# PDA/FDA Glass Quality Conference

**June 4-5, 2012**

Renaissance Washington, D.C. Downtown Hotel
Washington, D.C.

**An Alternative Glass Packaging Solution to Reduce Delamination Risks**

**www.pda.org/glass2012**

**Exhibition: June 4-5 | Courses: June 6-7**

Christophe Wagner - SGD

# Agenda

- Background:
  - Brief review of Delamination
  - Overview of pharma glass packaging options
- Comparison study between molded glass and current glass packaging solutions
- Observations / Conclusions

# Background

# SGD

- Independent Molded 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.

# SGD's evolving view of the delamination issue

- Pre -2010: aware of possible issues with organic acids such as NaHCO3 8.4% or Calcium Gluconate

- 2010 ~ mid-2011: Tracking the heightened industry concern about the more severe form of dissolution known as delamination and lamella formation

- Mid-2011 ~ Present: Conducting studies with clients to characterize molded glass chemical durability characteristics; in particular relative to other glass containers they are using

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delamination
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# Drugs

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  - Importing Prescription Drugs
  - Medication Guides
  - Drug Integrity and Supply Chain Security

## Advisory to Drug Manufacturers: Formation of Glass Lamellae in Certain Injectable Drugs

[3-25-2011] The U.S. Food and Dru
of glass lamellae (glass fragments
have recently been recalled due to t

s over o
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e is the
thrombo
evelopment of foreign body granuloma, local injection sit
6]

e been associated with a higher incidence of the form glass lamellae:

by tubing process (and thus manufactured under higher heat). These vials are
ed glass vials and may shed lamellae more easily.[6] The processing conditions
glass vials can be designed to mitigate the potential for later delamination.
tions formulated at high pH (alkaline) and with certain buffers. Common buffers associated with
rmation include citrate and tartrate.[7]
ne the drug product remains exposed to the inner surface of the container. The time duration
correlation to the potential for glass lamellae formation to occur during the product shelf life.3

- L s with room temperature storage requirements. Drugs stored at room temperature have a
  grea e of glass lamellae formation than do products stored at colder temperatures.[8]
- Termin ation has a significant effect on glass stability.[4]

The referenced ature, below, includes recommended actions to help prevent the formation of glass lamellae. For example, for products "at risk" the vial surface alkalinity can be minimized by proper selection of glass composition (e.g., highly resistant, non-alkaline earth borosilicate glass) appropriate selection and qualification of vendors, and proper quality control of the incoming vials. Accordingly, FDA advises drug manufacturers of products to re-examine their supplier quality management program with the glass vial manufacturers to assure that this phenomenon is not occurring. Further, the Agency reminds finished drug

ault.htm | Internet

"... for products "at risk" the vial surface alkalinity can be minimized by proper selection of glass ..."

"Glass vials manufactured ...under higher heat... are less resistant than molded glass vials and may shed lamellae more easily."

Rx-360 is using this flash r

It has been reporte the lit
respect to glass resistance and
are superior to others in pertaining to preventing glass delamination. For example:

vial forming makes the glass more durable and less susceptib
delamination.[3,6] For example:

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."[6]

| | | | ence |
|---|---|---|---|
| pH | | >7.0 | 5 |
| Buffer Type | N/A | Citrate | 4, 8 |
| Ionic Strength | N/A | >100 mM NaCl | 8 |
| Vial Configuration | Listed in order of preference<br>Best to Worst<br>1. Molded vial<br>2. Silica coated tubing vial<br>3. Regular tubing vial<br>4. Ammonium sulfate treated tubing vial | | 4,5,6,7,8 |

"... not all Type I glass is equivalent with respect to glass resistance and delamination... For example: Molded vials are more durable and less susceptible ."

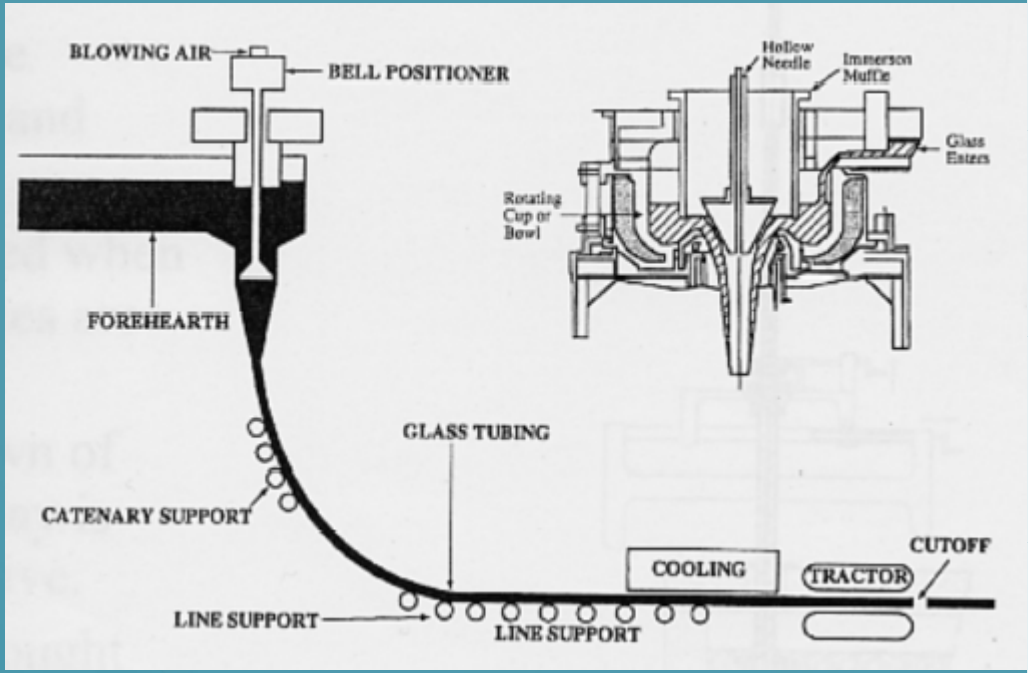
"... increasing surface alkalinity and reducing chemical durability..."

