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All about Pre-filled Syringe Systems Training Course

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Fill and Finish
- Introduction -

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

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**

First edition
2015-04-01

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

PDA Technical Report

Technical Report No. 73

Prefilled Syringe User Requirements for Biotechnology Applications

Bulk Processing – some remarks

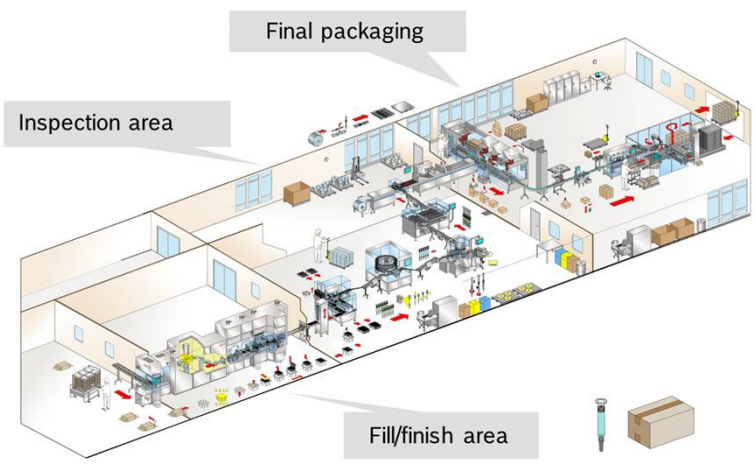
Challenges:

- 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

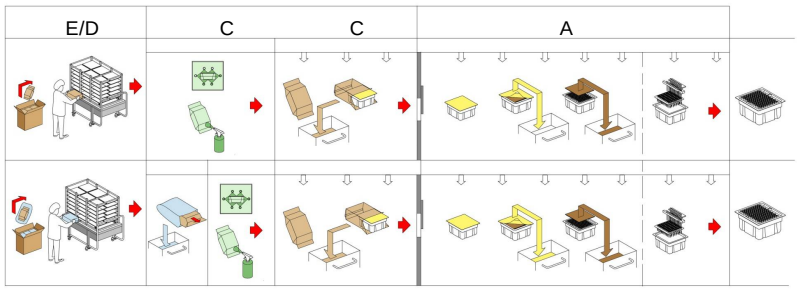
Advantages:

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

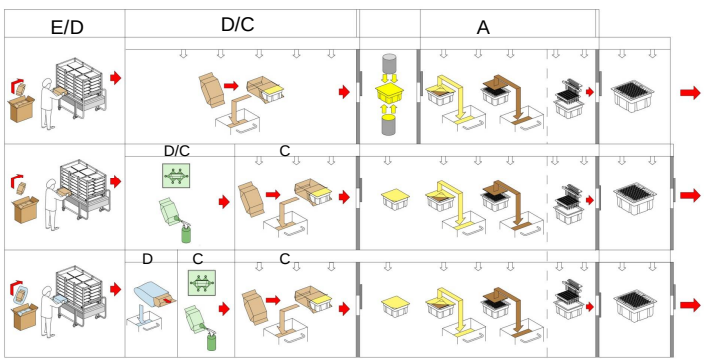
Nested syringe processing



Tub introduction into a RABS/Cleanroom

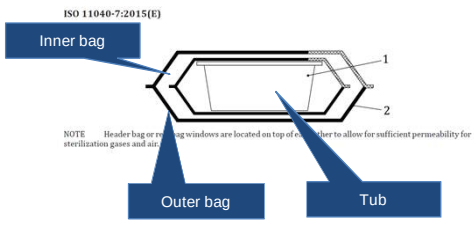


Tub introduction into an Isolator

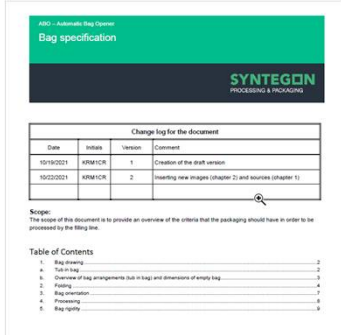


Trend for (high speed) fill/finish lines

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



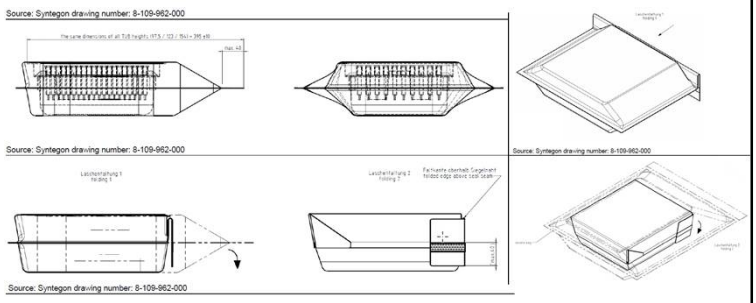
Picture ISO 11040-7



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



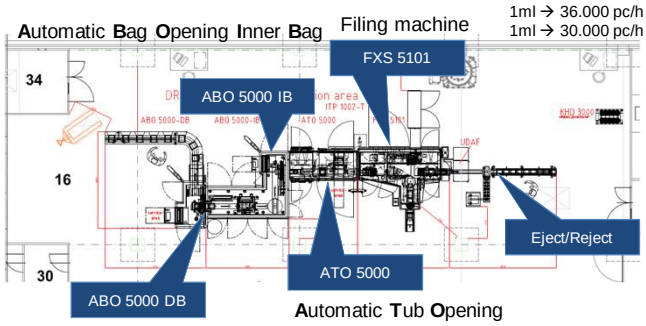
Fill and Finish

Automatic Bag Opening

Line Layout – high speed line

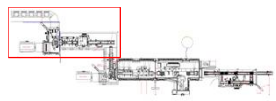
Capacity:

