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How to assure quality in glass vials: controlled manufacturing processes focused on particle reduction

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Product Manager Vial Platform

How to assure quality in glass vials

- **Stevanato Group at a glance**
- Bulk manufacturing process optimization
- State-of-the-art solutions for EZ-fill products
- Visible Particle Reduction Program
- Conclusions

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Stevanato Group Brand Structure

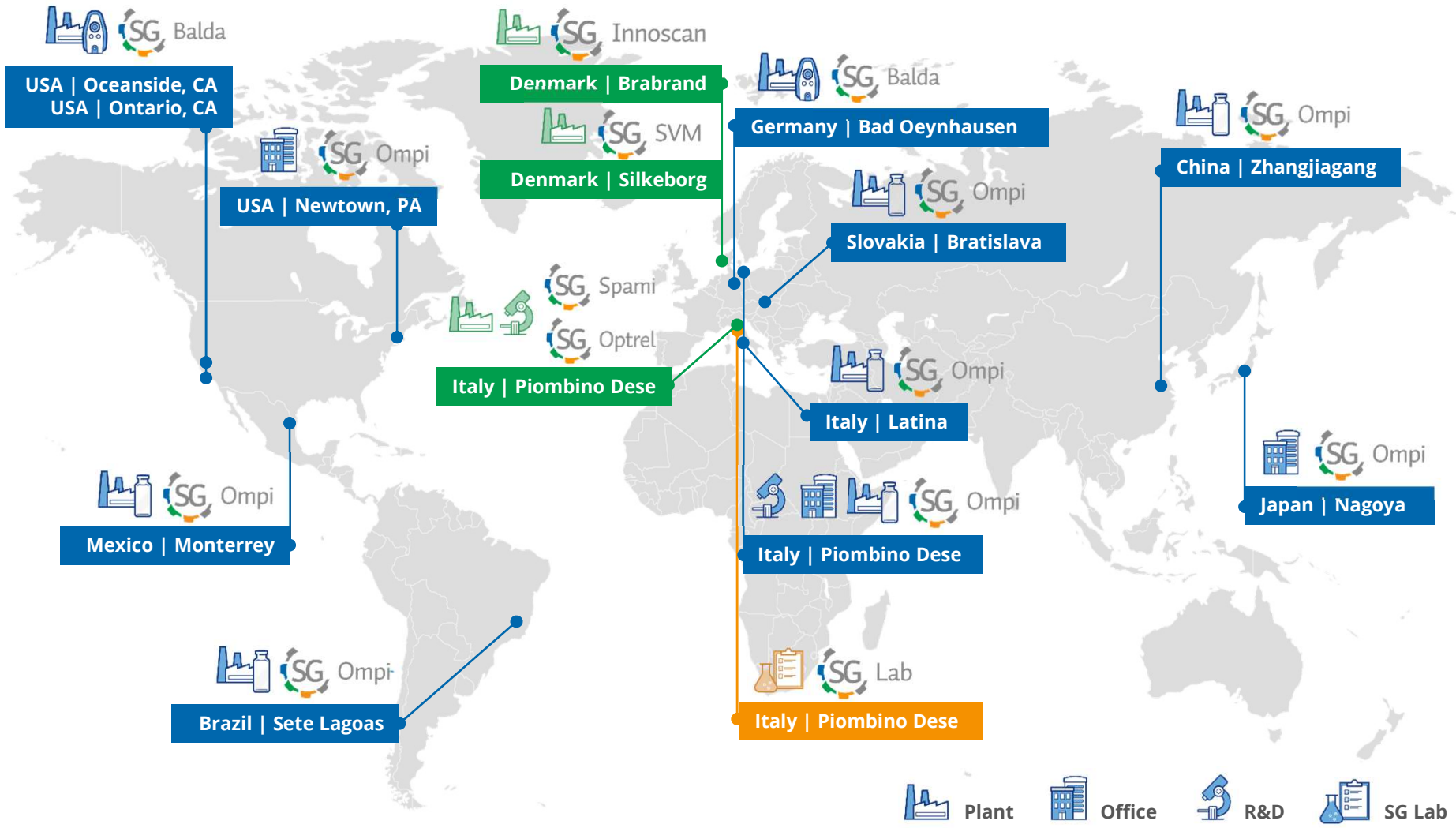
Stevanato Group

PHARMACEUTICAL SYSTEMS

ENGINEERING SYSTEMS

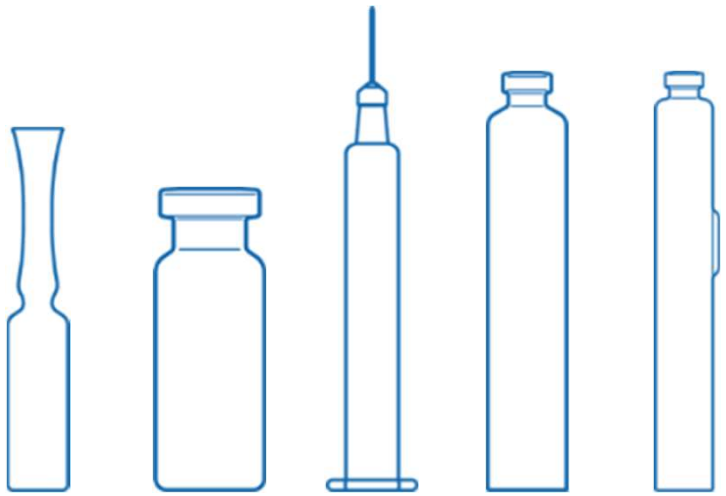
SERVICES

Stevanato Group Today – Global Footprint



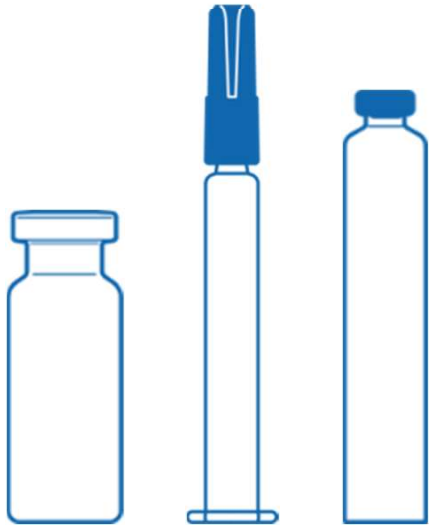
Ompi Range of Products

Bulk Containers



Ampoules | Vials | Syringes | Cartridges | Special Containers

Ompi EZ-fill®



Vials | Syringes | Cartridges

A Complete Range of Containers for Injectables

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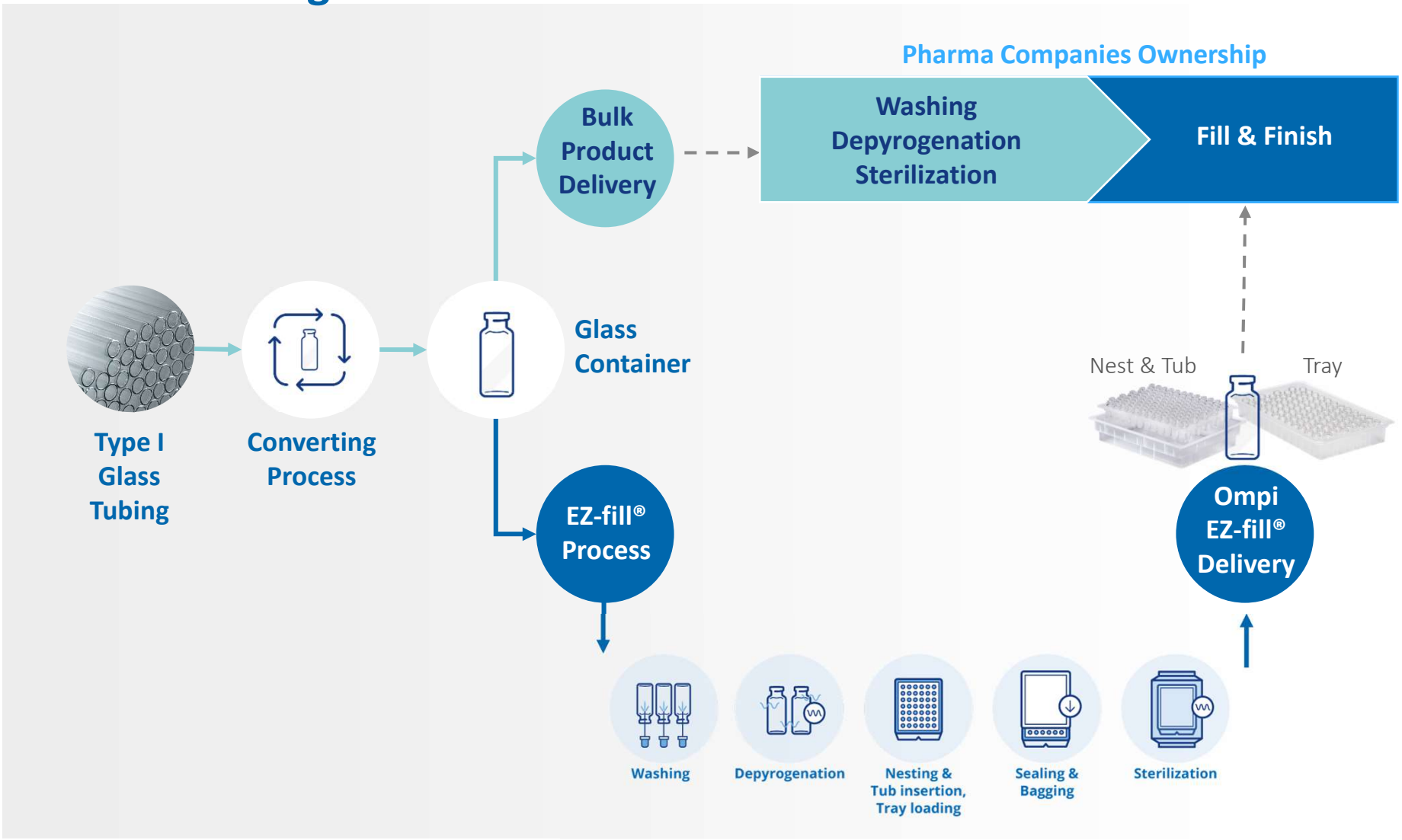
Glass Forming Process: from Bulk to EZ-fill®



