CORNING

Attacking delamination by addressing root cause

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Corning Incorporated

Founded:
1851

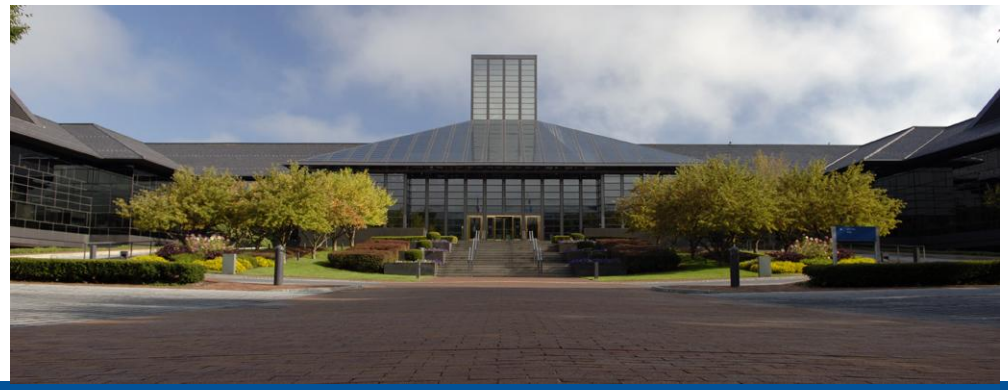
Headquarters:
Corning, New York

Employees:
~29,000 worldwide

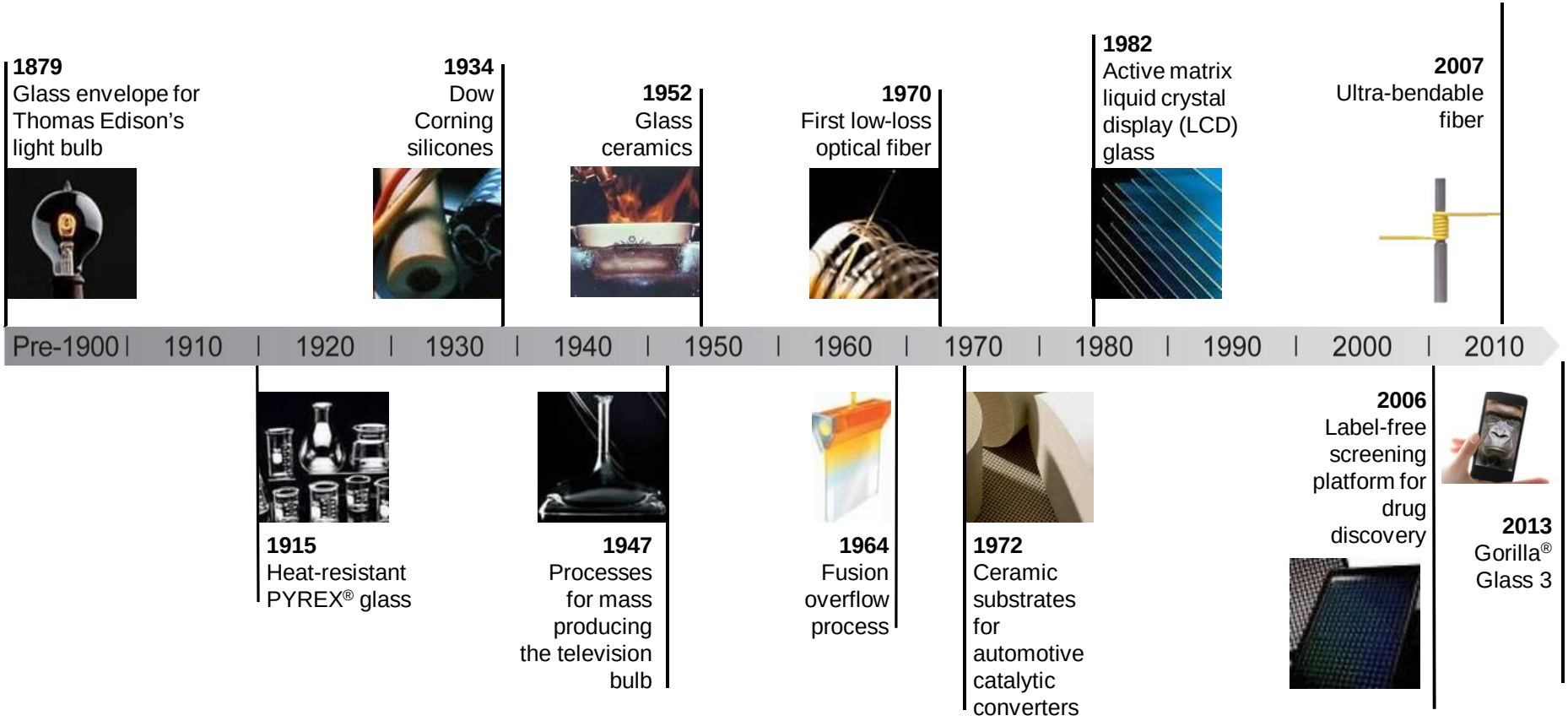
2013 Sales:
$7.9B

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.

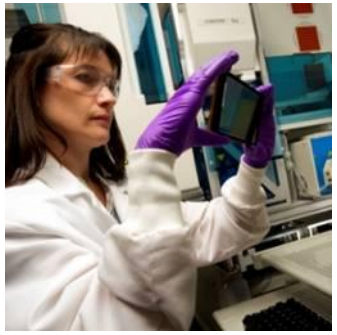


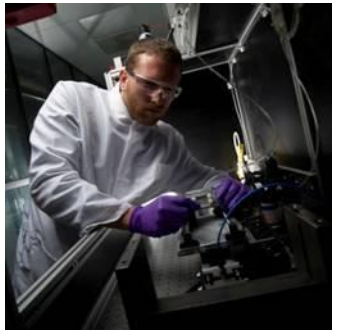
A Culture of Innovation



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

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

… 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" [2]– 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

FDA U.S. Food and Drug Administration

Advisory to Drug Manufacturers: Formation of Glass Lamellae in Certain Injectable Drugs[1]

[3-25-2011] The U.S. Food and Drug Administration is advising drug manufacturers of the potential formation of glass lamellae (glass fragments) in injectable drugs filled in small-volume glass vials [1]. Several drugs have recently been recalled due to this problem.[2]

Glass has many advantages over other packaging materials, but one well-known disadvantage is the potential for glass under certain conditions to shed thin, flexible fragments called "glass lamellae." [3] [4] These lamellae are shed from the interior surface of the glass container directly into the drug and are difficult to detect by visual inspection.

