# General Filling Line Design

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Manage Your Aseptic Filling Line
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PDA TRAINING

# General Filling Line Design

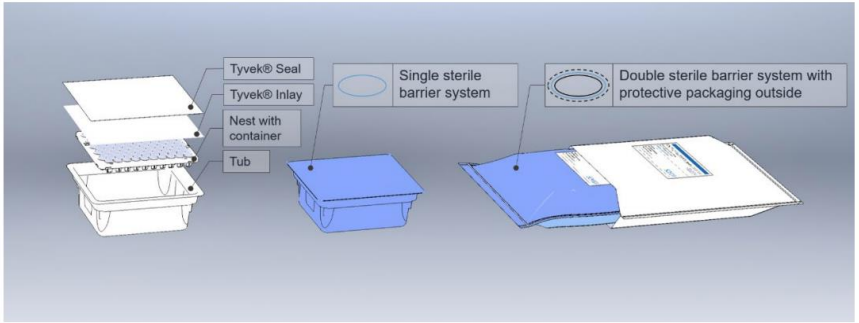
Facility, equipment and process should be appropriately designed, qualified and/or validated and where applicable, subjected to ongoing verification according to the relevant sections of the Good Manufacturing Practices (GMP) guidelines. (1)

In the first instance, QRM priorities should include appropriate design of the facility, equipment and processes, followed by the implementation of well-designed procedures, and finally application of monitoring systems as the element that demonstrates that the design and procedures have been correctly implemented and continue to perform in line with expectations. Monitoring or testing alone does not give assurance of sterility. (1)

# Which primary packaging material do I want to process?

The packaging material selection has one of the biggest impact on the design consideration of a filling line. Generally, it must be distinguished between Ready-to-Use (RTU) or Bulk material and the container types (syringe, cartridge or vial).
The selection of the primary packaging material has a direct impact on the processes of the filling line especially for the transfer of the container into the Grade A space.

Ready-to-Use primary packaging material (2)




Bulk Vials in Akylux box

# Ready-to-use primary packaging material

Ready-to-Use primary packaging material (3)

Syringes, Vials and Cartridges are being provided pre-assembled (e.g., needle, tip cap, combi seal, etc.) and are pre-sterilized by the primary packaging material supplier. Typical sterilization methods of these components are either Ethylene Oxide (ETO) or Dry Heat.

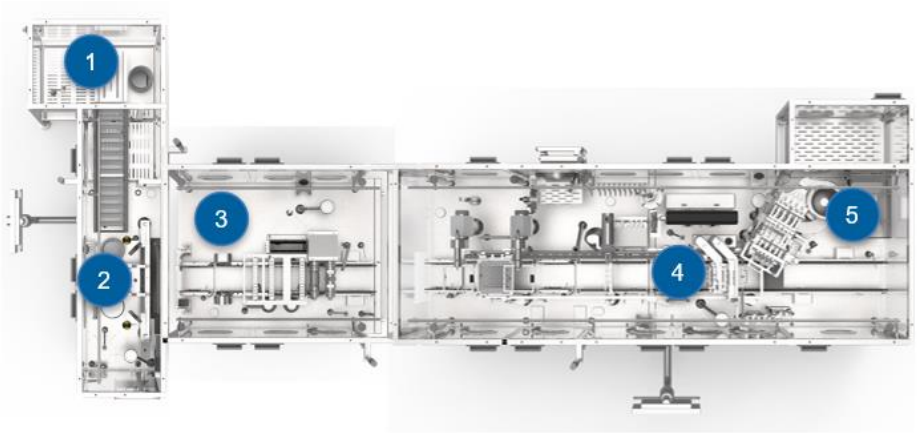
These packaging material are typically transferred into a filling line by usage of either a No-Touch-Transfer (NTT), Electron Beam (E-Beam) or H2O2 outside bio-decontamination.

The containers can be filled within the nest configuration or can be individualized if required by the process.

Note: As the sterilization of this primary packaging material is done by a 3rd party supplier a strong supplier, shipping and storage qualification is required. This must be reflected in the Contamination Control Strategy (CCS).