Bulk Products | Technology Steps and Improved Solutions

MANUFACTURING STEPS
CONTROLS

1. GLASS TUBING LOADER

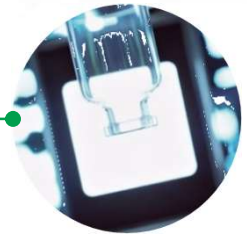
CAMERA FOR INTERNAL DIAMETER AND BOTTOM/FLANGE AREA

2. GLASS FORMING

4. ANNEALING LEHR

5. FINAL PACKING

3. AFTERFORMING LINE



CAMERA FOR NECK PROFILE AND FLANGE AREA

COSMETIC CONTROLS

Reduction of Variability in Dimensions

CONTINUOUS IMPROVEMENT OF THE TECHNOLOGY

Forming tools are designed to reduce glass container tolerances and to maintain their precision for long forming runs

INCREASED NUMBER OF FORMING STEPS

Forming steps are designed to guarantee high precision forming and high repeatibility of the process

NEW GENERATION INSPECTION SYSTEM

100% in-line camera inspection gives a real-time feedback on the quality of the batch

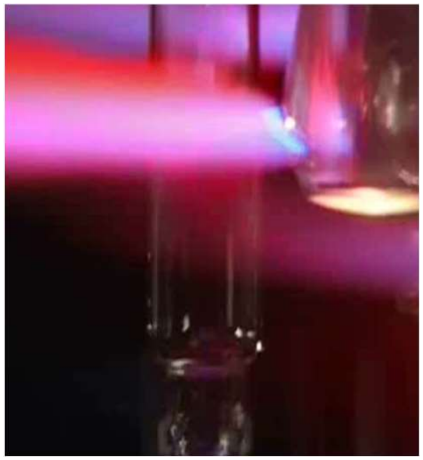
Example of Improved Manufacturing Process in Vial Bottom Forming Step

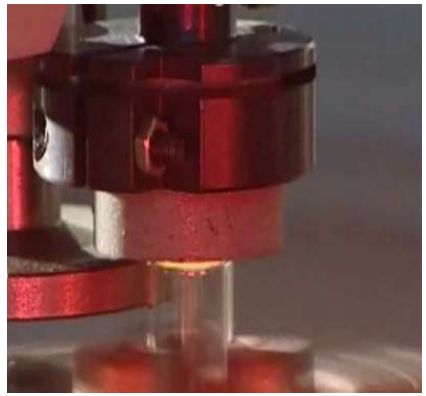
- Increased number of forming steps
- Introduction of a mold for final manufacturing
- Pyrometer Technology for 100% temperature control

Higher stability of vials

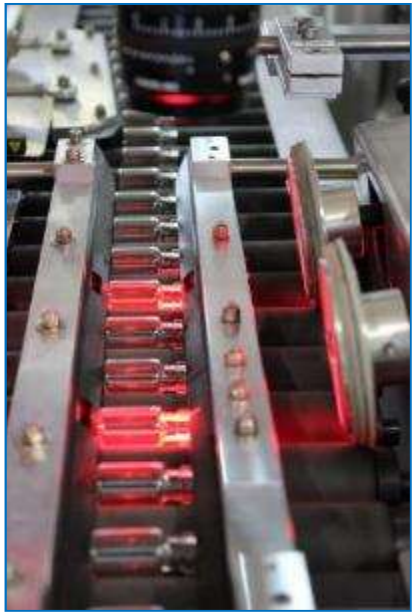
Homogeneous glass distribution and small concavity

More resistant glass in lyophilization cycles



Accurate Handling to Preserve Cosmetic and Mechanical Properties of Glass Container

- No glass-to glass contact
- No buffer stations
- New contact materials to reduce the risk of thermal shock and avoid metal to glass
- Soft handling of the glass container to limit vibrations

