



**The complete process
to manufacture
prefilled syringes**



- **Material**
- **Forming**
- **Cleaning**
- **Siliconization**
- **Pre-Assembly**
- **Sterilization**

Part 1

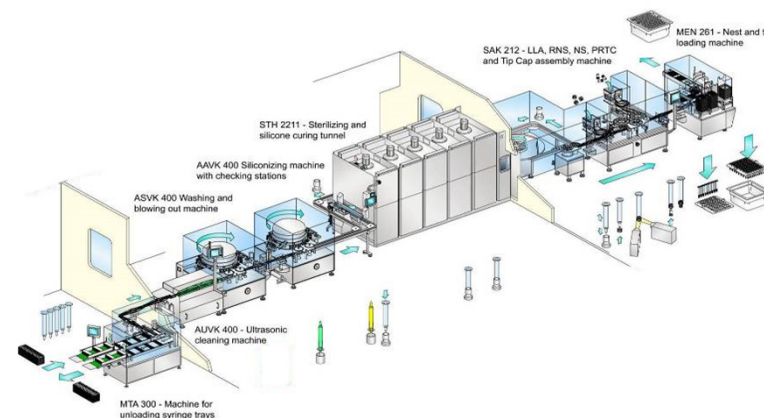
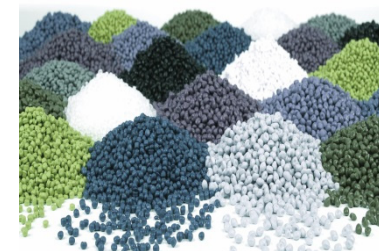
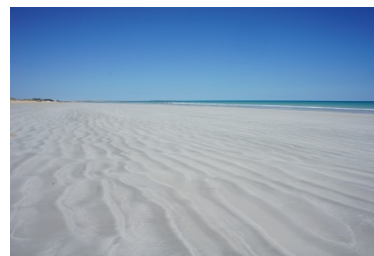
- **Unpacking**
- **Filling**
- **Control & Closing**
- **Labeling**
- **Secondary packaging**

Part 2

The complete process to manufacture prefilled syringes

Overview

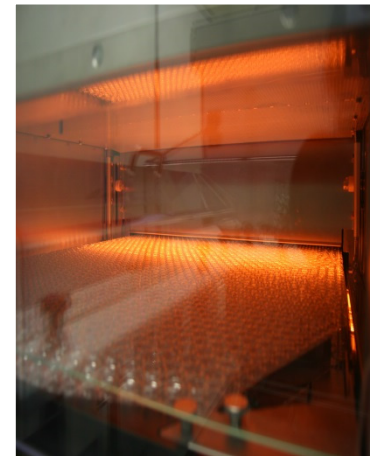
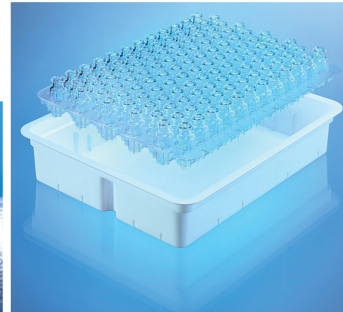
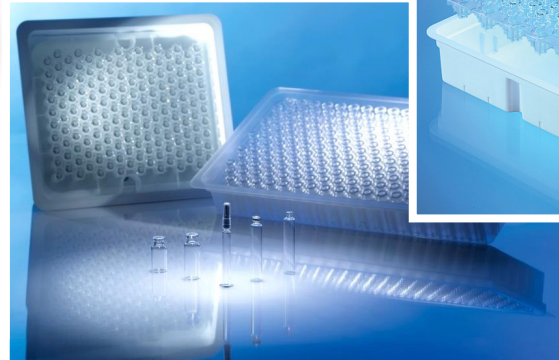
- Material
- Forming
- Cleaning
- Sterilization
- Functionality / Components
- Labeling
- Secondary packaging





The complete process to manufacture prefilled syringes

Two concepts: bulk and nested





The complete process to manufacture prefilled syringes

Two concepts: Process flow

- Infeed
- Cleaning
- Siliconization
- Assembly
- Sterilization
- Intermediate packaging
- Unpacking & outside decontamination
- Infeed on line
- Filling
- Control & Closing
- Labelling
- Packing

optional process step for
ready-to-fill/nested objects
at glass supplier





The complete process to manufacture prefilled syringes

Two concepts: Process flow

- Infeed
- Cleaning
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- Assembly
- Sterilization
- Intermediate packaging
- Unpacking & outside decontamination
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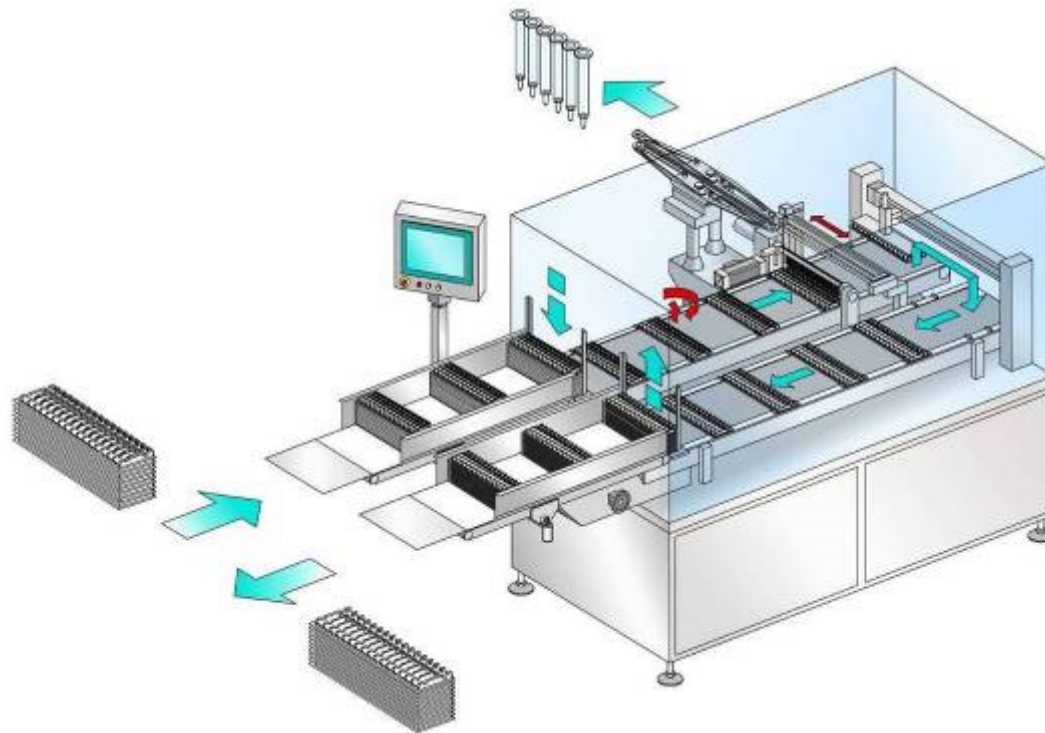
optional process step for ready-to-fill/nested objects at glass supplier

Process steps for already nested objects at pharma company



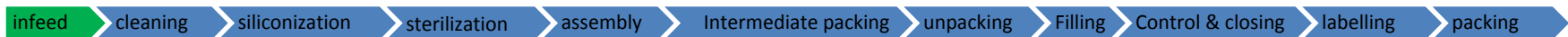
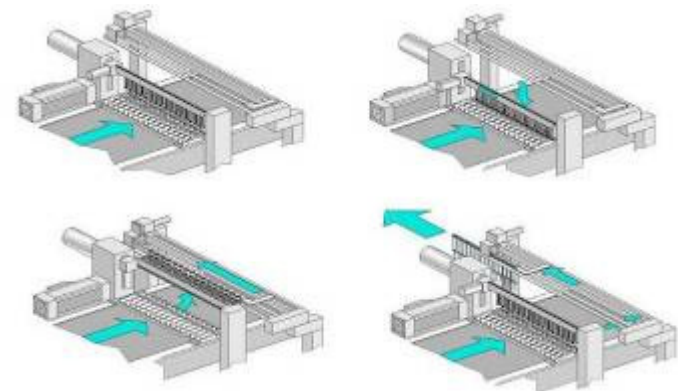
Pre-sterilized = bulk

Removing syringes from trays



traditional stressful version

New contactless version



Pre-sterilized = bulk

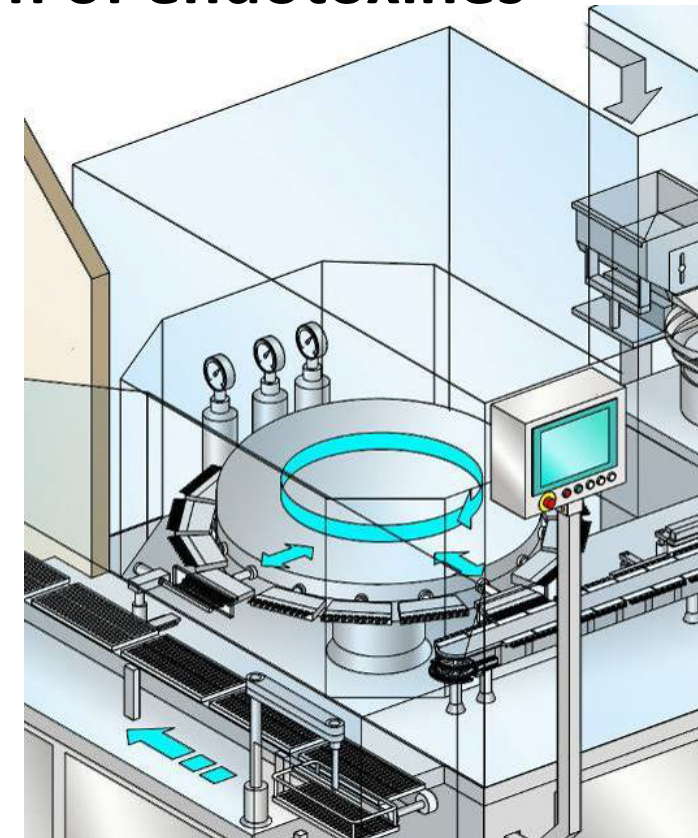
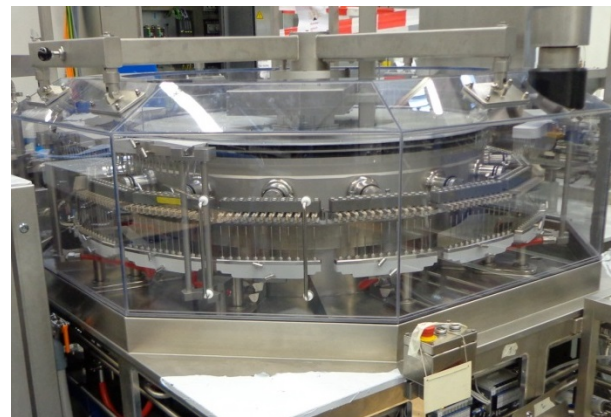
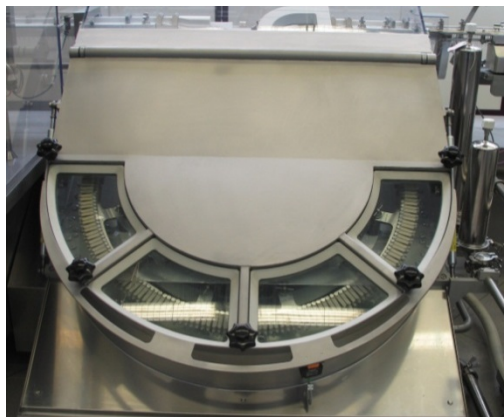
Separation of objects

Objects are removed from their packaging system (magazines or trays) and singularized for further processing



Pre-sterilized = bulk

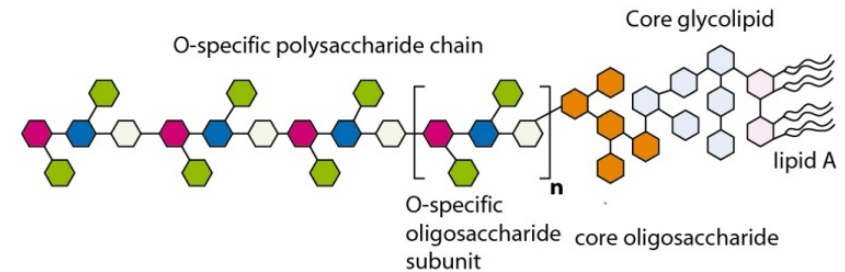
WFI cleaning
removal of „dirt“ and 3log-reduction of endotoxines
(polymer syringes are often just blown out before processing)



Endotoxines:

- Contained in cell-membranes of gram-negative microorganisms
- = Lipopolysaccharides
- Heat stable
- Cause fever and disease when injected
- Testing: clot formation of blue amoebocyte lysate of horseshoe crab (measured by e.g. turbidimetry)
- Washing process must show 3log-reduction of previously contaminated objects

Gram-negative bacterial endotoxin (lipopolysaccharide, LPS)



