Influence of aggressive screening conditions and glass composition on the extractables and leachables from glass containers
Agenda

• Background: Overview of pharma glass packaging options
• Comparison study between molded glass and tubing glass
• Extractables evaluation from USP <1660> Chapter
• Leachables
• Conclusion
Glass Surface Technology

- Technical Expertise in glass packaging and technology to solve packaging challenges
- Design and analysis of accelerated aging tests and extractions
- Design of solutions and coatings to improve inner durability and product contact

SGD

- Independent Glass Producer (formerly Saint-Gobain Desjonquères)
- Dedicated Pharmaceutical glass operations in France and Germany
- R&D lab is located in Mers-Les-Bains Facility, France, where Type I glass is produced
Agenda

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Tubing Glass

• 2 step process:
  - Cane manufacturing
  - Converting

• Capabilities:
  - Vials
  - Cartridges
  - Syringes
Molded Glass 1 step process

SGD Capabilities: Vials and IV bottles from 3 ml to 1 L.
- Neck finish 20 mm and higher
- Can also produce non round vials and bottles
Agenda

- **Background**: Overview of pharma glass packaging options
- **Comparison study between molded glass and tubing glass**
- **Extractables evaluation from USP <1660> Chapter**
- **Leachables**
- **Conclusion**
Method: X-Ray Fluorescence Spectrometry

Vials are cut in pieces
Samples flattened at 750°C
Surface is polished
X-Ray Fluorescence on 34mm diameter samples
FX S8 TIGER BRUKER
Type I glass composition

• NEUTRAL GLASS is an alkaline borosilicate glass with main components of (typical moulded glass composition):
  • Network Formers : SiO2+Al2O3 - 73%
    B2O3 - 12%
  • Network Modifiers: Na2O;K2O - 10%
    CaO;BaO;ZnO - 5%

• NEUTRAL GLASS may be composed of 2 primary phases
  • Silica-rich phase with low alkaline content
  • Boron-rich phase with most alkaline elements of the glass; it may be separated into micro-droplets within the silica rich matrix, depending on the composition
## Composition by X-Ray Fluorescence Spectrometry

<table>
<thead>
<tr>
<th>(%)</th>
<th>Molded</th>
<th>Tubing 1</th>
<th>Tubing 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Network Formers</td>
<td>85.7</td>
<td>90.2</td>
<td>91.1</td>
</tr>
<tr>
<td>Network Modifiers</td>
<td>14.2</td>
<td>9.6</td>
<td>8.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Main elements (%)</th>
<th>Moulded Flint</th>
<th>5ml Tubing 1</th>
<th>10ml Tubing 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>SiO₂</td>
<td>69.1</td>
<td>70.8</td>
<td>74.3</td>
</tr>
<tr>
<td>Na₂O</td>
<td>6.1</td>
<td>7.1</td>
<td>7.2</td>
</tr>
<tr>
<td>K₂O</td>
<td>3.1</td>
<td>1.2</td>
<td>0.0</td>
</tr>
<tr>
<td>CaO</td>
<td>1.1</td>
<td>1.2</td>
<td>1.5</td>
</tr>
<tr>
<td>MgO</td>
<td>0.0</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Al₂O₃</td>
<td>4.0</td>
<td>7.3</td>
<td>5.6</td>
</tr>
<tr>
<td>Fe₂O₃</td>
<td>0.02</td>
<td>0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>B₂O₃</td>
<td>12.6</td>
<td>12.1</td>
<td>11.2</td>
</tr>
<tr>
<td>BaO</td>
<td>2.8</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>TiO₂</td>
<td>0.02</td>
<td>0.01</td>
<td>0.03</td>
</tr>
<tr>
<td>ZnO</td>
<td>1.1</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

- Stronger network for bulk tubing glass, less modifiers
- Network modifiers needed to soften the glass to shape the vials for molded glass

12/6/13

Extractables and Leachables Europe - 2013
Surface SIMS analysis by Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS)

- 4 glass vial samples: 2 molded and 2 tubing vials
- ToF SIMS Profile by alternating analysis and abrasion cycles

**Analysis:**
- Primary Ions Bi$^{1+}$ 25 keV, I = 1 pA
- Surface analyzed 100 x 100 µm², 128x128 pixel
- Positive Secondary Ions analyzed

**Abrasion:**
- Primary Ions O$^{2+}$ 500 eV, I = 100 nA
- Surface: 300 x 300 µm²

**Cycle**
- Analysis: acquisition of 1 scan
  - (time of max flight = 100 µs)
- Abrasion: 1.6 s, Pause: 1 s
Glass Composition: from internal surface to inside the glass (SIMS)

