Best Practices for Glass Primary Containers

PDA Training Course, Mainz, June 11th/12th

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EMEA TEC Stevanato Group

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PDA Parenteral Drug Association

PDA TRAINING

Agenda

- Glass Containers for Pharmaceutical Application
- Container Production from Glass Tubing
- Factors that Affect Surface Chemistry in Glass Converting Process
- Case Studies
- Additional proprieties with internal and/or external treatment/coating
- Molded Vials

Glass Containers for Pharmaceutical Application

The main and general principle of the EP is the following:

«The container chosen for a given preparation shall be such that the glass material does not release substances in quantities sufficient to affect the stability of the preparation or to present a risk of toxicity».

Syringes and Ready to Use (RTU) containers expected to be the fast-growing container types

Glasstubing Primary Packaging (2022)

KEY CAGR 22-27: = STABLE ➚ LSD ↗ HSD ↑ DD

	SYRINGES	CARTRIDGES	VIALS	AMPOULES
Volume *(in billion)*	~4,5	4+	11-12	20+
Overall Volume CAGR	↑ (DD)	➚ (LSD)	➚ (LSD)	= (STABLE)
RTU Growth	↑ (DD)	↑ (DD)	↑ (DD)	-

Source: IQVIA, SG internal elaborations

Container Production from Glass Tubing

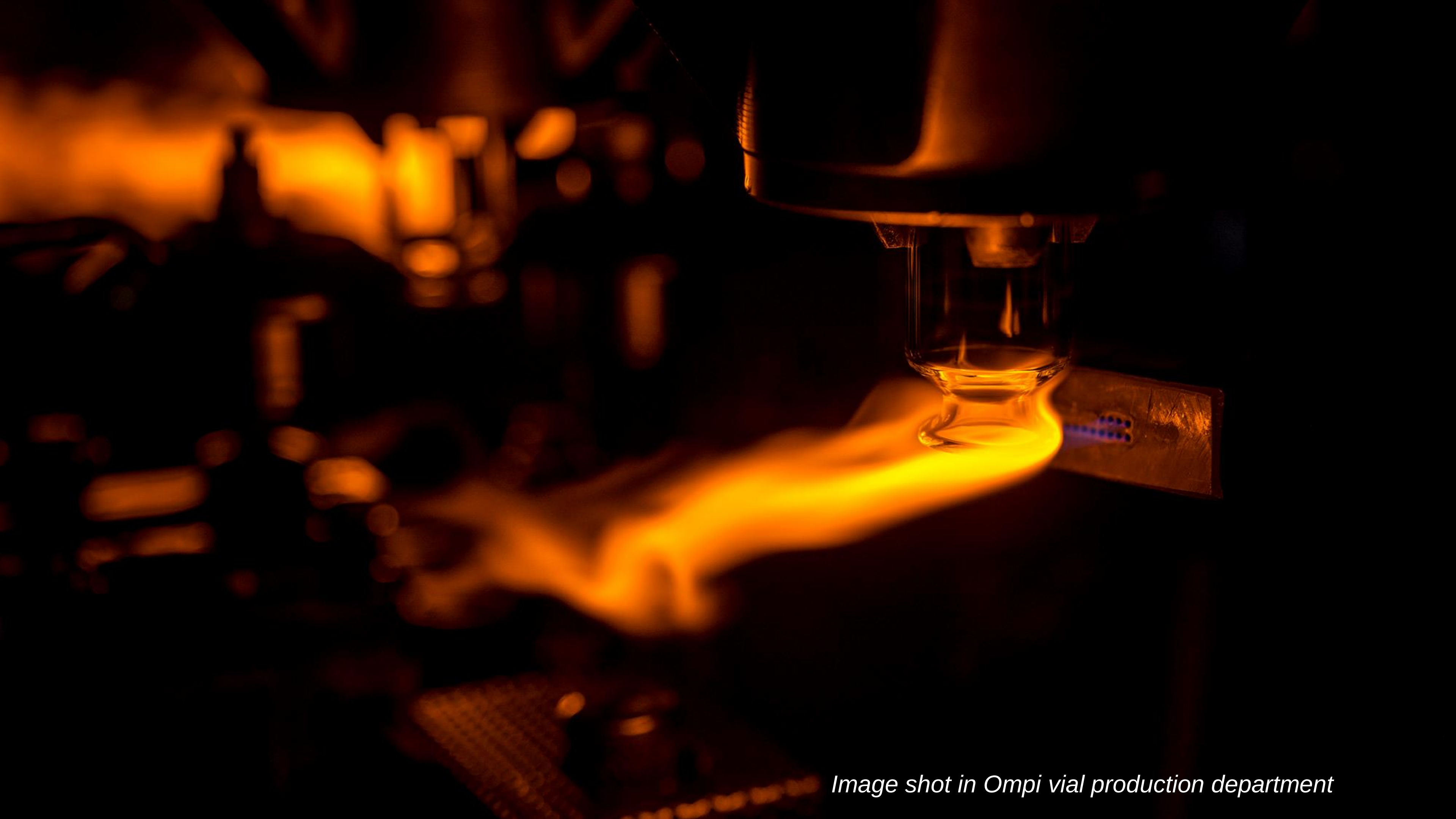
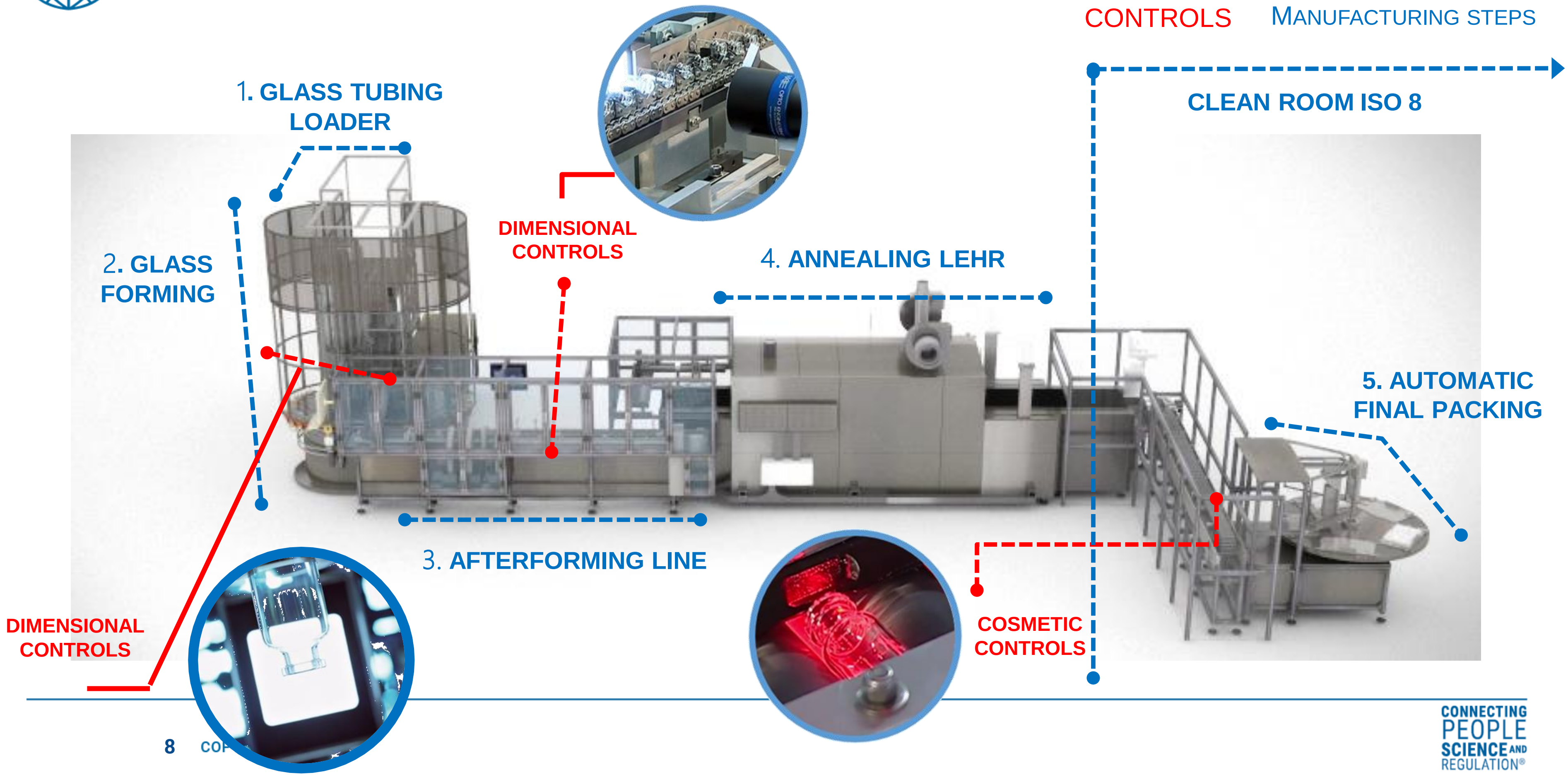


