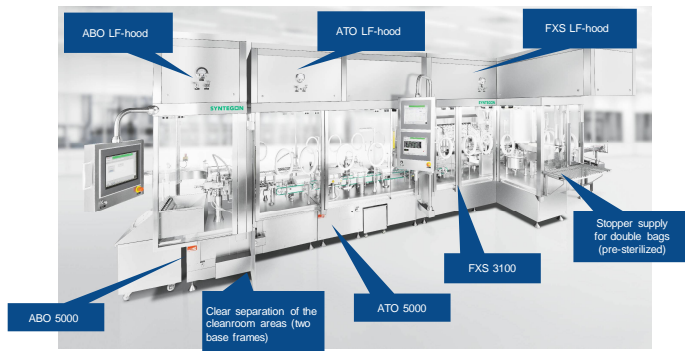
Arrangement / preparation for cutting the inner bag (patented system)



Vacuum chamber (patented system)



Filling line in RABS with Automatic Bag and Tub Opening





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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



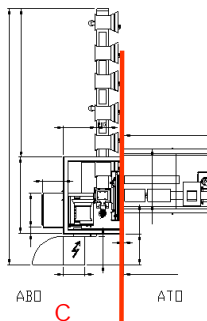
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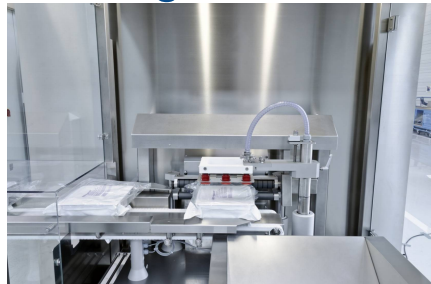
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Automatic Bag Opening



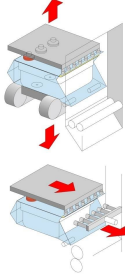
Automatic Bag Opening – Basic Configuration

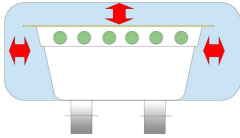


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Aseptic Tub Transfer – a Bundle of Measures






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

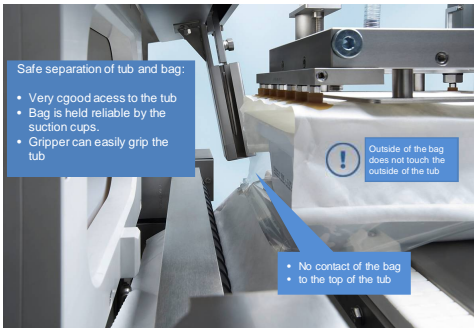
Protection of the tub (by the bag) as long as possible. Removal just before the transfer.

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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



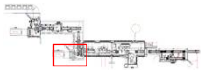
Line video



NTT video



NTT animation

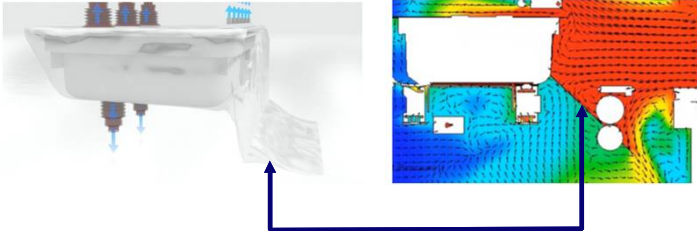


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Automatic Bag Opening – CFD Simulation



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Automatic Tub Opening



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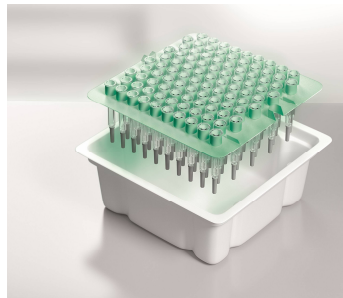


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Tub Opening

Requirements

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



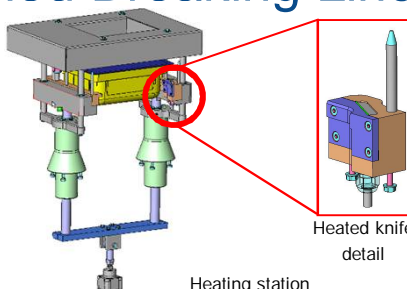
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Coffee Cream Concept – pre-Determined Breaking Line