Source: Biomin



Source: sea-life_Pfeilschwanzkrebs.jpg

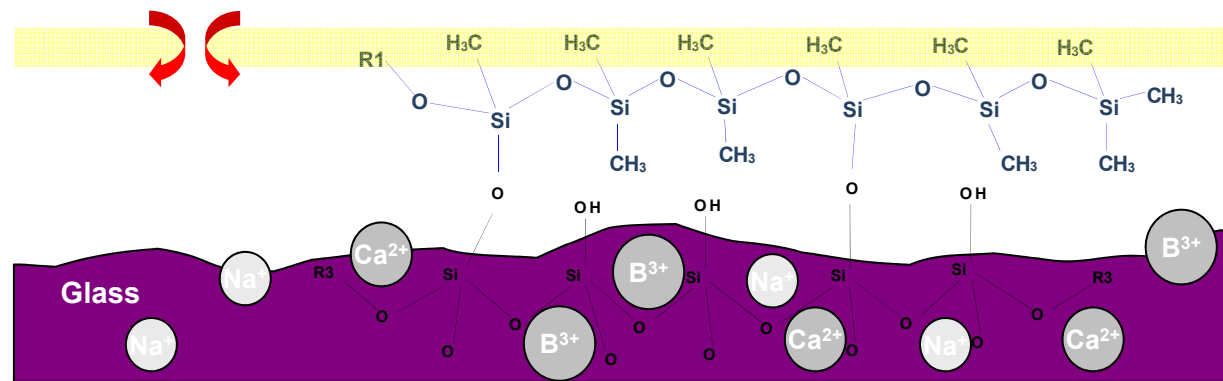


Source: nationalgeographic.de

infeed → cleaning → siliconization → sterilization → assembly → Intermediate packing → unpacking → Filling → Control & closing → labelling → packing

Reasons for siliconization

- Historically to improve **draining of vials, minimize residual vol.**
- **Chemical inactivation** of glass surface
- ↓ **frictional forces between needle and skin**
- ↓ **gliding forces** (frictional forces between stopper and glass) for **autoinjectors etc.**



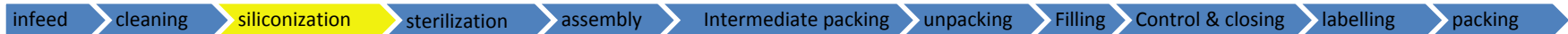
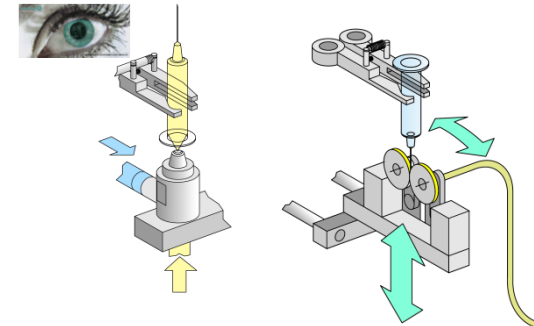
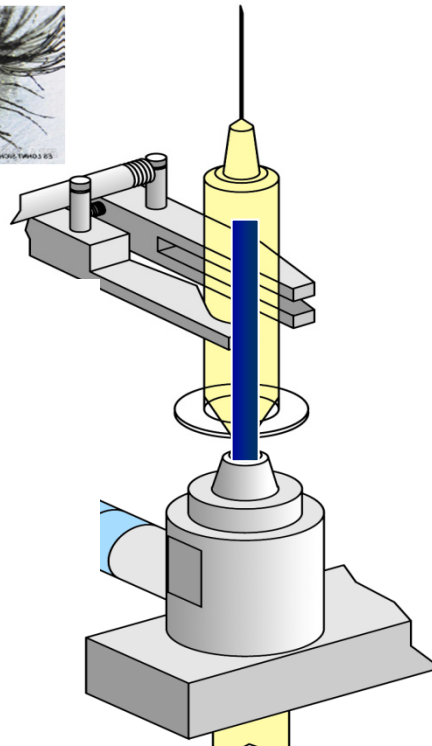
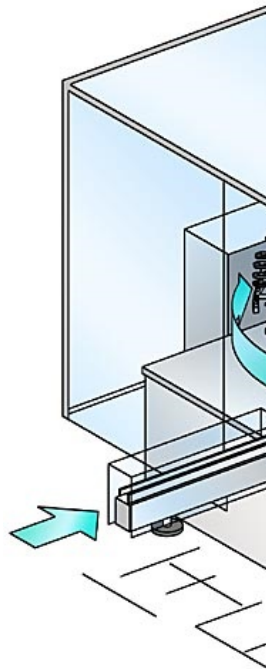


The complete process to manufacture prefilled syringes

Process flow: Siliconization

Syringes
Cartridges

Pre-sterilized = bulk

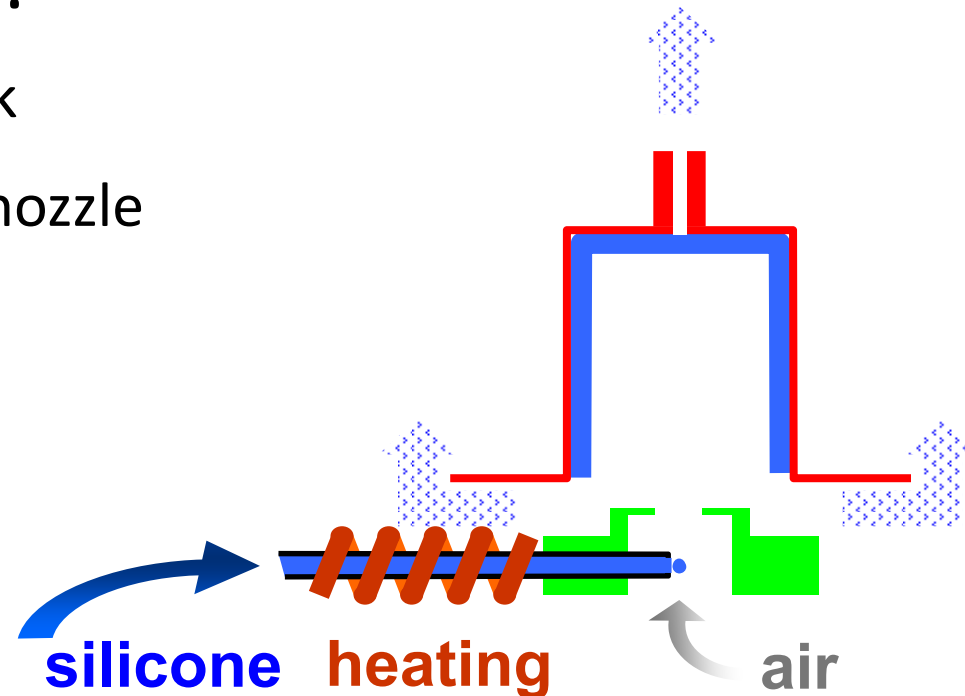
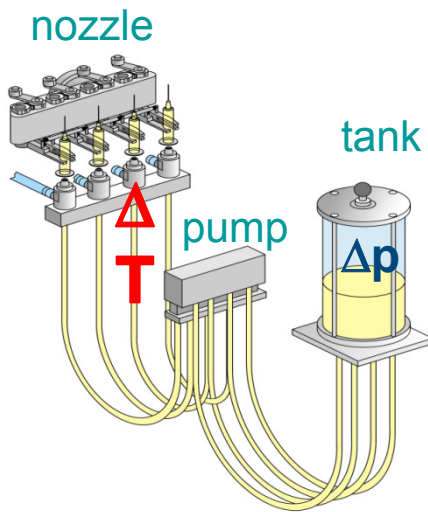


Pre-sterilized = bulk

Additional pre-heating for higher silicone oil – viscosity

High viscosity silicone oil involves different adjustments depending on higher viscosity:

- Pressurized silicone tank
- Heatable siliconization nozzle

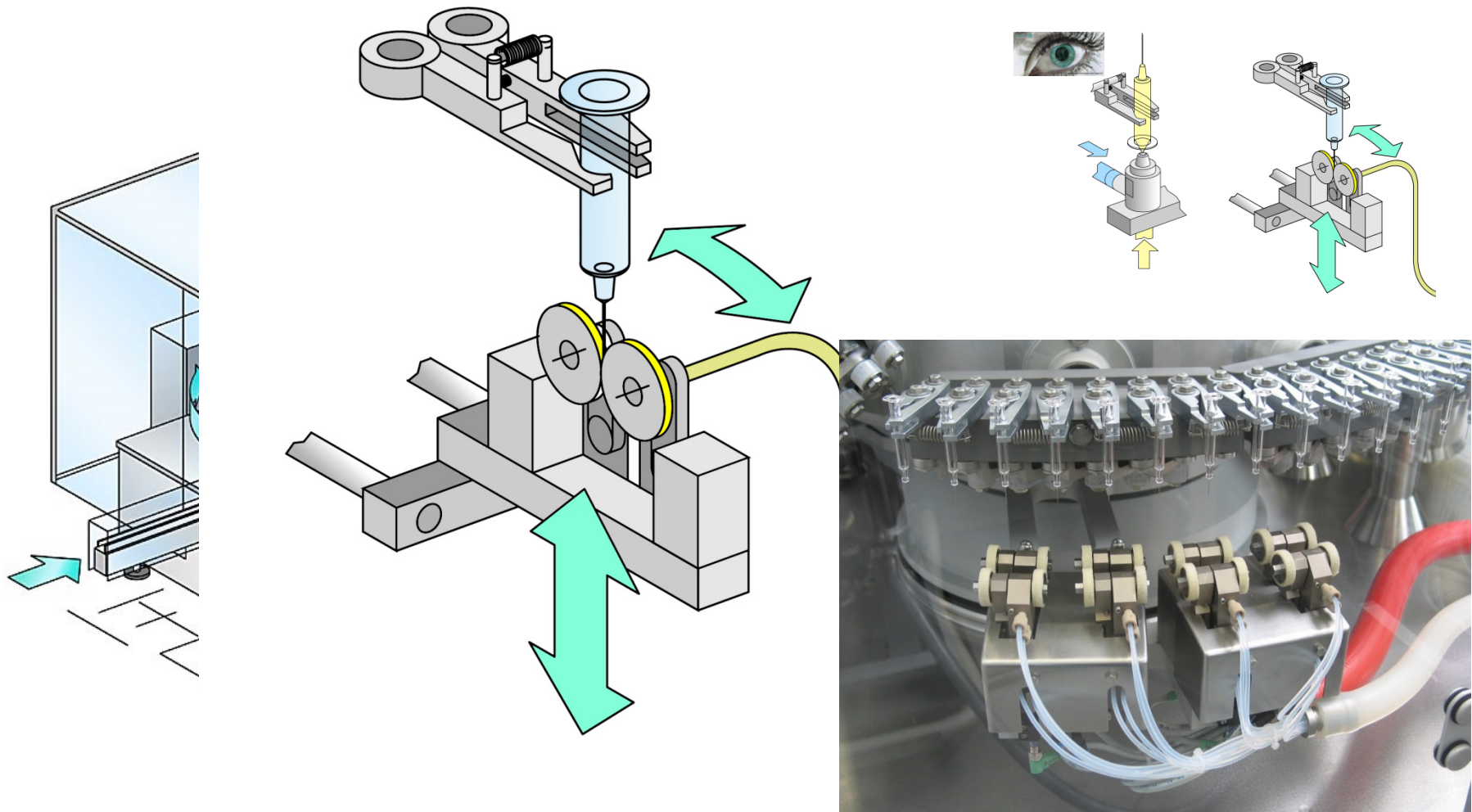


The complete process to manufacture prefilled syringes

Process flow: Siliconization

Syringes

Pre-sterilized = bulk



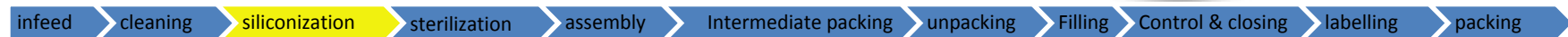
infeed → cleaning → **siliconization** → sterilization → assembly → Intermediate packing → unpacking → Filling → Control & closing → labelling → packing

Attribute to check: Amount - indirectly

	Control consumed amount silicone via scale at tank	Control air pressure and pump movement
Advantage	Simple After batch run	Simple 100% inline
Disadvantage	No information whether silicone is inside syringe or not No information about individual syringes and distribution Very imprecise approx. 0,5- 1,5mg/syringe => 100g resp.100ml /100.000 syringes	No information whether silicone is inside syringe or not No information about distribution within the syringe

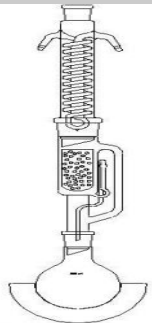


Source: mk-druckluft.de



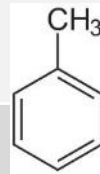
Attribute to check: Amount - directly

	Silicone extraction with Toluene in Soxhlet extractor	Brutto / Tara weighing before and after spraying
Advantage	Information about total amount of non-covalent bounded silicone on the glass surface	Simple Immediate result
Disadvantage	No information about distribution within syringe	Residual / volatile moisture influences result (Emulsions)
	Costly & time consuming	Emulsions: no information about water / oil distribution
	Delayed results	Only statistical
	Hazardous chemicals needed	Destructive



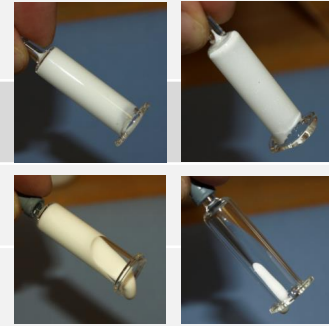
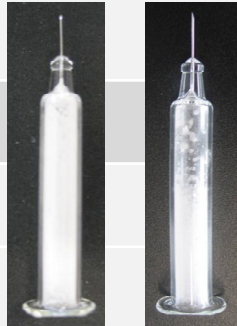
Extraction app.