To date, no adverse events have been reported nor can any be directly attributed to this phenomenon. However, there is the potential for drugs administered intravenously that contain these fragments to cause embolic, thrombotic and other vascular events (e.g., phlebitis); and, when administered subcutaneously, to lead to development of foreign body granuloma, local injection site reactions, and increased immunogenicity.[5]

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124780.htm
[2]http://www.contractpharma.com/issues/2013-06/view_features/glass-flakes/

Delamination related recalls continue

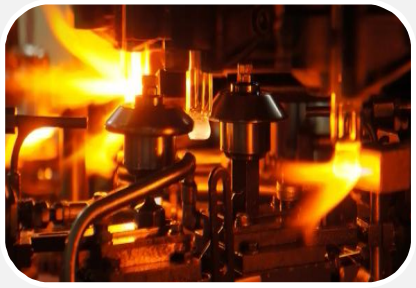
~30 recalls due to delamination 2010-2013

Within the last year …

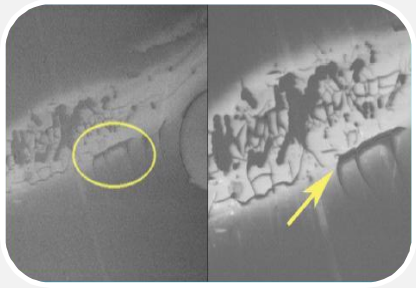
- "Some vials …have been found to contain ***glass-related particles that may not be easily visible*** under normal lighting conditions." (Apr 2013)
- "Firm is recalling a small number of vials with very small ***reflective flakes consistent with delamination*** of the glass vial." (June 2013)
- "... 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

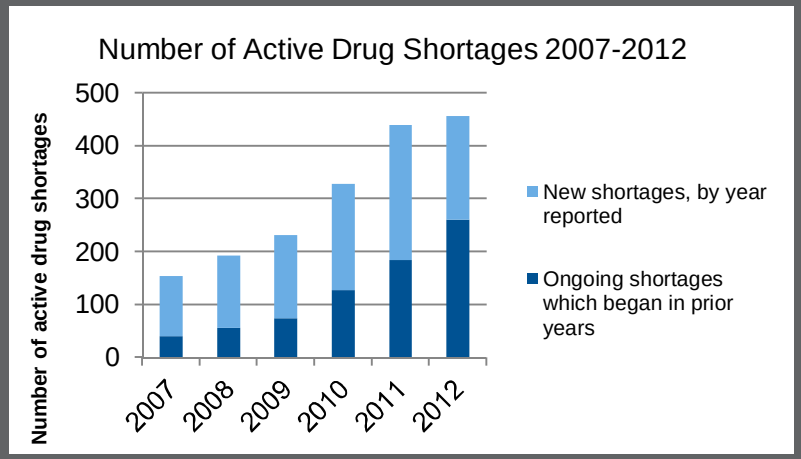
- Current delamination “solutions” have limitations and slow adoption
- They have not addressed root cause

Recalls can lead to shortages, which have risks

9 recalls (2011-2013) that resulted in drug shortages were due to delamination[2]

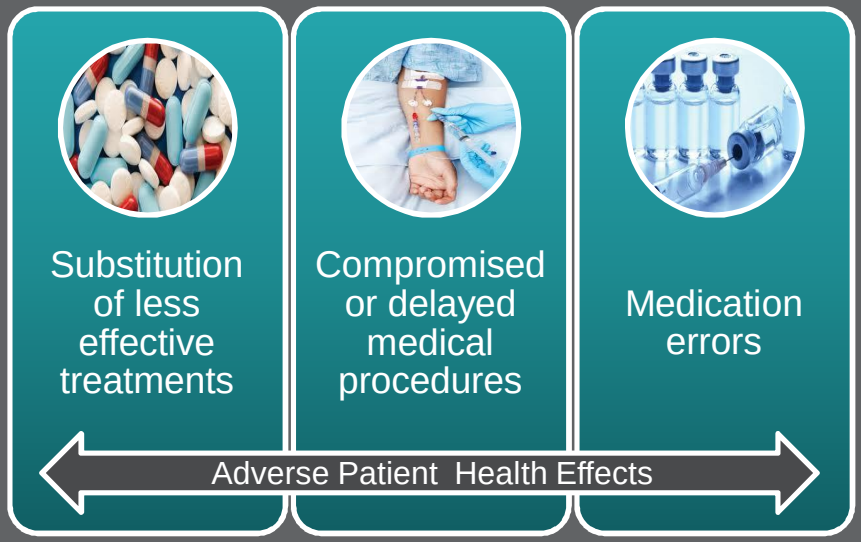
GAO

DRUG SHORTAGES
Public Health Threat Continues, Despite Efforts to Ensure Product Availability[1]



Pharmacy and Therapeutics P&T A Peer-Reviewed Journal for Managed Care and Hospital Formulary Management

The Drug Shortage Crisis in the US[3]



[1]DRUG SHORTAGES Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability http://www.gao.gov/assets/670/660785.pdf
[2]www.fda.gov; Corning Analysis
[3]The Drug Shortage Crisis in the US 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]

[1]DIMBLEBY, V. (1953). Glass for pharmaceutical purposes. *The Journal of Pharmacy and Pharmacology, 5*(12), 969-989.
[2]Bacon, F. R. and Burch, O. G. (1940), RESISTANCE OF GLASS BOTTLES TO NEUTRAL ALCOHOLIC SOLUTIONS. Journal of the American Ceramic Society, 23: 147–151.

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]

Suggests that delamination is linked to boron evaporation

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.

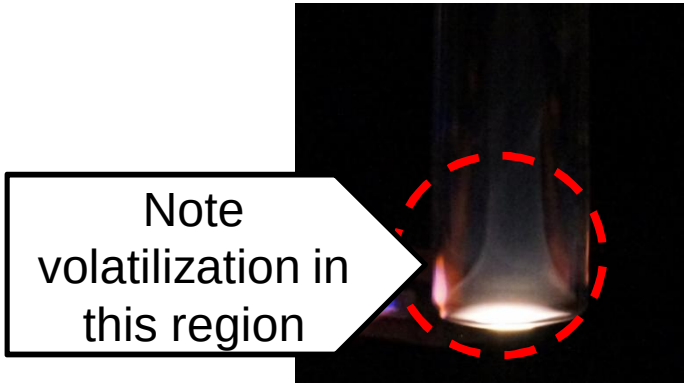
3. Haines, D. Glass delamination mechanisms: An update (2012 PDA/FDA Glass Quality Conference presentation).