Image shot in Ompi vial production department

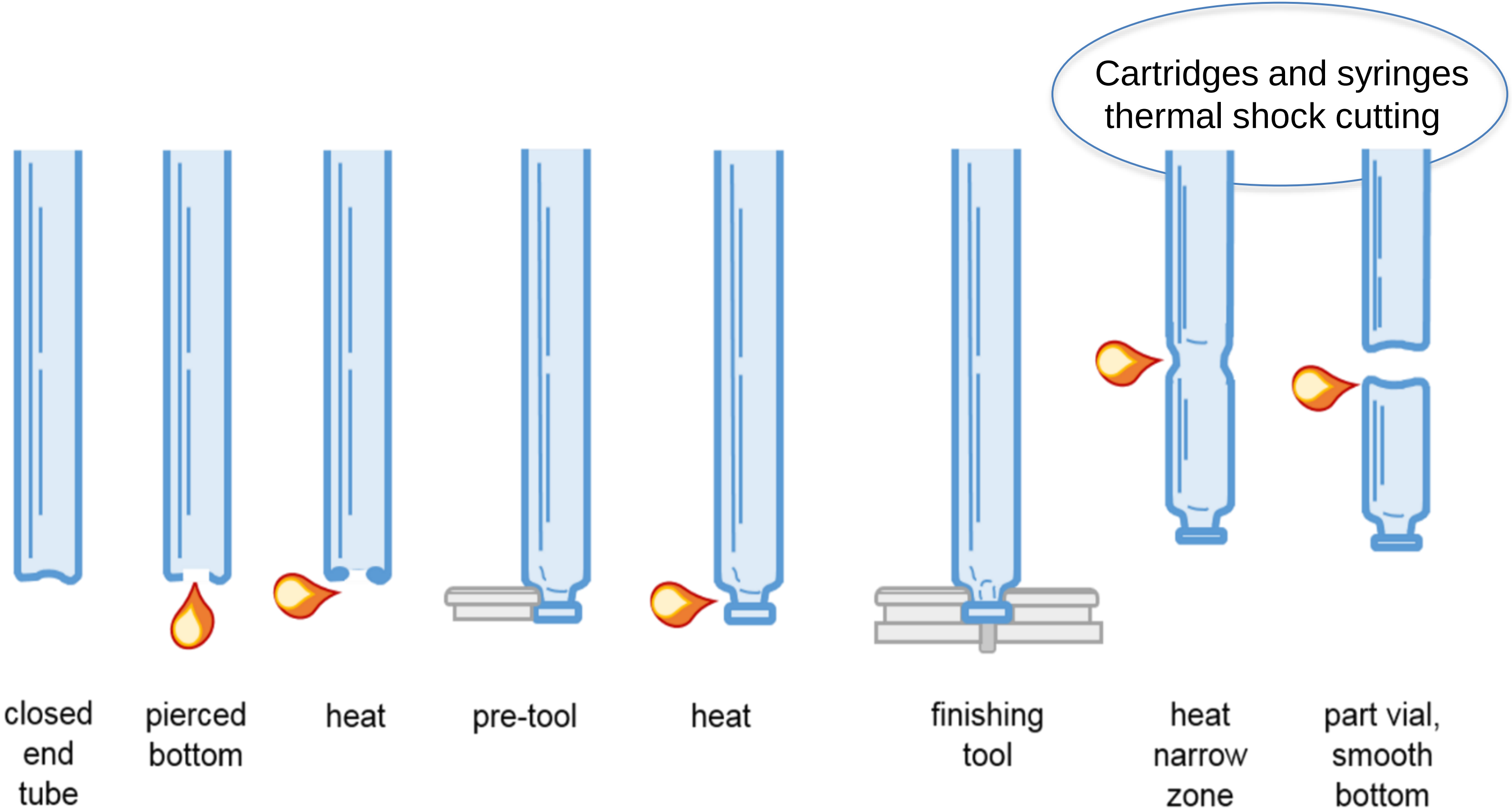
Container converting process from glass tubing into the final glass container