<http://www.chempage.de/lexi/soxhlet.htm>



Attribute to check: distribution

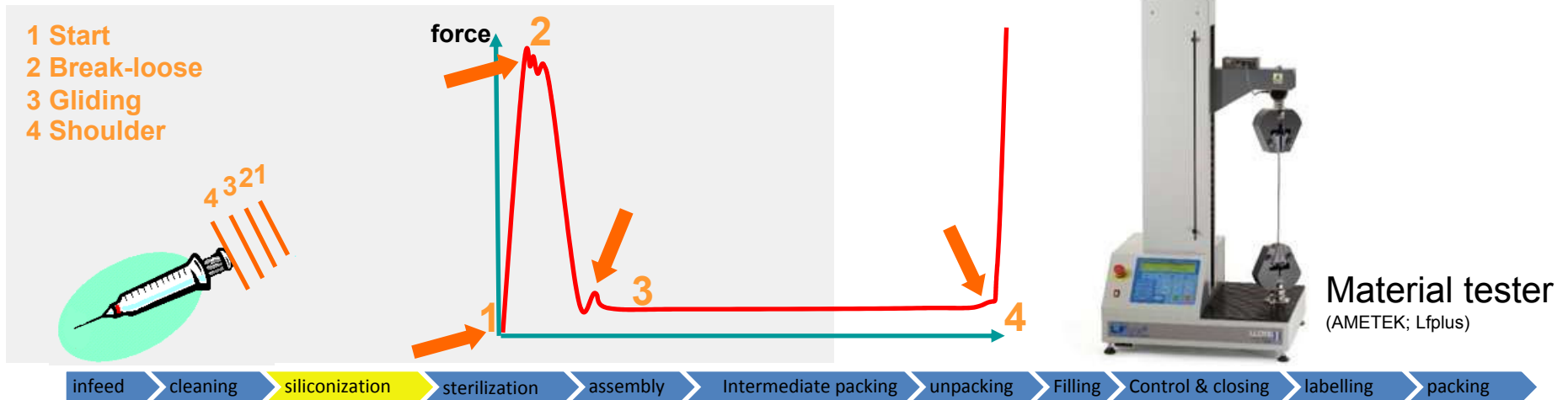
	Visualize with glass dust	Visualize with zink-alginate
Substrate	Glass powder <63µm grain size	Zink-alginate suspension
Principle	Sticks to siliconized surfaces	Sticks to non-siliconized surfaces
Advantage	Information siliconized yes / no	Information siliconized yes / no
	Distribution within the syringe	VERY sensitive
Disadvantage	Statistical	Statistical
	Manual	Manual
	Destructive	Destructive
		Protracted



Attribute to check: effect of siliconization

Measuring of forces during stopper movement

Advantage	Information about gliding effects (goal of siliconization)
Disadvantage	No in-line procedure
	Costly & time consuming
	No information about distribution within the syringe

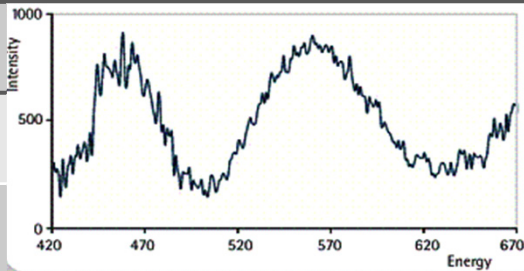




The complete process to manufacture prefilled syringes

Process flow: Siliconization Check

	Interferometry	Light dispersion
Attribute	Layer thickness distribution	distribution
Principle	reflected waves Elimination correlates to thickness	silicone droplets change light dispersion
Example	RapID	groninger
Properties	Manual	Automated
	Statistic	
Duration	Minutes	Inline: 400 parts/min

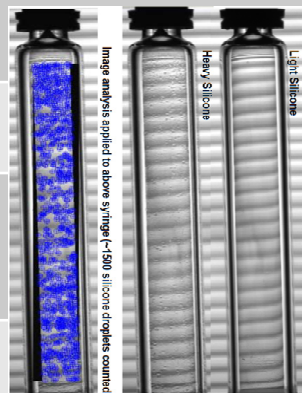
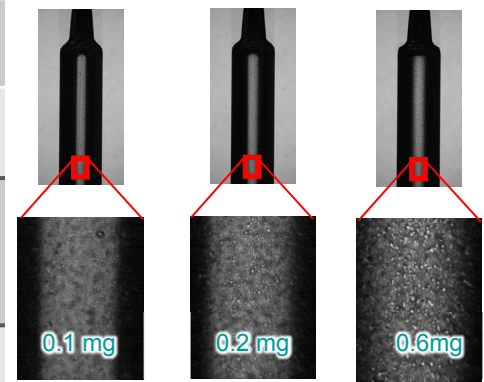




The complete process to manufacture prefilled syringes

Process flow: Siliconization Check

	Blacklight variation	Darkfield microscopy
Attribute	distribution	Droplet size distribution
Principle	Black & white stripes visualize droplets	Darkfield optics show droplets boundaries
Example	ZebraSci	ISRA vision & groninger
Properties	Manual	Automated
	Statistic	100% IPC at 600 parts/min
	Up to 100%	without rotation 3-30% of surface investigable
		graduated areas not detectable
Duration	Seconds	Milliseconds



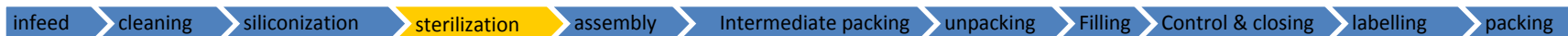
Pre-sterilized ≠ ~~bulk~~

Also stove process for emulsive siliconizations

Sterilization principles

- Chemical sterilization
- Dry heat
- Autoclaving
- Gamma irradiation

Depyrogenisation by cleaning
or „inactivation“ of pyrogens with
dry heat (at least 180° for 3h)





The complete process to manufacture prefilled syringes

Process flow: Siliconization “baked on”

All objects

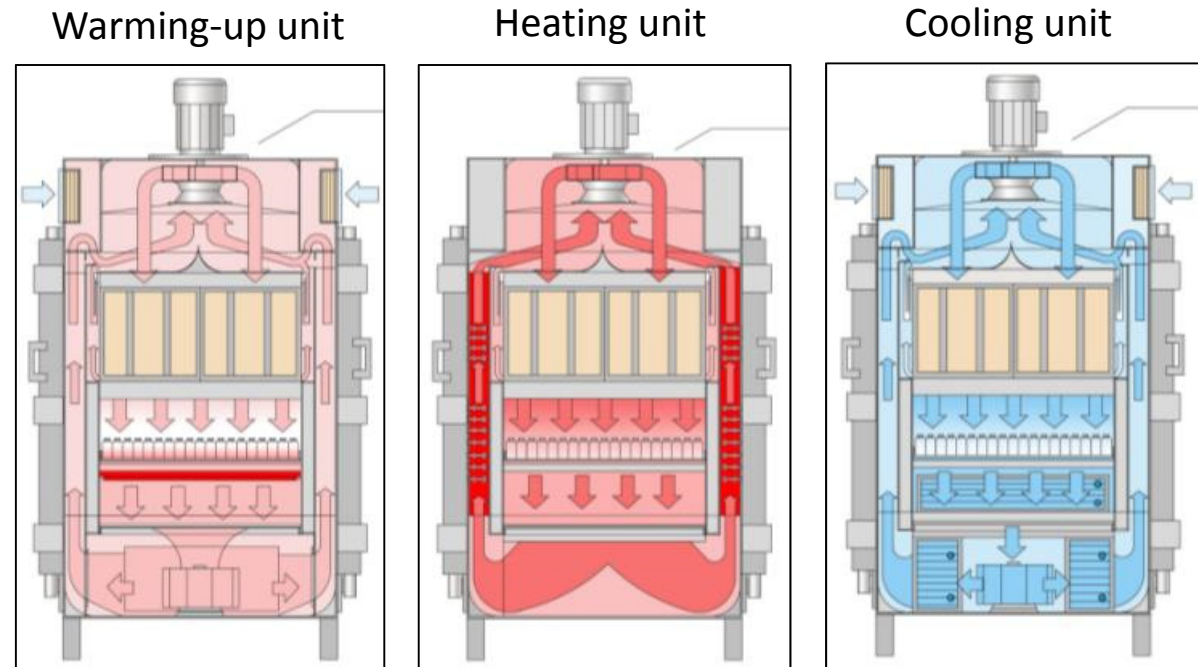
Pre-sterilized ? bulk

Depyrogenization included



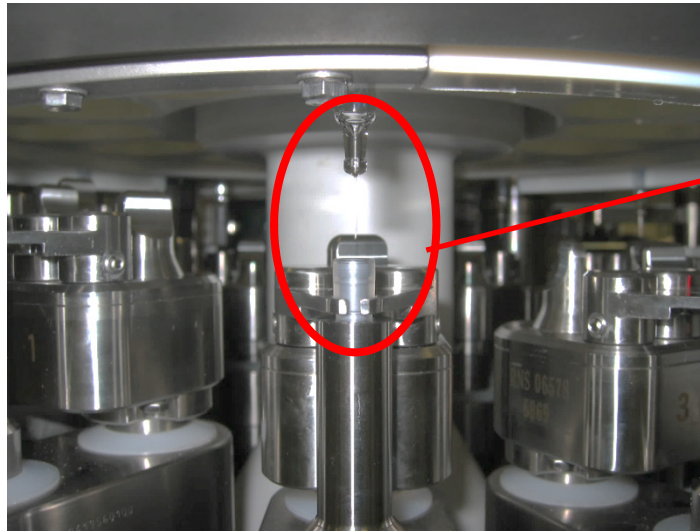
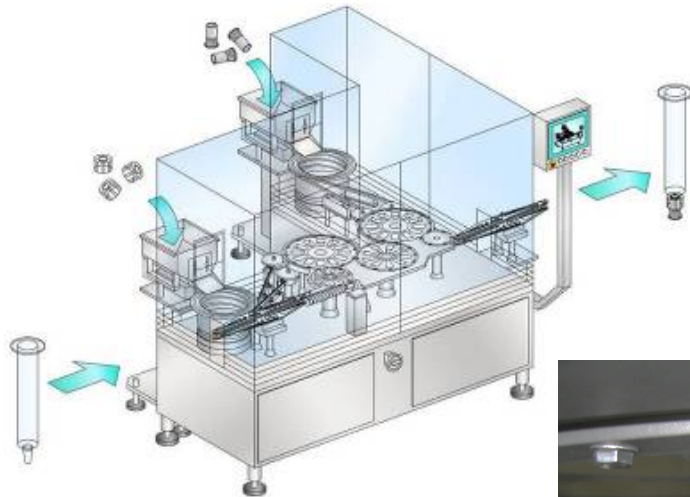
PREVIOUS TO assembly of rubber or plastics!

Removal of hydrogen coverage!