# Typical filling line execution for RTU packaging material

## Processing Syringes & Cartridges

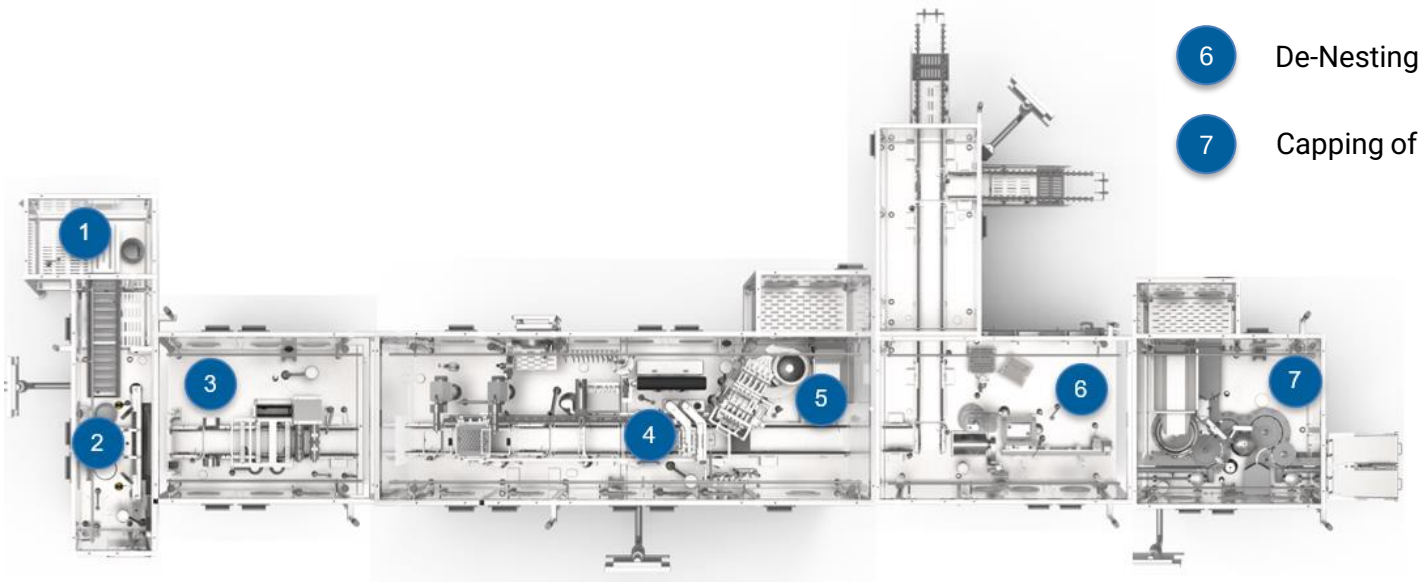



**Process Step Overview:**

1. Opening of Bag 1
2. Opening of Bag 2 and transfer to Grade A
3. Delid/Deline and exposing container to Grade A
4. Filling
5. Stoppering

# Typical filling line execution for RTU packaging material

## Processing Syringes & Cartridges **& Vials**



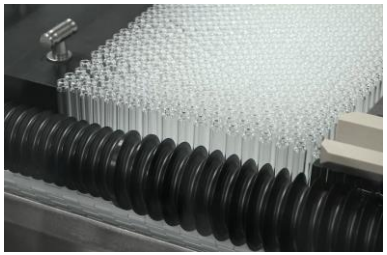

**Process Step Overview:**

6 De-Nesting

7 Capping of the vial for final closure

# Bulk primary packaging material

Vials and Cartridges (Syringes are very uncommon) are provided as bulk in Akylux boxes and the containers are neither sterile nor assembled in case of cartridges.



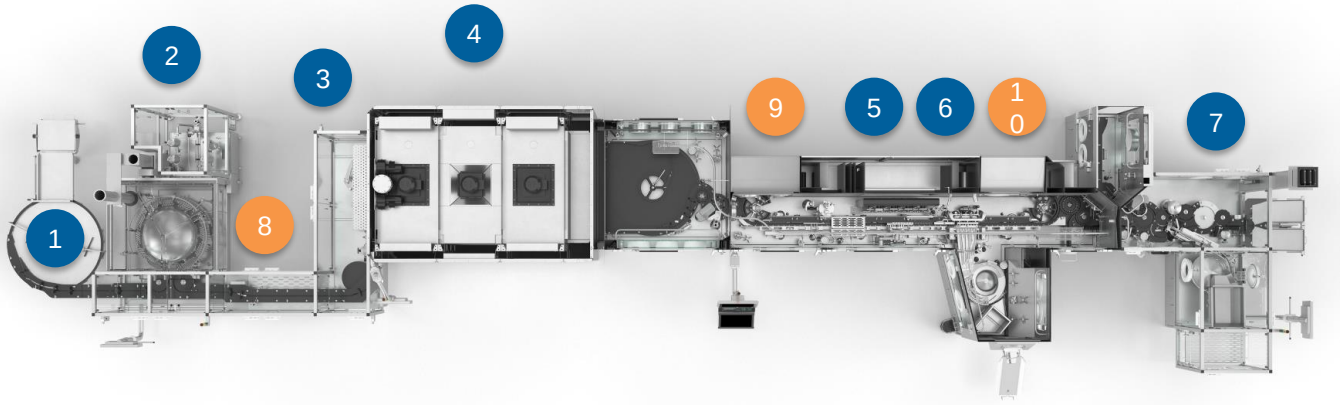
The typical process of transferring this containers into the Grade A space by several process steps which are including washing with WFI and dry heat sterilization (depyrogenation) before entering the filling line.

The containers are filled and processed as individuals.

Note: Depending on the process and container type additional treatments might be required as e.g., coating with silicone emulsion of the inside of the container before entering the depyrogenation tunnel.

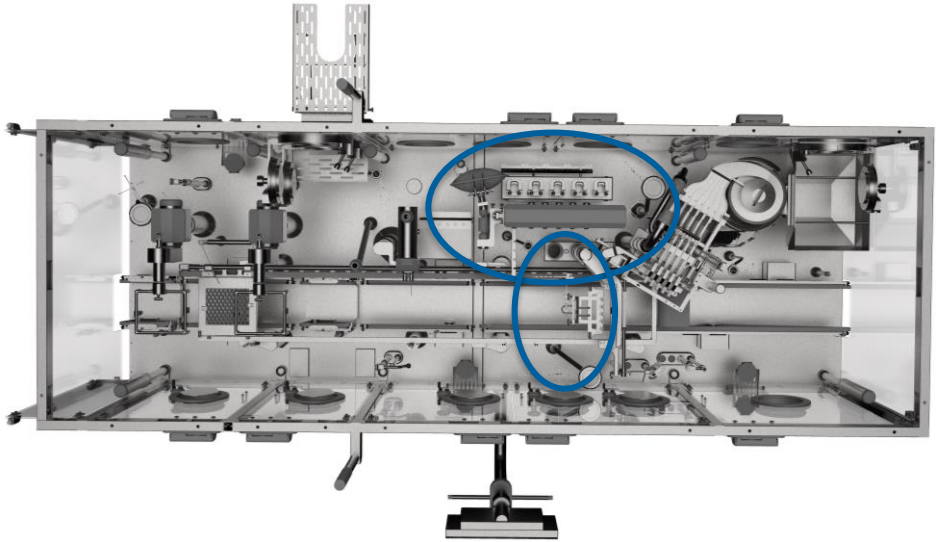
# Typical filling line execution for Bulk packaging material

## Processing of Vials & Cartridge




1. Feeding of container
2. Washing and drying
3. Tunnel loading
4. Depyrogenation (dry heat)
5. Filling
6. Stoppering
7. Capping of the vial
8. Siliconization of cartridge barrel
9. Cartridge stopper placement from the bottom
10. Closing of the cartridge with combi seal

# Filling Systems



Most common are three types of filling systems:

1. Rotary Piston Pump (RPP)
2. Peristaltic Pump (PP)
3. Time Pressure (TP)

The filling system typically contains the direct product contact parts.