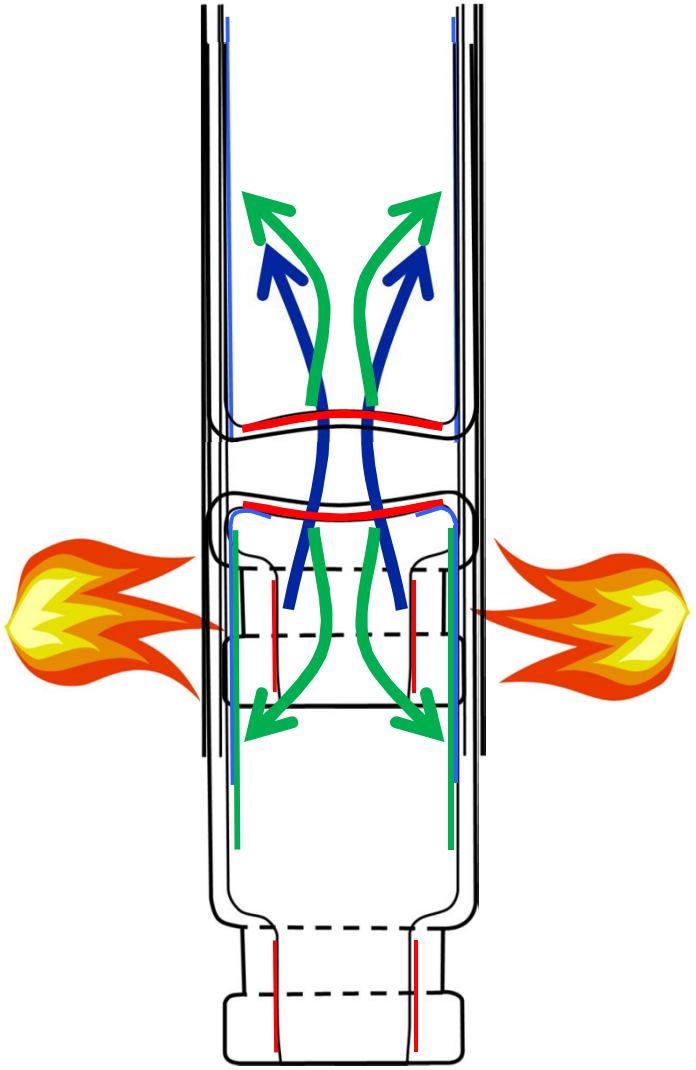
4. Schmid, B., Zuccato, D. Recommendations on delamination risk mitigation & prediction for type I pharmaceutical containers made of tubing glass (2012) *ONdrugDelivery*, (January), pp. 40-42.

5. Kreski, P.K., Varshneya, A.K. Microstructural phase separation and delamination in glass for pharma applications (2012) *Ceramic Transactions*, 231, pp. 85-90.

Surface chemistry changes are induced during converting

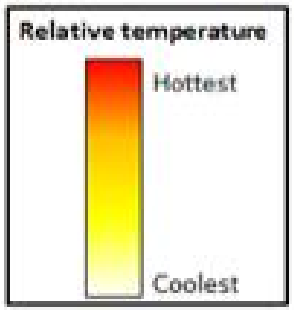
1. Tubing has uniform surface composition
2. Neck is formed, evaporating some boron
3. Separation from tube, base formation evaporates much more boron and alkali
4. Boron and alkali reincorporates into the heel regions

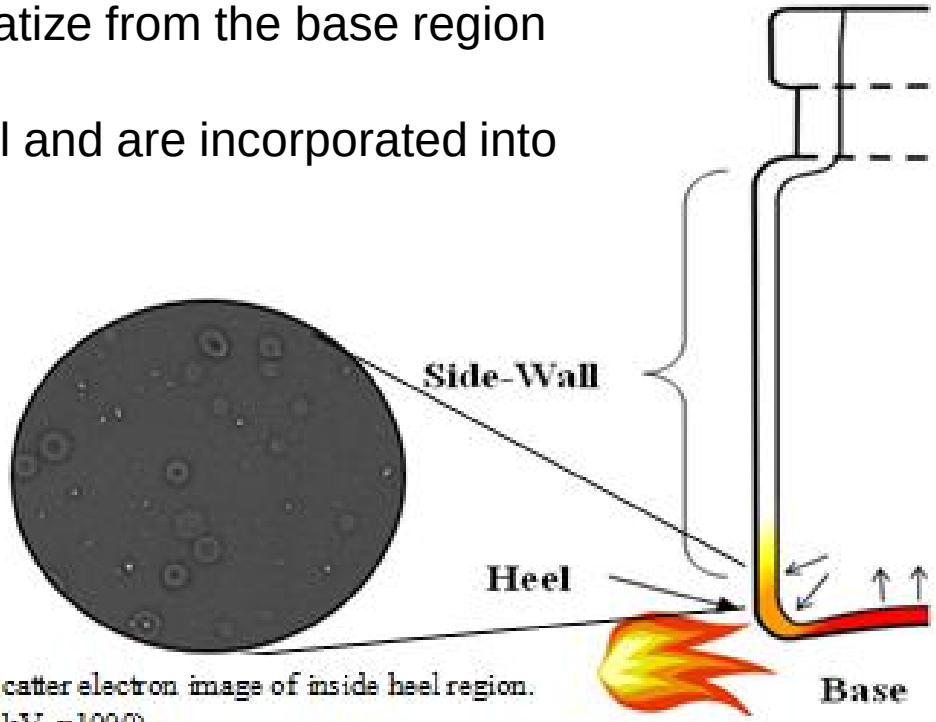




Boron is preferentially volatilized from the vial base to the heel due to extreme heat during converting

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





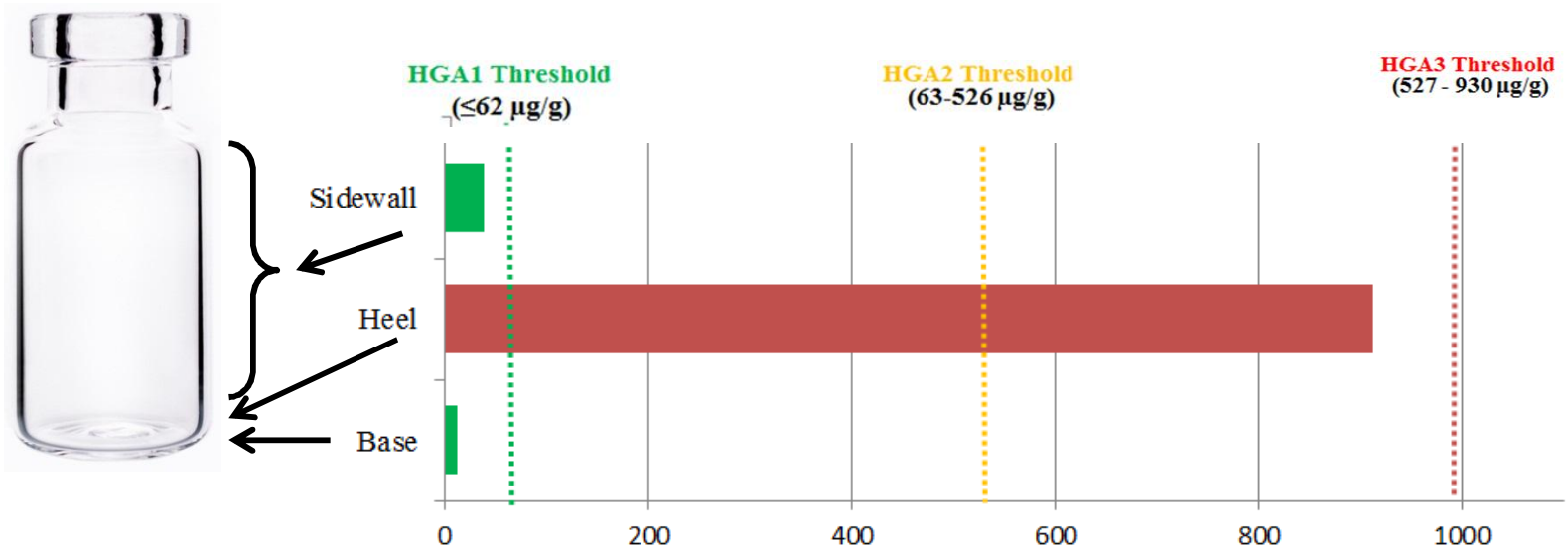
Backscatter electron image of inside heel region.
(20.0 kV, x1000)