Pre-sterilized = bulk

Assembly of syringe components from beneath





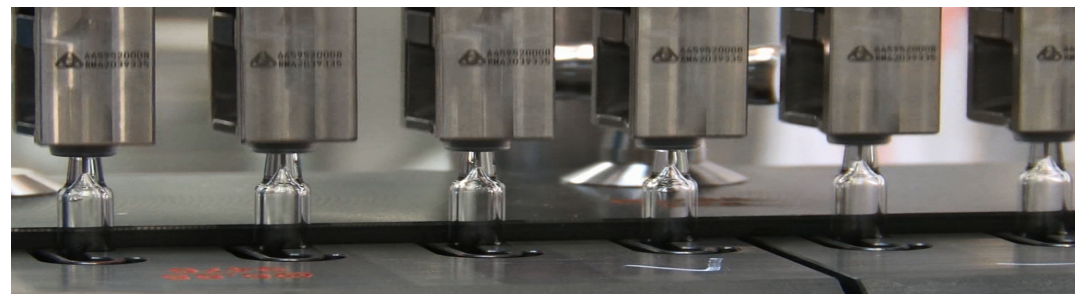
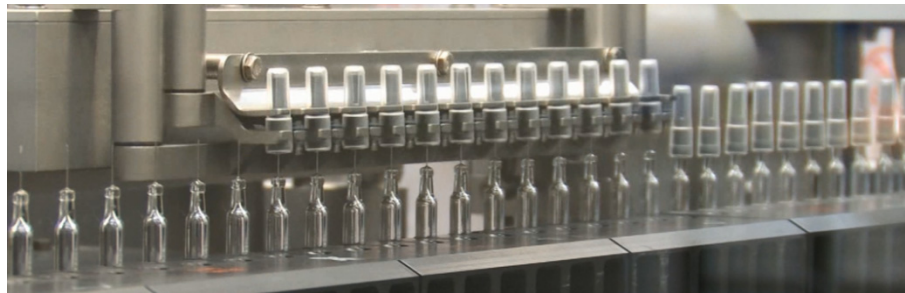
The complete process to manufacture prefilled syringes

Process flow: Assembly RNS

Syringes

Pre-sterilized = bulk

Assembly of syringe components from top



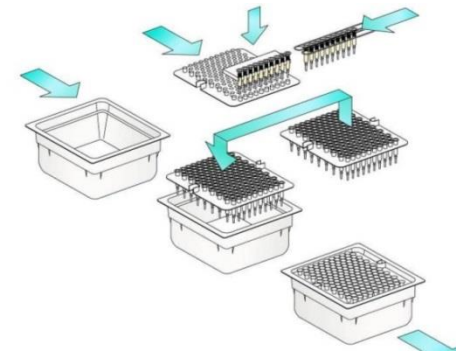
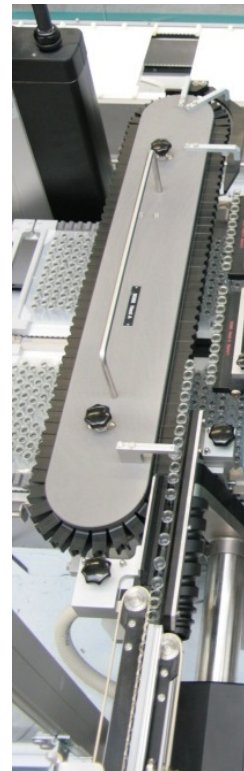
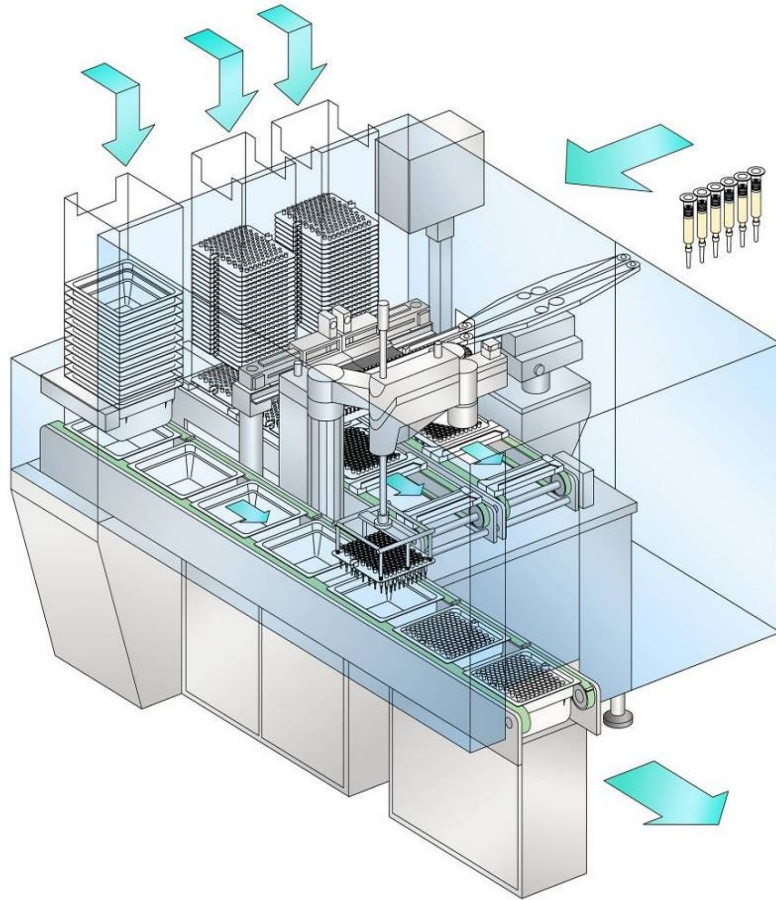


The complete process to manufacture prefilled syringes

Process flow: Intermediate packaging “nested” All objects

Pre-sterilized ~~≠ bulk~~

Nesting sterilized objects



infeed → cleaning → siliconization → sterilization → assembly → **Intermediate packing** → unpacking → Filling → Control & closing → labelling → packing

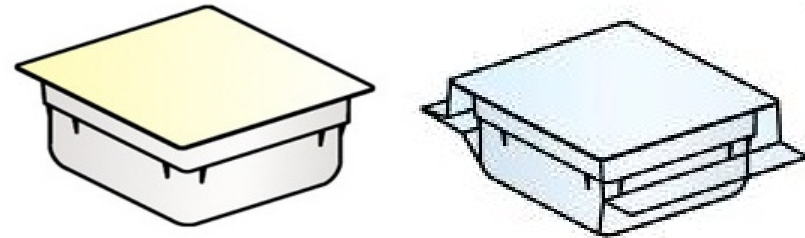


The complete process to manufacture prefilled syringes

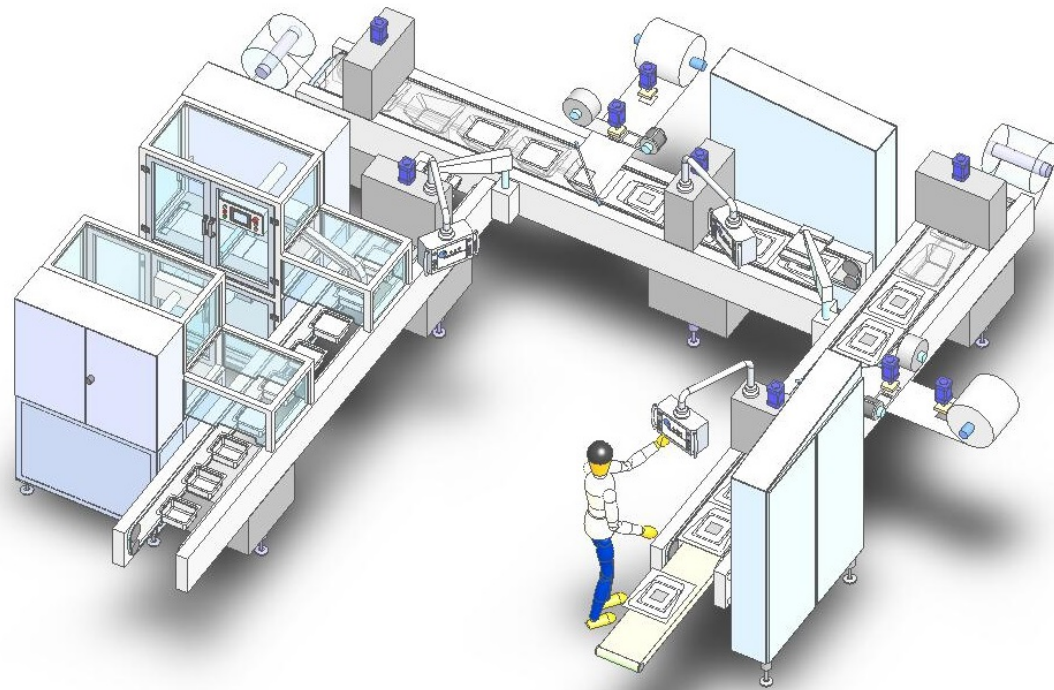
Process flow: Intermediate packaging “nested” All objects

Pre-sterilized ≠ ~~bulk~~

Manual or
automated handling of:



- intermediate tyvek
- sealing layer
- pouch





- **Material**
- **Forming**
- **Cleaning**
- **Siliconization**
- **Pre-Assembly**
- **Sterilization**

Part 1

- **Unpacking**
- **Filling**
- **Control & Closing**
- **Labeling**
- **Secondary packaging**

Part 2



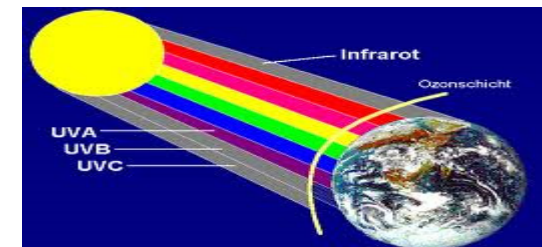
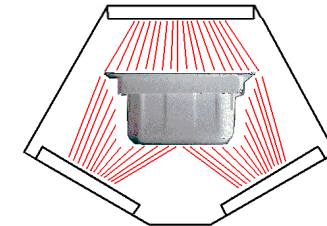
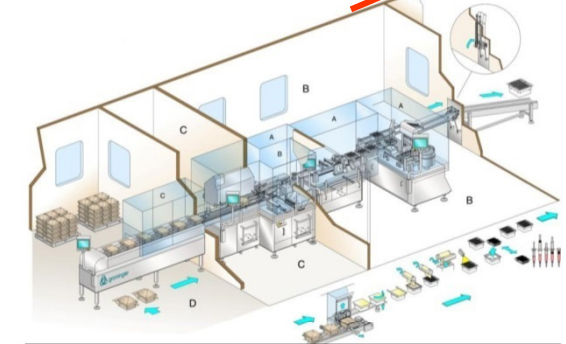


The complete process to manufacture prefilled syringes

Process flow: Outside Decontamination

All nested Objects

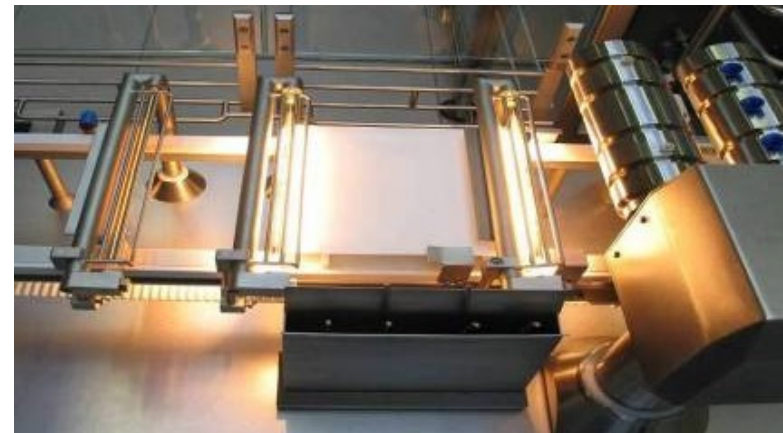
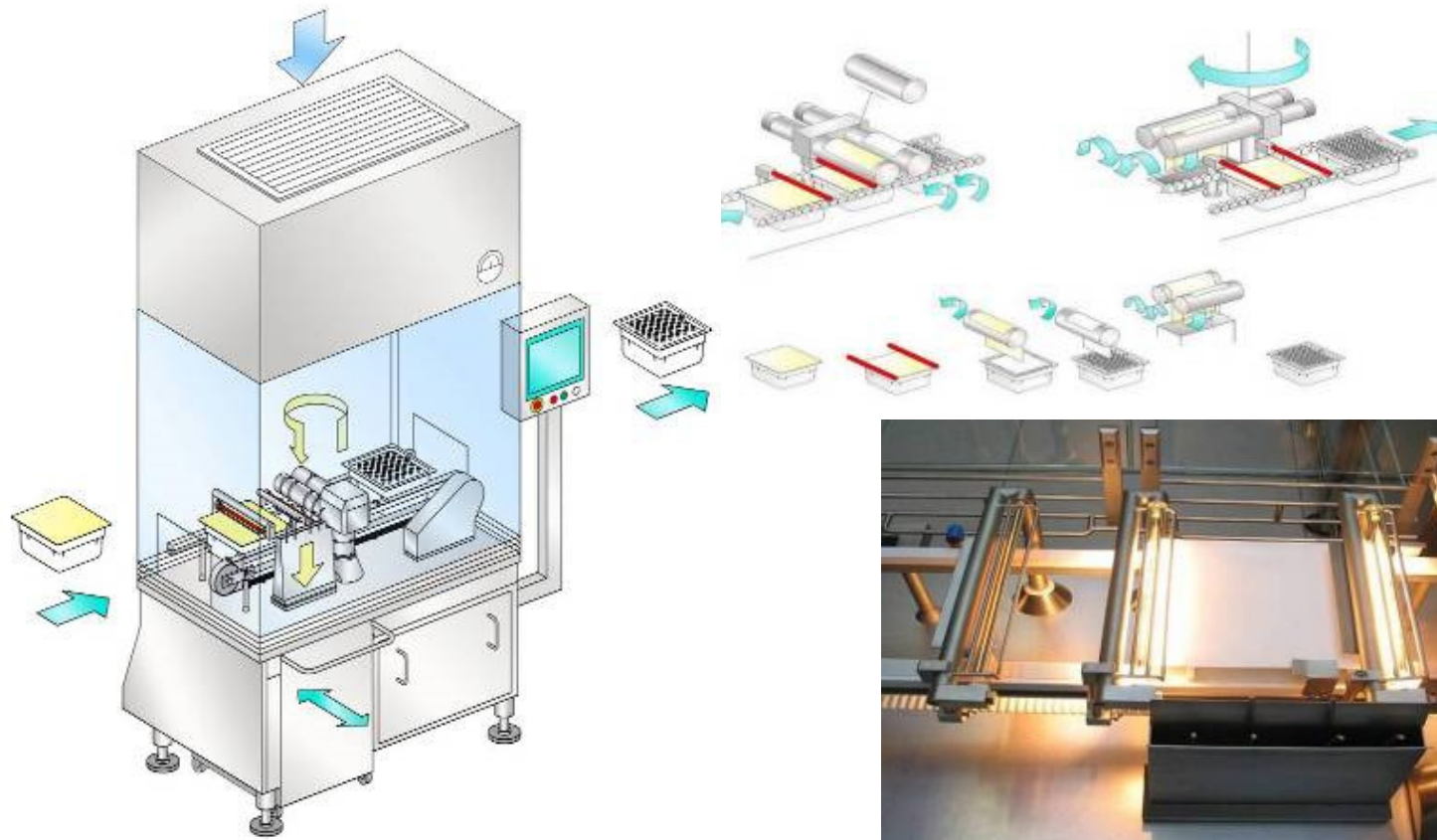
Pre-sterilized ~~≠ bulk~~



procedure	note
zone concept	no disinfection
spraying alcohol	not sporicidal; difficult validation; 10^2 kill
Aerosol (VHP) / wetting by H_2O_2	15min - 6h erosion of material residuals (Tyvek)
E-beam	Radicals; oxidation; radiation; expensive
UV-light	max. killing rate 10^3 shadowing effects
Plasma	New technology