*Note: Further filling systems like Mass flow and Diaphragm Pump are also existing but more uncommon. Therefore, we will highlight only the three major systems above.*

# Direct product contact parts

For aseptic processes, direct and indirect product contact parts should be sterilised. Direct product contact parts are those that the product passes through, such as filling needles or pumps. Indirect product contact parts are equipment parts that do not contact the product, but may come into contact with other sterilised surfaces, the sterility of which is critical to the overall product sterility (e.g. sterilised items such as stopper bowls and guides, and sterilised components). (1)

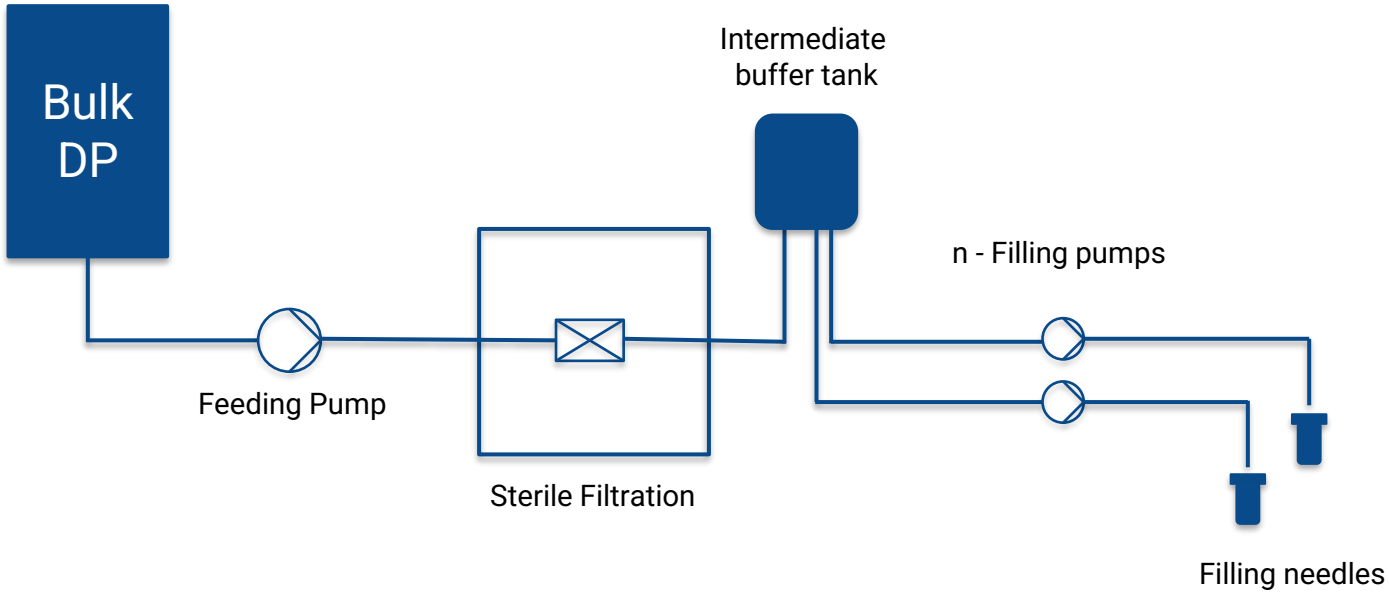
A sterilization of direct product contact parts can be achieved with typically two methods:

a) Single Use System (SUS) – All parts that are in contact with the product are supplied pre-sterilized e.g., gamma irradiated before usage. Transfer in grade A aseptically through a validated transfer system e.g., a rapid transfer port (RTP).

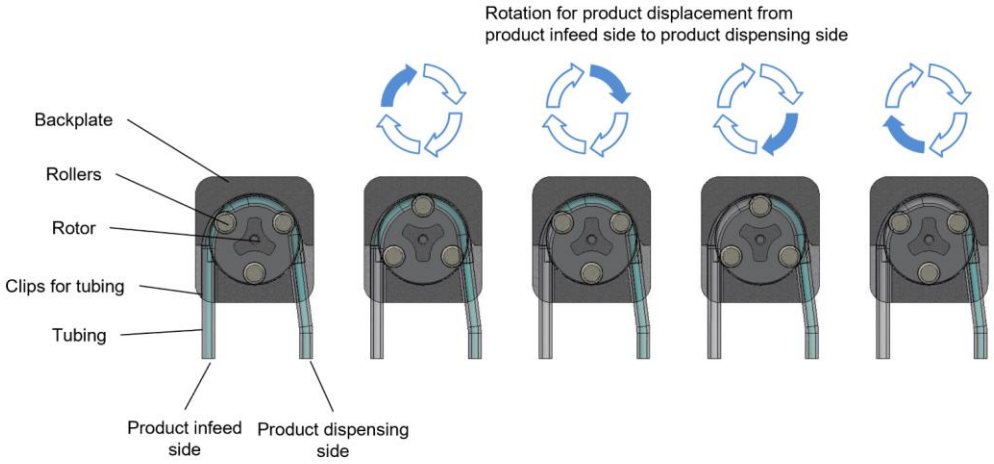
b) Stainless Steel System – All parts that are in contact with the product and are either

   1. cleaned (CIP) and sterilized in place (SIP) – the parts remain on the filling line or
   2. cleaned and sterilized out of place, transferred aseptically into grade A through a valid transfer system e.g., RTP, Tyvek wrapping, etc.

