Rx-360 Flash Report

www.Rx-360.org

A Nonprofit Organization

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Rx-360 is using this flash report to provide important information concerning glass vials, which are a critical component used in many sterile parenteral products.

There have been additional product recalls since our last glass delamination report. The following is a list of recent recalls associate with glass particles or flakes:

• American Reagent recalled several injectables including Dexamethasone, 23.4% Concentrated Sodium Chloride for Injection, Bacteriostatic Water for Injection, Potassium Phosphates, Sodium Thiosulfate and Sodium Bicarbonate (December 2010, February & March 2011)

• Cumberland Pharmaceuticals recalled six lots of Acetadote (December 2010)1

• EBEWE Pharma recalled Fluorouracil 50 mg/ml Solution for Injection 10 ml and Methotrexate 100 mg/ml Solution for Injection (November 2010)2

• Sandoz recalled 24 lots of Methotrexate (October 2010)1

• Amgen and Centocor Ortho Biotech recalled multiple lots of Epogen and Procrit (September 2010)1

• Baxter International and Halozyme Therapeutics recalled about 3,200 vials of Hylenex (May 2010)1

The phenomenon described as glass delamination is well-described in the literature, but not well-understood. Delamination occurs when top layers of a glass surface separate and flake off, typically at a scale barely visible or invisible to the naked eye, which makes the detection of glass delamination difficult.

Glass delamination is the result of several factors including the aggressiveness of the product formulation, the glass resistance and process control within the glass manufacturing process.
It has been reported in the literature that not all Type I glass is equivalent with respect to glass resistance and delamination. Some glass manufacturing processes are superior to others in pertaining to preventing glass delamination. For example:

- Molded vials are more durable and less susceptible to glass delamination than tubing vials.

- Processing the glass at lower temperatures during glass cane production and vial forming makes the glass more durable and less susceptible to glass delamination.

“Elevating the temperature of the glass melt can increase production rates; however, this can have a measured impact on product quality. Throughout the initial cane and vial formation processes, the thermal profile of the glass must be closely controlled. Excessive heat will cause sodium to migrate to the inside surface of the vial (where the vial contacts the liquid), thereby increasing surface alkalinity and reducing chemical durability. This physical change continues for the entire life of the vial.”

Studies conclude that the degree of vulnerability to glass delamination increases in order from molded vial to silica coated tubing vial to regular tubing vial to ammonium sulfate treated tubing vial. Citrate buffers and sodium chloride accelerate glass delamination.

The literature has reported that product formulations can be a contributing factor in glass delamination. Some product attributes to consider would be formulation, such as:

- pH
- Buffer type
- Ionic strength
- Vial type
- Vial size

Product formulations with a basic pH (>7.0); that contain citrate buffers; have a high ionic strength (>100 mM NaCl); vial type (tubing) or vial size (>5cc) can contribute to glass delamination.

The following table can serve as a guide to pharmaceutical scientists when developing formulations and to quality professionals when monitoring and controlling ongoing production activities:
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mitigating Factors</th>
<th>Contributing Factors</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>&lt;5.5</td>
<td>&gt;7.0</td>
<td>5</td>
</tr>
<tr>
<td>Buffer Type</td>
<td>N/A</td>
<td>Citrate</td>
<td>4, 8</td>
</tr>
<tr>
<td>Ionic Strength</td>
<td>N/A</td>
<td>&gt;100 mM NaCl</td>
<td>8</td>
</tr>
<tr>
<td>Vial Configuration</td>
<td>Listed in order of preference Best to Worst</td>
<td>4,5,6,7,8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Molded vial</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Silica coated tubing vial</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Regular tubing vial</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Ammonium sulfate treated tubing vial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vial Size</td>
<td>N/A</td>
<td>&gt;5cc</td>
<td>3,6,7</td>
</tr>
</tbody>
</table>

One question remains unanswered: why is there a cluster of glass delamination events leading to recalls in the second of half of 2010? Many of the products that have been recalled are established products with good quality histories. We do know that several different glass suppliers produced vials that were impacted by the recalls. Has something changed in the glass supply chain? Is the industry better at detecting glass delamination? Has the industry been sensitized to the issue and is now looking harder for this phenomenon? We may never fully understand the answer to these questions, since pieces of the data and information are located in many independent organizations. However, Rx-360 believes this information is important to disseminate, and encourages the community to utilize and share this information broadly.

Next Steps:

Rx-360 will be hosting a one-day scientific symposium on May 25, 2001 at the Key Bridge Marriott in Arlington, Virginia designed to share glass delamination experiences and scientific data, so that this information can be summarized in one document for everyone’s benefit. Interested parties should contact Rx-360 at kim.rouse@dbr.com

The PDA is sponsoring a Glass Quality Conference on May 23 -24, 2011, at the Key Bridge Marriott in Arlington, Virginia. Pharmaceutical manufacturers, regulators, and glass suppliers all share a common goal of assuring the highest quality products (including packaging) for patients. This meeting will discuss these issues; best practice to preventing and/or detecting at risk glass packaging; and review current expectations to ensure that recalls are avoided and container closure integrity is assured.
For more information contact PDA at (301) 656-5900 or www.pda.org

References:

1. US Food and Drug Administration Web Site
Dexamethasone Injection Recall
Concentrated Sodium Chloride Injection Recall
Bacteriostatic water for Injection Recall
Potassium Phosphate Injection Recall
Sodium Thiosulfate Recall
Sodium Bicarbonate Injection
Acetadote Recall
Methotrexate Recall
Epogen/Procrit Recall
Hylanex Recall

2. MHRA Web Site for Rapid Alerts
Fluorouracil and Methotrexate Recall