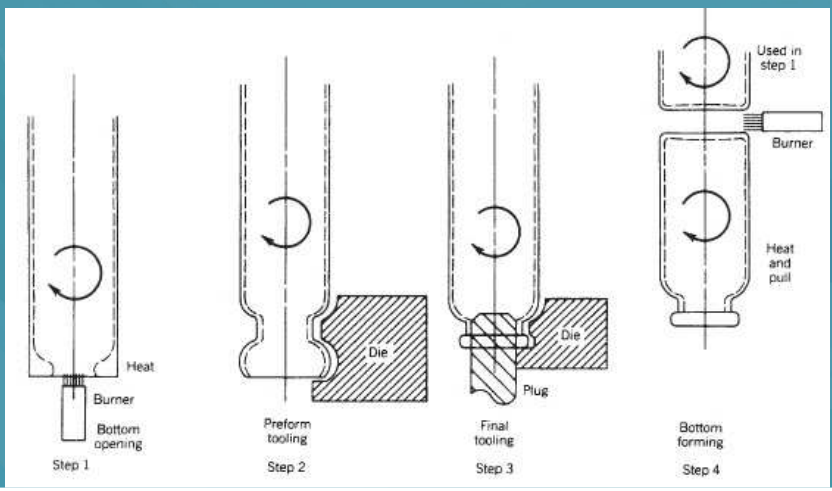
"Listed in order of preference
Best to Worst
1. Molded vial ..."