Container converting process from glass tubing into the final glass container

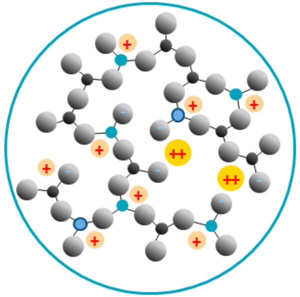
Vial Manufacturing Process

Container converting process from glass tubing into the final glass container



Factors that Affect Surface Chemistry in Glass Converting Process

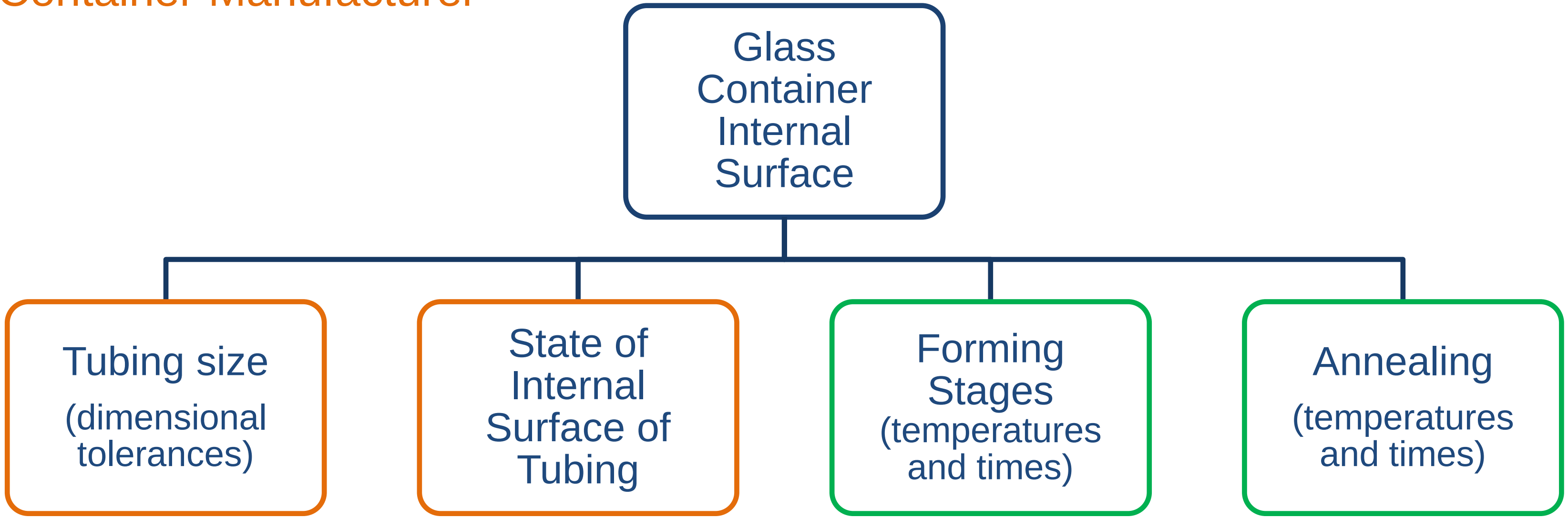
Mechanism of degradation for borosilicate glasses and factors that affect their corrosion propensity