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

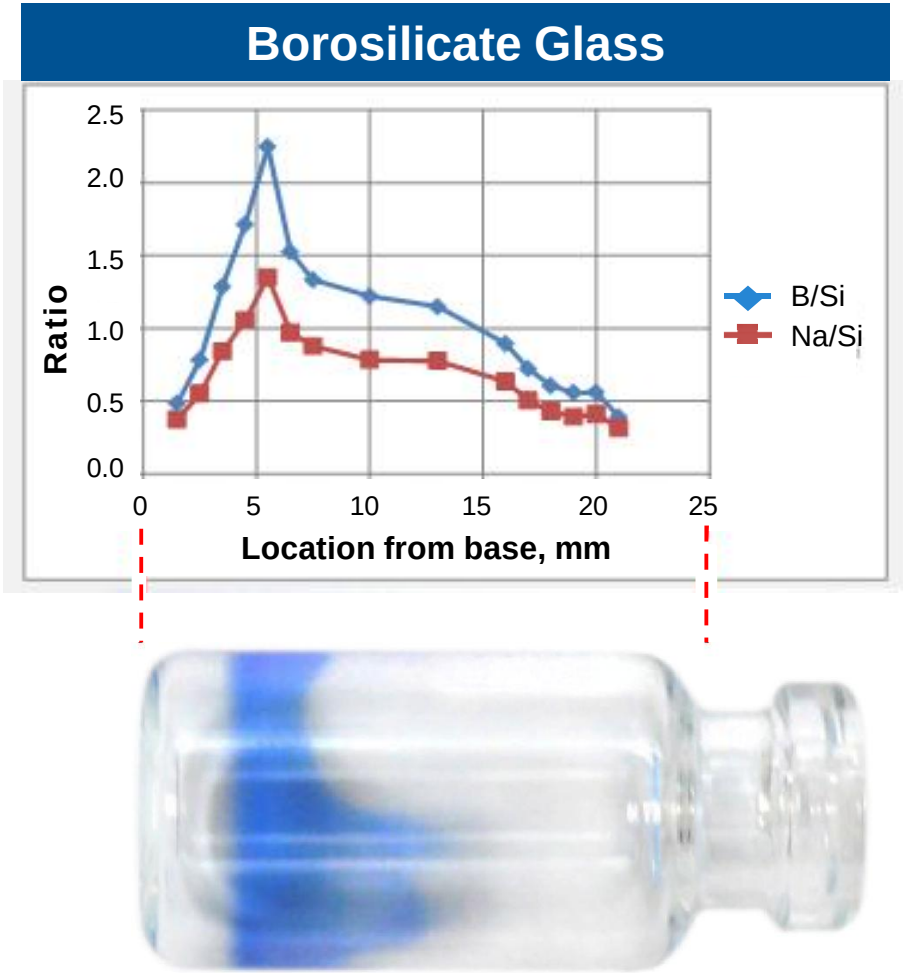
ISO 720 hydrolytic resistance tests



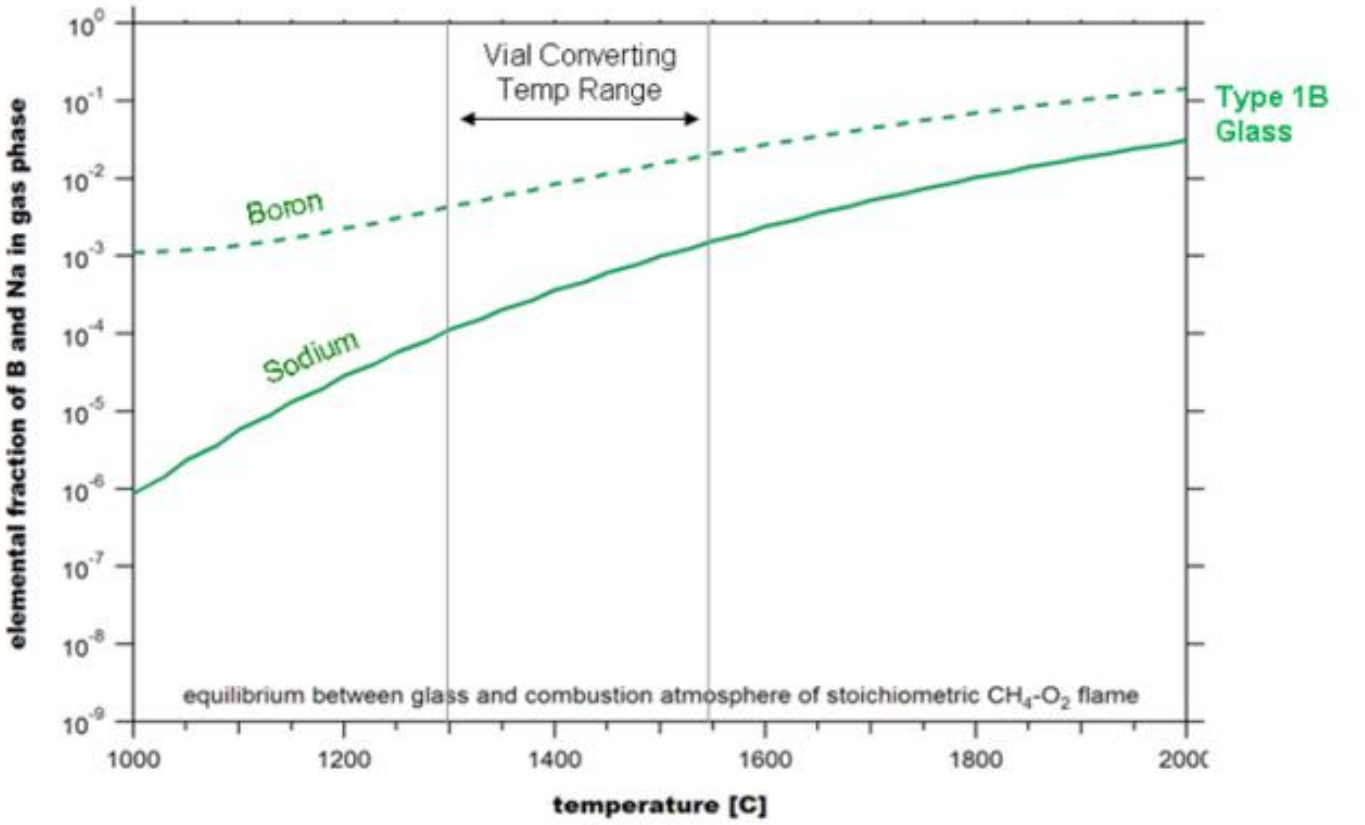
Evidence exists showing evaporation in borosilicates

