Quality and Risk-Based Approach for Particulate Matter and Endotoxin Control in Ophthalmic Products - Case Studies

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Ophthalmic Products Pose Unique Challenges

- Eye is a very sensitive organ and administration locally to the organ directly poses many challenges to the formulator
  - Ocular tolerability issues limit excipients to choose from
  - Critical to keep within a narrow range of other parameters (pH, Osmolarity, etc)
- Unique container-closure requirements present additional challenges, especially for particulate matter and endotoxin control

It all starts with good product and process design!!
Potential Safety Concerns of Particulate Matter in Ophthalmic Preparations

Particulate matter administered topically have the potential to damage the epithelial layer, which may lead to infection and scarring.

Particulate matter administered intraocularly can block the canals of Schlemm, disrupting the outflow mechanism for the aqueous humor and leading to a rapid increase in intraocular pressure and the onset of an acute attack of glaucoma.
PM Acceptance Limits are More Stringent than Small Volume Parenterals!

<table>
<thead>
<tr>
<th>Particle Size</th>
<th>Small Vol Parenterals USP &lt;788&gt;</th>
<th>Ophthalmic Products USP &lt;789&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 10 , \mu m$</td>
<td>$\leq 3000 \text{ particles/container}$</td>
<td>$\leq 50 \text{ particles/mL}$</td>
</tr>
<tr>
<td>$\geq 25 , \mu m$</td>
<td>$\leq 300 \text{ particles/container}$</td>
<td>$\leq 5 \text{ particles/mL}$</td>
</tr>
</tbody>
</table>

• Typical multi-dose Ophthalmic containers have 5-10 mL fill volume – so even per container limits are 10 fold more stringent than SVP
Sources of Particulate Matters

**Inherent (from formulation):**
- Undissolved drug
- Formation of less soluble drug polymorphs
- Incompatibility with primary container

**Intrinsic (from manufacturing process)**
- Raw materials
- Processing equipment and transfer line
- Primary container-closure

**Extrinsic (from outside the process)**
- Environmental contaminants
- Operators
- Cleaning process
- Transport of Container-closure

**Particulate matter Testing Procedure**
- Contamination during testing
- Low Fill Volume, especially in UD containers require sample pooling
- High viscosity solutions require dilutions
Quality and Risk Based Approach to Particulate Matter Control

**Prevent** formation in drug product
- Understand sources of particulate matter

**Eliminate** at the point of filling
- Assess risk, design mitigation plan and develop control points

**Avoid** introduction into the product train

**Monitor** through statistical sampling and release testing
Control Points for Intrinsic and Extrinsic Particulate Matter

- Filtration
- Equipment cleaning
- Environment control
- Human intervention

- Reduce particulate matter in RM
- Particulate-free container
- Handle RM under controlled condition

- Filtration and rinsing product path
- Particulate-free primary package
- Equipment cleaning/rinsing
- Qualify product contact parts
- Isolator/barrier tech
- Human intervention

Some Control Points may be more important dependent upon type of dosage forms
Case Example 1 – A Topical Ophthalmic Solution

Situation:
Visible particles observed in stability samples during formulation development

Investigation:
Particles were collected and found to be a degradation impurity that was insoluble in the formulation

Solution:
Estimated maximum amount of impurity could be formed (accelerated stability study)
Identified a suitable solubilizer and incorporated in formulation
Case Example 2 – A Gel Suspension for IVT Injection

Situation:
Product is a gel suspension filled in pre-filled syringe
To perform particulate matter test, a solvent/water mixture is used to dissolve both water insoluble drug and water soluble excipients in the formulation
High level of particulate matter was consistently observed in all analytical samples

Investigation:
ID of particles suggests these are mixture of drug and silicon oil
Solvent used for sample preparation was able to dissolve drug, but not able to dissolve drug particles encapsulated by trace level of silicon oil from pre-filled syringe

Solution:
Revised solvent system to ensure complete dissolution of drug particles in test samples
Additional Challenges – Test Procedures

• Testing limitations continue to pose the biggest challenges to PM control

• Low volume fills in UD containers (typically 100-300 μL) require pooling large no. of UD vials for PM testing
  • Contamination introduced during sampling process

• Microscopic methods often introduces artifacts and may not be the most representative

• For dispersions (suspensions/emulsions), although use of solvents to dissolve drug particles allow for testing, error may be introduced if extraneous particles are also removed.
Endotoxin

Where does it come from?

- The outer membrane of Gram-negative bacteria
- Lipopolysaccharide and protein
Endotoxin

Why is it important?

• A pyrogen (fever producing)
• Inflammation of the eye (e.g. Toxic Anterior Segment Syndrome - TASS)
• It survives sterilization (e.g. autoclaving, filtration)
• Control is a regulatory requirement for parenteral products
• For the eye:
  • OVDs or viscoelastics, irrigation fluids used in surgery, intraocular lenses and injectables into the eye (e.g. intra-vitreal gels and implants)
  • Topical ophthalmic products (in the past by FDA only) — current thinking is to not require this for topical products
Major sources/variabilities of Endotoxin

- Water (both in product as well as used for cleaning equipment)
- Manufacturing Equipment
- Container Closure
- Raw materials
- Environment/Operators

- Testing methods
  - Assay variability
  - Detection methods (Kinetic Chromogenic vs Gel Clot methods)
  - Contamination during testing
  - Control limits set close to detection/quantification limits
Endotoxin Control of Product Manufacturing Controls