# General Filling System Set-up



# Peristaltic Pump

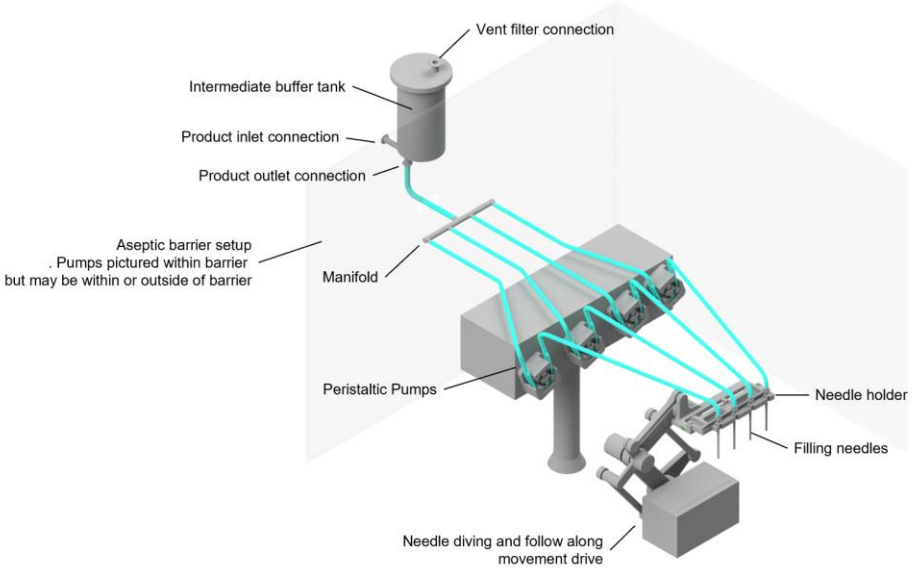



The operation principle is a dynamic circular squeezing of a flexible tube which is placed between the backplate and the rollers of the pump.

The rotation is generating a positive displacement in the tube and thereby moving the liquid product from the inlet to the outlet. By the dynamic movement a vacuum is generated on the infeed side drawing the product.

The filling volume is determined by number of revolutions executed by the rollers.

# Peristaltic Pump Filling System Set-up




The setup is considered as a closed system and therefore all the parts before the filling needles (pumps, buffer tank, etc.) could be placed outside the Grade A area. The product itself is never in direct contact with the pump system.

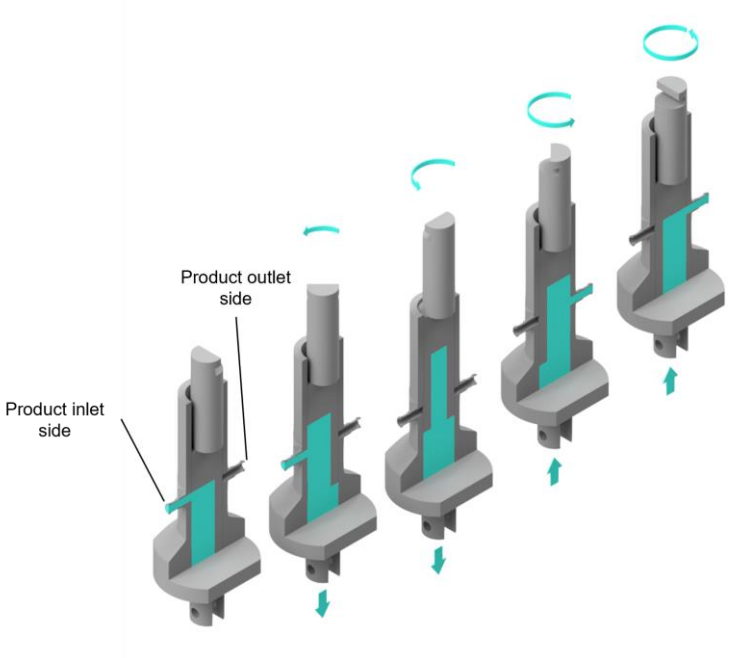
The peristaltic pump filling line setup is most commonly being used as a single use systems which is delivered pre-sterilized (typically gamma irradiated) from a 3rd party supplier.

*Note: Profound supplier validation for the SUS is mandatory due to the criticality of the parts and should be part of your CCS.*

# Peristaltic Pump Attributes

| | Advantages | Disadvantages |
|---|---|---|
| **Viscosity** | | Not good for high viscosity products |
| **Durability** | Product not in direct contact with moving parts, only moving parts are the rotors in the pump head | Tubing wears, so tubing longevity / particle generation studies required |
| **Single Use** | Designed for SU | Tubing may need to be changed or moved during filling due to tubing wear, especially on prolonged fills |
| **Change Over** | Rapid change over of filling path | For high dose accuracy applications, rigid tubing between pump and needle can be hard to aseptically install |
| **Sterilization** | Entire train can be disposable and sterilized together from surge bag to filling needle | System can be CIP/SIP but tubes need to be dismounted from pump. Nevertheless CIP/SIP is rarely used for PP |
| **Shear Level** | Very gentle low shear technology | |
| **Dosing Range** | Wide dosing volumes achievable just by changing disposable tubing sets | Very wide dosing ranges may require change of pump occlusion bed change part |
| **Operability** | Can institute feedback control / dosing to compensate for tubing deformation | Tubing deforms over time – potentially impacts dosing for long fills |
| | | Slower filling speed required to avoid splashing if soft tubing is used between pump and filling needle |

