GMP Requirements for Stopper Processing for sterile filling applications
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
• Foundation of Atec Pharmatechnik in 1996, 170 employees
• specialised in equipment for sterile manufacturing
• over 150 qualified Stopper Processing Systems 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
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
- Caps
- Lined Seals
- Plungers
- Needle Shields
- Caps
- Lyo and Liquid Stoppers
- Plungers
- Glass and Steel Beads
- Tip Caps
- and more!
Key Requirements for stoppers

- Bioburden
- Moisture
- Particles
- Temperature
- Endotoxin
- Machinability
<table>
<thead>
<tr>
<th>Requirement</th>
<th>Endotoxin</th>
<th>Particulate</th>
<th>Bioburden</th>
<th>Sterilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requirement</td>
<td>≥ 3 log reduction</td>
<td>Fewer than 2000 &gt; 10µm, Fewer than 200 ≥ 25µm</td>
<td>SAL ≥ 10⁻⁶, Spore log reduction ≥ 12</td>
<td>F₀ ≥ 15</td>
</tr>
</tbody>
</table>

*Requirement is inferred, not specific to stopper processing
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

<table>
<thead>
<tr>
<th>Pharmacopeia</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>“…practically free of visible particles”</td>
</tr>
<tr>
<td>European</td>
<td>“…essentially free of visible particles” (Parenteral Preparations)</td>
</tr>
<tr>
<td></td>
<td>“…without visible particles, unless otherwise justified and authorised” (MABs for human use)</td>
</tr>
<tr>
<td>Japan</td>
<td>“… must be clear and free from readily detectable particles”</td>
</tr>
<tr>
<td>Test</td>
<td>Product</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Light Obscuration</td>
<td>Small volume Parenterals</td>
</tr>
<tr>
<td></td>
<td>Large volume Parenterals</td>
</tr>
<tr>
<td>Microscope</td>
<td>Small volume Parenterals</td>
</tr>
<tr>
<td></td>
<td>Large volume Parenterals</td>
</tr>
</tbody>
</table>

- 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.

<table>
<thead>
<tr>
<th>Reporting Category</th>
<th>Historical Specification</th>
<th>Enhanced Specification (particles / 10cm(^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI</td>
<td>≤ 3.4</td>
<td>≤ 2.5</td>
</tr>
<tr>
<td>&gt; 25µm but ≤ 50µm</td>
<td>Not specified</td>
<td>≤ 13</td>
</tr>
<tr>
<td>&gt; 50µm but ≤ 100µm</td>
<td>Not specified</td>
<td>≤ 3.5</td>
</tr>
<tr>
<td>&gt; 100µm</td>
<td>Not specified</td>
<td>≤ 0.9</td>
</tr>
</tbody>
</table>

Values expressed in (particles / 10 cm\(^2\))
• Atec on-site laboratory Standard Operating Procedures

• Sample stoppers after processing and recover particles. Count particles by with a liquid particle counter.
Atec has selected the criteria from West Pharmaceuticals:

<table>
<thead>
<tr>
<th></th>
<th>PCI</th>
<th>25-50 µm</th>
<th>50-100 µm</th>
<th>&gt;100 µm</th>
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</thead>
<tbody>
<tr>
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<td>3.4</td>
<td>Not defined</td>
<td>Not defined</td>
<td>Not defined</td>
</tr>
<tr>
<td>Enhanced</td>
<td>2.5</td>
<td>13.0</td>
<td>3.5</td>
<td>0.9</td>
</tr>
</tbody>
</table>

with one additional category for small particles

\[
n_{an} = n_{a0} \cdot 0,01 + n_{a1} \cdot 0,1 + n_{a2} \cdot 0,2 + n_{a3} \cdot 1
\]
Graphic representation for 3 samples for unprocessed stoppers:
Graphic representation for 3 samples for unprocessed stoppers:

<table>
<thead>
<tr>
<th>Results Overview of Unprocessed and Processed Stoppers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Unprocessed Stoppers</td>
</tr>
<tr>
<td>Processed Stoppers</td>
</tr>
</tbody>
</table>
Washing Process
Requirements for Stoppers in sterile filling

Process steps to achieve the requirements:

- Endotoxin reduction
- Particle reduction
- Silicone layer
- Bioburden
- Residual moisture
- Final temperature of stoppers

Steps:
- Washing
- Siliconisation
- Sterilization
- Drying
- Cooling
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

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
Component Transfer with Process Vessel
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
Choose the right process parameters and qualification method to meet and verify regulatory requirements

Process steps to achieve the requirements:

- Endotoxin reduction
- Particle reduction
- Silicone layer
- Bioburden
- Residual moisture
- Final temperature of stoppers

Steps:
- Washing
- Siliconisation
- Sterilization
- Drying
- Cooling
We made it!

Thank you for your attention