- Equipment surfaces coming in contact with product should be cleaned using validated procedures and maintained dry
  - De-pyrogenation/Autoclaving/SIP/CIP processes and rapid drying after cleaning
  - Endotoxin spiking studies using coupons to demonstrate 3 log reduction of endotoxin to verify cleaning processes
  - Rinsing equipment and testing carry over water to demonstrate consistency of cleaning processes (limit 0.25 EU/mL)
- Hold time studies
  - To establish pre-sterile bulk hold times to control bioburden
  - To establish storage conditions and timelines for endotoxin testing
Whereas glass vials can be de-pyrogenated, plastic container closures can’t. The likelihood of endotoxin contamination from plastic containers into the product should be investigated:

- Testing of plastic resins over the seasons
- Testing of molded container closure after endotoxin spiking of plastic resins followed by molding
- Testing of several lots of plastic container closures to collect historical data and application of an appropriate endotoxin limit (action limit)
Endotoxin Control of Product Raw Materials

• RM pose the biggest risk and hence appropriate controls is critical

  • Audit vendors and negotiating setting additional limits as part of Certificate of Analysis

  • Raw materials utilizing synthetic steps are of lower risk than those from animal and plant origin

  • Preservatives, strong acids/bases and dry solids are of lower risk than water containing liquids

  • Testing frequency and raw material limits (action limits) should factor in these risks

  • Consider the weighted contribution of individual raw material endotoxin limits to the finished drug product specification

  • Alert limits below action limits to be aware of OOT data
A risk-based approach to the choice of method for testing water, raw materials, container closure, in-process bulk sub-parts and drug product should be taken.

- Use kinetic test methods when greater sensitivity is desired.
- Gel clot method is better suited for some insoluble materials.
- Choose at least 2-fold greater dilution than the minimum non-inhibitory dilution to accommodate for variability from lot to lot and at product stability.
- Utilize method detection limits and historical data from multiple lots to set endotoxin limits (action limits) using risk-based approaches.
# Case Study

Topical Ophthalmic Product (10 mL Fill)

DL for Product Method is 2 EU/mL and Specification is NMT 6 EU/mL

<table>
<thead>
<tr>
<th>Component</th>
<th>mg/mL</th>
<th>Property</th>
<th>Detection Limit (DL)</th>
<th>Component Limit (Risk Based)</th>
<th>Weighted Contribution (EU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Substance</td>
<td>1</td>
<td>Synthetic</td>
<td>0.5 EU/mg</td>
<td>1 EU/mg</td>
<td>1</td>
</tr>
<tr>
<td>Excipient 1</td>
<td>1</td>
<td>Preservative</td>
<td>1 EU/mg</td>
<td>2 EU/mg</td>
<td>2</td>
</tr>
<tr>
<td>Excipient 2</td>
<td>10</td>
<td>Natural Source, Vendor Controlled</td>
<td>0.025 EU/mg</td>
<td>0.1 EU/mg</td>
<td>1</td>
</tr>
<tr>
<td>Excipient 3</td>
<td>10</td>
<td>Natural Source, No Vendor Control</td>
<td>0.005 EU/mg</td>
<td>0.05 EU/mg</td>
<td>0.5</td>
</tr>
<tr>
<td>Water</td>
<td>QS</td>
<td>Purified, WFI limit</td>
<td>0.01 EU/mL</td>
<td>0.25 EU/mL</td>
<td>0.25</td>
</tr>
<tr>
<td>Container Closure (CC)</td>
<td>NA</td>
<td>Plastic</td>
<td>0.1 EU/CC</td>
<td>0.5 EU/CC</td>
<td>0.05</td>
</tr>
<tr>
<td>Process</td>
<td>NA</td>
<td>Endotoxin Controlled</td>
<td>(0.1 EU/mL)</td>
<td>(0.25 EU/mL)</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.05</td>
</tr>
</tbody>
</table>
# Case Study

## Intra-Vitreal Injection (100 µg Implant and Needle)

Specification is NMT 2 EU/Dose/Eye

<table>
<thead>
<tr>
<th>Implant (IM) Component</th>
<th>[ ] mg/IM</th>
<th>Property</th>
<th>Detection Limit EU/mg</th>
<th>Component Limit EU/mg</th>
<th>Weighted Contribution EU/IM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Substance</td>
<td>0.02</td>
<td>Synthetic, Vendor Controlled</td>
<td>2</td>
<td>4</td>
<td>0.08</td>
</tr>
<tr>
<td>Excipient 1</td>
<td>0.02</td>
<td>Synthetic, Vendor Controlled</td>
<td>3</td>
<td>6</td>
<td>0.12</td>
</tr>
<tr>
<td>Excipient 2</td>
<td>0.06</td>
<td>Synthetic, Vendor Controlled</td>
<td>5</td>
<td>10</td>
<td>0.6</td>
</tr>
<tr>
<td>Total</td>
<td>0.1</td>
<td></td>
<td></td>
<td></td>
<td>0.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Finished Product Component</th>
<th>Detection Limit</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant</td>
<td>1 EU/IM</td>
<td>NMT 1.8 EU/IM</td>
</tr>
<tr>
<td>Needle</td>
<td>0.1 EU/Needle</td>
<td>NMT 0.2 EU/Needle</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>NMT 2 EU/Dose/Eye</td>
</tr>
</tbody>
</table>
Summary

• Control of PM and Endotoxin begins at Product Design Stages

• Unique nature of Ophthalmic products pose additional challenges and needs to be carefully considered

• Understanding the sources of origin as well as the variabilities at every level (Product, process, material, distribution, etc) is important to effectively place controls throughout

• Emphasis on final product testing can lead to poorly controlled product – Final testing should only confirm and monitor the controls.