Heating station

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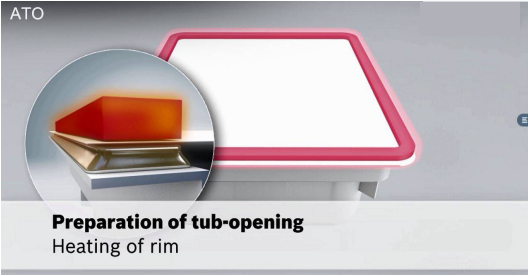
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Automatic Tub Opening – Pre-heating

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




ATO
Preparation of tub-opening
Heating of rim

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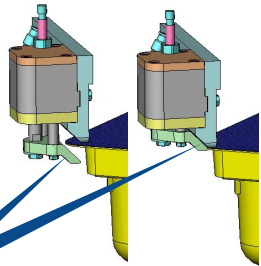


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Tub Opening – Detail






gripper open gripper closed

Coffee cream concept allows very safe gripping of the lid

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Automatic Tub Opening



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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

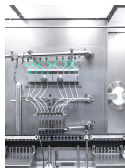


Overview of Filling Systems

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



Piston Pumps



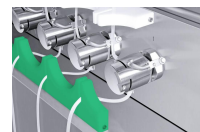
Time Pressure



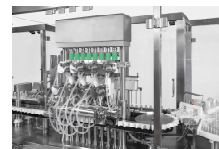
Rolling Diaphragm Pumps



Mass Flow



Peristaltic Pumps



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	+

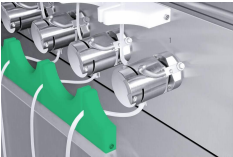


- not possible / not reasonable
 0 possible with restrictions
 + possible solution
 ++ preferred solution

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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

- 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

Points to consider

- Viscous products



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



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Peristaltic Pump on syringe filler




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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

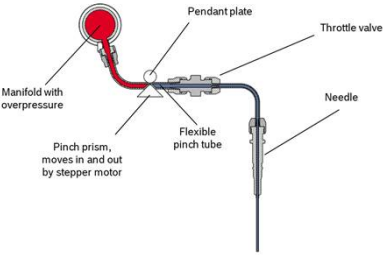
Benefits	Points to consider
<ul style="list-style-type: none"> Accurate, repeatable fill volumes, also at high speed Most popular pump type, very well known No seals Simple assembly Easy to clean and sterilize 	<ul style="list-style-type: none"> Crystallising products Longer CIP/SIP cycle time than TPF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

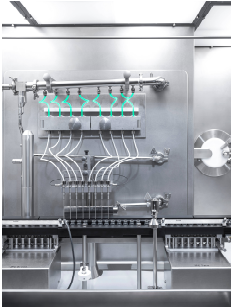
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Time Pressure Filling System

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

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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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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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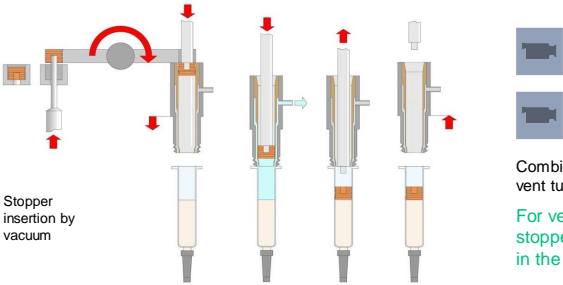


Slides for hands on Training

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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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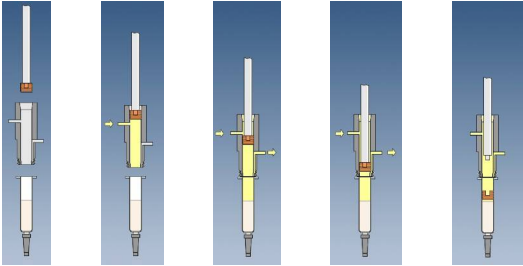
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Stopper insertion principles


To minimize air bubble and the residual oxygen

Stopper insertion
by vacuum
+ gassing



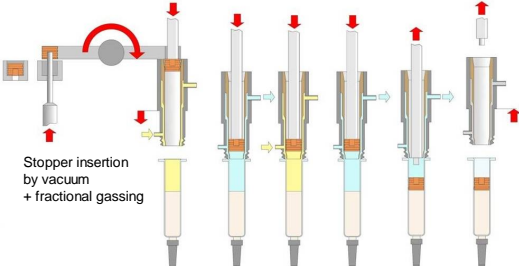
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Stopper insertion principles