# Overview of pharma glass packaging options

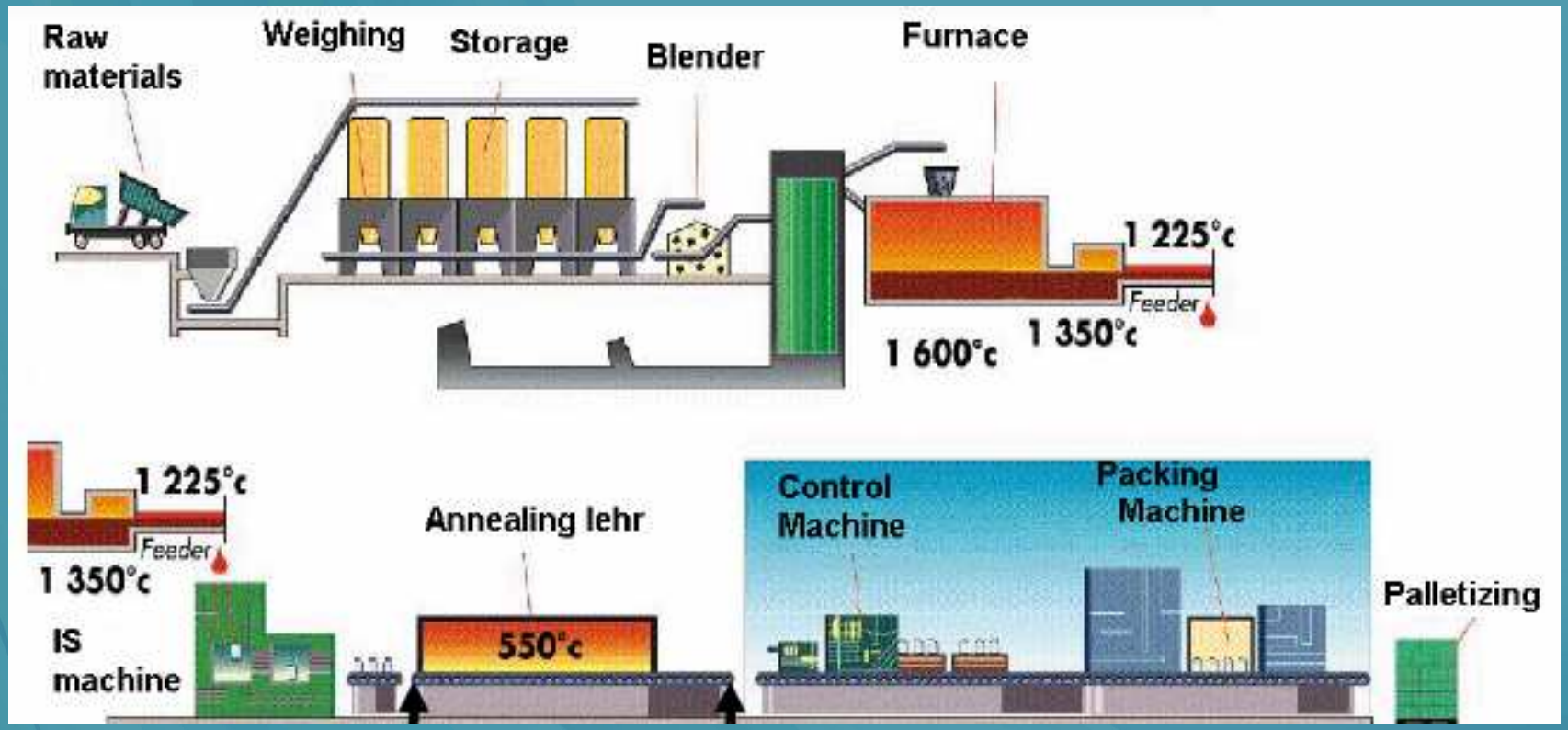
# Tubing Glass

- 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 produce non round vials and bottles

# Comparison study between molded glass and current glass packaging solutions

# For Type I Vials 5 ml and 10 ml

# Study overview

| Objective: | To characterize leachable/extractable profile of molded and tubing vials across a range of pH; and to further our understanding of the referenced correlations to hydrolytic resistance | |
|---|---|---|
| Scope: | Sample id | Description |
| | M-5 | Asolvex® molded (SGD) vials; 5ml x 20mm |
| | M-10 | Asolvex® Molded (SGD) vials; 10ml x 20mm |
| | T-5 | Tubing vials, European Supplier 1; 5ml x 20mm |
| | T-10 | Tubing vials, European Supplier 2; 10ml x 20mm |

# Study overview (cont.)

| Analysis: | Methods |
|---|---|
| 1- Mass Composition | X-Ray Fluorescence Spectrometry |
| 2- Surface Composition | Time-of-Flight Secondary Ion Mass Spectrometry (TOF-SIMS) |
| 3- Hydrolytic Resistance | Grain and Surface per European Pharmacopeia, 3.2.1 |
| 4- Extractables | Aqueous extraction at elevated temperature and across a pH range of 1 – 10 + Emission Spectrometry ICP |

# Study 1: Mass Composition Analysis

- 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

# Reminder: Type I glass composition

- NEUTRAL GLASS is an alkaline borosilicate glass with main components of (typical moulded glass composition):
  - Network Formers : $SiO_2+Al_2O_3$ - 73%
    $B_2O_3$ - 12%
  - Network Modifiers: $Na_2O;K_2O$ - 10%
    $CaO;BaO;ZnO$ - 5%

- NEUTRAL GLASS may be composed of 2 primary phases
  1. Silica-rich phase with low alkaline content
  2. 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

# Results / Conclusion

| (%) | Molded | Tubing 1 | Tubing 2 |
|---|---|---|---|
| Network Formers | 85.7 | 90.2 | 91.1 |
| Network Modifiers | 14.2 | 9.6 | 8.7 |

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

| Main elements (%) | Moulded Flint | 5ml Tubing 1 | 10ml Tubing 2 |
|---|---|---|---|
| $SiO_2$ | 69,1 | 70,8 | 74,3 |
| $Na_2O$ | 6,1 | 7,1 | 7,2 |
| $K_2O$ | 3,1 | 1,2 | 0,0 |
| CaO | 1,1 | 1,2 | 1,5 |
| MgO | 0,0 | 0,2 | 0,0 |
| $Al_2O_3$ | 4,0 | 7,3 | 5,6 |
| $Fe_2O_3$ | 0,02 | 0,03 | 0,02 |
| $B_2O_3$ | 12,6 | 12,1 | 11,2 |
| BaO | 2,8 | 0,1 | 0,0 |
| $TiO_2$ | 0,02 | 0,01 | 0,03 |
| ZnO | 1,1 | 0,0 | 0,0 |

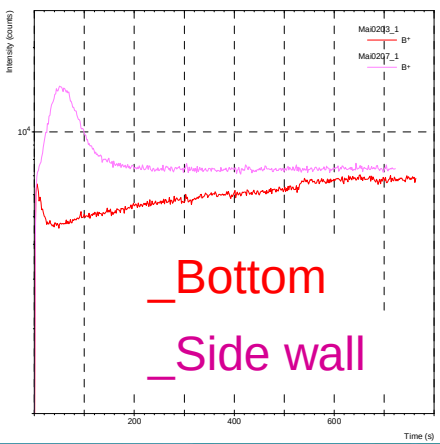
# Study 2: Surface Composition Analysis - SIMS

- 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 =1pA
    - Surface analyzed 100 x 100 µm², 128x128pixel
    - Positive Secondary Ions analyzed
  - **Abrasion:**
    - Primary Ions $O_2^+$ 500eV, I = 100nA
    - Surface : 300 x 300 µm²
  - **Cycle**
    - Analysis : acquisition of 1 scan (time of max flight = 100 µs)
    - Abrasion : 1.6s, Pause : 1s

