GMP Requirements for Stopper Processing for sterile filling applications

PDA Parenteral Drug Association

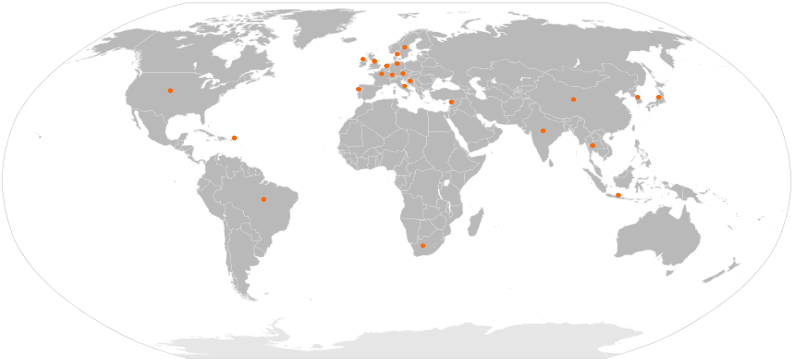
CONNECTING PEOPLE SCIENCE AND REGULATION®

Agenda

1. Atec Pharmatechnik GmbH - Introduction
2. Requirements on stoppers in sterile filling
3. Stopper Processing Equipment
4. Stopper Supply to filling lines
5. Question and Answer

Atec Pharmatechnik - Process Equipment for sterile filling

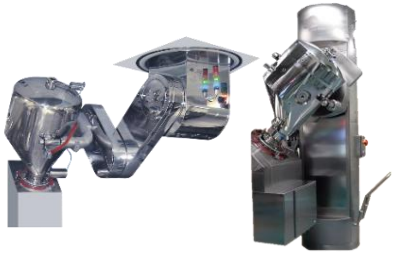
- Foundation of Atec Pharmatechnik in 1996, 170 employees
- spezialised in equipment for sterile manufacturing
- over 150 qualified Stopper Processing Sytems worldwide
- a worldwide distribution, customer and technology network
- ASME & ISO 9001 certification



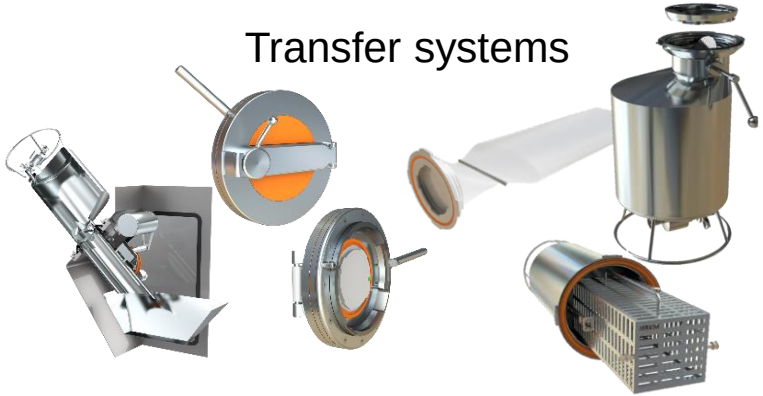
Made in Germany - Customized products & services

Component Processing Systems

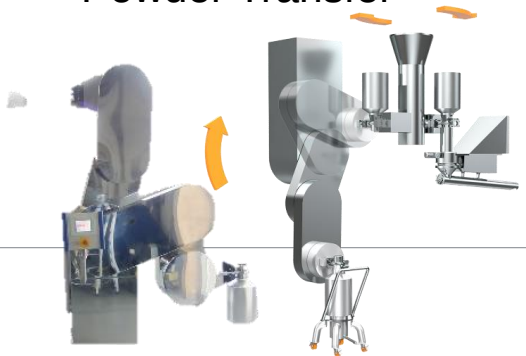
Cleanroom Lifts



Transfer systems



Powder Transfer



Bag Filling Equipment

Formulation and CIP/SIP Systems

Requirements for stoppers in sterile filling

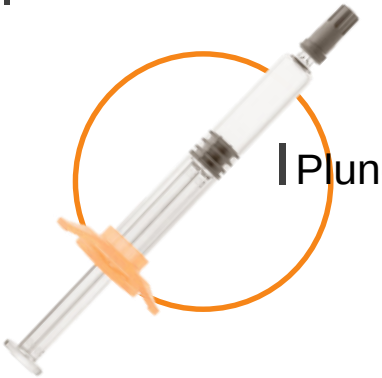
Quality is critical for primary product contact surfaces, specifically for the final container and closure

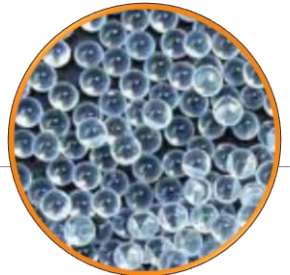
Clean and sterile stoppers are needed at the filling line for vial closure of parenteral drug products