Glass Composition: from surface to internal

B+  Na+  TUBING 5ml  Al+  K+
_Bottom
_Side wall

B+  Na+  MOLDED 5ml  Al+  K+
_Bottom
_Side wall
Surface Composition differences

- All samples show a different composition at the surface from the bulk
- Small and curved samples may explain different bulk compositions between the bottom and the side wall
- More surface composition differences between side wall and bottom for tubing vials
- Sodium depletion at surface on the vial bottom for tubing, Boron-rich at the surface on side wall from Vial Forming
- Sodium depletion during forming for Asolvex Type I glass, both on bottom and on side walls (blowing effect)
• Standard test for Pharma Glass - Hydrolytic stability, expressed by the resistance to the release of soluble mineral substances into water under the prescribed conditions of contact between:
  • the inner surface of the container (Test A, surface test according to European Pharmacopeia, 3.2.1)
  • glass grains (Test B, glass grain test according to European Pharmacopeia, 3.2.1)

• The hydrolytic resistance is evaluated by titrating released alkali.

• The glass grain test is performed on crushed glass pieces, so represents the chemical resistance of the bulk glass
Hydrolytic Resistance Comparison in (ml) 
HCl N/100

<table>
<thead>
<tr>
<th></th>
<th>Type I Molded</th>
<th>Tubing T-5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grain</strong> Hydrolytic Resistance (ml)</td>
<td>0.53</td>
<td>0.43</td>
</tr>
</tbody>
</table>

- Better grain resistance for Tubing than molded because more network formers and less modifiers, Type I Limit 1 ml

<table>
<thead>
<tr>
<th></th>
<th>Type I Molded M-5</th>
<th>Tubing T-5</th>
<th>Type I Molded M-10</th>
<th>Tubing T-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vol 90% (ml)</td>
<td>8.1</td>
<td>8.3</td>
<td>12.25</td>
<td>12.4</td>
</tr>
<tr>
<td>Type I Limit</td>
<td>1</td>
<td>1</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Surface</strong> Hydrolytic Resistance (ml)</td>
<td>0.15</td>
<td>0.50</td>
<td>0.17</td>
<td>0.41</td>
</tr>
</tbody>
</table>

- More critical for product interaction
- All vials are lower than type I surface limit, as required
- Better surface Hydrolytic resistance for molded vials
Extractables evaluation

• Autoclave solution analysis with ICP

• Solution Preparation
  - Deionized water pH (18 MΩ.cm resistivity) adjusted:
    - with HCl for acid pH
    - with NaOH for base pH

• Vials Extraction
  - filled at nominal capacity with the solution
  - Vials in autoclave at 121°C for 1h, Eur. Pharma. HR cycle, 3 to 5 for each pH

• ICP Preparation
  - Acidification HNO3 Suprapur 2% before ICP measurement
  - Equipment Calibration with certified PE multielements solution and acidification HNO3 Suprapur 2%

• Results
  - Equipment: Emission Spectrometry ICP (Perkin Elmer Optima 7300 DV)
  - The blank solution is analyzed and subtracted from the autoclaved solutions.
Vial comparison: Total Extractables by ICP after 1h at 121°C – 5 & 10ml

- Less elements extracted with Molded vials, for all pH
- Higher pH (10 or more) causes higher extractions
- Less extraction in volume for bigger vials, surface/volume ratio lower
No visible attack of the glass, no flake (methylene blue test shows nothing)

Different local / surface glass compositions with tubing may cause higher extractions

ICP detection limit on the blank solution $3\sigma<4\mu g/L$ ($\sigma$ calculated on 10 measurements of the blank solution), Vial to vial variation +/- 10%
• **Tubing**: more Na and Ca extracted, but also Al, Si and B which are the glass network formers.

• **Molded**: more K (not in the tubing 10ml glass composition) and Ba (traces in the tubing glass composition), which are mainly glass modifiers and less impacting the glass chemical robustness.

• Bulk hydrolytic resistance is good for tubing, but surface resistance is not at the same level.