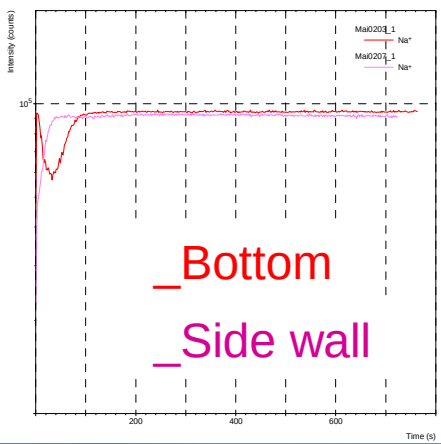
# Glass Composition : from surface to internal

## TUBING 5ml

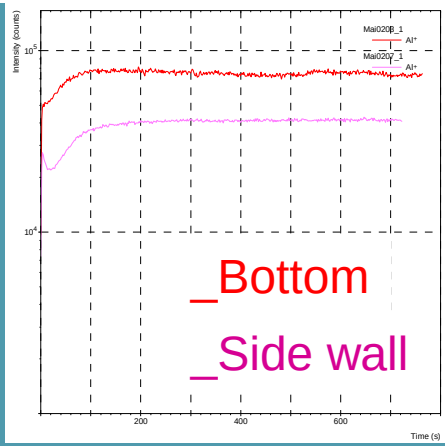
B+



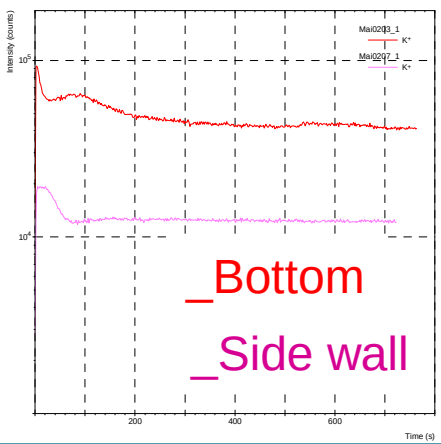

Na+




Al+

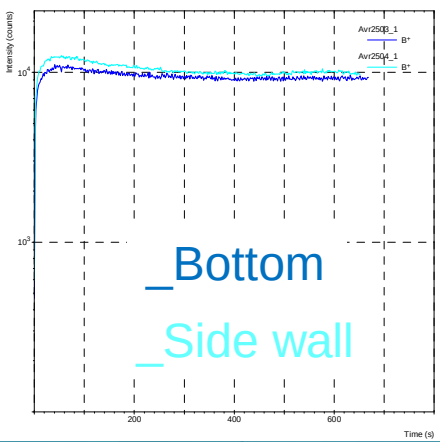



K+

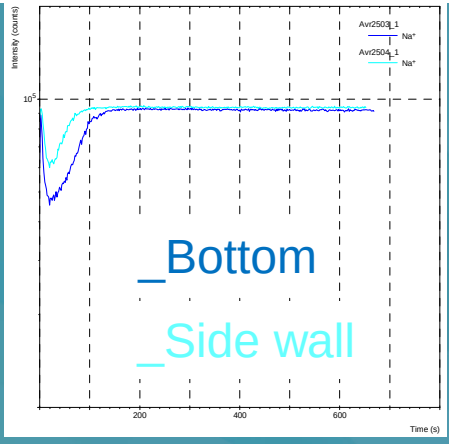



## MOLDED 5ml

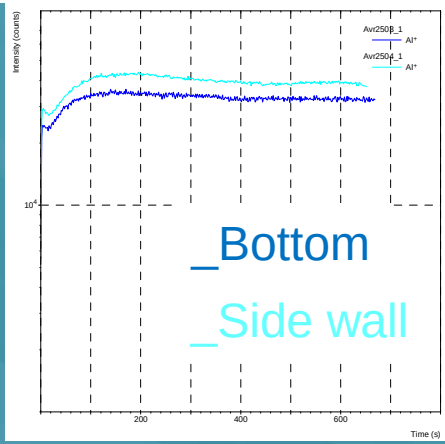
B+



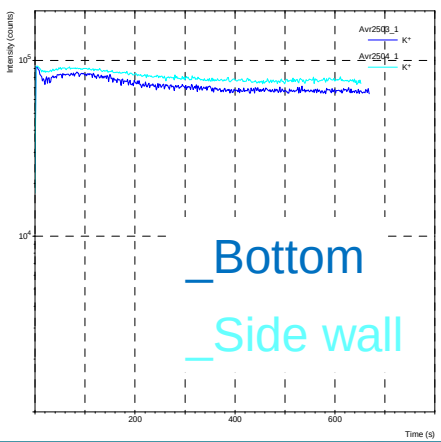

Na+




Al+



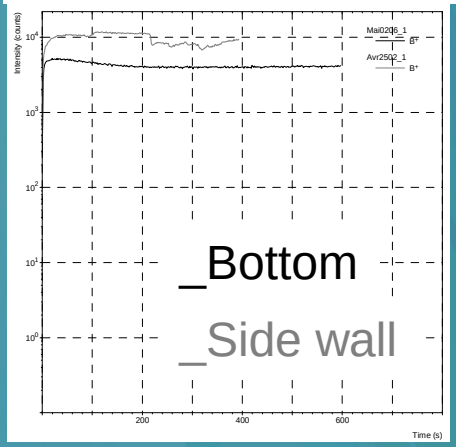

K+



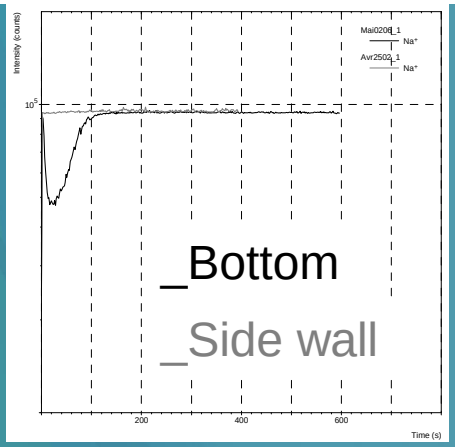
# Glass Composition : from surface to internal

## TUBING 10ml

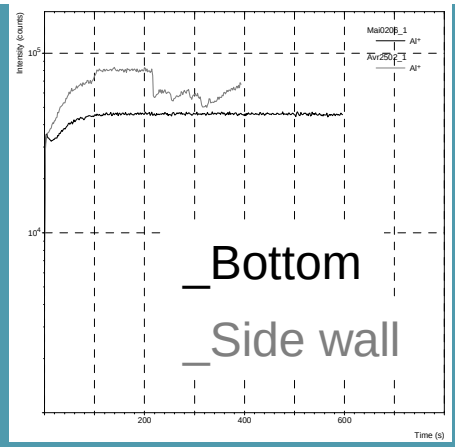