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

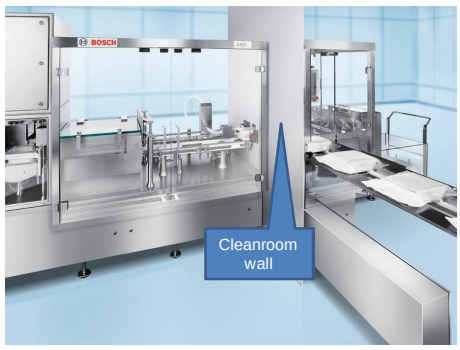


Automatic **B**ag **O**pening **D**ouble **B**ag = outer bag

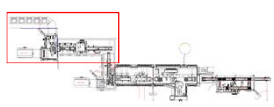
Double bag opening



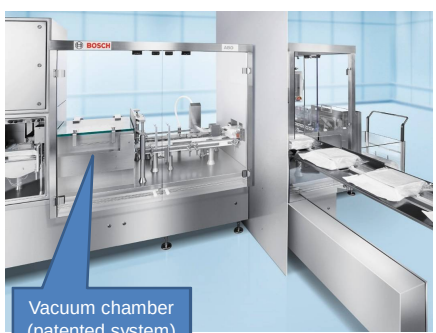
View from ABO Double Bag



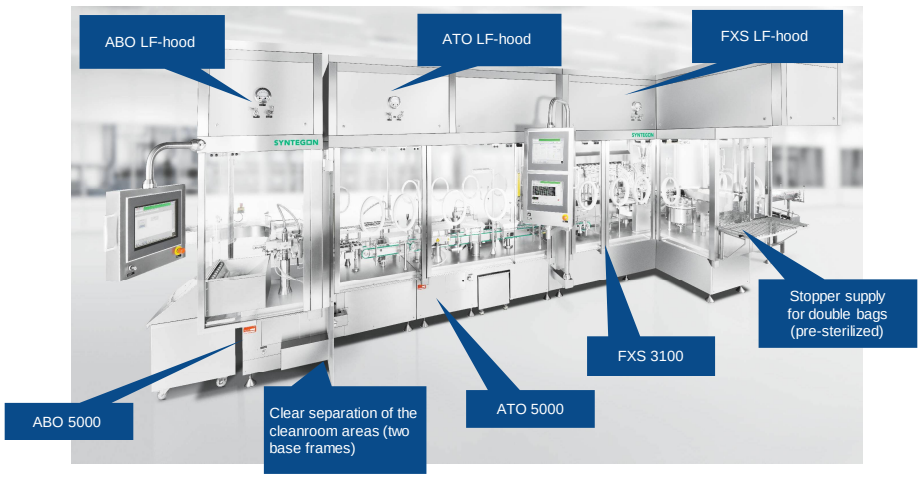
Double bag opening



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



Filling line in RABS with Automatic Bag and Tub Opening



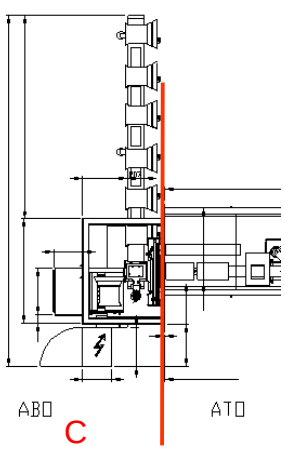
Filling line under isolator with Automatic Bag and Tub Opening

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



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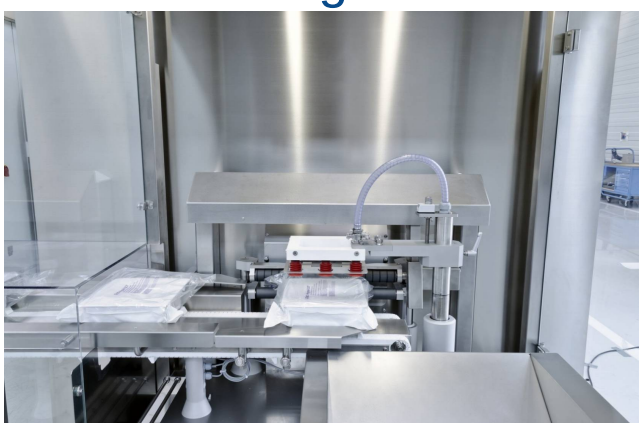
Automatic Bag Opening – Basic Configuration