100% in-line Inspection Controls are in Place to Assure Product Conformity

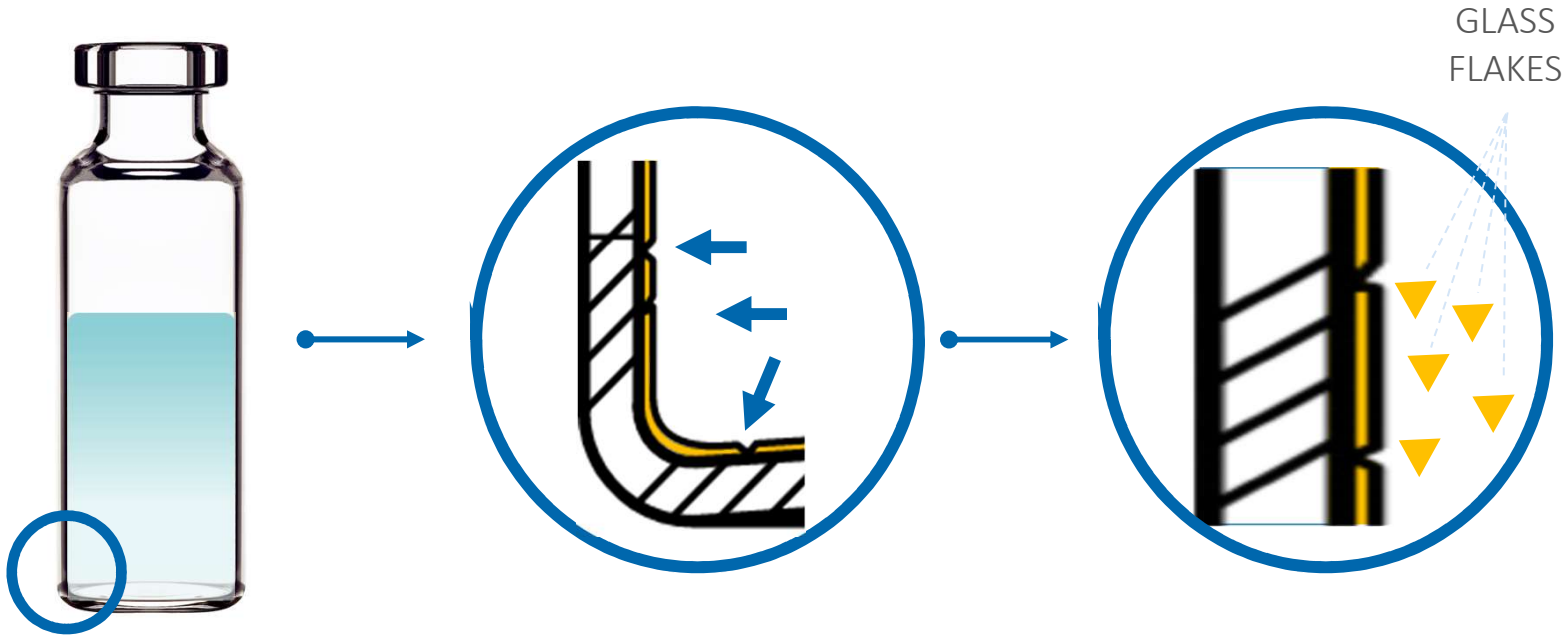
- 100% inspection of all dimensions
- Automatic rejection of defective pcs
- Automatic calibration system
- Performance per chuck
- Measurements and statistics in real time

Cracks	*Scratch*	*Chip*	*Contamination*
			

Specific Line Settings Contribute to Achieve Different Quality Levels

	Ompi Fina	Ompi Nexa
Critical Chip (sealing) Crack Glass particles	0,1 – 0,04	0,1 – 0,025 & ppm
Major Contamination Bull eye Groves and notches	0,65 – 0,1	0,15 – 0,04
Minor Notch, external Scratch Folds	2,5 – 0,4	1,0 – 0,25

Glass Chemical Properties
Glass-Liquid Interactions Can Lead to Creation of Altered Layer