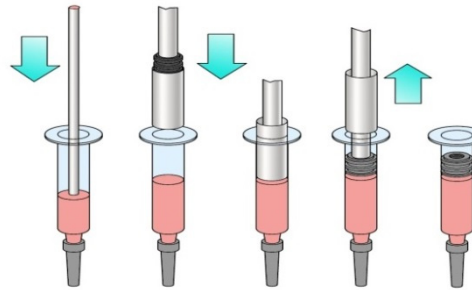
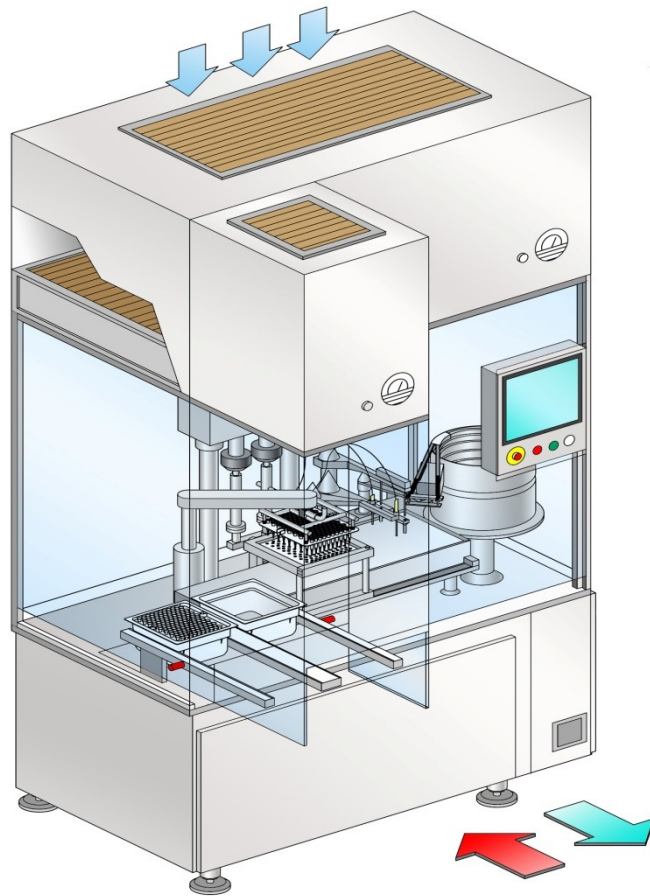


Removal of lid foils & fleece inserts



Pre-sterilized ≠ ~~bulk~~

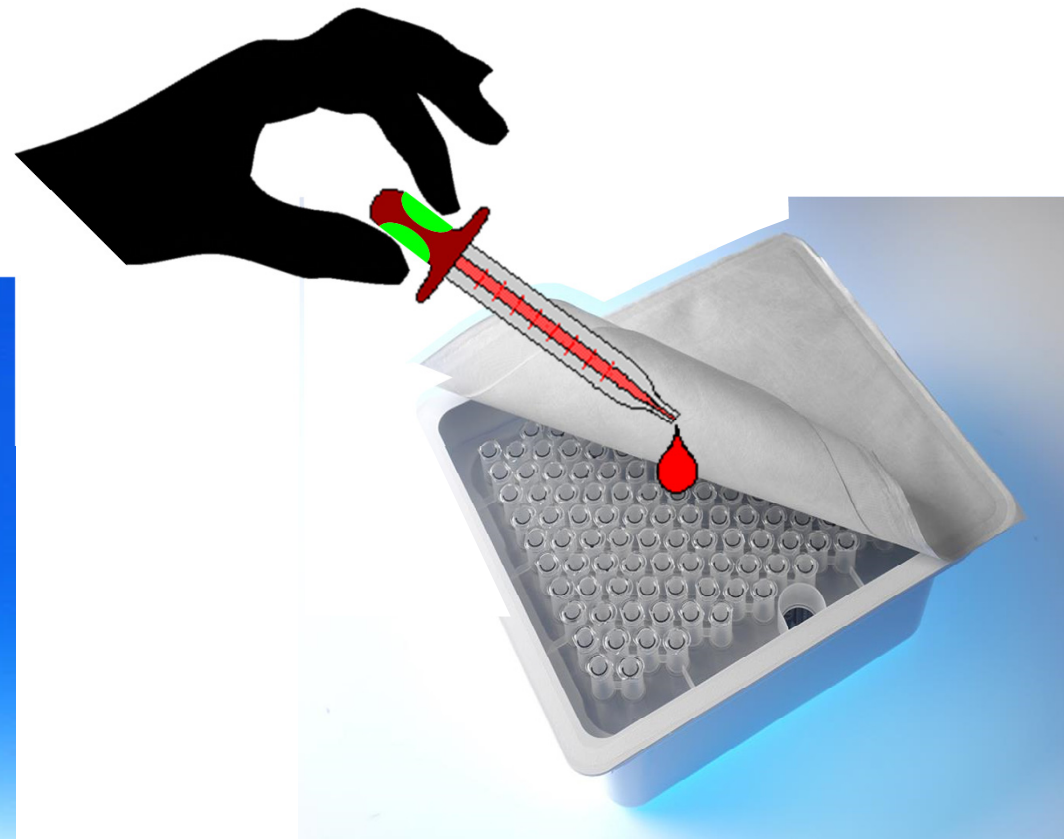
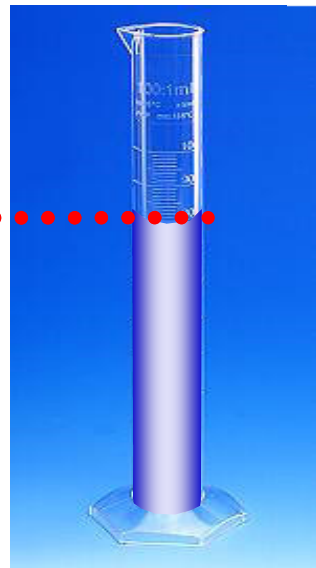
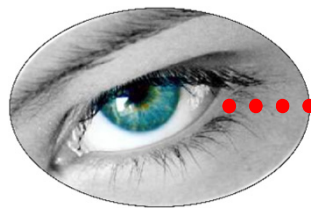
Filling of nested objects in nest



infeed → cleaning → siliconization → sterilization → assembly → Intermediate packing → unpacking → **Filling** → Control & closing → labelling → packing

Filling – the theory behind

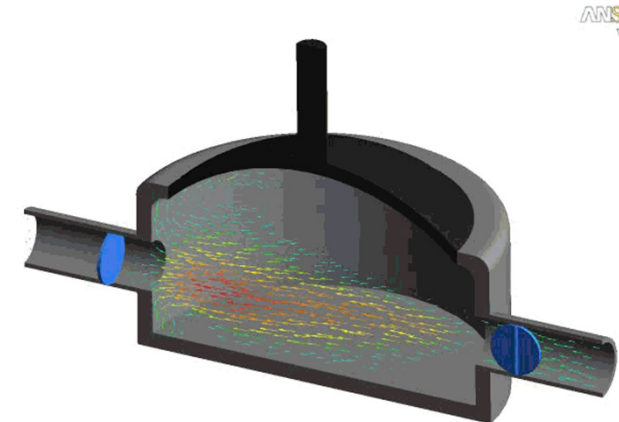
- Volumetric filling
- Controlled filling



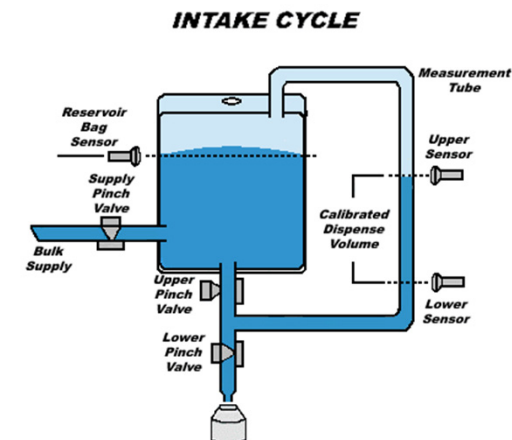
The complete process to manufacture prefilled syringes

Filling pumps

- Diaphragm pump
- Gravimetric pump
- Magnetic-inductive
- Filling on a weighing cell
-



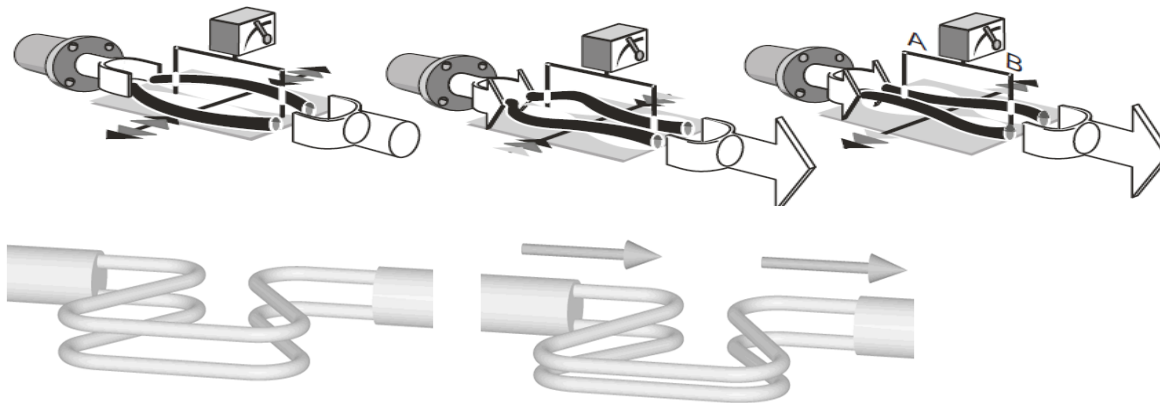
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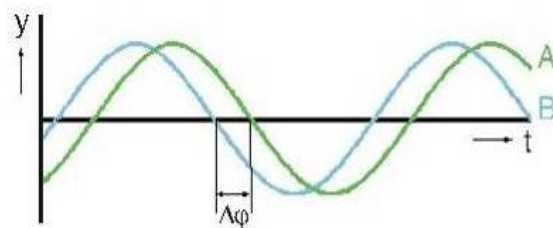
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Mass flow