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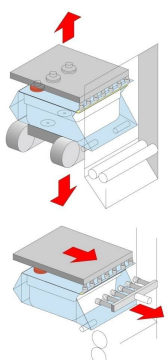
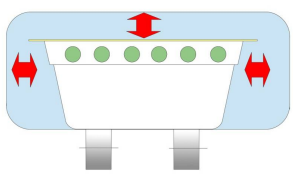
Aseptic Tub Transfer – a Bundle of Measures

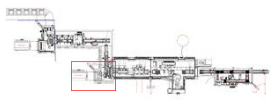


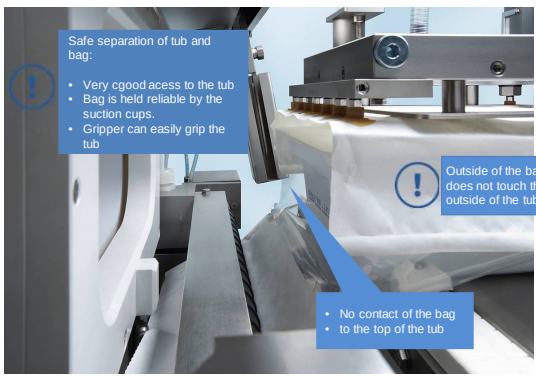


No contact bag outside – tub outside, especially at the top of the tub.

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

Automatic Bag Opening



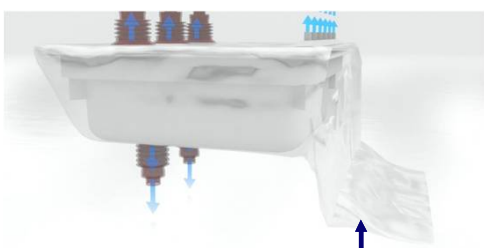


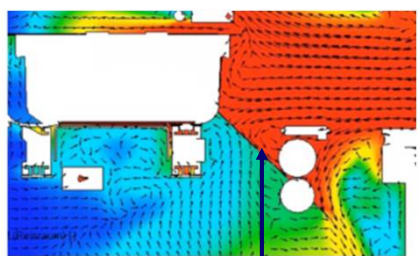
Line video

NTT video

NTT animation

Automatic Bag Opening – CFD Simulation





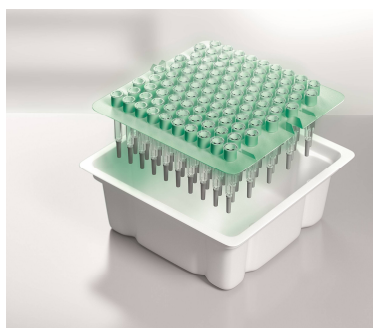
Fill and Finish

Automatic Tub Opening

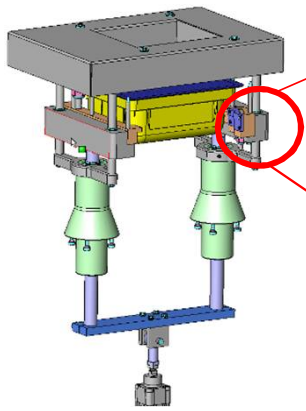
Tub Opening

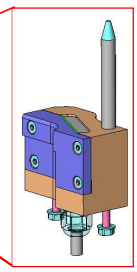
Requirements

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



Coffee Cream Concept – pre-Determined Breaking Line

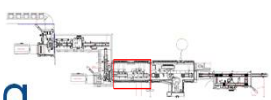




Heated knife - detail

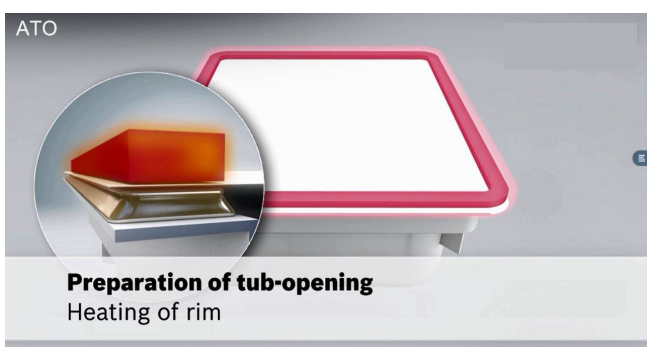
Heating station

Automatic Tub Openening – Pre-heating

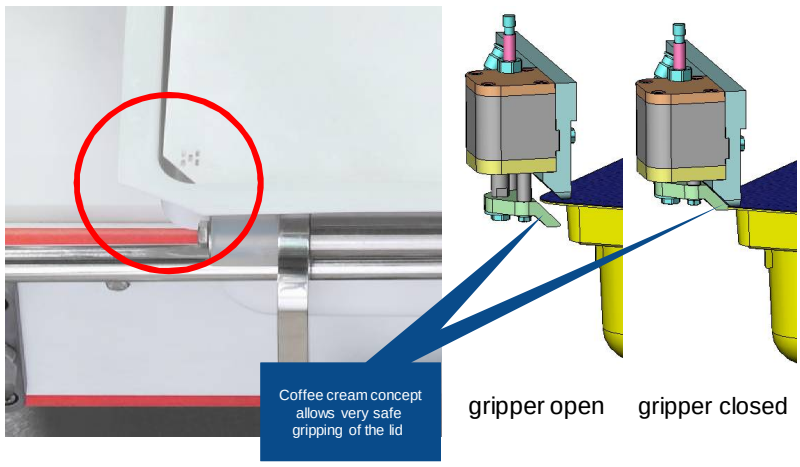


Pre-heating of the tub rim. Temperatures adjustable at HMI for different qualities of packaging material (range from approx. 80°C to 120°C , typically around 100°C ➔