Stopper insertion
by vacuum
+ fractional gassing



For lowest residual oxygen values

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Basic Configuration Stopper Supply



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

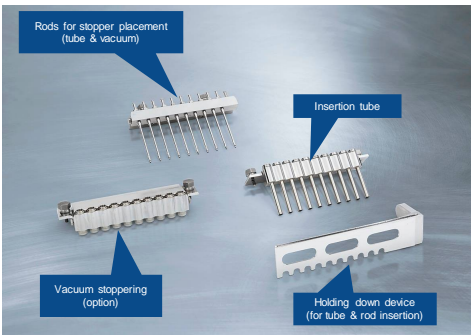
Stopper re-supply, made of stainless steel

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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



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



Exchangeable port for stopper supply

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Exchangeable Port for Stopper Supply

Port Getinge




Outside view



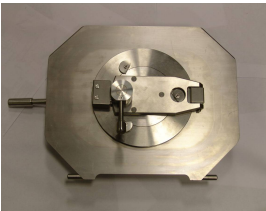
Inside view

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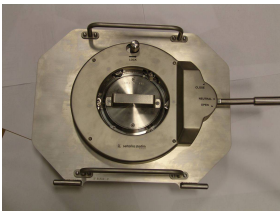
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Exchangeable Port for Stopper Supply

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



Outside view



Inside view

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



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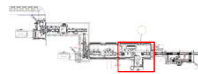
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Stoppering station



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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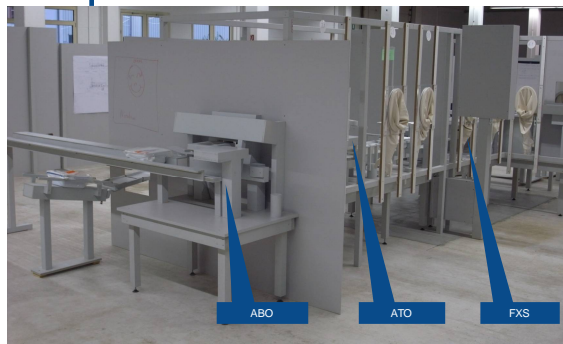
Topics for Mock-Up (Selection)

- 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.



Mock Up for Isolator & RABS





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Mock Up for Isolator & RABS



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Tub Reject



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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

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Combi nest filler for syringes, vials, cartridges

Single use filling system PreVAS

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Combi Nest filler line

MBO

Glass bead insertion for "old" insulins (suspension)

FXS Combi

Unique at Syntegon: Glass bead insertion for nested cartridges

ATO

USD 2200

VRK

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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



Machine and Isolator = one unit



Versynta FFP – Flexible Filling Platform



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Machine and Isolator = one unit

Versynta FFP – Flexible Filling Platform







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FFP - Detail filling station



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


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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





PDA DRUG DELIVERY
INNOVATION AWARD
2021
PARTNERSHIP

Joint development with



VETTER



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3 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.

No aseptic interventions by personnel – even no set-up.

Instead, robotics will take over all main activities.

R. Friedman: "Use of robotics in aseptic processing has the potential to profoundly reduce contamination risks"

Source: FDA Guidance for Industry: Sterile Oculars, produced by aseptic processing (CDER, Sep 2004)


Connecting Pharmaceutical Knowledge


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 blog, commenting on EU Annex 1 Ed4. Website article available by [link](#)

The clean sterilized equipment is unloaded into a H₂O₂ decontaminated or 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

Connecting Pharmaceutical Knowledge ISPE.org

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Gloveless isolator

Versynta microBatch

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Gloveless isolator

Versynta microBatch



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Manufacturing Aspects

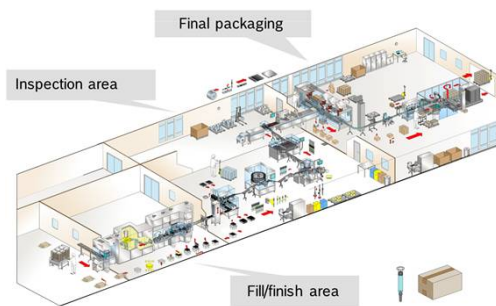
Regarding Filling, Finishing and Assembly

Rod insertion and labelling

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Nested syringe processing



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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