# Rotary Piston Pump

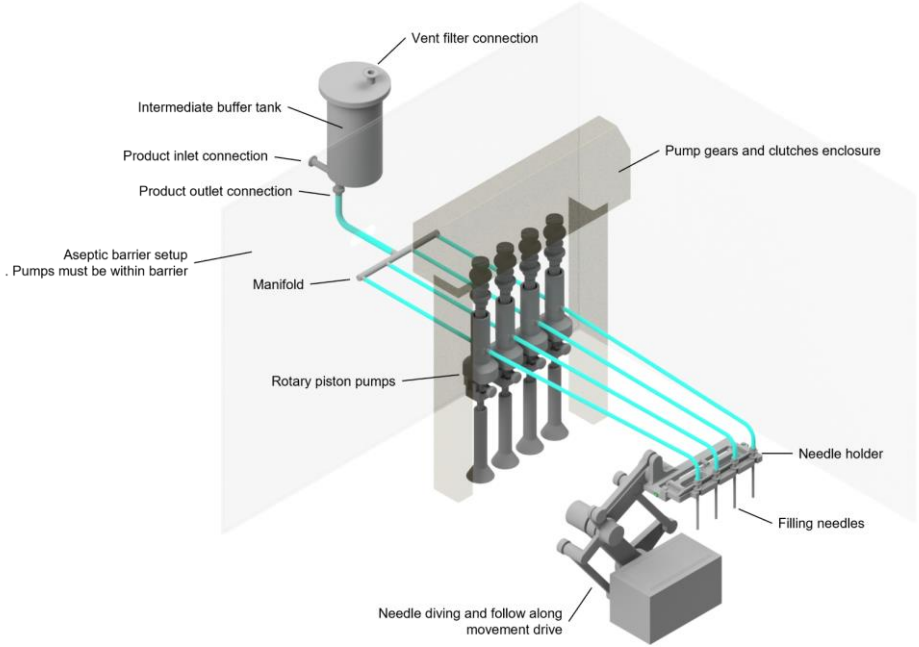



The operation principle is based on a stroke and rotation movement of the pump which is consisting of a piston and cylindrical housing (product is the lubricant).

In the suction position (the pump piston at the lowest position of the pump cylinder), the pump piston is then raised, creating an under pressure, through which the product is drawn into the pump. The pump piston rotates towards the dosing side. Once at the dosing position the pump piston is immediately lowered again, displacing the product from the pump and pushing it into the filling tube.

The filling volume is determined by the pump stroke and the size of the machined pouch in the piston.

# Rotary Piston Pump Filling System Set-up




The rotary piston pump is considered as an open system as there is no sealing between the piston and the cylindrical housing. For that reason the product can be exposed to the environment with the result that the pumps need to be placed within Grade A.

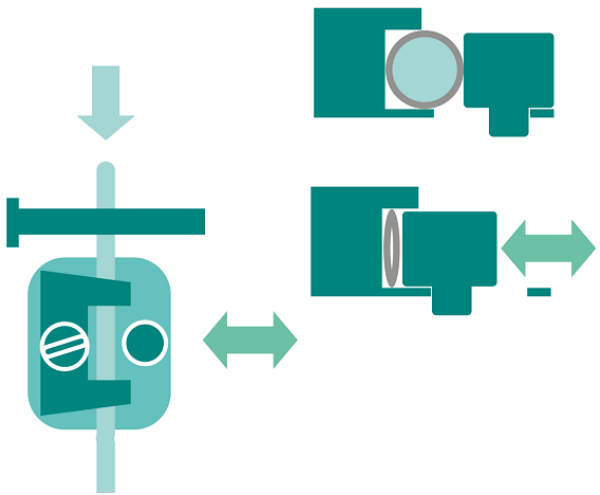
The rotary piston pump filling line setup is most commonly being used as a re-usable system. The pumps are prone to either an offline cleaning and aseptic setup or a fully automated CIP/SIP (Clean- and Sterilize in Process) process which should be preferred.

*Note: Both systems require a cleaning validation process which should be part of your CCS.*

# Rotary Piston Pump Attributes

| | Advantages | Disadvantages |
|---|---|---|
| **Viscosity** | Compatible with high viscosity products | |
| **Durability** | Durable, long equipment life when handled properly. Different materials of construction may experience different handling risks (e.g., ceramic is susceptible to sudden changes in temperature, stainless steel is susceptible to deformation, glass is subject to fracture) | |
| **Single Use** | | Usually not used for SU because of price, however some manufacturers do offer SUS RPP |
| **Change Over** | CIP/SIP capable in most designs. | When not purchased with CIP/SIP, aseptic installation requires extensive training and is not an approach that easily fulfils Annex 1 (1) objectives. |
| **Sterilization** | SIP is an advantage for sterility assurance. | Extra connections are required for CIP/SIP for all models. Some models may require additional valving to make CIP/SIP which adds to the complexity. Whether the additional valves are present or not, it will be required to demonstrate steam penetration to all surfaces. |
| **Shear Level** | | Significant shear force is exerted on the product due to the compression of the fluid within the cylinder and piston movement. |
| **Dosing Range** | 10-fold filling range for each pump size is typical | Several pump sizes may be required if wide filling volume ranges are required, which may restrict campaign flexibility |
| **Operability** | Dosing is stable across the batch, even for campaign manufacture (which may permit statistical weight check control). | Air entrainment in product (e.g., foam, air bubbles, air entrained from mixing or recirculation) can be detrimental to dosing control. Priming is essential for proper dosing control. |
| | Optimized filling curves can control splashing and foaming very effectively while still filling quickly. | Filling curve (e.g., start, acceleration, stop) is more complex to establish initially. |
| | Separate drives are possible for each pump which makes individual fine tuning and operation simpler (including the disconnection of any individual pump mid-run). | Separate drives are a more complex design which is more expensive. Common drives (simpler, less expensive design) are possible but will require physical disconnection of any individual pump in case of failure (e.g., leakage, dose control failure) and does not enable product savings during priming, redosing and emptying (see Topic E). |