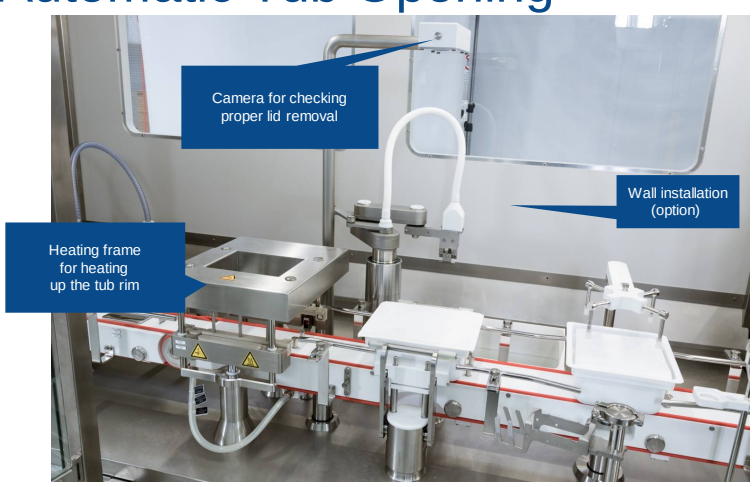
- Less particles
- Facilitates the opening process



Tub Opening – Detail



Automatic Tub Opening



Fill and Finish

Filling

Fill/finish - Requirements

Syringe specific requirements:

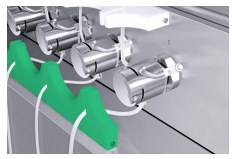
- Up to 600 syringes / min [1)]
- Precise transport system
- No contact of the insertion tube with the syringe
- Suitable for all available filling systems
- Stoppering immediately after filling
- Transport of the tub

[1)] 16head up to 57.600/h

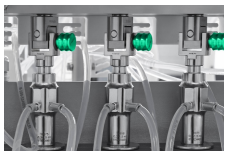
Overview of Filling Systems

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

Rolling Diaphragm Pumps

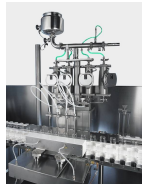


Peristaltic Pumps

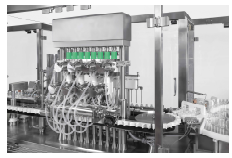


Piston Pumps

Time Pressure



Mass Flow



Combi Filling Station

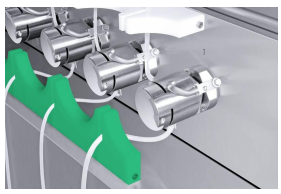
Filling System Comparison

FILLING SYSTEM	PRODUCT PROPERTIES							
	Similar to water	High viscosity	Protein / Biotech	Sus-pension	Warm / Cold filling	Crystallizing / Sugar containing	Minimum product loss	Repro-ducibility / Speed
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

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



Peristaltic Pumps Filling System

Benefits	Points to consider
• 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	• Viscous products

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

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 Zr02
- 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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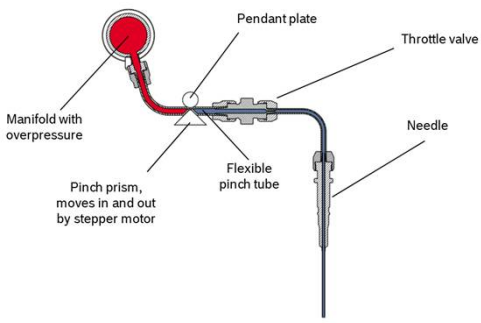
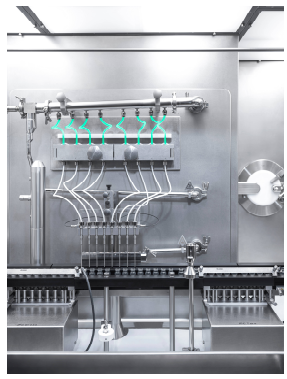
Rotary Valve Piston Pump Filling System

Benefits	Points to consider
• Accurate, repeatable fill volumes, also at high speed • Most popular pump type, very well known • No seals • Simple assembly • Easy to clean and sterilize	• Crystallising products • Longer CIP/SIP cycle time than TPF (more steel) • Not applicable for high temperature filling >35°C