Requirements for stoppers in sterile filling

- Cleanable and sterilizable components such as:

- Needle Shields

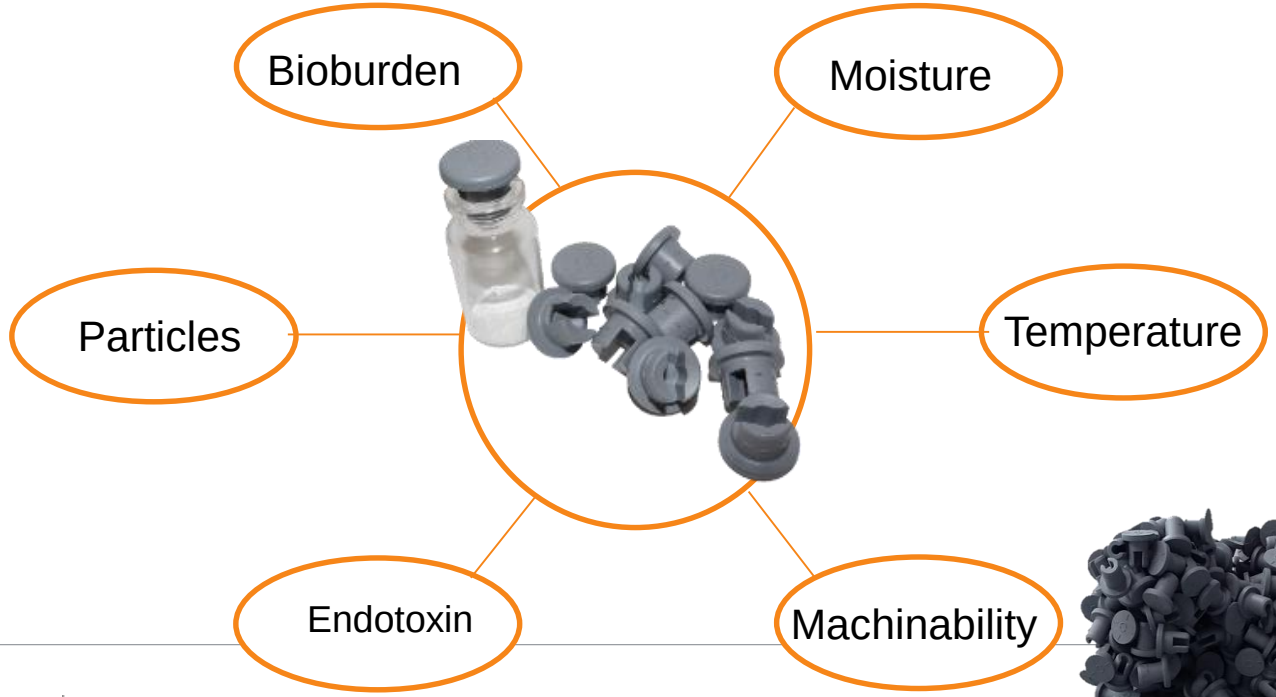




- **Tip Caps**
- **Glass and Steel Beads**
- **and more!**

Requirements for Stoppers in sterile filling

Key Requirements for stoppers



Regulatory requirements

	Endotoxin	Particulate	Bioburden	Sterilization
Requirement	$\geq$ 3 log reduction	Fewer than 2000 $\geq$ 10µm, Fewer than 200 $\geq$ 25µm	SAL $\geq 10^{-6}$, Spore log reduction $\geq$ 12	$F_o \geq 15$
Reference	FDA Guidance for Industry, Sept 2004 and Nov 1994	USP <788>*	FDA Guidance for Industry, Sept 2004 and Nov 1994	EN285* PDA Technical Monograph 1

*requirement is inferred, not specific to stopper processing

Guidance for the industry

Sterile Drug Products Produced by Aseptic Processing

Rubber closures (e.g., stoppers and syringe plungers) can be cleaned by ***multiple cycles of washing and rinsing*** prior to ***final steam or irradiation sterilization***. At minimum, the initial rinses for the washing process should employ at ***least Purified Water, USP, of minimal endotoxin content, followed by final rinse(s) with WFI*** for parenteral products.

The adequacy of the depyrogenation process can be assessed ***by spiking*** containers and ***closures with known quantities of endotoxin***, ***followed by measuring endotoxin content after depyrogenation***. The challenge studies can generally be performed by directly applying a reconstituted endotoxin solution onto the surfaces being tested. The endotoxin solution should then be allowed to air dry. Positive controls should be used to measure the percentage of endotoxin recovery by the test method. ***Validation study data should demonstrate that the process reduces the endotoxin content by at least 99.9 percent (3 logs)*** (see Section VII).1.