- 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?

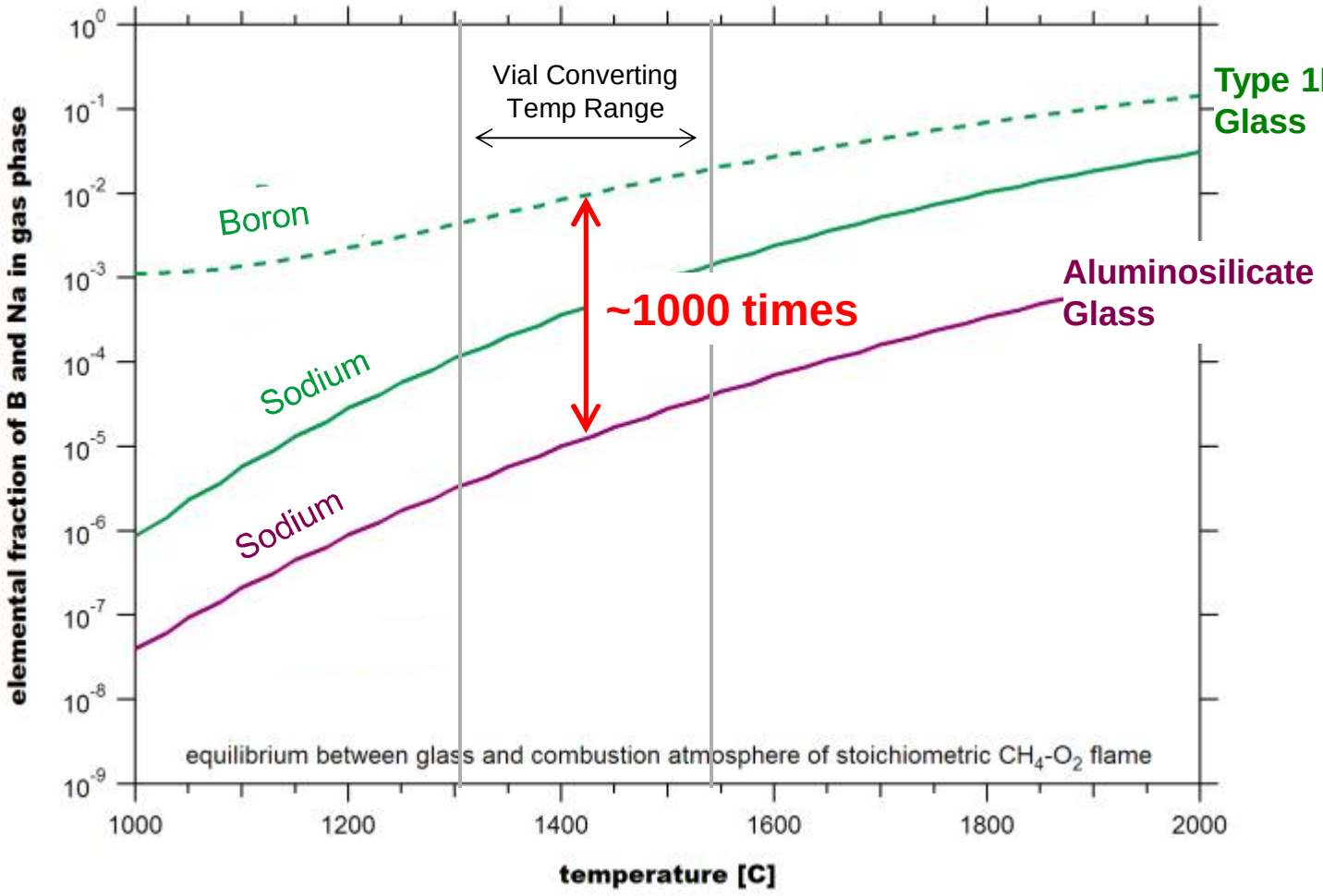
Necessary characteristics of pharmaceutical glass

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

What other glasses could produce these same characteristics?

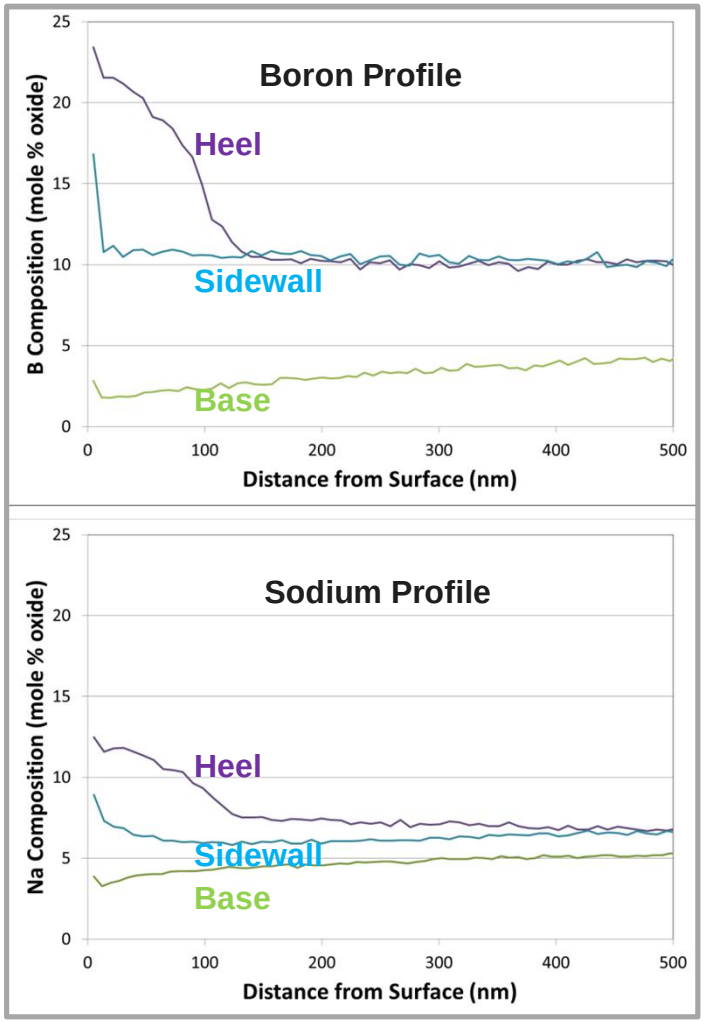
Al_2O_3 binds alkali like B_2O_3, making aluminosilicates a potentially chemically durable glass

