Attaching delamination by addressing root cause

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Corning Incorporated

Founded:
1851

Headquarters:
Corning, New York

Employees:
~29,000 worldwide

2013 Sales:
$7.9B

Fortune 500 Rank (2013):
326

- Corning is the world leader in specialty glass and ceramics.
- We create and make keystone components that enable high-technology systems for consumer electronics, mobile emissions control, telecommunications, and life sciences.
- We succeed through sustained investment in R&D, more than 160 years of materials science and process engineering knowledge, and a distinctive collaborative culture.
A Culture of Innovation

- **1879**: Glass envelope for Thomas Edison’s light bulb
- **1915**: Heat-resistant PYREX® glass
- **1934**: Dow Corning silicones
- **1947**: Processes for mass producing the television bulb
- **1952**: Glass ceramics
- **1964**: Fusion overflow process
- **1970**: First low-loss optical fiber
- **1972**: Ceramic substrates for automotive catalytic converters
- **1982**: Active matrix liquid crystal display (LCD) glass
- **2006**: Label-free screening platform for drug discovery
- **2007**: Ultra-bendable fiber
- **2013**: Gorilla® Glass 3

Research and Development (R&D)

• Our growth is fueled by a commitment to innovation and a passion for conquering complex material and technology challenges

• We invest approximately 10% of our sales in R&D

• We maximize the results of our R&D by engaging cross-functional teams and senior leadership at all stages of innovation

• Our technology leadership and R&D environment attract and enable the best scientific minds in the world

• We have core competencies in numerous areas including inorganic materials and processes, modeling and simulation and life sciences.
Glass is the ideal material for parenteral packaging

<table>
<thead>
<tr>
<th>Glass Attributes</th>
<th>Parenteral Needs</th>
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</thead>
<tbody>
<tr>
<td>Chemically durable</td>
<td>• Acid, Base, and Neutral solutions</td>
</tr>
<tr>
<td>Hermeticity</td>
<td>• Gas impermeable</td>
</tr>
<tr>
<td>High elastic modulus</td>
<td>• Survive high stresses</td>
</tr>
<tr>
<td>Transparency</td>
<td>• Ability to view/inspect drug</td>
</tr>
<tr>
<td>Low expansion</td>
<td>• Survive rapid thermal cycles</td>
</tr>
<tr>
<td>Thermal stability</td>
<td>• Enable depyrogenation</td>
</tr>
<tr>
<td>Viscous phase transitions</td>
<td>• Formable into complex shapes</td>
</tr>
<tr>
<td>Sterilizable</td>
<td>• Able to be sterilized by many methods</td>
</tr>
</tbody>
</table>

Chemically durable, Hermeticity, High elastic modulus, Transparency, Low expansion, Thermal stability, Viscous phase transitions, Sterilizable

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… but it is not without issues

“Glass delamination has emerged as a significant problem for the pharmaceutical industry…at a cost of as much as $50 million per recall” – ContractPharma 2013

What is delamination?

- Corrosion of a glass surface which results in glass lamellae from the original container

- Not contamination; but, high aspect ratio lamellae from the original surface

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Delamination related recalls continue

~30 recalls due to delamination 2010-2013

Within the last year …

- “Some vials …have been found to contain glass-related particles that may not be easily visible under normal lighting conditions.” (Apr 2013)

- “Firm is recalling a small number of vials with very small reflective flakes consistent with delamination of the glass vial.” (June 2013)

- “… voluntarily recalling four lots of …single dose vials due to the potential presence of glass particles (glass delamination) in the vials.” (June 2013)

- “All product made in these tube glass vial sizes over the last three years are subject to this voluntary recall… evidence of glass delamination during a routine stability study check conducted at the 18-month dating checkpoint.” (July 2013)

- “Glass bits force recall … Four lots … have been recalled because of glass particles found in some vials, the FDA and the drug’s manufacturer said.” (Aug 2013)
Industry has responded, but delamination remains an issue

**Manufacturing “solutions”**
- Rigorous converting process controls
- Predictive testing
- Interior coating

**Pharmaceutical “solutions”**
- Reduced shelf life

- Current delamination “solutions” have limitations and slow adoption
- They have not addressed root cause
Recalls can lead to shortages, which have risks

9 recalls (2011-2013) that resulted in drug shortages were due to delamination

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2 www.fda.gov; Corning Analysis

3 The Drug Shortage Crisis in the US [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278171/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278171/)
Glass delamination is not a new phenomenon

- Water has been known to react with glass and produce flakes since at least the 1700’s\(^1\)

- Soda-lime glasses are known to produce flakes and treatments have been suggested since the 1940’s\(^2\)

- Delamination in pharmaceutical glass has been discussed as early as 1953\(^1\)


While borosilicates can be chemically durable, the boron leaves it susceptible to delamination.