# Time Pressure

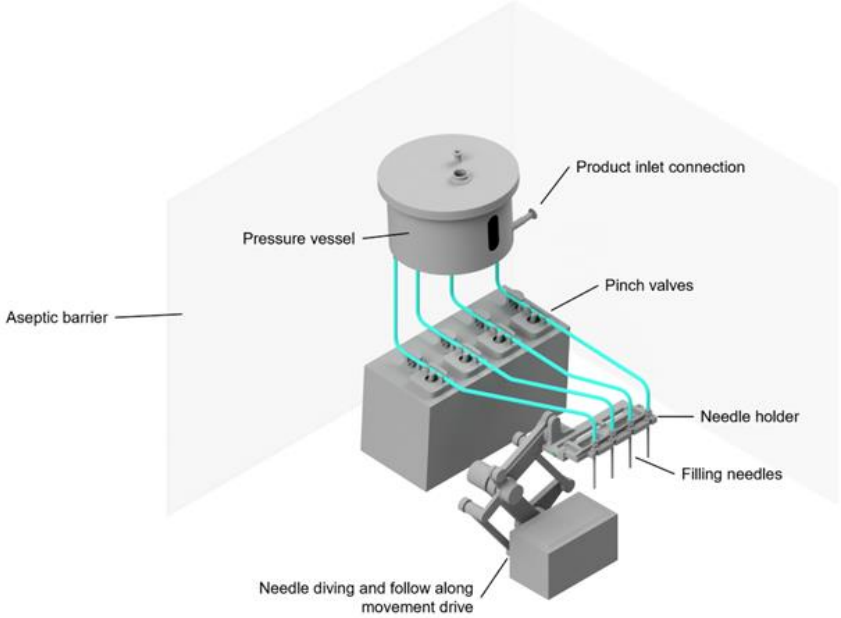


The operation principle is based on a slight over pressure that is applied typically to an intermediate tank and a pinch valve is opened and closed for a specific time to control the flow of the product to the filling needle.

The “pressure” that is applied to the bulk vessel makes use of air, inert gas, or gravity.

The time pressure dosing system has an independent control, which calculates the actual time required for filling from the current pressure and temperature. Without this independent control, a pure time control would lead to deviations in the filling accuracy when the pressure or the temperature change.

# Peristaltic Pump Attributes




The setup is considered as a closed system and therefore all the parts before the filling needles could be placed outside the Grade A area. The product itself is never in direct contact with the pump system.

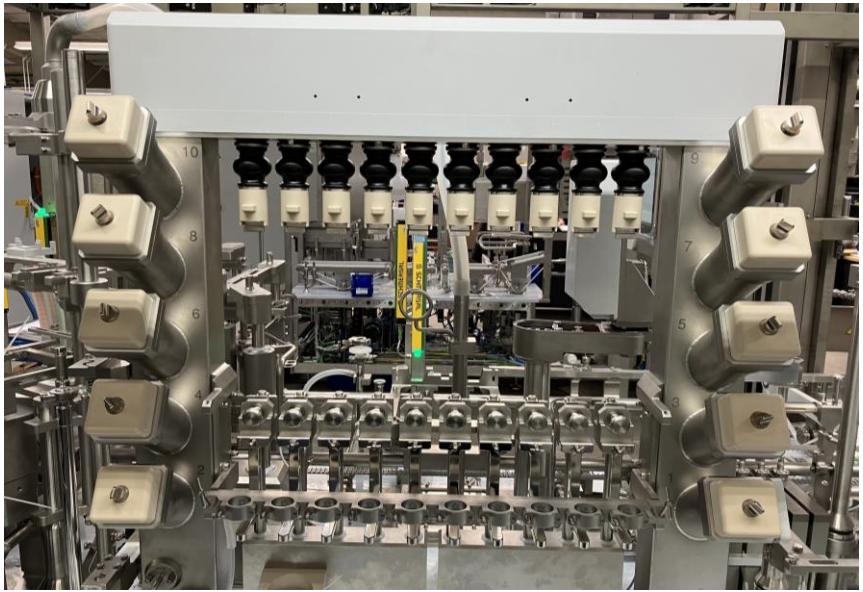
The pressure vessel is typically from stainless steel and therefore requires CIP/SIP process for cleaning and sterilization. Due to the size of the tanks offline cleaning and sterilization is very uncommon.

*Note: The system requires a cleaning validation process which should be part of your CCS.*

# Time Pressure Attributes

| | Advantages | Disadvantages |
|---|---|---|
| **Viscosity** | | Not good for high viscosity products |
| **Durability** | Product not in direct contact with moving parts, only moving parts are the pinch valves | Hose transiting the pinch valve is subject to wear and must be changed |
| **Single Use** | | Usually not adopted for SU because bulk vessels and fluid pathway must be pressure rated |
| **Change Over** | CIP/SIP capable in most designs. Only tubing, orifice and filling needle to be changed when changing filling recipe. | Only a small filling range is possible with each orifice / filling needle combination. Change parts are required for greater flexibility. |
| **Sterilization** | System is well suited for CIP/SIP | |
| **Shear Level** | Very gentle low shear technology | Compatibility of the product with the selected orifice and applied pressure should be confirmed due to the potential for shear at the orifice |
| **Dosing Range** | Wide dosing volumes, achievable just by changing orifice, tubing and needle | Design should take into account any requirements for large volume fills (which will take more time to fill) |
| **Operability** | | Tubing at the pinch valve deforms over time – potentially impacting dosing accuracy for long fills |
| | | Filling accuracy depends upon pressure and temperature variation; therefore, temperature compensation is typically necessary |

# Combination of Filling Systems



Typical combinations of filling systems are:

Peristaltic Pump and Rotary Piston Pump with the target to gain product flexibility e.g., to process different viscosities or shear sensitive products. Both systems can be accommodated in one filling setup. Other combinations as Peristaltic Pumps and Time Pressure are also a possibility.