Thermodynamic modeling can identify glasses with reduced evaporation

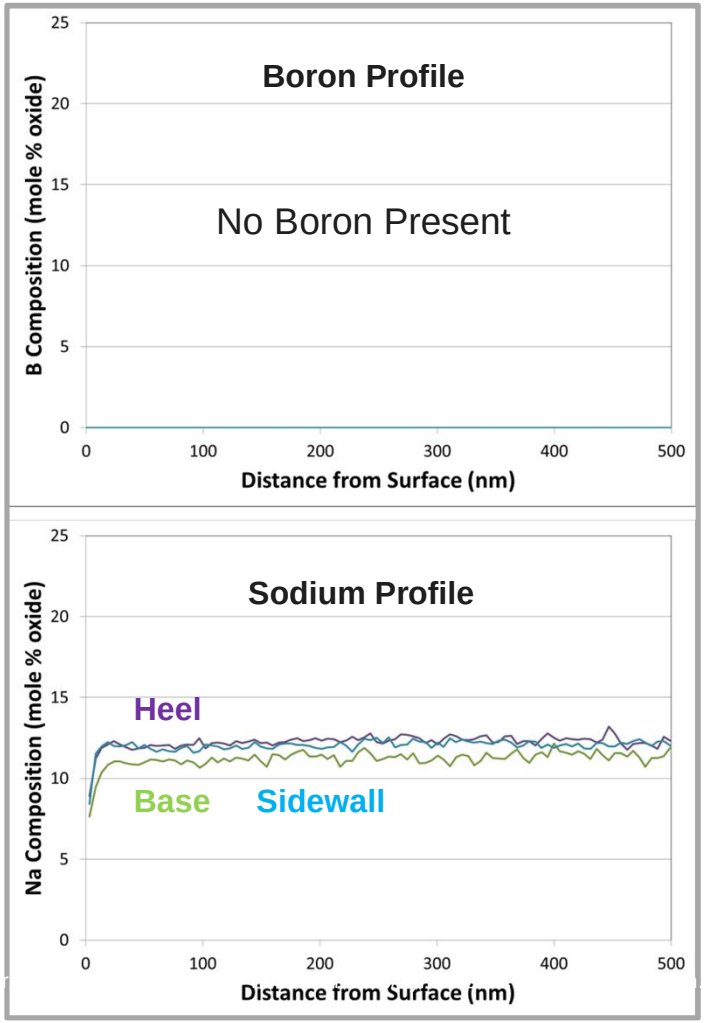


Aluminosilicate glass has uniform chemistry with depth

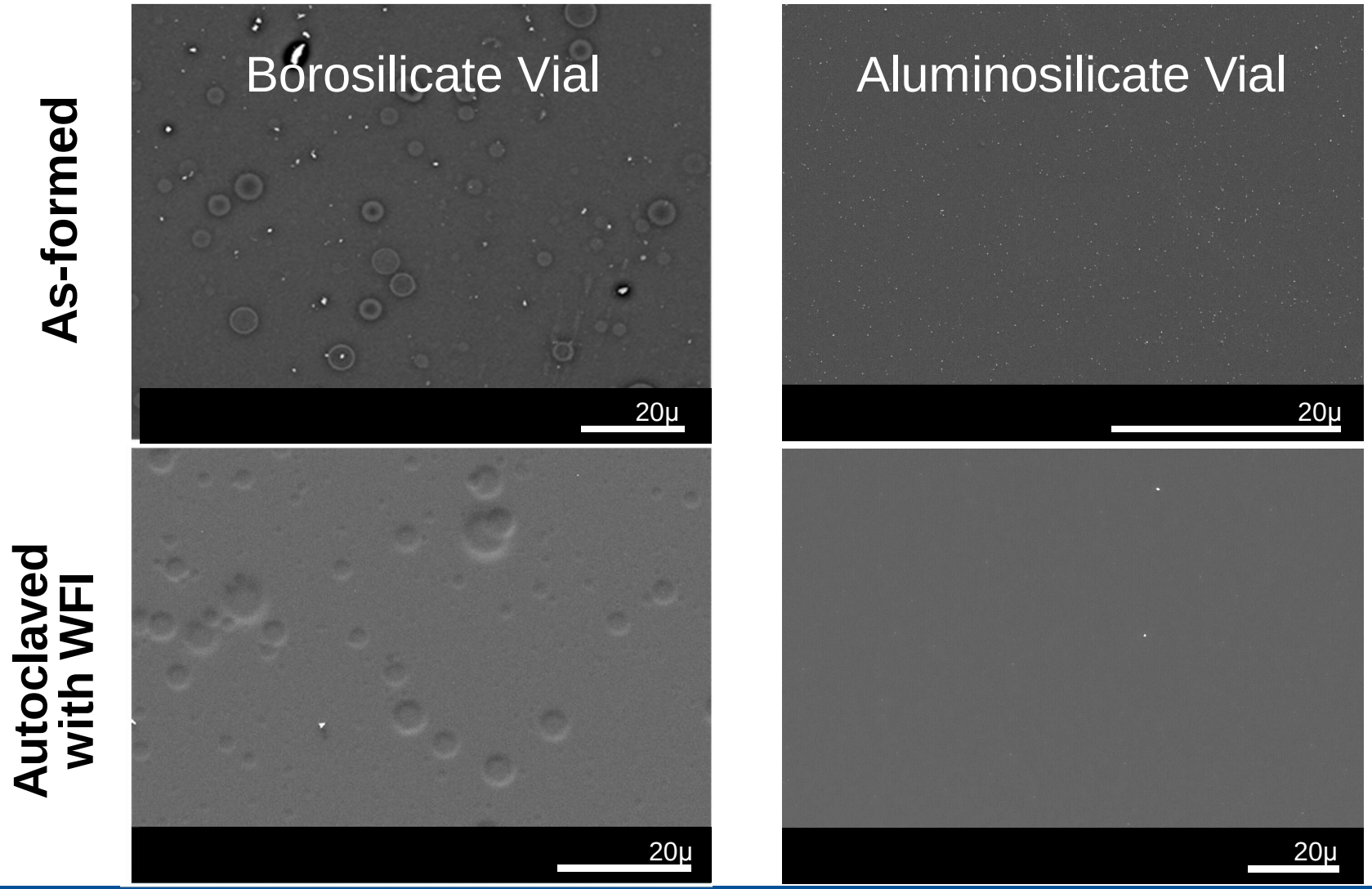