Controlled filling by pressure, mass controlled



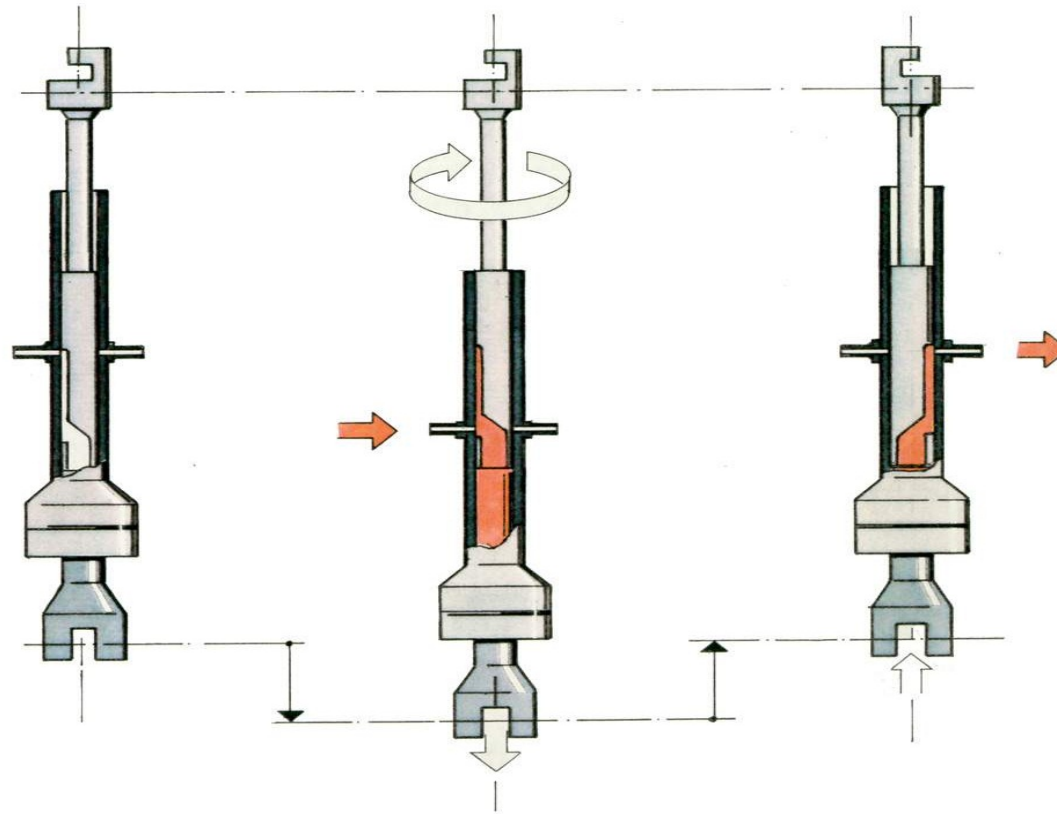
Source: wikipedia



- infeed
- cleaning
- siliconization
- sterilization
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Rotary piston pump (RPP)

Volumetric filling

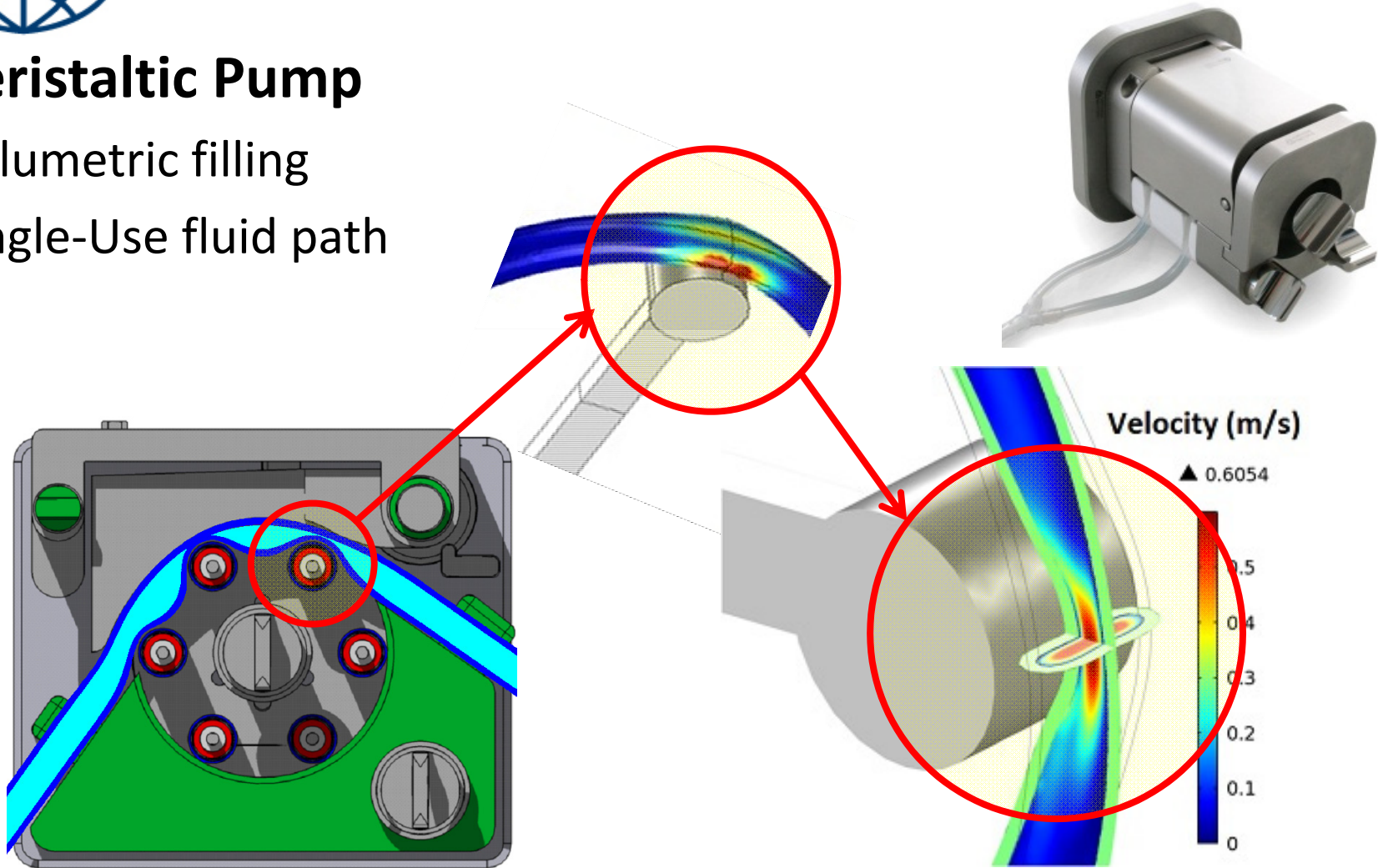


infeed > cleaning > siliconization > sterilization > assembly > Intermediate packing > unpacking > **Filling** > Control & closing > labelling > packing

Peristaltic Pump

Volumetric filling

Single-Use fluid path

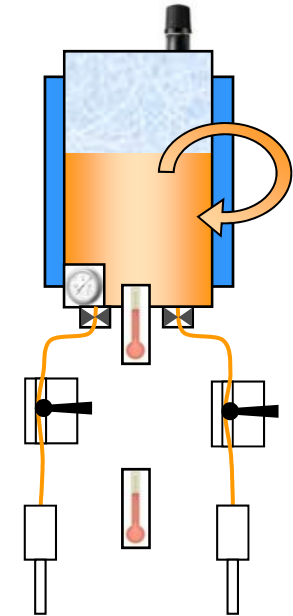
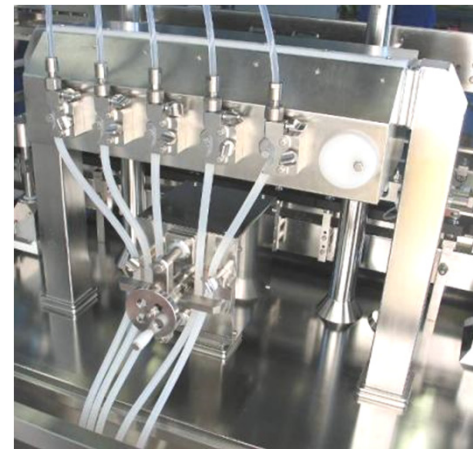
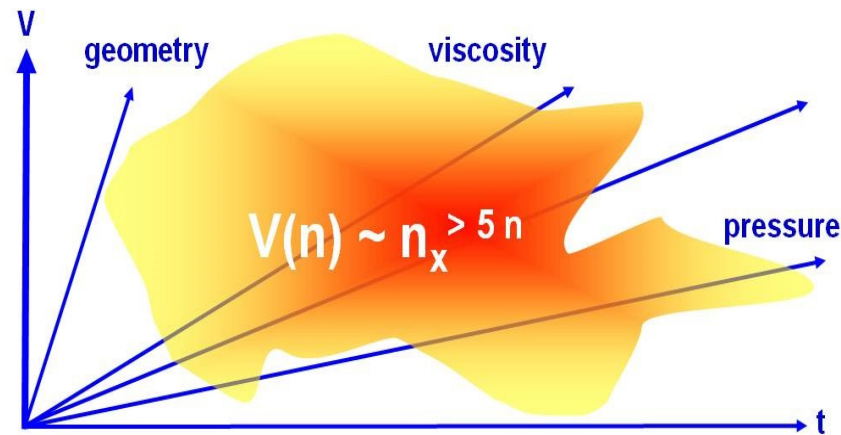


Time pressure system

Filling volume $V = F(p, t, \mu)$

Resistance $\mu = F(\text{geometry } [x], \text{velocity, viscosity } F [T])$

F(x): Function of
p: pressure
t: time
T: temperature



Single-Use rotary piston pump

- Stainless steel
- well established filling system
- well established material
- multipurpose filling lines
- useable on all servo-driven
groninger filling lines
- Ready-to-use & completely validated



The complete process to manufacture prefilled syringes

Single-use product flow path





The complete process to manufacture prefilled syringes

Comparing Filling pumps

Criteria	Rotary piston	Peristaltic	Time-pressure	Mass flow
High viscosity	++	-	+	-
Filling accuracy	++	+	+ (+)	+
Easy in production	++	+	--	+
No system-IPC required	++	-	--	++
Product temperature	++	++	-	++
CIP/SIP – compatible	+	++	+ (+)	++
Performance	++	+	++	-
Filling range	+	++	++	-
shear forces	-	+	++	++
Single-Use	+	++	-	--

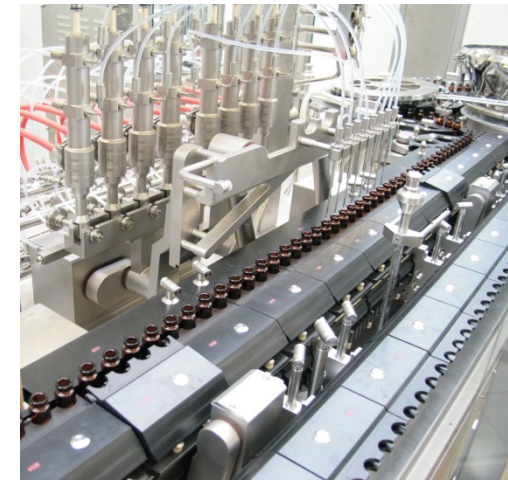


Pre-sterilized = bulk

In process control (IPC)

Control of filling amount

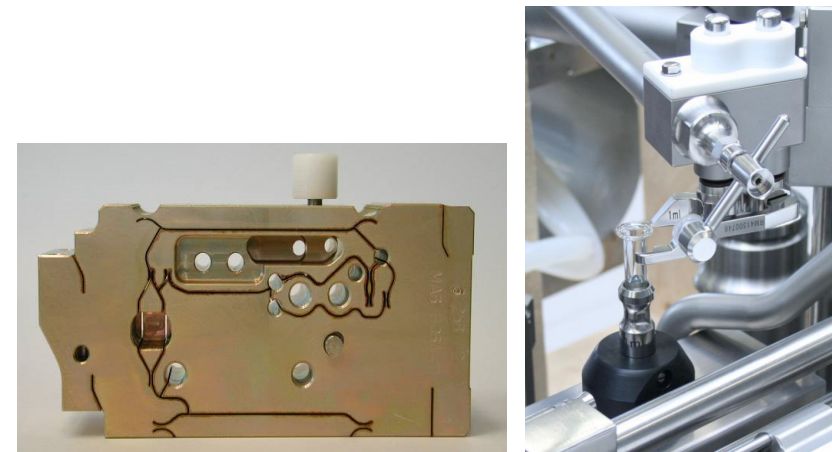
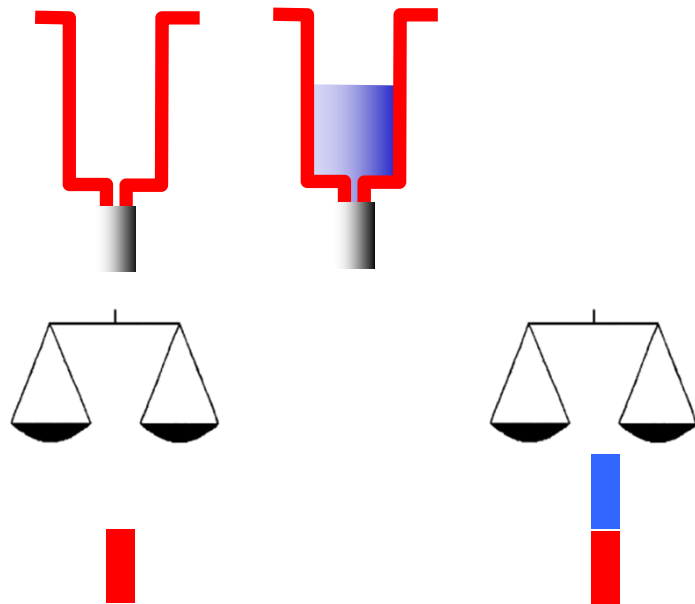
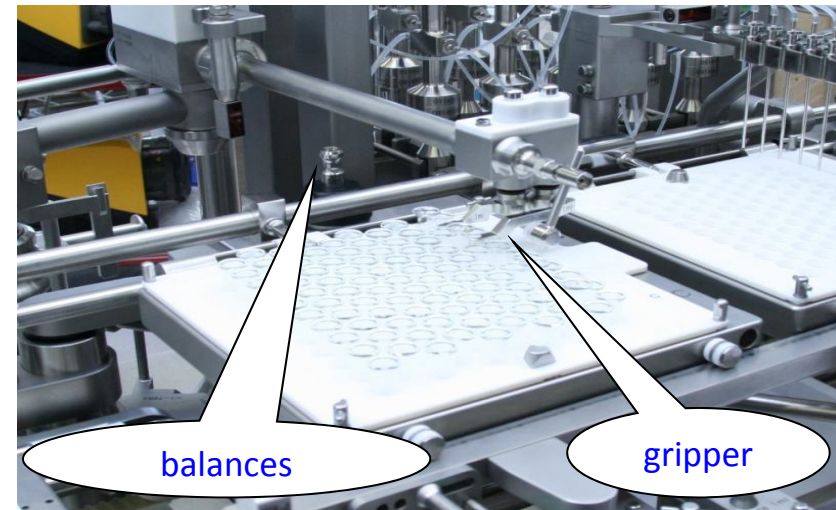
- Optical (sensor filling of cartridges)
- Gravimetric (syringes & vials)



infeed > cleaning > siliconization > sterilization > assembly > Intermediate packing > unpacking > Filling > Control & closing > labelling > packing