Literature shows:

- Delamination scales with adsorption of methylene blue\(^1\)
- Boron is known to evaporate at temperatures reached during forming\(^2,3\)
- Delamination scales with forming speeds\(^4,5\)

1. Various presentations from: Alfred U & Gerresheimer, OMPI, BD, etc.
2. Guadagnino, E., Zuccato, D. Delamination propensity of pharmaceutical glass containers by accelerated testing with different extraction media (2011) PDA Letters, (July/August), pp40-42.
Surface chemistry changes are induced during converting

1. Tubing has uniform surface composition
2. Neck is formed, evaporating some boron
3. Separation from tube, base formation evaporates much more boron and alkali
4. Boron and alkali reincorporates into the heel regions

Note volatilization in this region
Boron is preferentially volatilized from the vial base to the heel due to extreme heat during converting.

- Boron and sodium species volatize from the base region.
- They condense on the sidewall and are incorporated into the glass structure in the heel.

The additional boron incorporated into the heel causes decreased chemical durability.
Current tests can mask the decreased chemical durability

- Container hydrolytic tests measure average chemical resistance for the entire vial
- If the surface chemistry changes, then the risk of delamination increases
- Results of the heel region were significantly different

ISO 720 hydrolytic resistance tests
Evidence exists showing evaporation in borosilicates

- XPS (X-ray Photoelectron Spectroscopy) can quantify changes in surface chemistry from forming

- Regions enriched in B and Na also indicated with methylene blue
Thermodynamic modeling supports evaporation as a mechanism.
Since boron volatilization is the root cause for delamination in borosilicates, can a boron-free glass function for parenterals?

Necessary characteristics of pharmaceutical glass

- Hydrolytic performance
- Acceptable extractables
- Drug product stability
- Other chemical, optical, thermal properties

Al₂O₃ binds alkali like B₂O₃, making aluminosilicates a potentially chemically durable glass.

What other glasses could produce these same characteristics?
Thermodynamic modeling can identify glasses with reduced evaporation

![Graph showing the elemental fraction of B and Na in gas phase versus temperature, with a red arrow indicating a 1000 times increase in the temp range for Aluminosilicate Glass compared to Type 1B Glass.](image)

equilibrium between glass and combustion atmosphere of stoichiometric CH₄-O₂ flame
Aluminosilicate glass has uniform chemistry with depth

**Borosilicate Vial**

- **Boron Profile**
  - Heel
  - Sidewall
  - Base

- **Sodium Profile**
  - Heel
  - Sidewall
  - Base

**Aluminosilicate Vial**

- **Boron Profile**
  - No Boron Present

- **Sodium Profile**
  - Heel
  - Base
  - Sidewall

SEM Images show homogeneous inner surface

As-formed

Borosilicate Vial

Aluminosilicate Vial

Autoclaved with WFI

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Aluminosilicates substantially reduce delamination

<table>
<thead>
<tr>
<th>Test</th>
<th>Solution</th>
<th>Autoclave / Storage</th>
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<tbody>
<tr>
<td>Condition 1: citrate buffer</td>
<td>25 mM citrate buffer at pH=7</td>
<td>121°C for 1 hour</td>
</tr>
<tr>
<td>Condition 2: glycine buffer</td>
<td>20 mM Glycine pH=10</td>
<td>121°C for 2 hours</td>
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</tbody>
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Borosilicate

Delam evaluation with citrate buffer

No flakes observed

Aluminosilicate

Delam evaluation with glycine buffer

No flakes observed
Aluminosilicates can exhibit excellent hydrolytic performance

- Variation in borosilicate performance resulting from changes in bulk composition and converting

- Aluminosilicates are capable of matching the best borosilicate performance
Aluminosilicates can exhibit low extractables

Similar extractables as Type 1B, without boron or arsenic

Results show overall lower extracted concentrations

Aluminum extractable levels are comparable to borosilicates
Aluminosilicate vials can exhibit drug stability

<table>
<thead>
<tr>
<th>Historical Borosilicate degradation</th>
<th>Aluminosilicate degradation</th>
</tr>
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<tr>
<td>-0.0795 ± 0.0383</td>
<td>-0.0566</td>
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</table>

Slope of product degradation is indistinguishable from historical product performance in borosilicates.
Aluminosilicates may offer advantages for parenteral packaging

- Delamination issues continue in the industry and recalls can lead to shortages
- Evidence exists that the root cause for delamination is due to boron evaporation creating less durable glass surfaces
- Current delamination “solutions” do not address the root cause
- Aluminosilicate glass may be suitable for parenteral packaging and averts risk of delamination
  - Testing shows no delamination in aluminosilicates
  - Hydrolytic and extractables comparable to the leading Type 1 borosilicates
  - Drug stability data shows acceptably-low product degradation