IMPACT ON GLASS SURFACE →  → **LEACHING** → **DISSOLUTION** → **GLASS PARTICLES/ FLAKES**

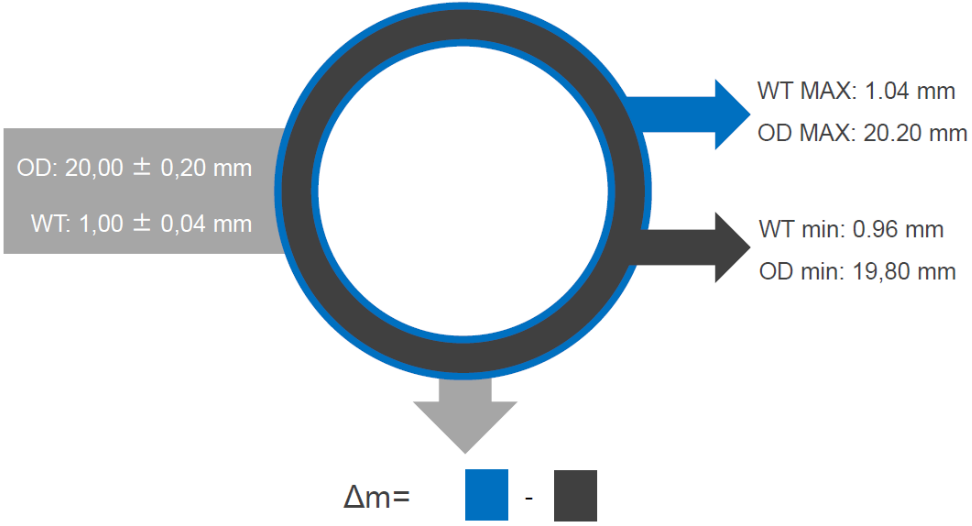
Influenced by

Influenced by	Factor	Responsible
Glass Vial	**Conversion manufacturing process** (e.g.: speed, temperature, type of glass)	Container Manufacturer
	Surface treatments (e.g.: sulfur)	
Drug	**Formulation** (e.g.: chemical composition, pH)	Pharma company
	Process (e.g.: depyro, sterilization)	
	Storage conditions (e.g.: temperature, time)	

Container Manufacturer



Dimensional Tolerances of Glass Tubing



Comparing MAX (20,20 x 1,04) **with MIN** (19,80 x 0,96)

$\Delta m = \pm 4\%$ (generally ≤ 2%)

m=mass

$$Q = m\,c\,\Delta T$$

Q= Kalories
m= glass mass
C= glass specific heat
T= temperature

Glass Tubing Internal Surface State

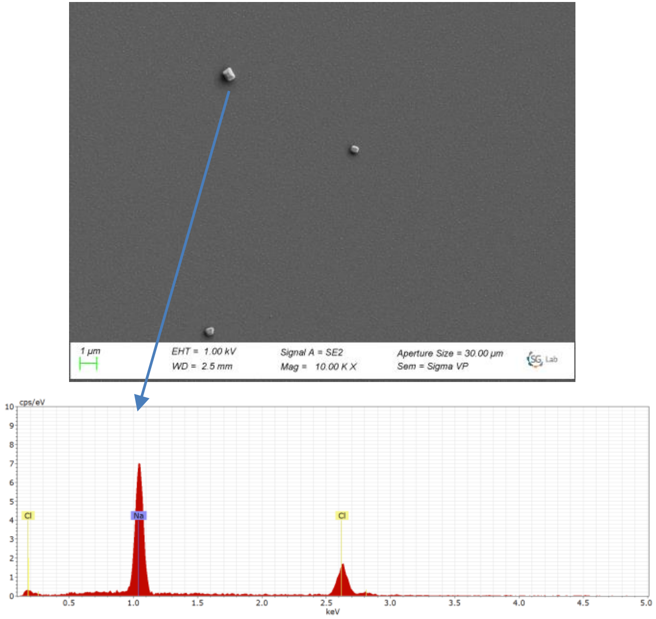
Glass Tubing Internal Surface State

Roughness

Increase of the surface area

Size of the elemental structure

Higher cooling rates generate larger structural units with lower chemical resistance