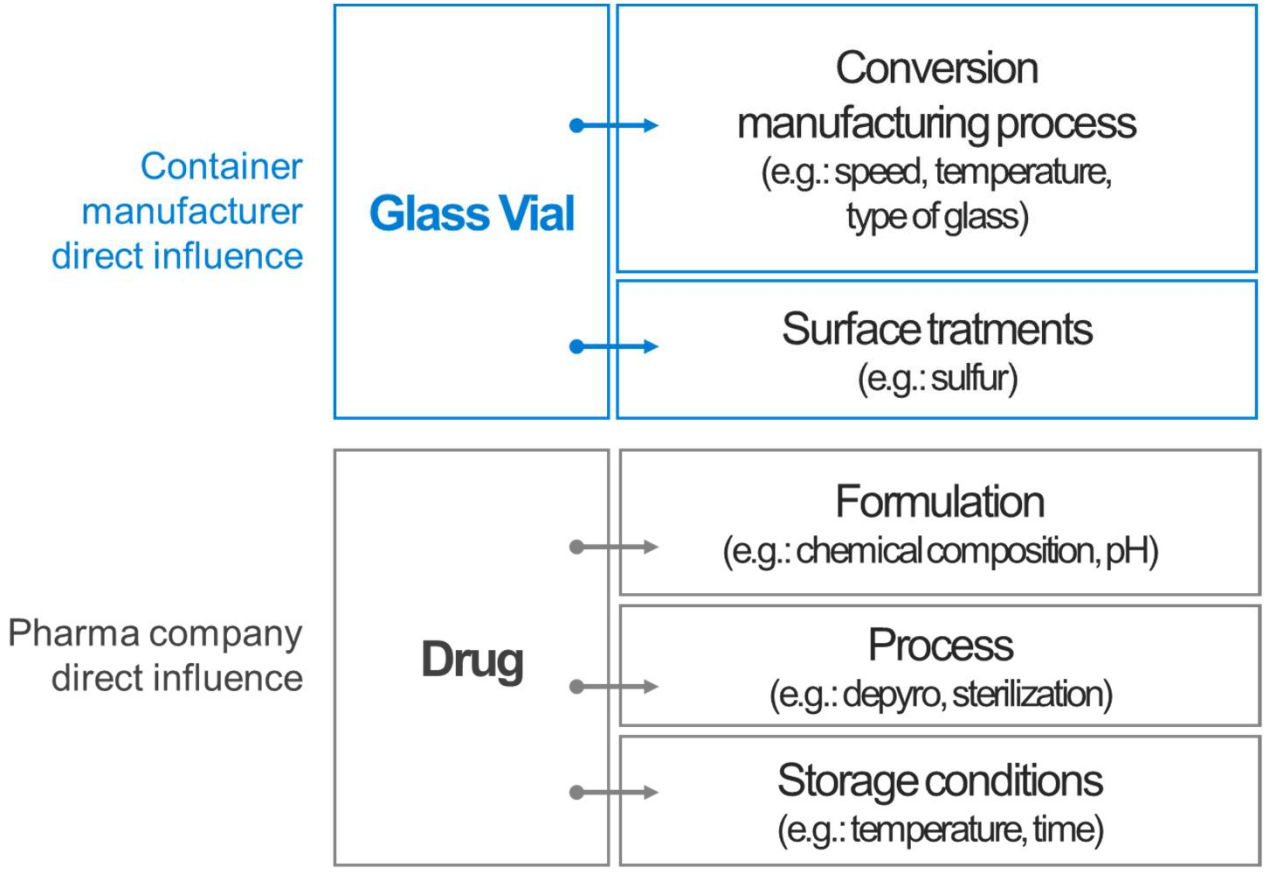


Alkaline solutions strongly affect the dissolution of the silica layer.
SiO2 concentration in the extraction liquid increases steeply

Flakes appears

Several Factors Affect Delamination Propensity of Pharmaceutical Glass

Morphological and Physicochemical properties of Glass Vials can affect the interaction with the drug



Source: USP 1660

Chemical Performances Can Be Guaranteed with Optimized Bulk Processes

LDP (Low Delamination Propensity) Vials

Forming process optimization with low heat/energy thermal cycle and reduced surface inhomogeneities formation

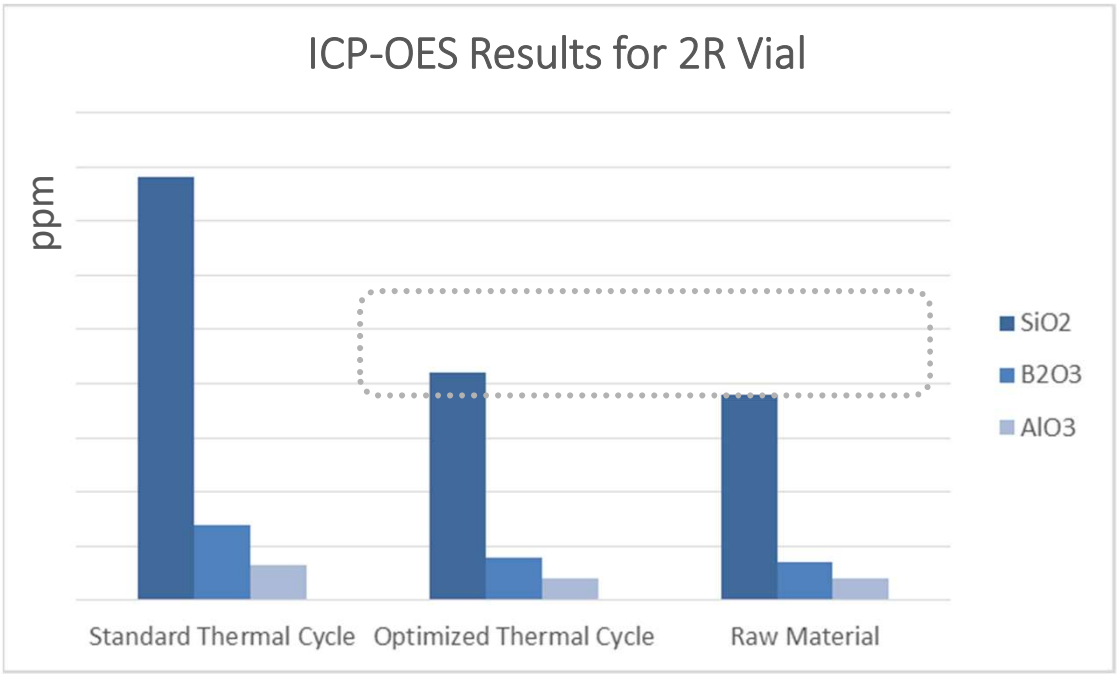
Quantitative and qualitative **tests** to guarantee the quality and the stability of vials production