Time Pressure Filling System

Product path from manifold to container





Time Pressure Filling System

Benefits	Points to consider
• Easy size changeover • Very simple mechanical set-up • Easy cleaning • Closed system • No problems with crystallising products • CIP/SIP handling, faster cycle	• Accuracy if product viscosity is highly dependent on temperature • Oily products • Control system needs educated staff

Combi Filling Station

Rotary valve piston pump

Peristaltic pump

Rolling diaphragm pump

Time-pressure-filling

In Process Checkweigh under Isolator – Detail

Filling Laboratory –
Content of typical test protocol

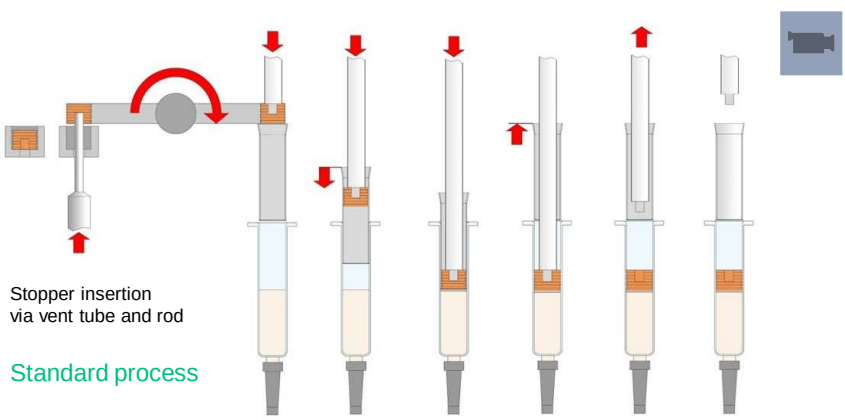
- Customer name
- Product name
- Filling Volume
- Filling size parts (needle, tubing, …)
- Output
- Design of filling system and product header
- Parameters of filling system (e.g. speed of peristaltic pump, acceleration)
- Parameters of filling needle movement

Fill and Finish
Stopper Insertion Principles

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

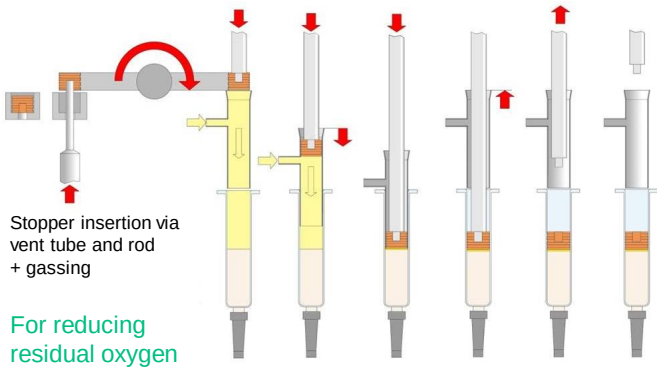
Stopper insertion principles



Stopper insertion
via vent tube and rod

Standard process

Stopper insertion principles

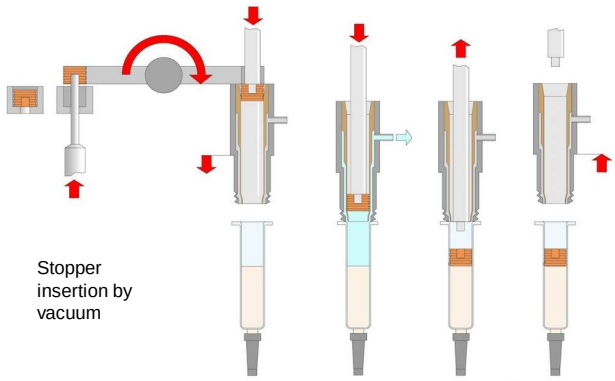


Stopper insertion via vent tube and rod + gassing

For reducing residual oxygen

Slides for hands on Training

Stopper insertion principles



Stopper insertion by vacuum

Combi vacuum+ vent tube

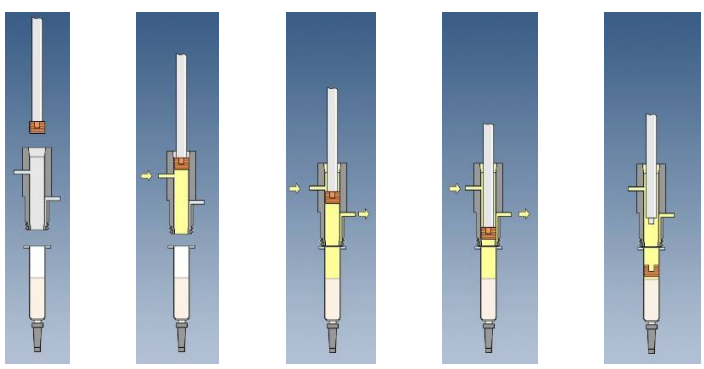
For very low stopper positions in the syringe