=> No definition on the level of spiking
=> No definition on the location of endotoxin spiking
=> No definition of the recovery rates

Particle requirements

Pharmacopeia	Requirement
United States	"…practically free of visible particles"
European	"…essentially free of visible particles" (Parenteral Preparations) "…without visible particles, unless otherwise justified and authorised" (MABs for human use)
Japan	"… must be clear and free from readily detectable particles"

USP <788>

Test	Product	≥ 10 µm	≥ 25 µm
Light Obscuration	Small volume Parenterals	6000/ container	600 / container
	Large volume Parenterals	25/ml	3/ml
Microscope	Small volume Parenterals	3000/ container	300 / container
	Large volume Parenterals	12/ml	2/ml

- Given that “product” includes three components (drug product, vial, stopper) then the industry approach is to split requirements 1/3 applied to stoppers:

- Not to exceed 2000 > 10µm size and 200 > 25µm size

Proved Clean Index" (PCI) from West

$$PCI = \frac{n_{(25-50\mu m)}}{10} \cdot 0{,}1 + \frac{n_{(51-100\mu m)}}{10} \cdot 0{,}2 + \frac{n_{(>100\mu m)}}{10} \cdot 1$$

Allows direct interpretation of certified value without calculations

4 specifications versus 1 provides assurance of consistency

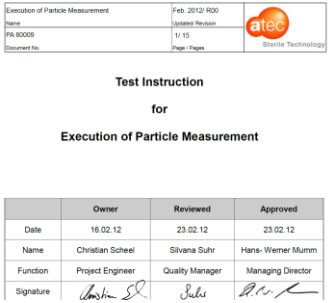
Reporting Category	Historical Specification	Enhanced Specification (particles / 10cm^2)
PCI	≤ 3.4	≤ 2.5
> 25µm but ≤ 50µm	Not specified	≤ 13
> 50µm but ≤ 100µm	Not specified	≤ 3.5
> 100µm	Not specified	≤ 0.9

Values expressed in (particles / 10 cm^2)

Particle Counting

- Atec on-site laboratory Standard Operating Procedures
- Sample stoppers after processing and recover particles. Count particles by with a liquid particle counter.

Lighthouse LS-20 Liquid Batch Sampler



Execution of Particle Measurement	Feb. 2012/ R00
Name	Updated Revision
PA 80009	1/ 15
Document No.	Page / Pages

atec Sterile Technology

Test Instruction

for

Execution of Particle Measurement

	Owner	Reviewed	Approved
Date	16.02.12	23.02.12	23.02.12
Name	Christian Scheel	Silvana Suhr	Hans- Werner Mumm
Function	Project Engineer	Quality Manager	Managing Director
Signature			

Particle Counting

Atec has selected the criteria from West Pharmaceuticals:

	PCI	25-50 µm	50-100 µm	>100 µm
Historical	3.4	Not defined	Not defined	Not defined
Enhanced	2.5	13.0	3.5	0.9

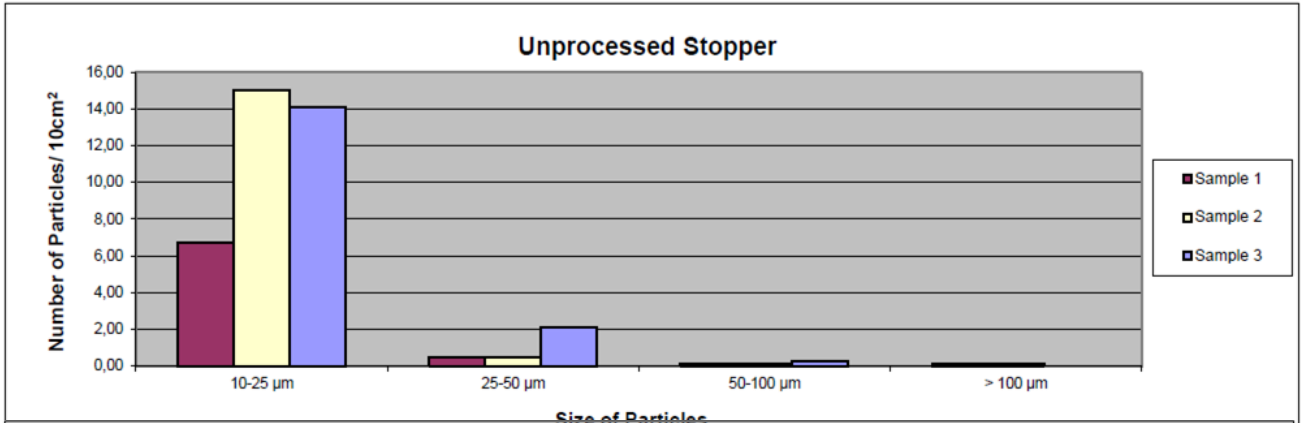
with one additional category for small particles