Glass tube inner surface_SEM-EDX

Forming Temperatures and Times

Forming Temperatures and Times

The migration of elements from bulk to the surface increases with increasing temperature and time

Phase separation and sublimation of alkali borates

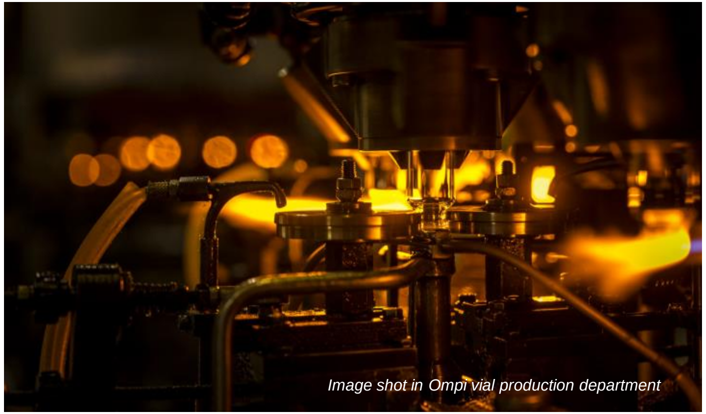
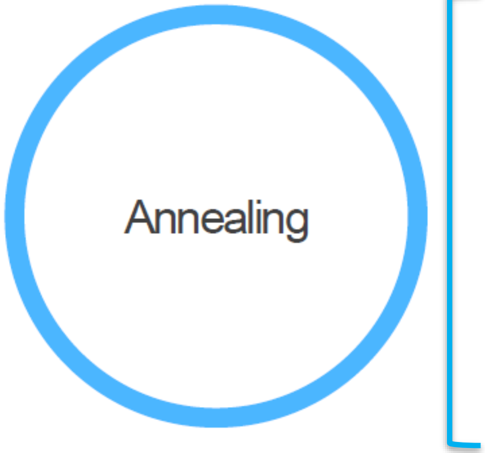


Image shot in Ompi vial production department

Glass Quality: factors that affect surface chemistry in glass converting process

Annealing



Alkali surfacing effect due to the increased thermal mobility of ions as a function of temperature and time

Increased alkali extractability

Annealing

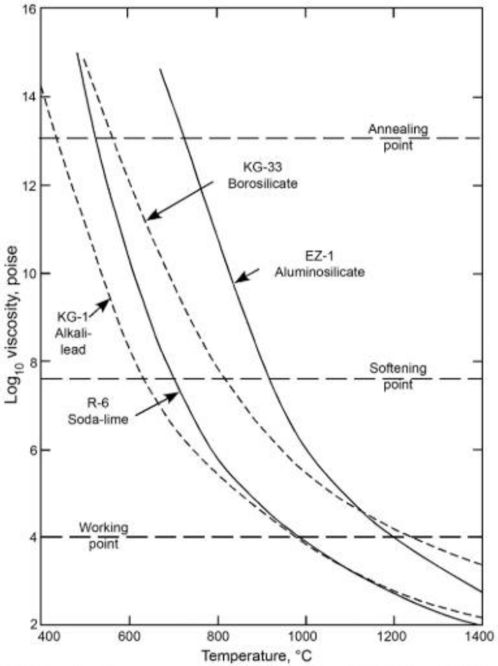


Fig. 9.11 Viscosity of some commercial silicate glasses. *(Modified from R.H. Doremus, Glass Science, John Wiley and Sons, New York, 1973, p. 103. Reproduced with permission of the publisher.)*