*Note: The selection of the filling systems always needs to be selected based on the product attributes and required processes to fill the product.*

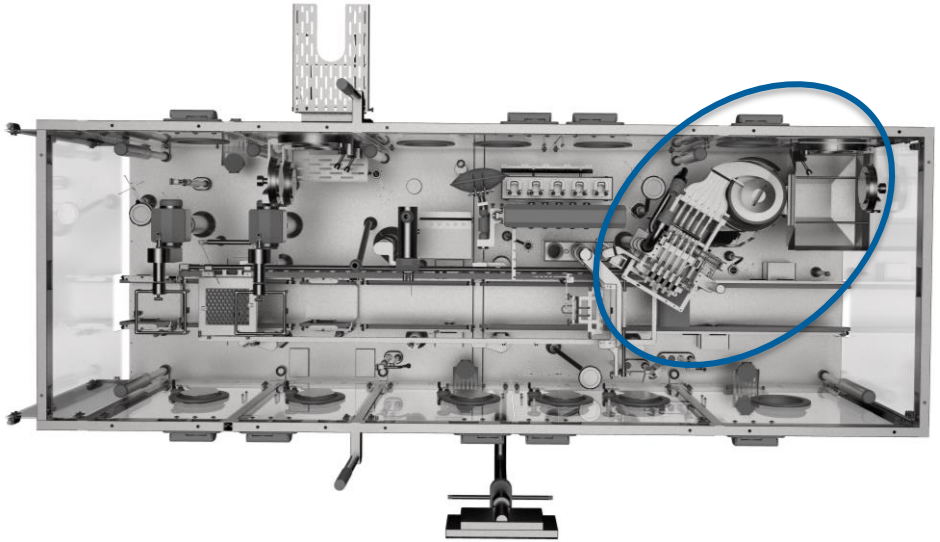
# Comparison of the filling systems

| Dosing System | Peristaltic pump (PP) | Rotary piston pump (RPP) | Time pressure (TP) |
|---|---|---|---|
| **Dosing Accuracy** | Very accurate<br>Pulsation, when present, can adversely influence dosing accuracy. Pulsation is more prevalent with single tube execution. | Very accurate | Very accurate |
| **Single Use fluid pathway** | Well-suited for single use (vast majority of PP is single use) | Possible with some vendors | At present option not available |
| **CIP/SIP Execution** | Possible but rare | Possible | Possible |
| **Campaign compatibility** | Wear of hoses is a limiting factor, so hoses must be either changed or repositioned for very large/long batches based on studies carried out to qualify hose durability | Compatible<br><br>Due to filling volume range, if the pump has to be exchanged, isolator must be opened or sterilized pumps must be introduced through an RTP port | Compatible<br><br>Wear of hoses due to single point of pinch wear is a limiting factor, so studies must be carried out to qualify hose durability |
| **Filling Range** | Typically, 0.1 ml to 100 ml (up to 500mL possible)<br><br>Potentially a different pump head for higher ranges | Typically, 0.1 ml to 100 ml (up to 250 ml possible; while larger volumes are possible, the trade-offs with the handling of the over-sized pumps often drives the selection of another filling technology)<br><br>Ranges are limited. Pumps typically cover decimal factor ranges | Typically, 0.1 ml to 100 ml (up to 500 ml possible) |
| **Viscosity Range** | Up to 60 mPa.s (depending on product characteristics) | Up to 300,000 mPa.s | Up to 100 mPa.s |
| **Execution Outside Isolator** | Possible | Not Possible as the pumps are "open" at the interface between the piston and cylinder | Possible |
| **Product Compatibility** | Could potentially be difficult with solvent-based products as the tubes could become brittle | Due to shear forces and long residence times inside the pump may not be the best system for long chain protein products (though some recent studies show potential compatibility) | Could potentially be difficult with temperature sensitive products (expansion and contraction could affect dosing volume if the pressure is directly affected) |

# Comparison of the filling systems based on product

| Product Examples | PP | RPP | TP |
|---|---|---|---|
| **Proteins** | Yes | No, creates too much shear force | Yes |
| **Suspensions** | Yes, as long as the viscosity is below approximately 60 mPa.s and as long as settling of the suspension is considered during potential downtime | Yes, as long particles do not disturb the pump surface | Yes- provided that the particle size is compatible with the orifice geometry |
| **High viscosity products** | No, as gaps will form in the hoses and cause underfills | Yes, up to approximately 300.000 mPa.s. A closing needle may be chosen depending on how high the viscosity is. See Filling Needle Design Topic C | No - Limited to approximately 10-100 mPa.s |
| **Low viscosity products** | Yes, up to approximately 60 mPa.s | Yes, the intermediate vessel level maintenance may be critical, and it may require ventilation of that vessel | Yes |
| **Small Volume Parenteral (SVP)** | Yes, very suitable and very accurate | Yes, very suitable and highly accurate | Yes, very suitable and highly accurate |
| **Large Volume Parenteral (LVP)** | Yes, considerations should be given to batch size and number of revolutions per fill in order to evaluate the rate of tubing wear. | For Large Volume Parenterals, pump sizes up to approx. 250 ml are routinely available, otherwise multi-stroke filling is necessary. In order to deliver large volumes, in addition to splitting the dosing, there might also be the possibility to use multiple pumps (at single stroke) to fill a single container. The larger the pump diameters the more awkward for handling during setup (assembly) and disassembly which risks contamination or damage. | Yes |
| **Antibody Drug Conjugate (ADC)** | Yes, highly recommended especially in SU execution. Some would opt against having the pump outside of the isolator in this case, to contain leakage should that occur. | Yes | Yes |
| **Solvent based products** | Not ideal if the concentration of solvent leads to brittleness in the hoses | Yes, see the additional considerations under low viscosity products | Yes, it might be required to use a housing to cover the pinch valves for safety reasons to prevent the pinch valve drive from coming into contact with any flammable vapors. |
| **Vaccines / Heparins** | Depending on batch size, it may not be ideal if running long campaigns (e.g., flu vaccines with 3-week long campaigns) à frequent hose replacement | Yes | Yes |

# Sorting Systems



The sorting system typically contains the following parts:

- Stopper hopper
- Sorting / Feeding Bowl
- Sorting / Feeding Tracks
- Stoppering Pins
- Stopper Lock (Vent tube or Vacuum)

The sorting system typically contains the indirect product contact part.