• Local changes in glass compositions (processing effect) may explain some of the increased extraction.
Agenda

- Background: Overview of pharma glass packaging options
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Testing Plan

- **3 Solutions for New USP 1660 Chapter** to evaluate glass containers
  - KCl 0.9% pH 8.0 Autoclave for 2H at 121°C (2 1h autoclave cycles)
  - 3% Citric Acid at pH 8.0 for 24h at 80°C
  - 20 mM (1.5g/L) Glycine at pH 10.0 for 24h at 50°C

- NaOH (contains K) added to bring pH to the right level, so Na and K not measured in extracted solutions
- Autoclave samples closed with borosilicate lab glass, Other vials closed with aluminum foil
- **Glass Samples**: 100ml Type I moulded vials from different glass makers
- **ICP Preparation**
  - Acidification HNO3 Suprapur 2% before ICP-OES measurement
  - Equipment Calibration with certified PE multielements solution and acidification HNO3 Suprapur 2%

- **Results**
  - Equipment: Emission Spectrometry ICP (Perkin Elmer Optima 7300 DV)
  - The blank solution is analyzed and subtracted from the autoclaved solutions
Citric acid extraction is quite extensive: modifiers and network formers. The 3 solutions are more aggressive than water. 1h 121°C testing extracts more with Citric acid and Glycin than 24H at 80 and 50°C.
Results

Citric Acid at pH 8 is more aggressive than the other solutions.
All Flint Glass are similar with the same chemical solution and testing procedure.
 Extractions depend on: solution, glass composition, and extraction conditions.
All glass are type I glass (Hydrolytic Resistance better than limit)

Composition differences (Flint vs. Amber) may impact chemical resistance

<table>
<thead>
<tr>
<th>(%)</th>
<th>Flint SGD</th>
<th>Amber SGD</th>
<th>Flint Gerresheimer Millville Wheaton (ref 1500)</th>
<th>Flint Bormioli (ref 1500)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SiO₂</td>
<td>69.1</td>
<td>65.4</td>
<td>66.3</td>
<td>67.4</td>
</tr>
<tr>
<td>Na₂O</td>
<td>6.1</td>
<td>7.3</td>
<td>9.6</td>
<td>8.3</td>
</tr>
<tr>
<td>K₂O</td>
<td>3.1</td>
<td>2.2</td>
<td>1.1</td>
<td>1.9</td>
</tr>
<tr>
<td>CaO</td>
<td>1.1</td>
<td>0.5</td>
<td>0.8</td>
<td>1.3</td>
</tr>
<tr>
<td>MgO</td>
<td>0.0</td>
<td>0.0</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Al₂O₃</td>
<td>4.0</td>
<td>6.6</td>
<td>5.5</td>
<td>5.6</td>
</tr>
<tr>
<td>Fe₂O₃</td>
<td>0.02</td>
<td>0.86</td>
<td>0.06</td>
<td>0.03</td>
</tr>
<tr>
<td>B₂O₃</td>
<td>12.6</td>
<td>11.6</td>
<td>12.8</td>
<td>12.0</td>
</tr>
<tr>
<td>BaO</td>
<td>2.8</td>
<td>2.0</td>
<td>2.7</td>
<td>2.7</td>
</tr>
<tr>
<td>TiO₂</td>
<td>0.02</td>
<td>2.70</td>
<td>0.02</td>
<td>0.05</td>
</tr>
<tr>
<td>ZnO</td>
<td>1.1</td>
<td>0.7</td>
<td>0.6</td>
<td>0.4</td>
</tr>
</tbody>
</table>
Agenda

• Background: Overview of pharma glass packaging options
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**Testing Conditions**

**Same 1660 Solutions** as previous part, with pH adjusted 2 ways
- Demineralized water at pH 5.6
- 3% Citric Acid at pH 8.0, pH adjusted with NaOH
- 3% Citric Acid at pH 8.0, pH adjusted with KOH
- 20 mM (1.5g/L) Glycine at pH 10.0, pH adjusted with NaOH
- 20 mM (1.5g/L) Glycine at pH 10.0, pH adjusted with KOH

**Glass Samples**: 100ml Type I moulded Flint SGD vials

All containers closed with Omniflex Helvoet stoppers

21 days aging at 50°C
All results with Citric Acid are similar, higher than Glycine and water. Adjusting the pH with KOH or NaOH gives similar results.
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Conclusions

- Choice of a vial is a complete decision depending on several parameters, including Extractables and Leachables and chemical resistance:
  - Product interaction with the vial depends on 1) composition 2) how it was formed
  - Process difference: 1 step forming process of molded vials seems to extract less glass formers than 2 step tubing process
  - Tubing glass starts off better at cane stage but chemical robustness is impacted by converting step, which can differ from 1 supplier to another

- Due to its chemical robustness, molded can be considered as an alternative in aggressive extraction conditions

- Not all vials are equal for chemical resistance: it depends on process, glass and solution composition, as well as storage conditions
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• Sébastien Dussardier

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