No coatings
No glass formulation changes
No need to re-file

Responsibilities

- Primary Packaging Supplier optimizes glass Converting Process
- Pharma Companies in charge of verifying impact of washing/depyrogenation

LDP Vials Show Chemical Performances Close to Non-Converted Raw Material



Example of extracted elements from converted glass in comparison to raw materials

Vials from Optimized Process shows comparable performances of Raw Material

Converting process can be controlled to reduce effect on chemical properties of the glass

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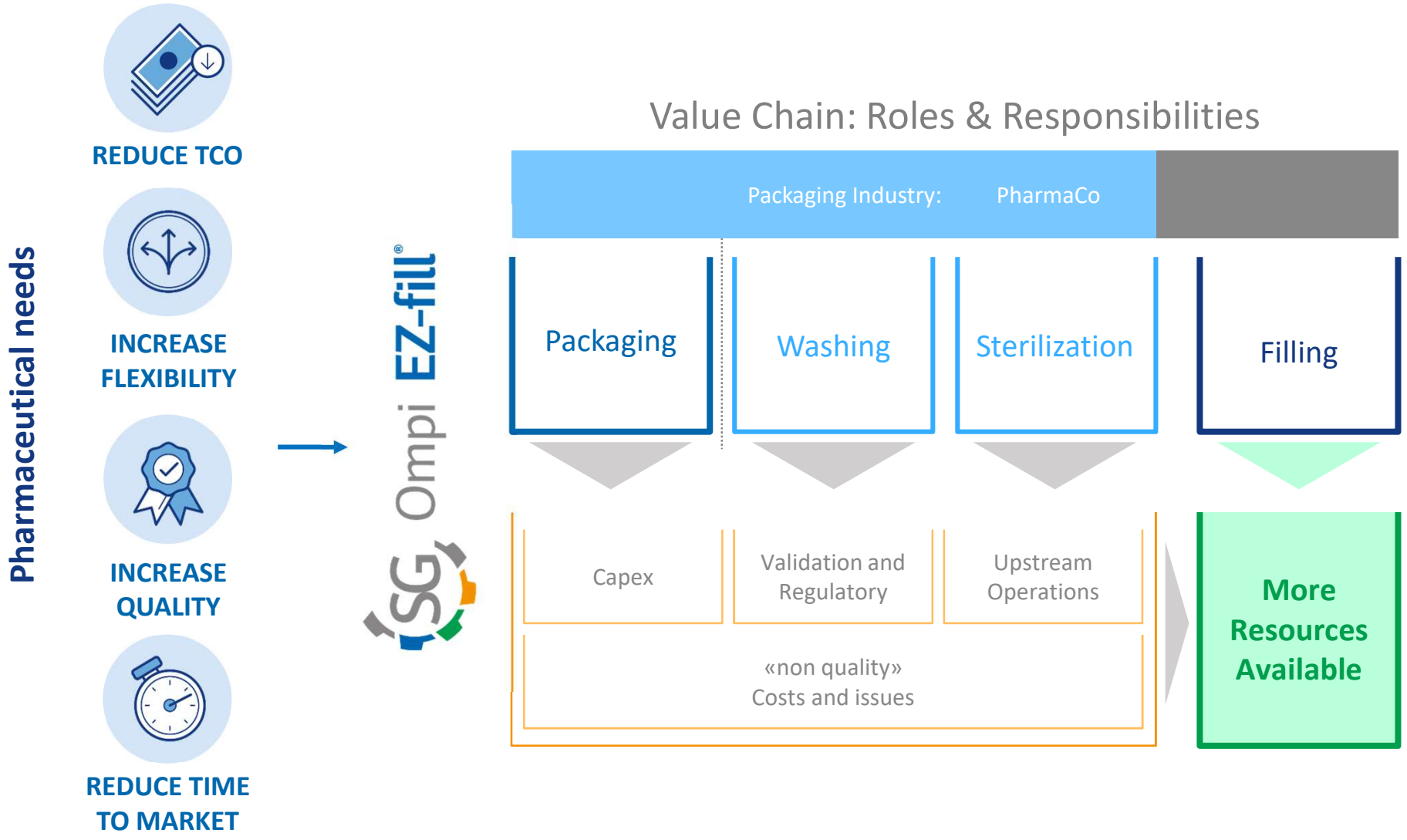
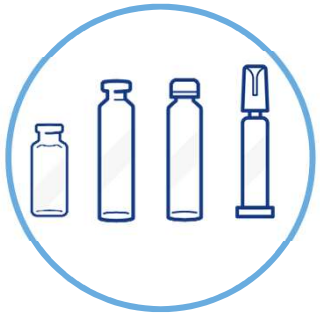
Ompi EZ-fill® Syringes, Vials and Cartridges | Concept Introduction