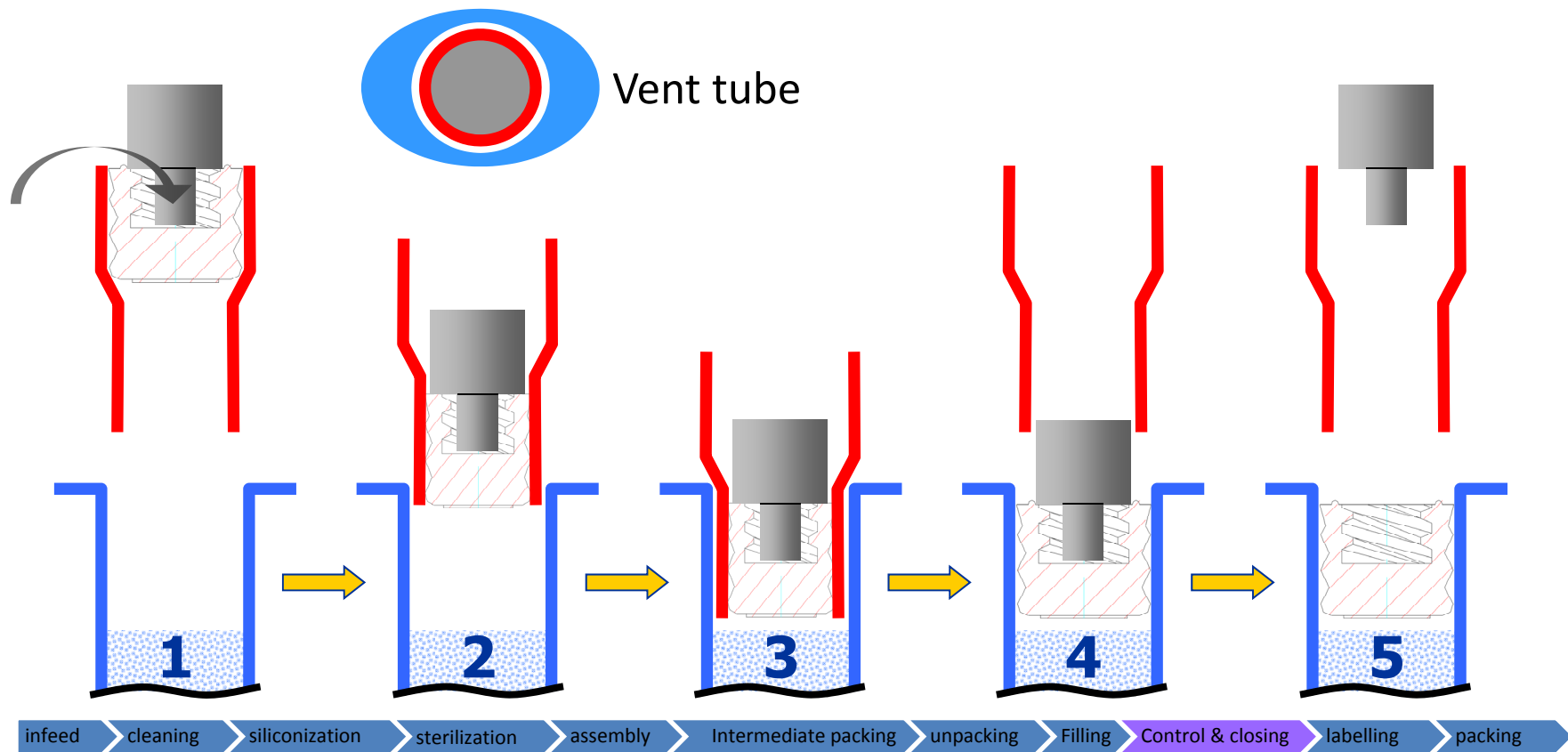
- Tare-Weighing
- Filling
- Cross-Weighing
- Stoppering

Pre-sterilized = bulk



Pre-sterilized = bulk

mechanical insertion - using a vent tube





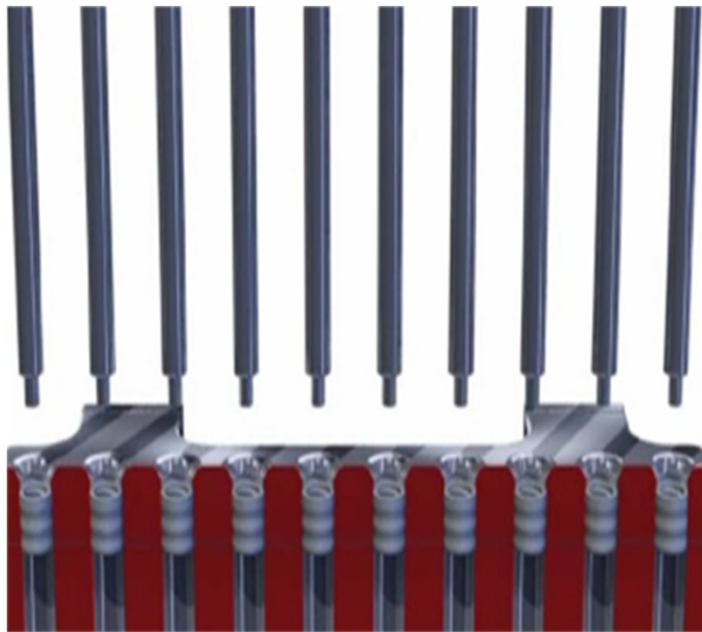
The complete process to manufacture prefilled syringes

Process flow: Stoppering

Syringes
Cartridges

Pre-sterilized = bulk

mechanical insertion - using a vent tube

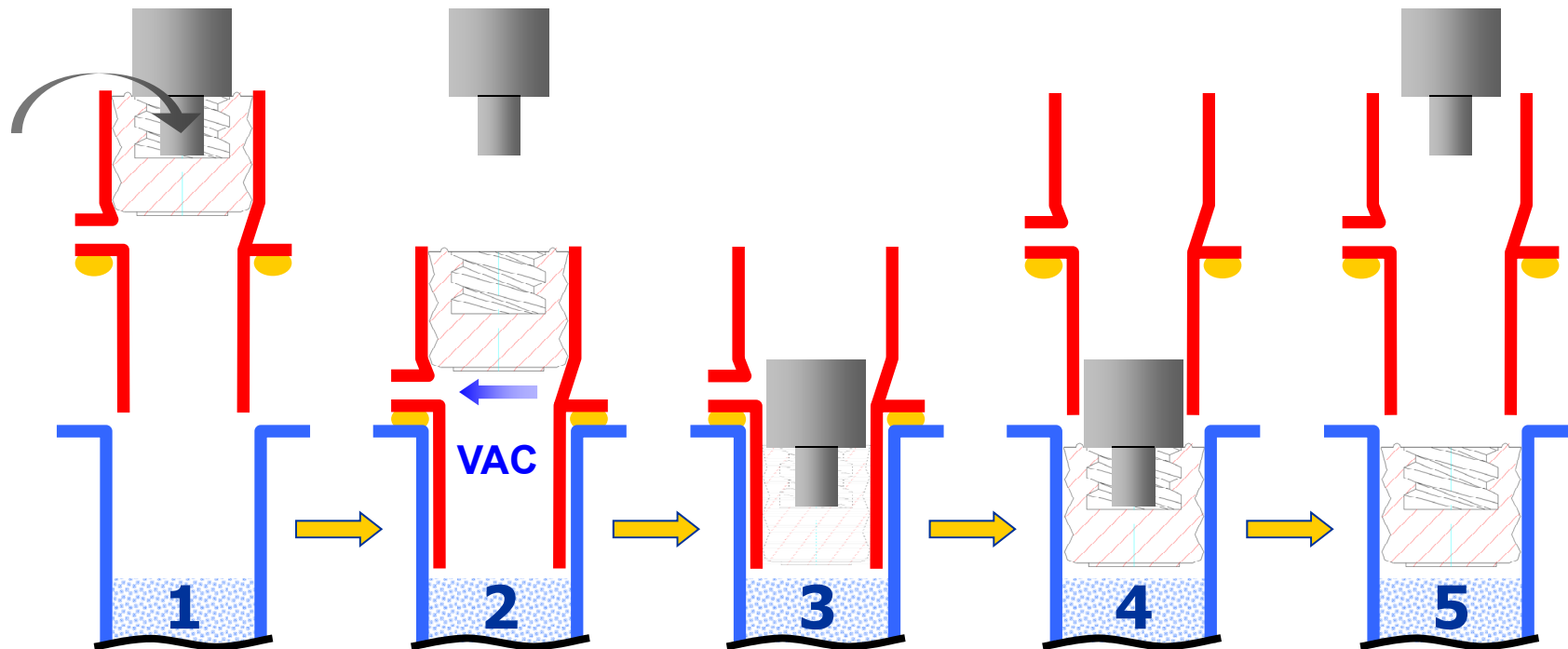


infeed > cleaning > siliconization > sterilization > assembly > Intermediate packing > unpacking > Filling > Control & closing > labelling > packing

Pre-sterilized = bulk

mechanical insertion – assisted by vacuum

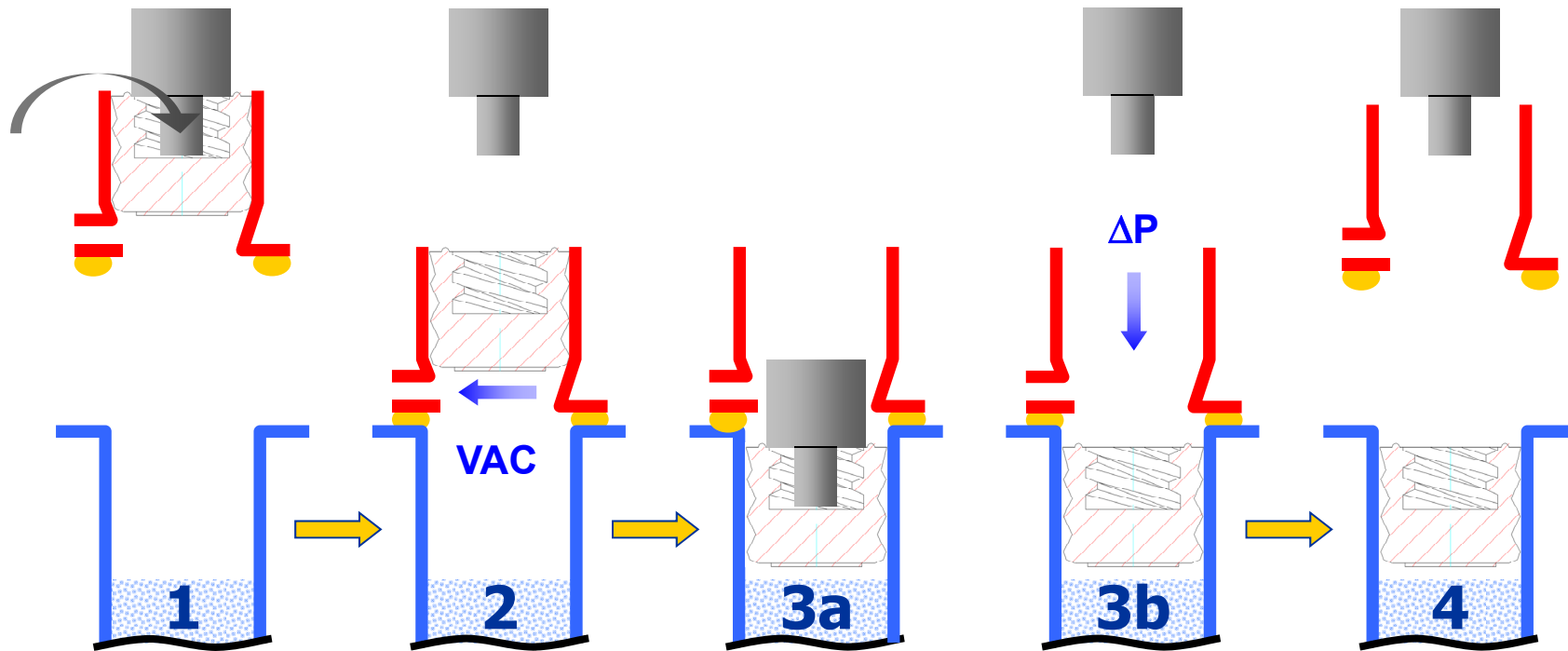
(still using a vent tube)



infeed > cleaning > siliconization > sterilization > assembly > Intermediate packing > unpacking > Filling > Control & closing > labelling > packing