B+



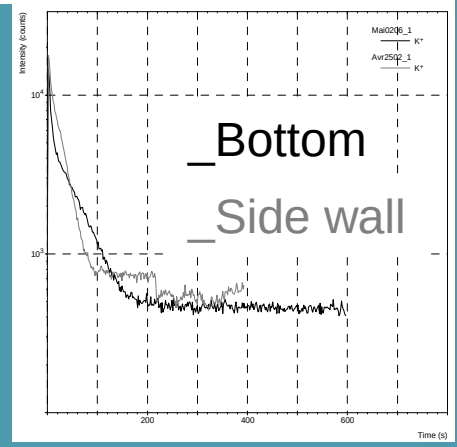

Na+




Al+

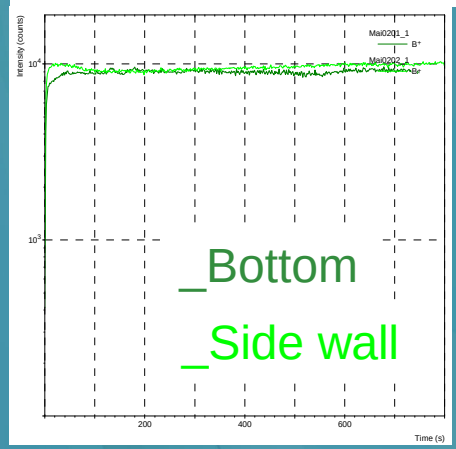



K+

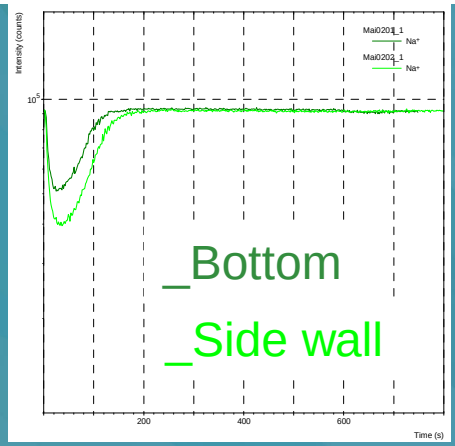



## MOLDED 10ml

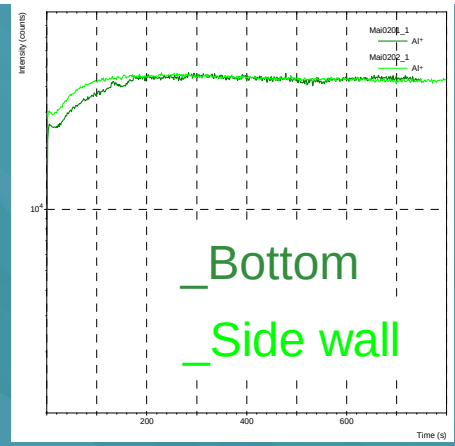
B+



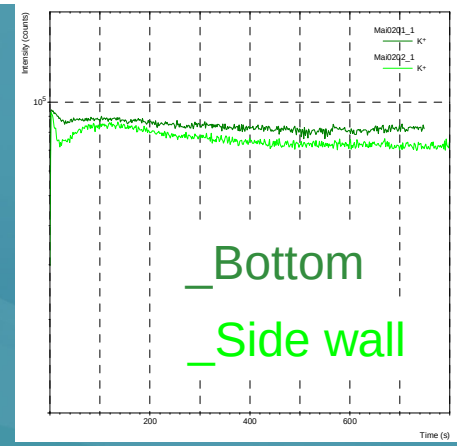

Na+




Al+




K+



# Conclusion – Surface Composition

- All samples show a different surface composition
- 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
- Sodium depletion during forming for Asolvex Type I glass, both on bottom and on side walls (blowing effect)