OMPI Designed Different Secondary Packaging Configurations to Support the Specific Needs of Pharma



Washing
(Siliconization)
Depyrogenation
Nesting (no G2G)
Final Sterilization

OMPI EZ-fill in Tray is a suitable solution for EZ-fill vials and cartridges for:

- High speed filling line
- Flexible lines processing different dimensions of the same container
- RTU lines working according to traditional filling process (i.e. for cartridges: plunger insertion, filling from the neck, capping)

OMPI EZ-fill in N&T is the best configuration for *combi lines* to fill vials, cartridges, syringes with a unique filling machine

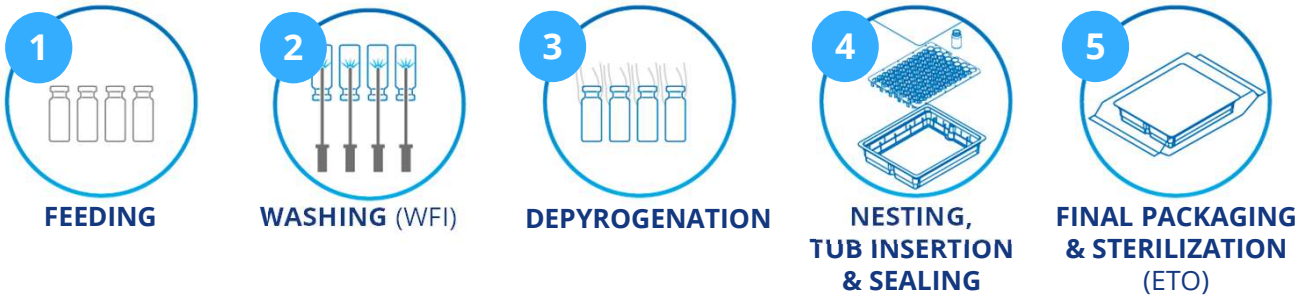
Ompi EZ-fill® | Pharma Production Area

Production Area
Designed and developed on GMP standard.

Different Clean Rooms
(from ISO8 to ISO5)

Internal Laboratories
(chemical, environmental and functional testing)

EZ-fill® Products | Technology Steps and Microbiological Focus



Product Microbiological Level

- Endotoxin Level < 0,25 EU/mL
- Bioburden (before sterilization)
- Final Sterility < 0 CFU

Utilities Microbiological Periodical Analysis

- Water for Injection
- Compressed Air
- Environmental monitoring (e.g. particle counting)

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Visible Particle Characterization on 10R EZ-fill® Vials in Nest&Tub

Specification on primary packaging prescribes a requirement for visible particles bigger than 0.3 mm^2

Focus on particles/fibers **bigger than 100 µm**

Characterization results on 2 tubs of 10R vials manufactured in 2016:

- Identified fibers (L>3W): Cellulose, Polyester.
- Identified particles: Proteins, Cellulose, Teflon, Poly-Acetal.
- No secondary-packaging-related materials were identified (e.g. Polypropylene, Tyvek, Polyethylene).

Samples were characterized through automatic scanning on filter (USP <788>), using a rinsing solution 0.2µm-filtered water (considered particle-free), added with 0.001% Tween 80.

Critical-to-Quality Attribute (CTQ's)

1. CTQ (OPERATIVE): Defect per Unit (DPU)

$$CTQ_{Ope} := DPU = \frac{N_{VP,tot}}{N_{vials,inspected}}$$

where:

- DPU is the mean number of visible particles per vial;
- $N_{VP,tot}$ is the total number of «generalized» particles (as sum of particles and fibers);
- $N_{vials,inspected}$ is the total number of inspected vials.