Borosilicate Vial



Aluminosilicate Vial

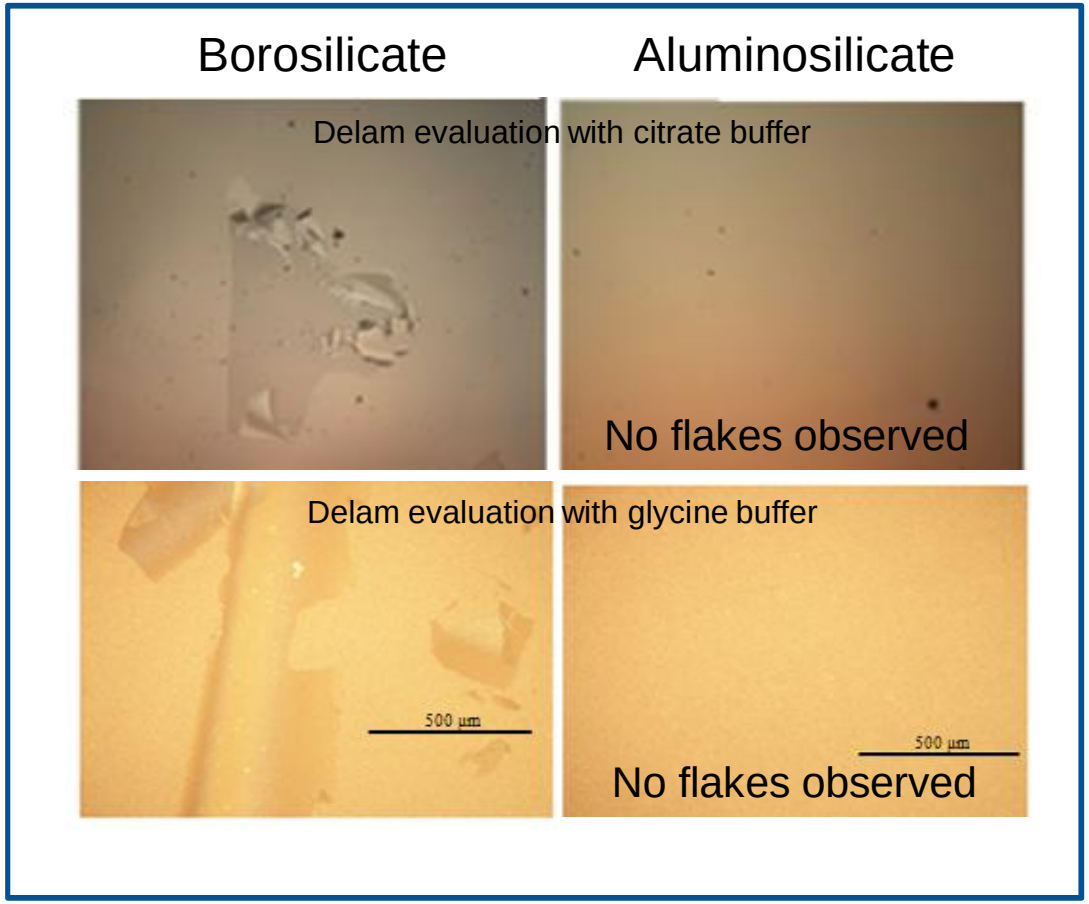


SEM Images show homogeneous inner surface



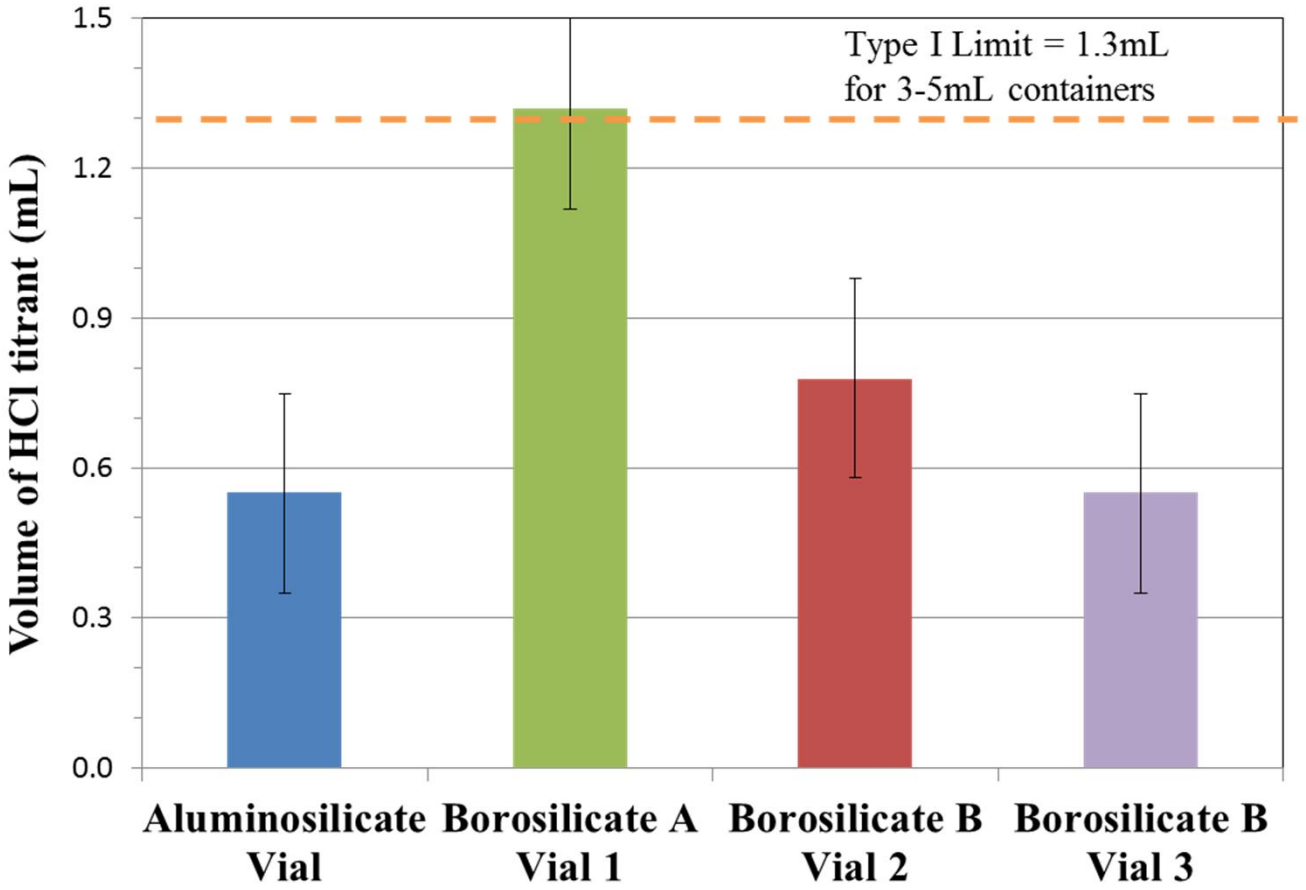
Aluminosilicates substantially reduce delamination