For coated stoppers and/or to reduce air bubble

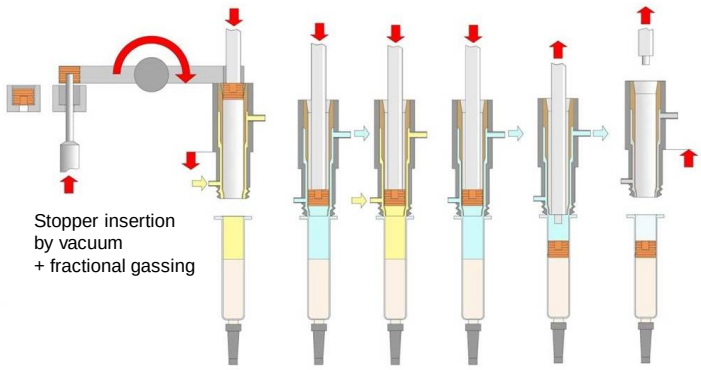
Stopper insertion principles

To minimize air bubble and the residual oxygen

Stopper insertion by vacuum + gassing



Stopper insertion principles



Stopper insertion
by vacuum
+ fractional gassing

For lowest residual oxygen values

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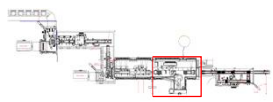
Stoppering station



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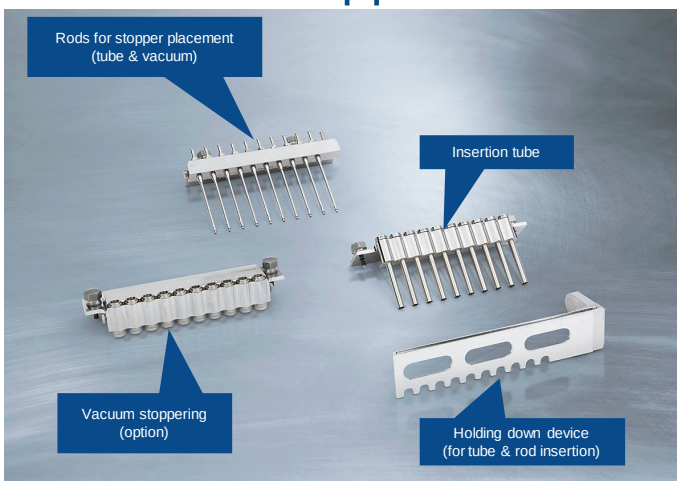
New Annex 1 - Stopper Supply via port operation from the outside

Size Parts Stopper Placement



Fill and Finish

Special topic: Vacuum filling

Vacuum filling / stoppering

Animation Video

Vacuum filling / stoppering

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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

RABS Stopper Supply Including Sliding Pane

- Stopper loading from operation side
- Easy logistics / no crossing of the line

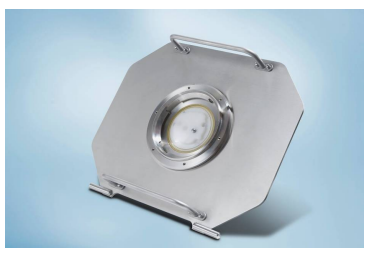
Nested Syringe Filling Machine with Isolator

- Stopper supply with exchangeable Port
- Wash down air ducts

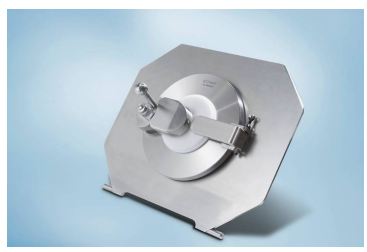
Isolator Stopper Supply

Exchangeable Port for Stopper Supply

Port Getinge



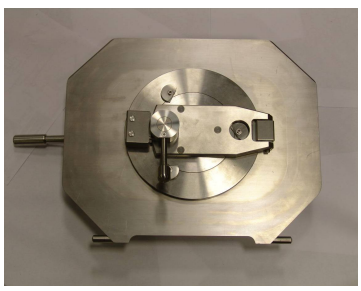
Outside view



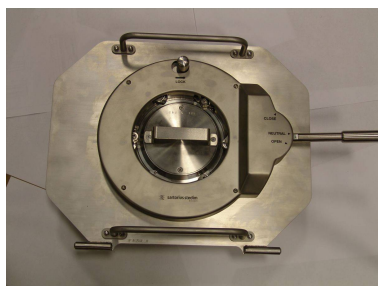
Inside view

Exchangeable Port for Stopper Supply

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



Outside view



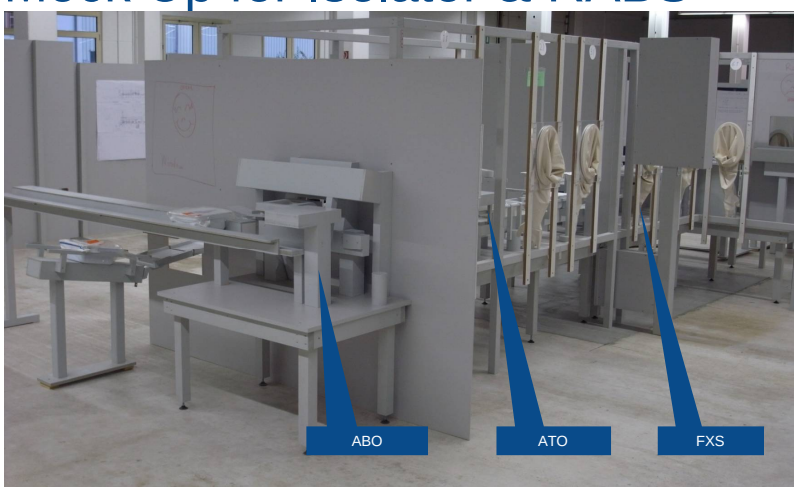
Inside view

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 adaptions of the machine design can be necessary for optimized barrier system use.