# Study 3 : Hydrolytic Resistance Testing

- 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 and water (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

| | Type I Molded | Tubing T-5 |
|---|---|---|
| Grain Hydrolytic Resistance (ml) | 0.53 | 0.43 |

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

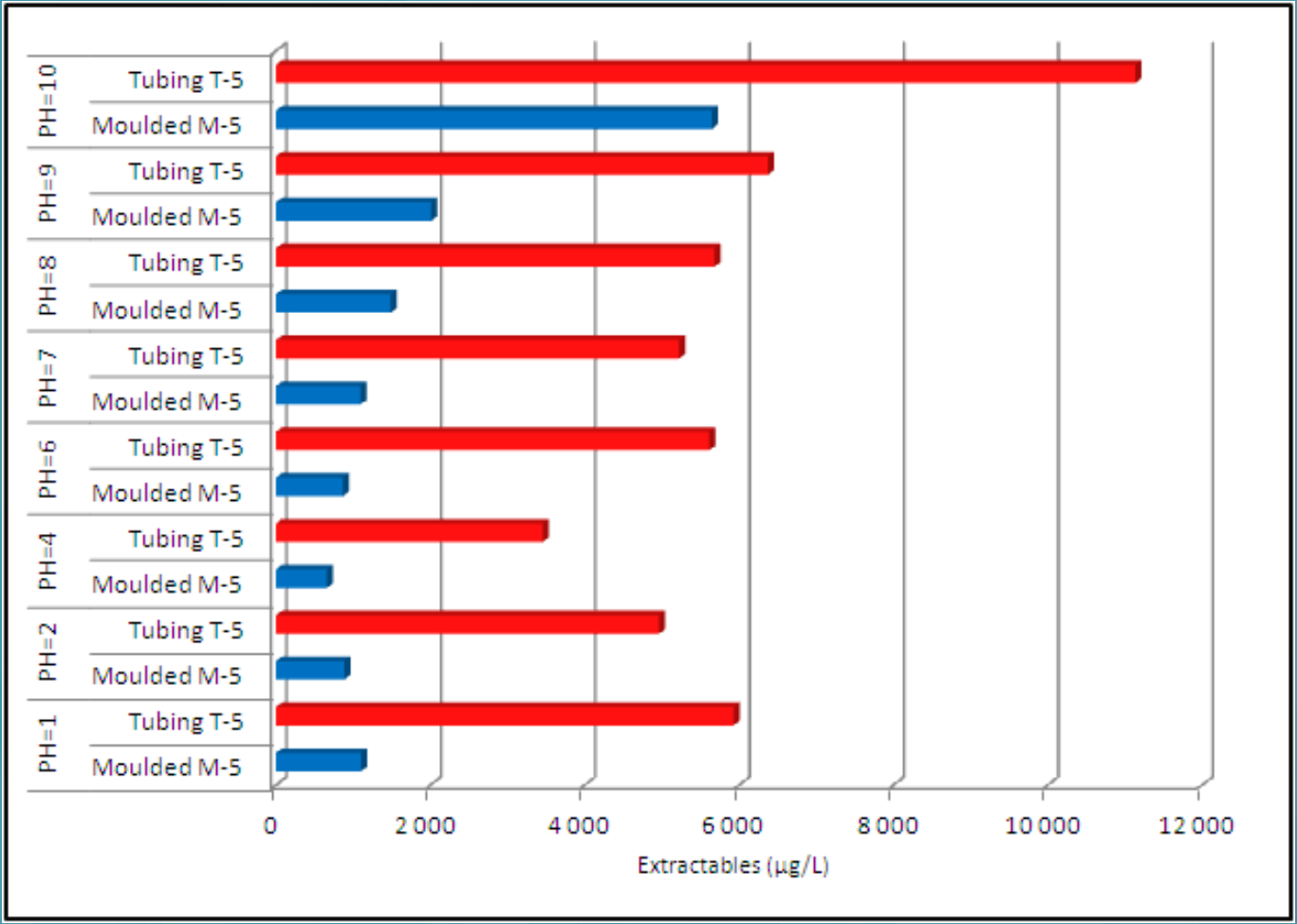
| | Type I Molded M-5 | Tubing T-5 | Type I Molded M-10 | Tubing T-10 |
|---|---|---|---|---|
| Vol 90% (ml) | 8.1 | 8.3 | 12.25 | 12.4 |
| Type I Limit | 1 | 1 | 0.8 | 0.8 |
| Surface Hydrolytic Resistance (ml) | 0.15 | 0.50 | 0.17 | 0.41 |

- More critical for product interaction
- All vials are under type I surface limit
- Better surface Hydrolytic resistance for molded vials

