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

Martina Largoni
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
Stevanato Group Brand Structure

PHARMACEUTICAL SYSTEMS  ENGINEERING SYSTEMS  SERVICES
Stevanato Group Today – Global Footprint
Ompi Range of Products

Bulk Containers

Ampoules  Vials  Syringes  Cartridges  Special Containers

Vials  Syringes  Cartridges

A Complete Range of Containers for Injectables
How to assure quality in glass vials

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Glass Forming Process: from Bulk to EZ-fill®

Type I Glass Tubing → Converting Process → Glass Container → EZ-fill® Process → Bulk Product Delivery

Pharma Companies Ownership

Washing Depyrogenation Sterilization

Fill & Finish

Ompi EZ-fill® Delivery

Washing
Depyrogenation
Nesting & Tub insertion, Tray loading
Sealing & Bagging
Sterilization

Nest & Tub
Tray
Bulk Products | Technology Steps and Improved Solutions

1. GLASS TUBING LOADER

2. GLASS FORMING

3. AFTERFORMING LINE

4. ANNEALING LEHR

5. FINAL PACKING

CAMERA FOR INTERNAL DIAMETER AND BOTTOM/FLANGE AREA

CAMERA FOR NECK PROFILE AND FLANGE AREA

COSMETIC CONTROLS

MANUFACTURING STEPS

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 repeatability 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
## Specific Line Settings Contribute to Achieve Different Quality Levels

<table>
<thead>
<tr>
<th></th>
<th>Ompi Fina</th>
<th>Ompi Nexa</th>
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</thead>
<tbody>
<tr>
<td><strong>Critical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chip (sealing)</td>
<td>0,1 – 0,04</td>
<td>0,1 – 0,025 &amp; ppm</td>
</tr>
<tr>
<td>Crack</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glass particles</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Major</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contamination</td>
<td>0,65 – 0,1</td>
<td>0,15 – 0,04</td>
</tr>
<tr>
<td>Bull eye</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Groves and notches</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Minor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notch, external</td>
<td>2,5 – 0,4</td>
<td>1,0 – 0,25</td>
</tr>
<tr>
<td>Scratch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folds</td>
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</tbody>
</table>
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

Pharmaceutical needs

- REDUCE TCO
- INCREASE FLEXIBILITY
- INCREASE QUALITY
- REDUCE TIME TO MARKET

Value Chain: Roles & Responsibilities

Packaging Industry: PharmaCo

Packaging | Washing | Sterilization | Filling

More Resources Available

Capex | Validation and Regulatory | Upstream Operations

«non quality» Costs and issues

REDUCE TCO
INCREASE FLEXIBILITY
INCREASE QUALITY
REDUCE TIME TO MARKET
OMPI Designed Different Secondary Packaging Configurations to Support the Specific Needs of Pharma

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

- **Washing** (Siliconization)
- **Depyrogenation**
- **Nesting (no G2G)**
- **Final Sterilization**
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 mm²

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)

\[
CTQ_{Ope} := DPU = \frac{N_{VP,\text{tot}}}{N_{\text{vials,inspected}}}
\]

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

<table>
<thead>
<tr>
<th>ASSESSMENT BEFORE IMPROVEMENT</th>
<th>Particles/ Fibers size &gt; 100 µm (Study threshold)</th>
<th>Particles/ Fibers size &gt; 0.3 mm(^2) (Specification threshold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPU</td>
<td>PY [%]</td>
<td>DPU</td>
</tr>
<tr>
<td>&gt;1</td>
<td>&lt;50%</td>
<td>0</td>
</tr>
</tbody>
</table>

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

BEFORE IMPROVEMENT

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

AFTER IMPROVEMENT
Performance Improvements Based on Manufacturing Flow Optimization: Effectiveness Verification

### Performance Improvements

#### Test Plan Before Improvement

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<td>&lt;50%</td>
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<tr>
<td>&lt;1</td>
<td>100.00%</td>
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Test plan: two (2) random tubs from 2016 batch (48 vials/tub) – tot. 96 vials

#### Test Plan After Improvement

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<tbody>
<tr>
<td>DPU</td>
<td>DPU</td>
</tr>
<tr>
<td>&lt;0.03</td>
<td>100.00%</td>
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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