Mock Up for Isolator & RABS



Mock Up for Isolator & RABS

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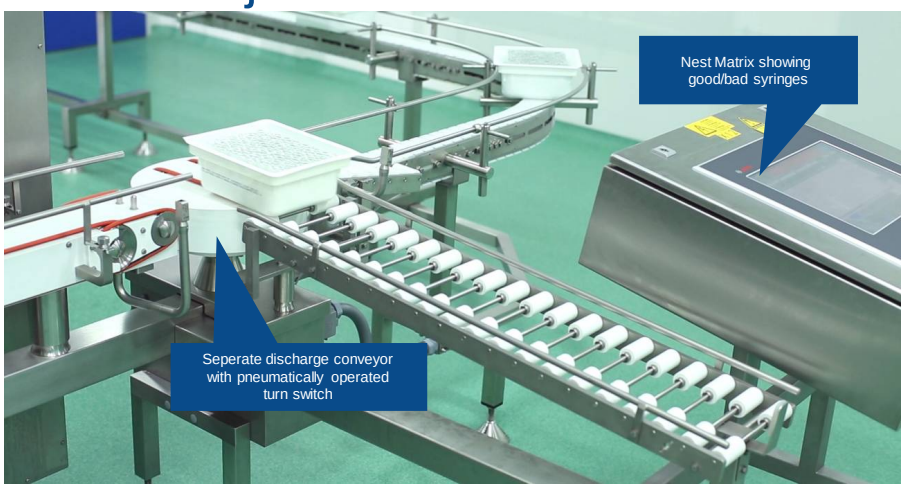
Tub Reject



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Manufacturing Aspects

Regarding Filling, Finishing and Assembly

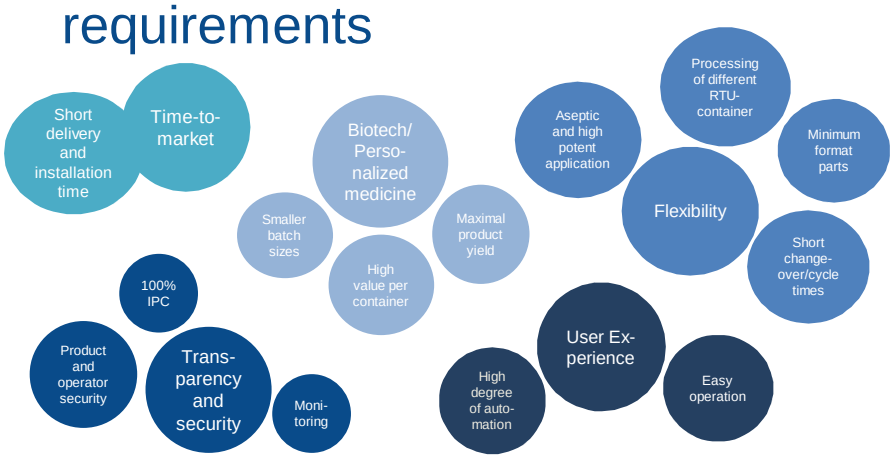
Combi Filling – Robotic Filling

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

Tub & nest approach (syringes, vials and cartridges)

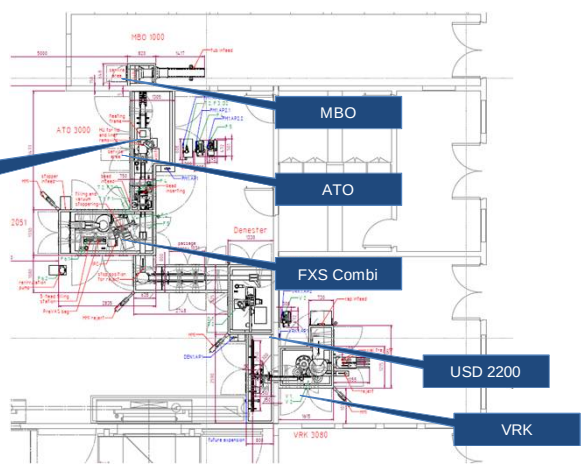
Packaging material pictures by Gerresheimer