# Study 4: Extractables evaluation

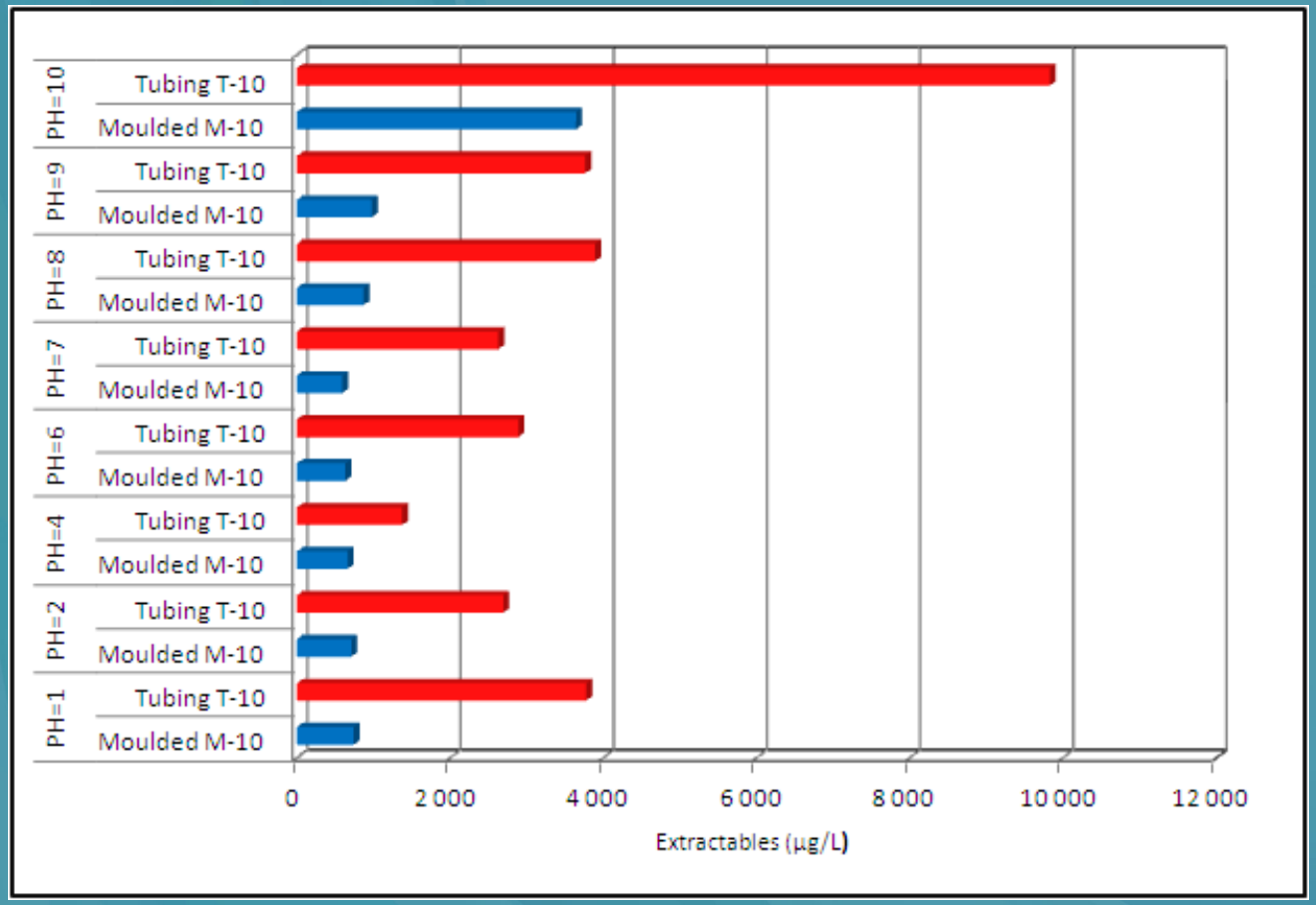
- Autoclave solution analysis with ICP
- **Solution Preparation**
  - Deionized water pH (18 MΩ.cm resistivity) adjusted :
  - with HCl for acid pH
  - with NaOH for base pH
- **Vials Extraction**
  - filled at nominal capacity with the solution
  - Vials in autoclave at 121°C for 1h, Eur. Pharma. HR 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 – 5ml




- Less elements extracted with Molded vials, for all pH
- Higher pH (10 or more) causes higher extractions

# Vial comparison : Total Extractables – 10ml




- Higher pH (10 or more) causes higher extractions
- Less extraction in volume for bigger vial, surface/volume ratio lower