2. CTQ (PROJECT): Process Yield (PY)

$$CTQ_{Prj} := PY = e^{-DPU}$$

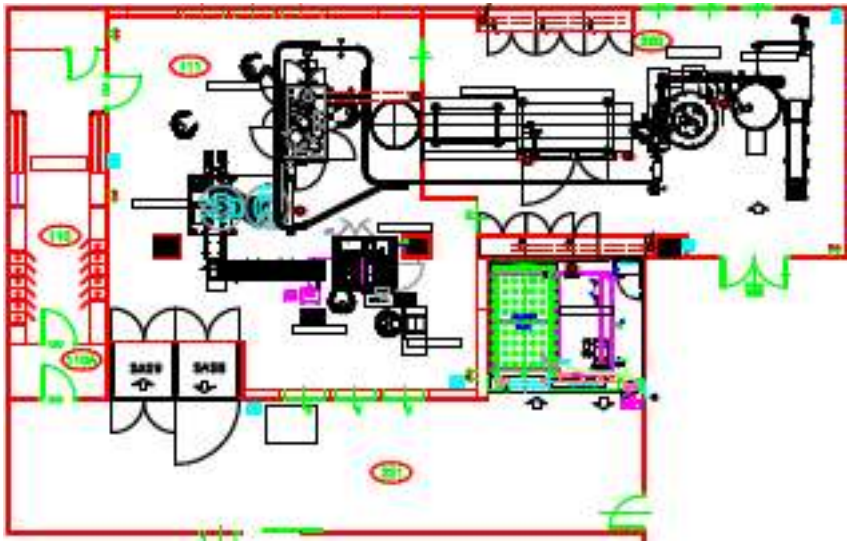
where e is the Euler's number.

ASSESSMENT BEFORE IMPROVEMENT			
Particles/ Fibers size > 100 µm (Study threshold)		**Particles/ Fibers size > 0.3 mm^2 (Specification threshold)**	
DPU	**PY [%]**	**DPU**	**PY [%]**
>1	<50%	0	100.00%

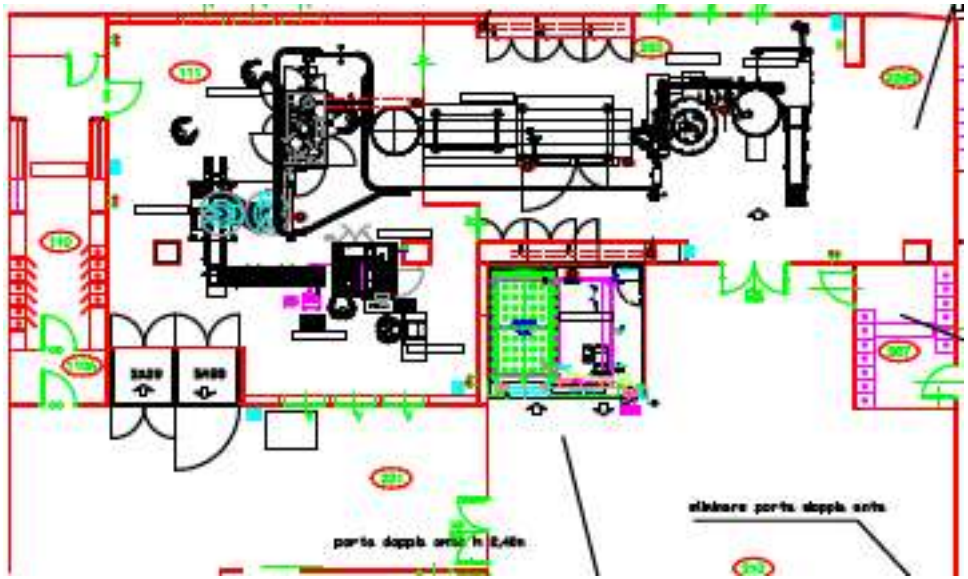
Test plan: two (2) random tubs from 2016 batch (48 vials/tub) – tot. 96 vials

Manufacturing Flow Optimization

BEFORE IMPROVEMENT



AFTER IMPROVEMENT



- Dedicated semifinished pallet loading area
- Improved material movimentation
- Additional changing rooms

Performance Improvements Based on Manufacturing Flow Optimization: Effectiveness Verification

ASSESSMENT BEFORE IMPROVEMENT			
Particles/ Fibers size > 100 µm (Study threshold)		Particles/ Fibers size > 0.3 mm^2 (Specification threshold)	
DPU	PY [%]	DPU	PY [%]
>1	<50%	0	100.00%

Test plan: two (2) random tubs from 2016 batch (48 vials/tub) – tot. 96 vials

SG OMPI PROCESS MAPPING			
Particles/ Fibers size > 100 µm (Study threshold)		Particles/ Fibers size > 0.3 mm^2 (Specification threshold)	
DPU	PY [%]	DPU	PY [%]
<0.03	>97%	0	100.00%

Test plan: twelve (12) tubs from 2017 production process mapping (48 vials/tub) – tot. 12 tubs (576 vials)

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Conclusions

- High quality level for glass primary packaging can be obtained starting from the optimization of manufacturing process
- The characteristics obtained during bulk forming process can be maintained through the EZ-fill step thanks to a state-of-the-art design of the lines
- Particle Reduction is possible acting on flow optimization in core area
  - Further improvements are possible through additional assessment on raw material Suppliers' processes
- The Ready-to-Use concept is today well established in the market since it allows to:
  - Reduce the total cost of ownership
  - Increase flexibility
  - Increase quality

Thank You for Your Attention!

For further information visit
www.sg-ompi.com

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