Test	Solution	Autoclave / Storage	
Condition 1: citrate buffer	25 mM citrate buffer at pH=7	121°C for 1 hour	42 days at 60°C
Condition 2: glycine buffer	20 mM Glycine pH=10	121°C for 2 hours	2 days at 50°C

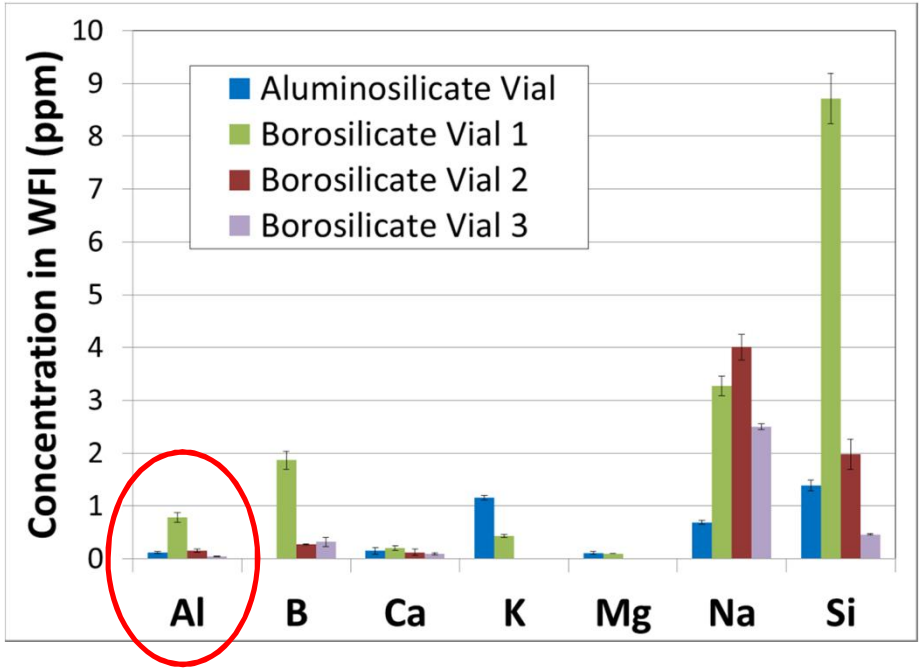


Aluminosilicates can exhibit excellent hydrolytic performance

- Variation in borosilicate performance resulting from changes in bulk composition and converting
- Aluminosilicates are capable of matching the best borosilicate performance



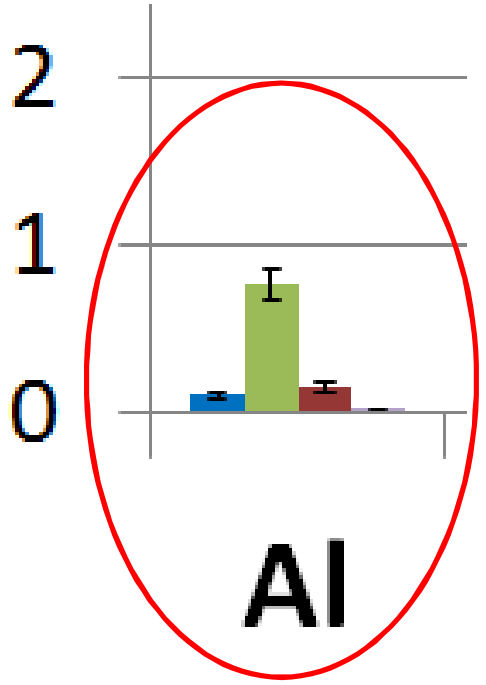
Aluminosilicates can exhibit low extractables



Similar extractables as Type 1B, without boron or arsenic

Results show overall lower extracted concentrations

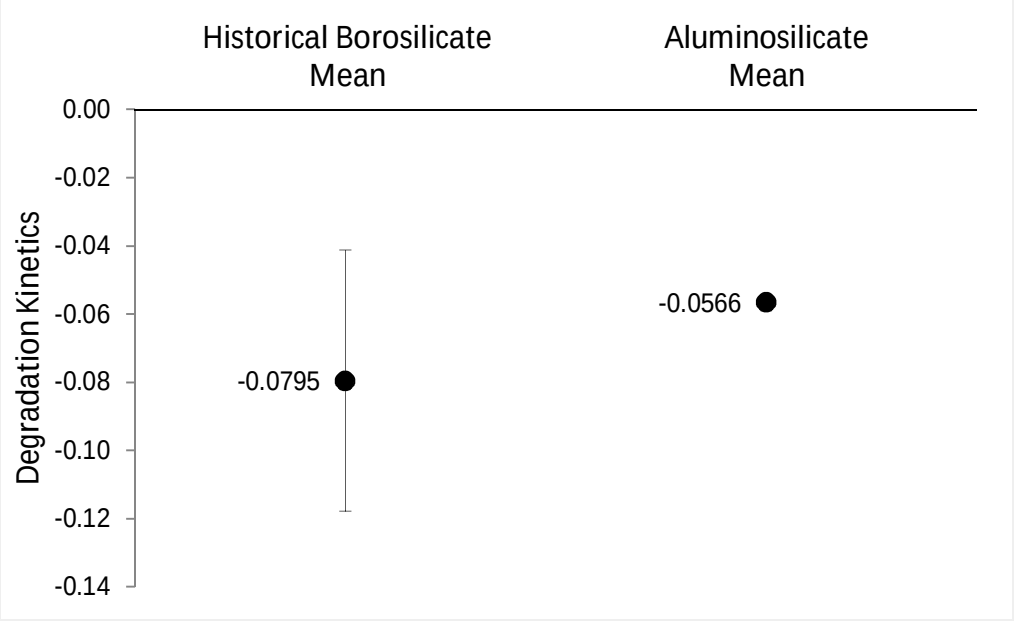
Aluminum extractable levels are comparable to borosilicates



Aluminosilicate vials can exhibit drug stability

Historical Borosilicate degradation	Aluminosilicate degradation
-0.0795 ± 0.0383	-0.0566

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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