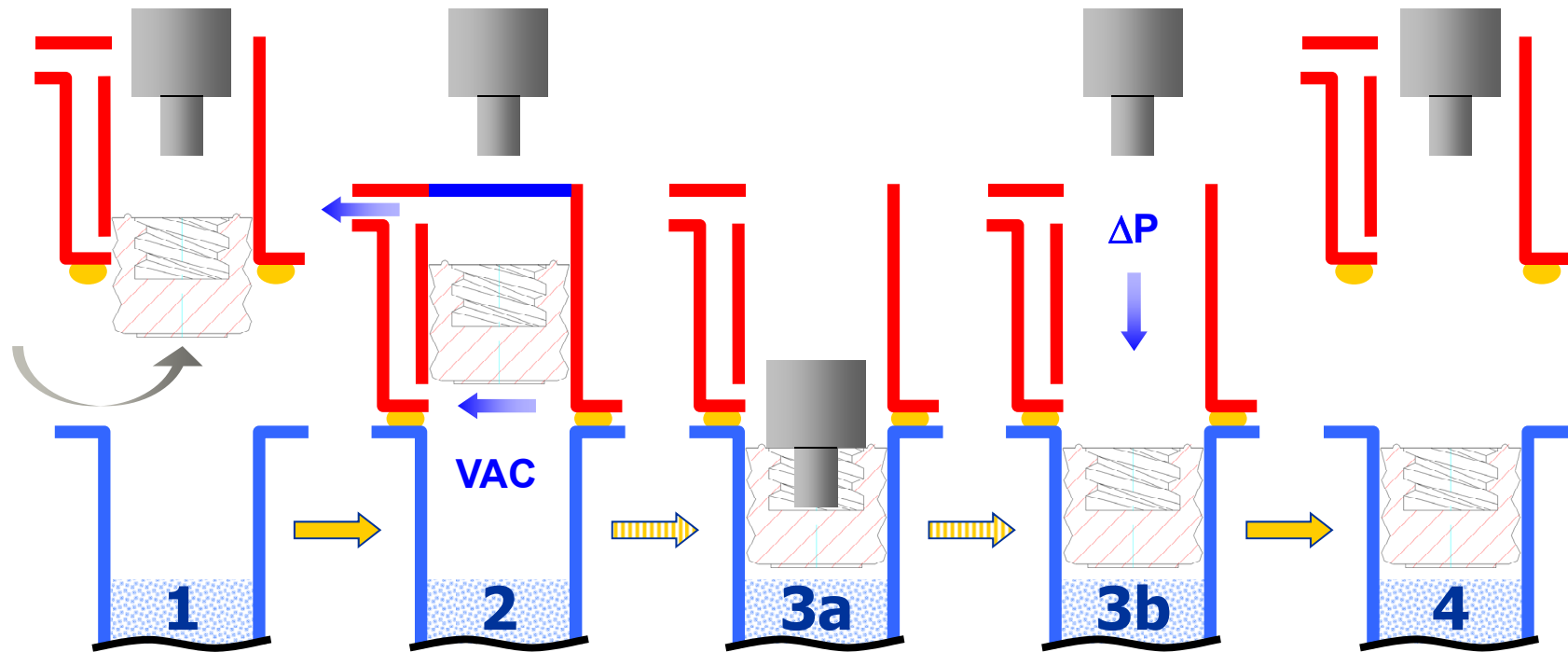
Pre-sterilized = bulk

vacuum insertion - "classic"



Pre-sterilized = bulk

vacuum insertion - improved

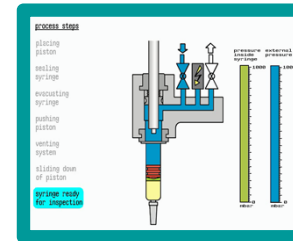
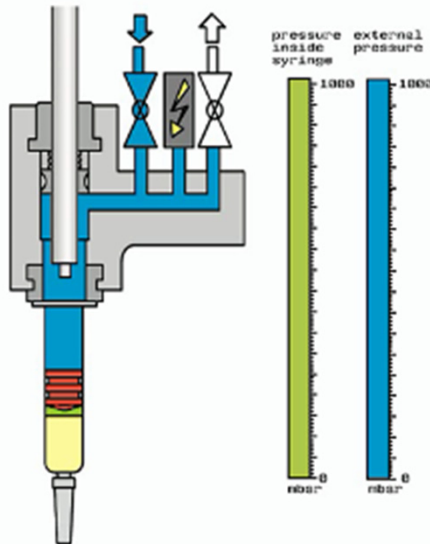


Pre-sterilized = bulk

vacuum insertion

process steps

- placing piston
- sealing syringe
- evacuating syringe
- pushing piston
- venting system
- sliding down of piston
- syringe ready for inspection**

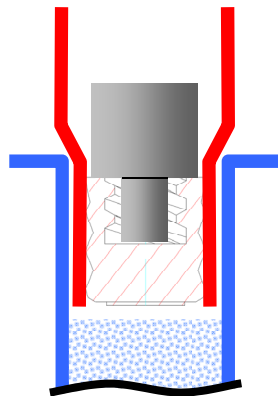


infed → cleaning → siliconization → sterilization → assembly → Intermediate packing → unpacking → Filling → **Control & closing** → labelling → packing

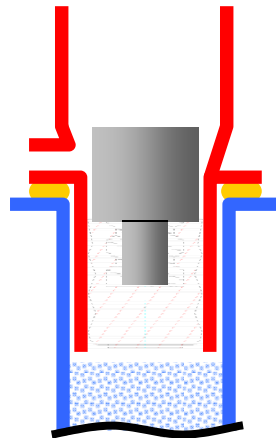
Pre-sterilized = bulk

“summary”

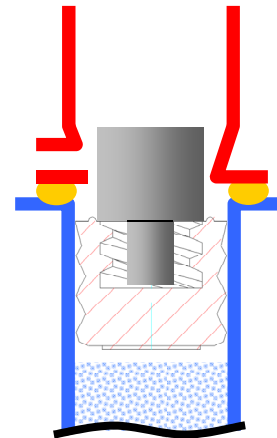
mechanical



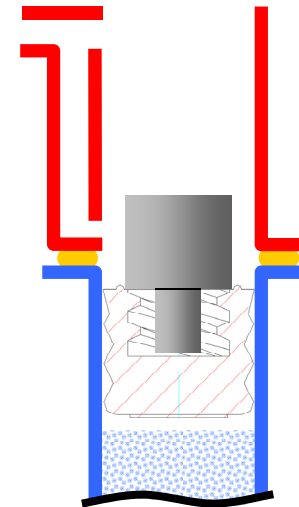
mechanical
+ vacuum



vacuum
“classic”



vacuum
“improved”



Note: filling by tip is not shown in special, as plunger insertion is similar to the above mentioned methods, but done by the primary packaging supplier





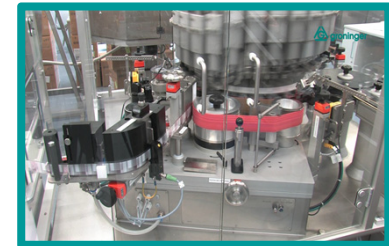
The complete process to manufacture prefilled syringes

Process flow: Labeling

All objects

Pre-sterilized = bulk

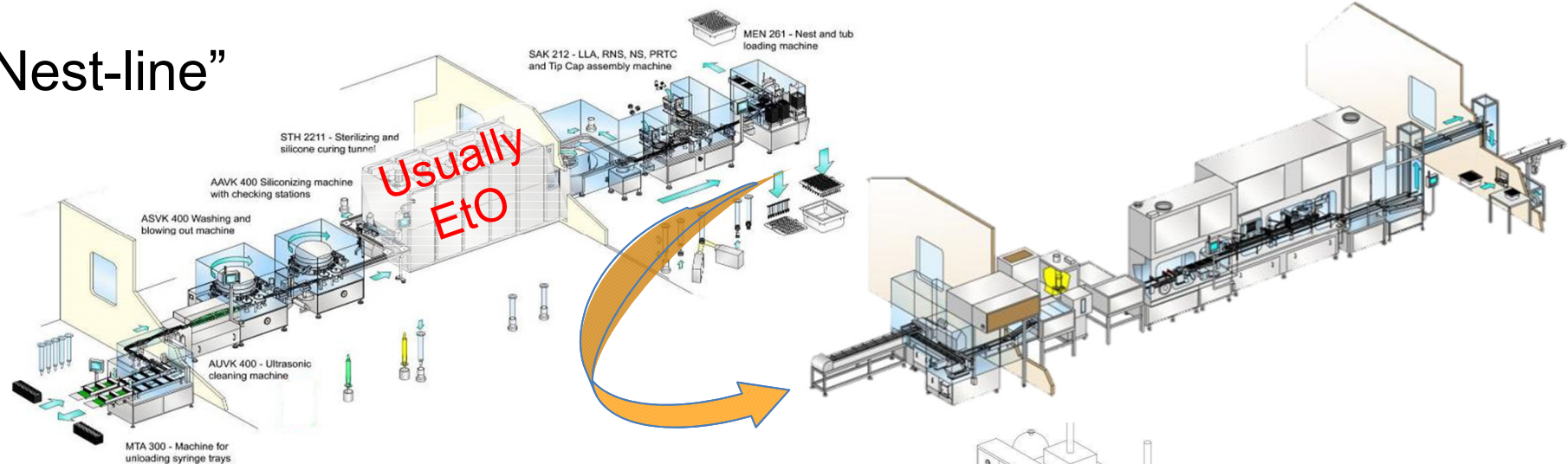
Same process for all objects
nested objects need to be denested



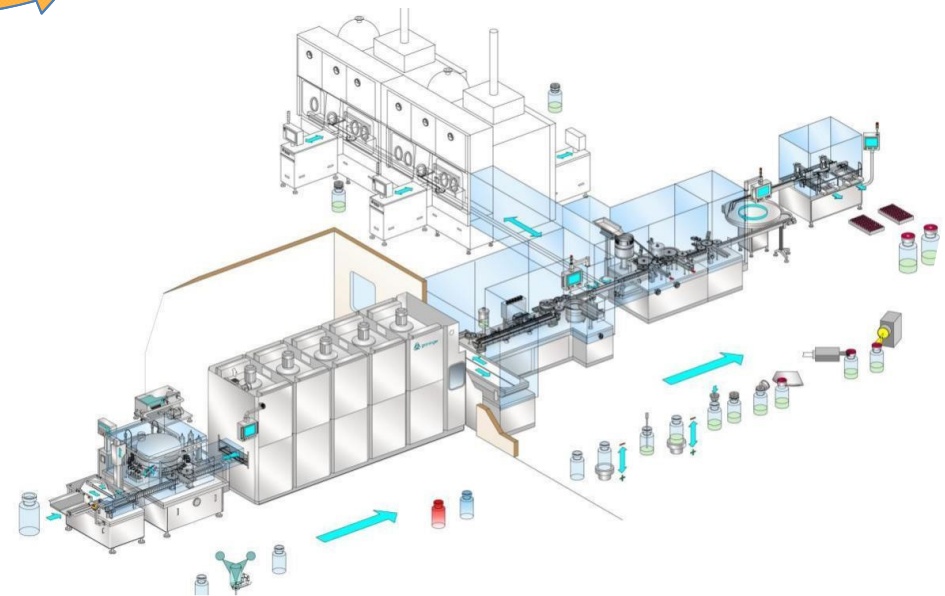
The complete process to manufacture prefilled syringes

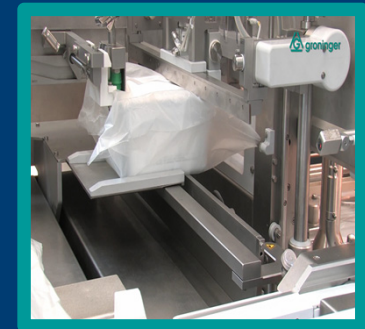
Two concepts: Comparing

“Nest-line”



“Bulk-line”





Thank you very much for your attention!

Any Questions?



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