# Extractables Analysis by element– 5ml

| | PH=1 | | PH=2 | | PH=4 | | PH=6 | | PH=7 | | PH=8 | | PH=9 | | PH=10 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Extracted Elements (µg/L) | Moulded M-5 | Tubing T-5 | Moulded M-5 | Tubing T-5 | Moulded M-5 | Tubing T-5 | Moulded M-5 | Tubing T-5 | Moulded M-5 | Tubing T-5 | Moulded M-5 | Tubing T-5 | Moulded M-5 | Tubing T-5 | Moulded M-5 | Tubing T-5 |
| Si | 241 | 1632 | 203 | 1320 | 188 | 1118 | 368 | 3216 | 640 | 3443 | 818 | 3253 | 1079 | 3447 | 3481 | 6315 |
| Na | 272 | 1913 | 246 | 1647 | 185 | 1162 | 137 | 883 | 146 | 808 | 158 | 881 | 209 | 1026 | 471 | 1735 |
| K | 126 | 213 | 111 | 190 | 75 | 119 | 65 | 111 | 78 | 99 | 87 | 127 | 109 | 135 | 334 | 250 |
| Ca | 136 | 326 | 74 | 281 | 60 | 122 | 94 | 218 | 93 | 199 | 131 | 263 | 143 | 381 | 229 | 606 |
| Mg | 6 | 7 | 2 | 7 | 2 | 4 | 3 | 6 | 4 | 6 | 3 | 9 | 5 | 10 | 5 | 15 |
| Al | 58 | 771 | 54 | 541 | 34 | 221 | 62 | 509 | 4 | 84 | 87 | 511 | 140 | 630 | 339 | 1068 |
| Fe | 20 | 5 | - | 4 | - | 2 | 8 | 3 | 0 | 0 | 7 | 3 | 13 | 10 | 10 | 14 |
| B | 123 | 1058 | 99 | 939 | 51 | 691 | 62 | 639 | 73 | 585 | 99 | 578 | 158 | 675 | 421 | 1075 |
| Ba | 64 | 4 | 52 | 22 | 34 | 15 | 39 | 21 | 32 | 9 | 68 | 47 | 89 | 42 | 228 | 34 |
| Ti | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 2 | 2 |
| Zn | 58 | 3 | 45 | 15 | 34 | 7 | 37 | 14 | 34 | 4 | 35 | 15 | 69 | 21 | 130 | 25 |
| Extractables Total (µg/L) | 1 105 | 5 931 | 887 | 4 967 | 663 | 3 459 | 872 | 5 618 | 1 101 | 5 227 | 1 491 | 5 684 | 2 012 | 6 377 | 5 648 | 11 137 |

- No visible attack of the glass, no flake (methylene blue test shows nothing)
- Different local / surface glass compositions with tubing may cause higher extractions

# Extractables Analysis by element– 10ml

| | PH=1 | | PH=2 | | PH=4 | | PH=6 | | PH=7 | | PH=8 | | PH=9 | | PH=10 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Extracted Elements (µg/L) | Moulded M-10 | Tubing T-10 | Moulded M-10 | Tubing T-10 | Moulded M-10 | Tubing T-10 | Moulded M-10 | Tubing T-10 | Moulded M-10 | Tubing T-10 | Moulded M-10 | Tubing T-10 | Moulded M-10 | Tubing T-10 | Moulded M-10 | Tubing T-10 |
| Si | 201 | 781 | 141 | 493 | 146 | 275 | 310 | 1535 | 312 | 1575 | 465 | 2116 | 497 | 1920 | 2320 | 5688 |
| Na | 200 | 1492 | 199 | 1195 | 213 | 752 | 93 | 567 | 117 | 540 | 112 | 741 | 129 | 754 | 329 | 1781 |
| K | 96 | 37 | 101 | 8 | 119 | 5 | 41 | 0 | 68 | 27 | 63 | 8 | 81 | 7 | 208 | 10 |
| Ca | 39 | 272 | 47 | 165 | 66 | 56 | 37 | 141 | 28 | 109 | 38 | 194 | 46 | 219 | 81 | 365 |
| Mg | 1 | 5 | 2 | 2 | 3 | 0 | 1 | 2 | 1 | 2 | 2 | 2 | 2 | 4 | 2 | 5 |
| Al | 49 | 457 | 49 | 305 | 33 | 68 | 46 | 277 | 1 | 68 | 61 | 368 | 81 | 396 | 244 | 964 |
| Fe | 6 | 11 | 6 | 7 | 4 | 2 | 6 | 11 | 0 | 0 | 3 | 5 | 3 | 6 | 3 | 13 |
| B | 86 | 707 | 83 | 506 | 33 | 212 | 51 | 341 | 41 | 304 | 63 | 447 | 69 | 431 | 252 | 978 |
| Ba | 44 | 0 | 53 | 0 | 29 | 0 | 30 | 4 | 14 | 0 | 44 | 0 | 45 | 6 | 141 | 0 |
| Ti | 0 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 5 |
| Zn | 24 | 15 | 29 | 14 | 18 | 7 | 19 | 15 | 14 | 8 | 22 | 13 | 28 | 21 | 67 | 21 |
| Extractables Total (µg/L) | 742 | 3 777 | 709 | 2 694 | 662 | 1 374 | 631 | 2 890 | 592 | 2 629 | 870 | 3 894 | 979 | 3 763 | 3 644 | 9 829 |

- Values lower than 20 µg/L may not be significant (pollution ?),
- Still refining our test method, ICP detection limit on the blank solution 3σ<4µg/L (σ calculated on 10 measurements of the blank solution)
- Vial to vial variation +/- 10%

# Comments on Extractables

- **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

# Conclusions

- Delamination is a last stage indicator of heavy extraction of glass by the product
- Product interaction with the glass depends on glass composition AND how it was formed
- Results seem to indicate 1 step forming of molded seems to extract glass formers less readily 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 could be considered as an alternative in high aggressive extraction conditions
- Further comparison studies with real products are being conducted with clients to confirm this theory

# Thank you for your attention !

## Acknowledgements

Work done by SGD lab in Mers-les-Bains, France
- Didier Pichard
- Joel Bourjot
- Sébastien Dussardier

SIMS profiles done by CRITT