Market trends and requirements



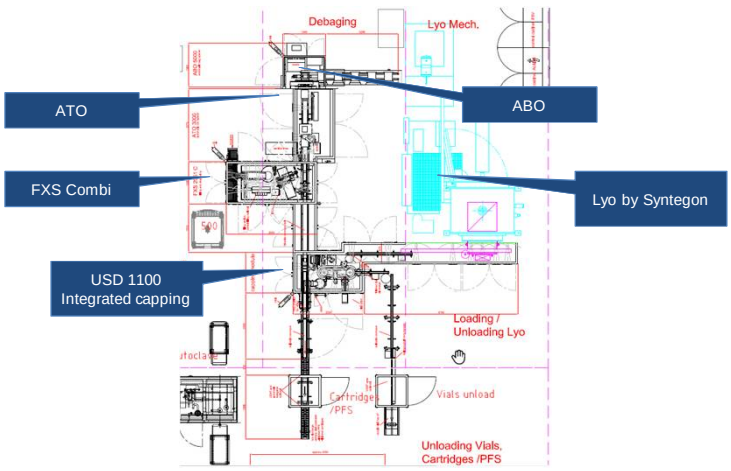
Combi nest filler for syringes, vials, cartridges

Combi Nest filler line



Combi nest filler for syringes, vials, cartridges

Combi Nestfiller line



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

Flexible Filler customized

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Machine and Isolator = one unit

Versynta FFP – Flexible Filling Platform

Klaus Ullherr, Senior Product Manager, Syntegon

pda.org

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Machine and Isolator = one unit

Versynta FFP – Flexible Filling Platform

Animation

Klaus Ullherr, Senior Product Manager, Syntegon

pda.org

FFP - Detail filling station

Video syringe

Video vial

Dose in 00:00 - 38

Gloveless isolator

Versynta microBatch

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

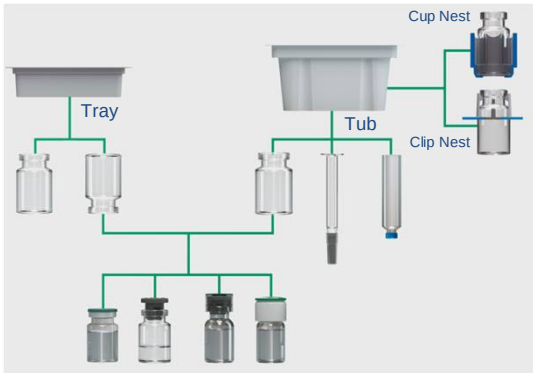
Joint development with

PDA DRUG DELIVERY INNOVATION AWARD 2021 PARTNERSHIP

VETTER

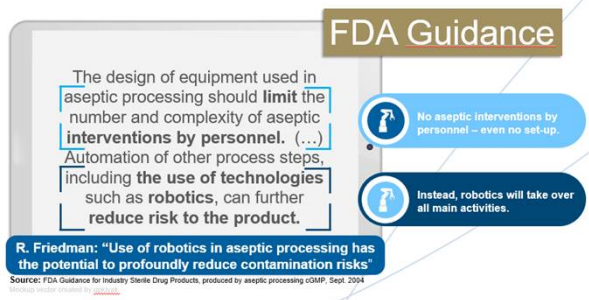
Gloveless isolator

Versynta microBatch



Requirements & Expectations

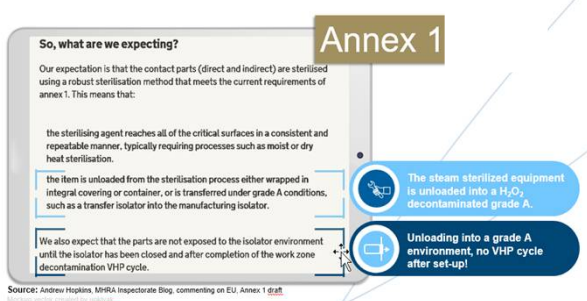
Regulatory expectations.



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

Requirements & Expectations

Regulatory expectations



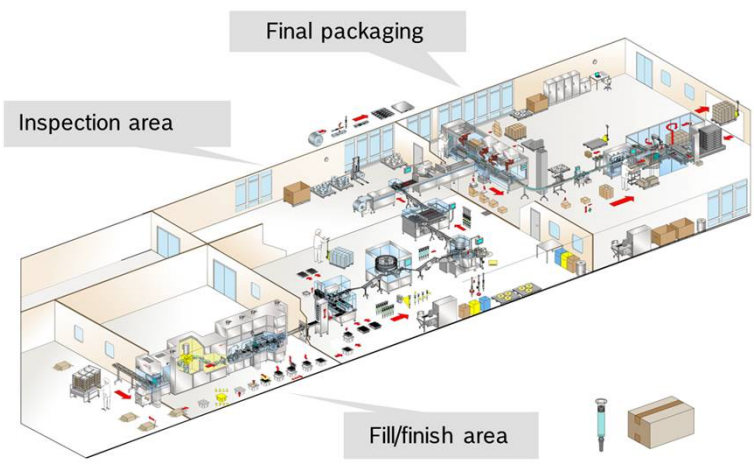
Presentation Ute Schleyer, Vetter and Klaus Ullherr Syntegon at ISPE Annual Meeting in Boston, Nov 1st 2021

Manufacturing Aspects

Regarding Filling, Finishing and Assembly

Rod insertion and labelling

Nested syringe processing



Rod Insertion and Labeling

Video

Animation

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)

Questions?

klaus.ullherr@syntegon.com