# Indirect product contact parts

For aseptic processes, direct and indirect product contact parts should be sterilised. Direct product contact parts are those that the product passes through, such as filling needles or pumps. Indirect product contact parts are equipment parts that do not contact the product, but may come into contact with other sterilised surfaces, the sterility of which is critical to the overall product sterility (e.g. sterilised items such as stopper bowls and guides, and sterilised components). (1)

A sterilization on indirect product contact parts can be achieved typically with moist heat (autoclave).

Note: H2O2 is not considered as a sterilizing agent for indirect product contact parts.

The cleaning and sterilization of these parts are most commonly performed offline. Transfer of the parts into grade A aseptically through a validated transfer system e.g., RTP, Tyvek wrapping.

Note: Stopper Hopper, Stopper Bowl and Tracks are typically large and heavy parts and therefore in most cases need to be installed by an open-door intervention. This requires strict adherence to aseptic techniques to not contaminate the filling line.

# Indirect product contact parts

The Installation of the parts happen as followed:

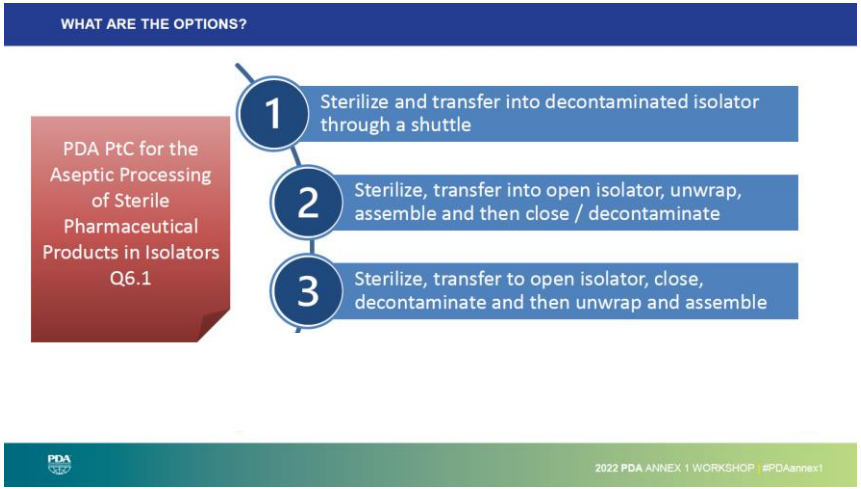
**Large and Heavy parts as stopper bowl, hopper and often feeding lanes**

Best practice procedures for introduction of these parts can be found in the PDA PtC for Isolators (5). The transfer can be also applied to RABS.

Best practice are two operators performing this task according to the doctor and nurse principle or often also referred to primary and secondary operator.

The primary operator is the only person that touching the parts and that is installing them into the filling line (additional gowning might be needed), the secondary operator assists the primary operator on the “dirty” side.

For the unwrapping procedure either procedure #2 or #3 are possible procedures that need to be applied acc. to a respective risk analysis.




Transfer methods of indirect product contact parts (4)

Note: Point number 4 is removed in this presentation as it is referred to an in-situ decontamination with the isolator which is no longer accepted by regulatory.

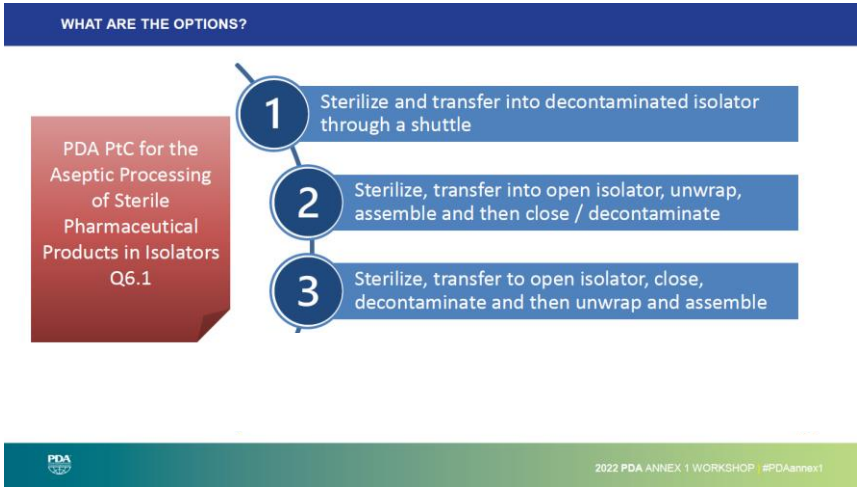
# Indirect product contact parts

The Installation of the parts happen as followed:

**Smaller indirect product contact parts**

Expectation for these parts is the transfer via an RTP (procedure #1) for isolator systems. Installation happens with barrier glove system.

For RABS these parts can be hung wrapped inside the RABS, transferred via and RTP or via sterile boxes depending on the risk assessment. Installation happens with barrier glove system.




Transfer methods of indirect product contact parts (4)

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# References

(1) 2022, 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, Brussels

(2) 2004, U.S. Department of Health and Human Services Food and Drug Administration, Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice, Rockville

(3) EJPPS – European Journal of Parenteral and Pharmaceutical Sciences Volume 26 Issue 4 https://www.ejpps.online/post/vol26-4-end-to-end-qualification-of-ready-to-use-rtu-product-containers-in-packaging-suitable#viewer-cltu5

(4) https://www.schott-pharma.com/shop/en/SCHOTT-iQ/c/iq_platforms

(5) Decontamination and Sterilization of Direct and Indirect Product Contact Surfaces from Patrick Nieuwenhuizen at PDA Annex 1 Workshop 2022 in Dublin

(6) PDA PtC for the Aseptic Processing of Sterile Pharmaceutical Products in Isolators, 2020