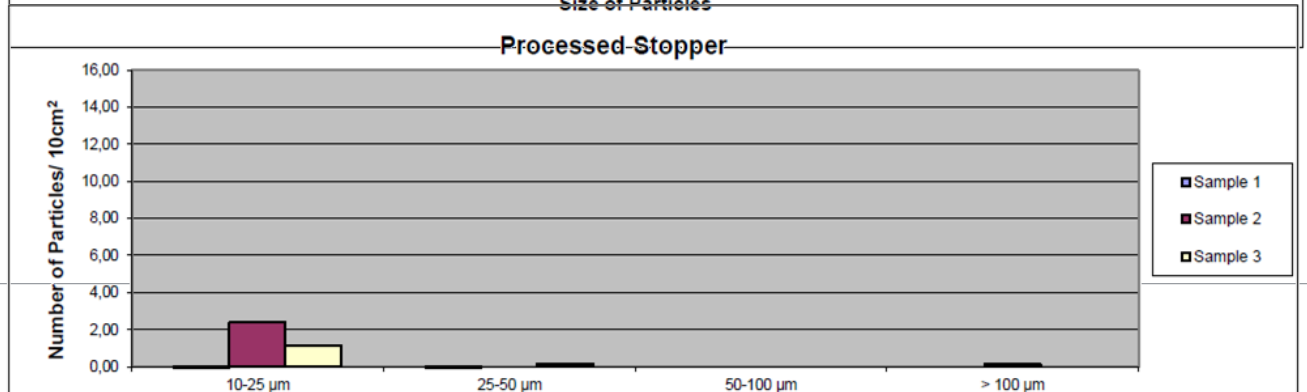
Particle Size				
	Class 0	Class 1	Class 2	Class 3
	10-25 µm n_{a0}	25-50 µm n_{a1}	50-100 µm n_{a2}	>100 µm n_{a3}

$$n_{an} = n_{a0} \cdot 0{,}01 + n_{a1} \cdot 0{,}1 + n_{a2} \cdot 0{,}2 + n_{a3} \cdot 1$$

Particle Counting

Graphic representation for 3 samples for unprocessed stoppers:

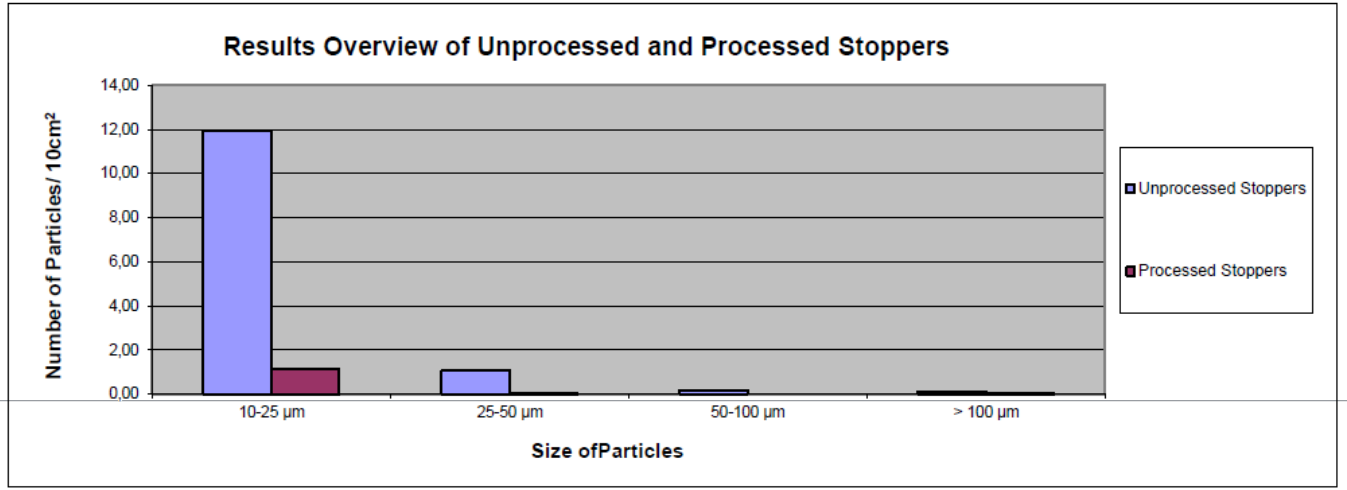




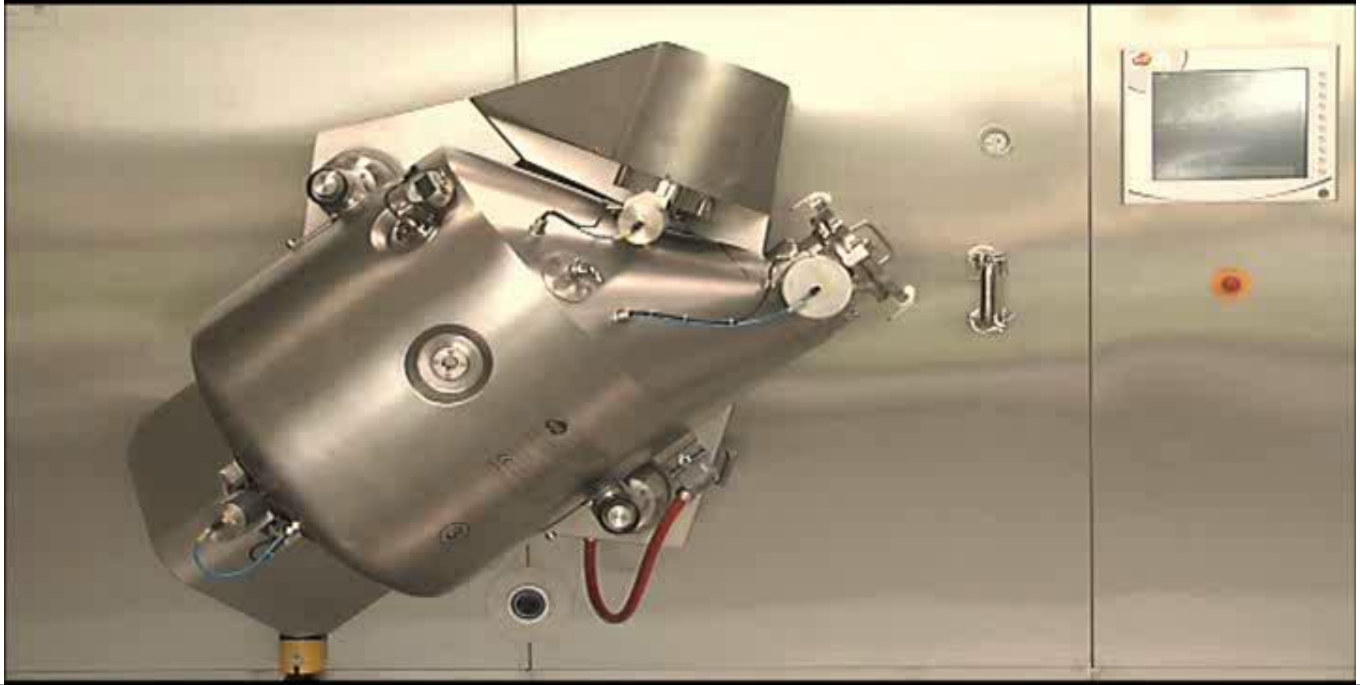
Particle Counting

Graphic representation for 3 samples for unprocessed stoppers:

Results Overview of Unprocessed and Processed Stoppers				
	10-25 µm	25-50 µm	50-100 µm	> 100 µm
Unprocessed Stoppers	11,95	1,05	0,17	0,08
Processed Stoppers	1,13	0,03	0,00	0,04



Washing Process



Requirements for Stoppers in sterile filling

Process steps to achieve the requirements:

Endotoxin reduction Particle reduction	Washing
Silicone layer	Siliconisation
Bioburden	Sterilization
Residual moisture	Drying
Final temperature of stoppers	Cooling

Washing - Qualification of Endotoxine removal

Process steps to achieve the requirements:

Endotoxin reduction
Particle reduction

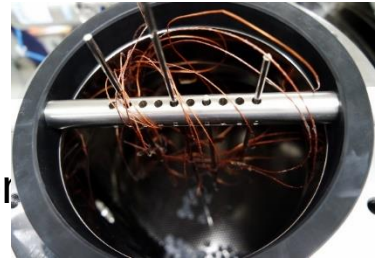
→ Washing

Testing of performance: Test with spiked components

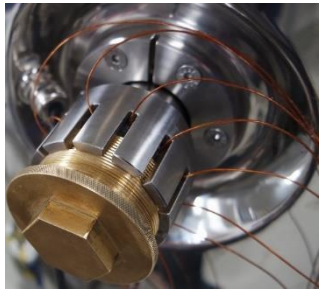
Typical spiking level:10.000 EU

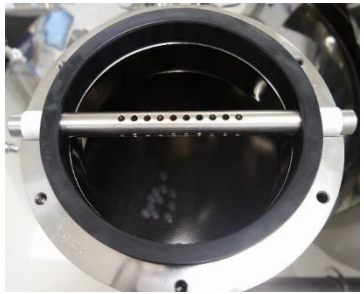
Process steps to achieve the requirements:

Bioburden → Sterilization



Testing of performance Temperature distribution
Tests with bio-indicators





Temperature Mapping Test Methods

Thermocouple in Piping

Pic.1 Remove lid (if applicable)

Pic.2 Remove flap valve incl. sealing

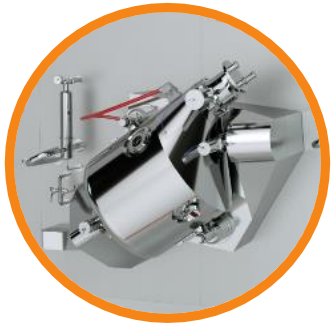
Thermocouples in Vessel

DART and Bowie Dick Test

Stopper Supply in Sterile Filling - Comparison of Component Supply

BULK COMPONENTS or
READY TO STERILISE
COMPONENTS

IN HOUSE
PROCESSING



READY TO STERILISE
COMPONENTS

IN HOUSE
STERILISATION

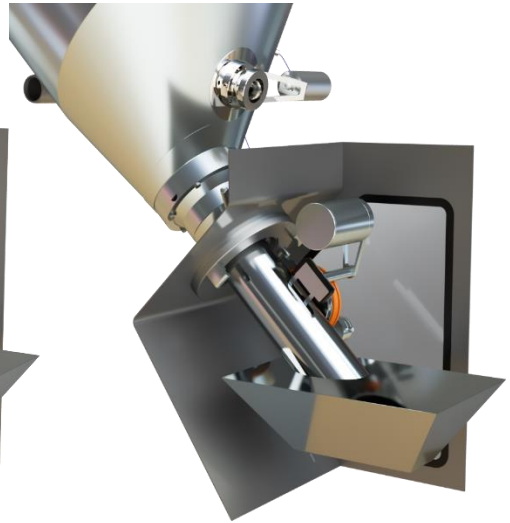
READY TO USE
COMPONENTS

Direct use

Production flow – Stopper transfer

Component Transfer with Bag

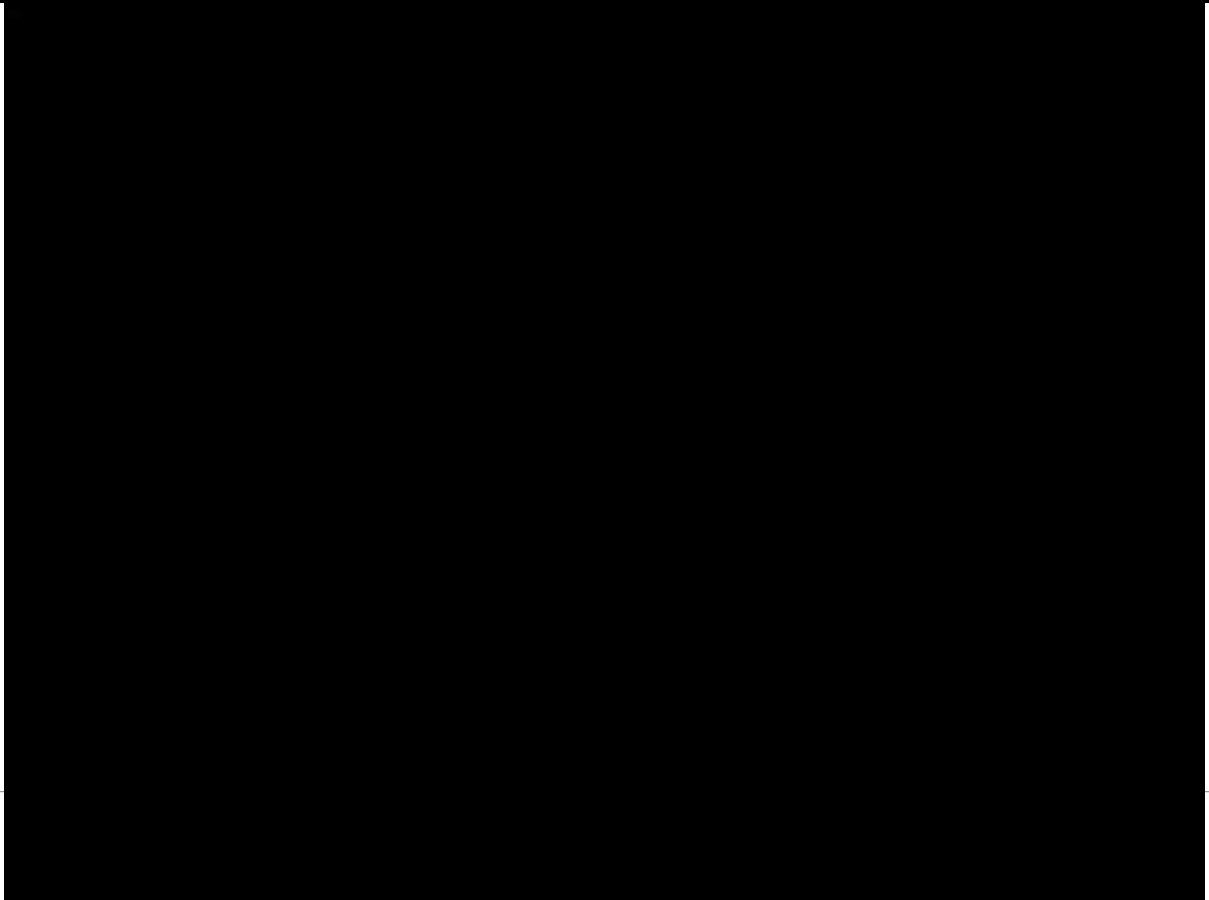
Component Transfer with Beta Port Container



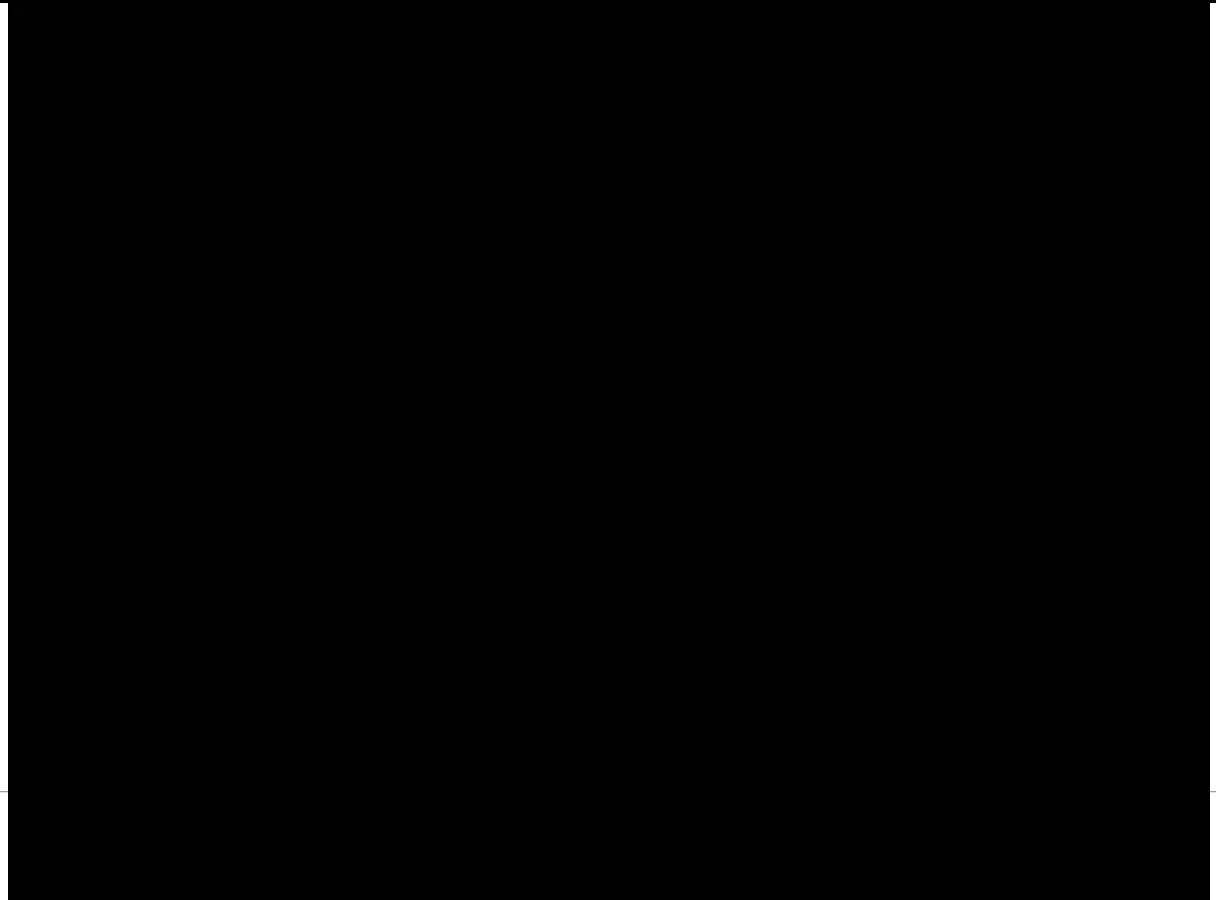
Component Transfer with Process Vessel

Stopper Processing System

Stopper Processing System - Loading Station



Stopper Processing System - Process Station

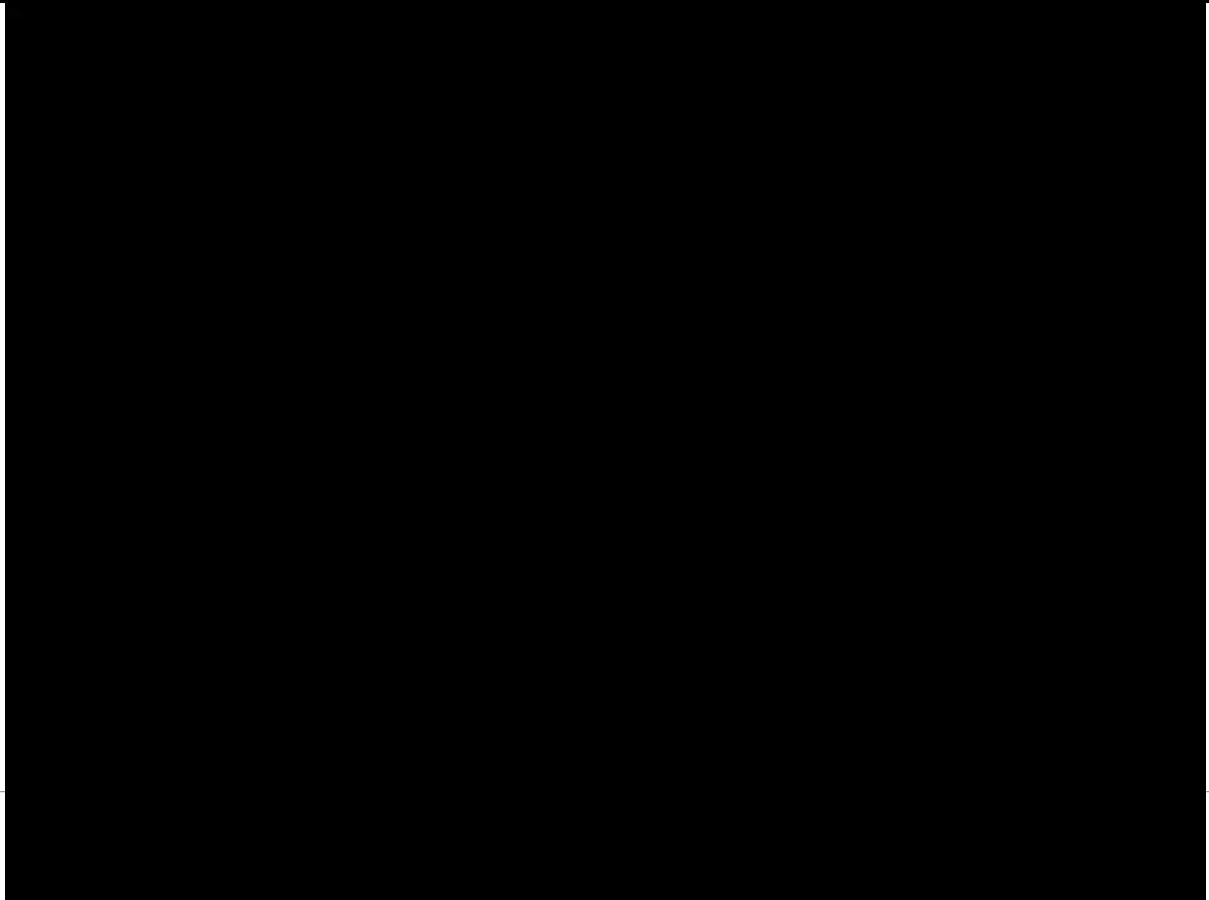


Stopper Processing System - Transfer Station

Automatic Stopper Transfer through
Alpha/Beta Port system

- Transfer of Stoppers from grade C directly to Isolator / Filling Line
- Sterile Transfer Stoppers cannot get in contact with ring of concern due to Transfer Chute Design

Stopper Processing System - Transfer Station

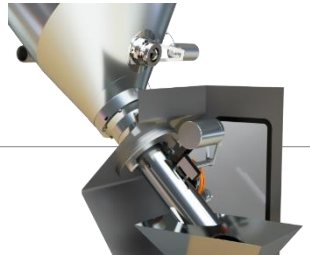


Summary

Choose the right process parameters and qualification method to meet and verify regulatory requirements

Process steps to achieve the requirements:

Endotoxin reduction Particle reduction	Washing
Silicone layer	Siliconisation
Bioburden	Sterilization
Residual moisture	Drying
Final temperature of stoppers	Cooling



Question & Answer

We made it!

Thank you for your attention