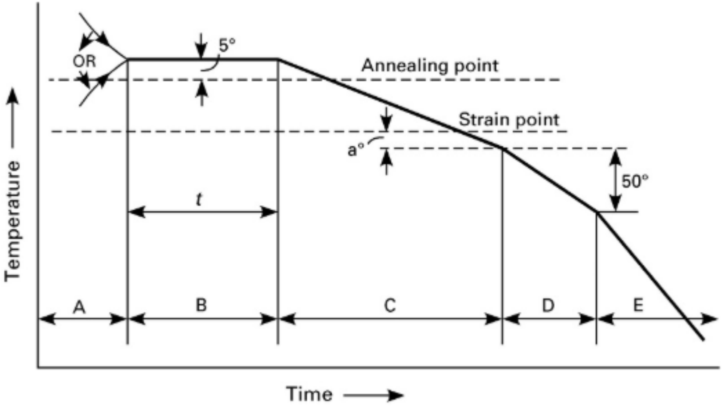
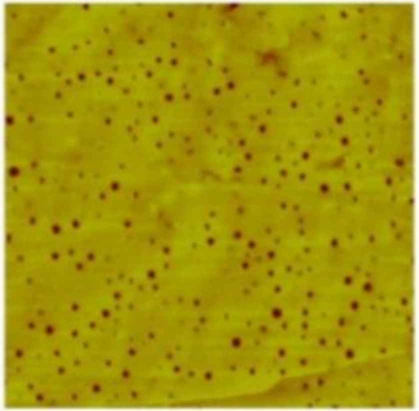


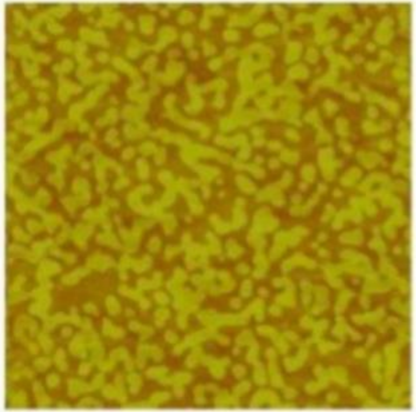
Fig. 13.46 Suggested schedules for commercial annealing of soda lime silicate glassware. (Courtesy Corning Incorporated.)

*Fundamentals of Inorganic Glasses, A.k. Varshneya and J. Mauro (2019)

Phase Separation in Borosilicate Glasses



Droplet in Matrix Morphology



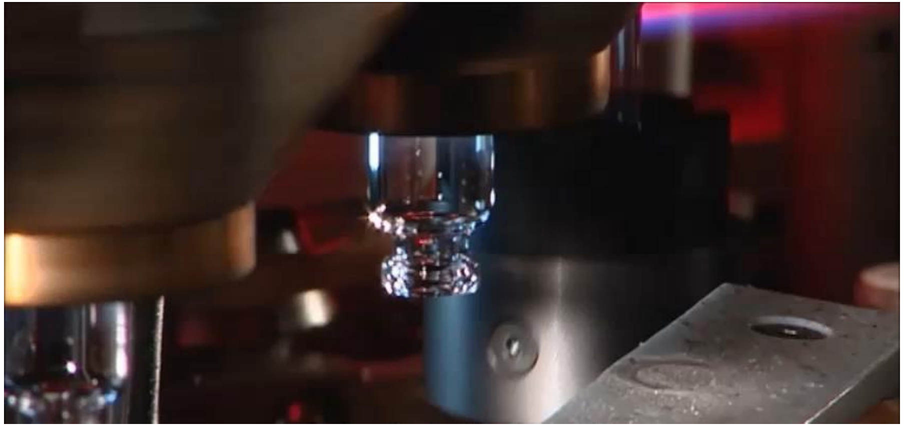
Interconnected Morphology

Depending upon composition, glasses may exhibit phase separation.

In images on the side, two basic phase separation morphologies are observed.

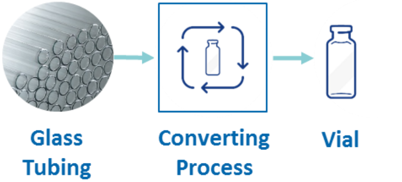
*B. Wheaton and A. Clare (2007). J. Non-Cryst. Solids, Vol. 353, pp. 4767-4778

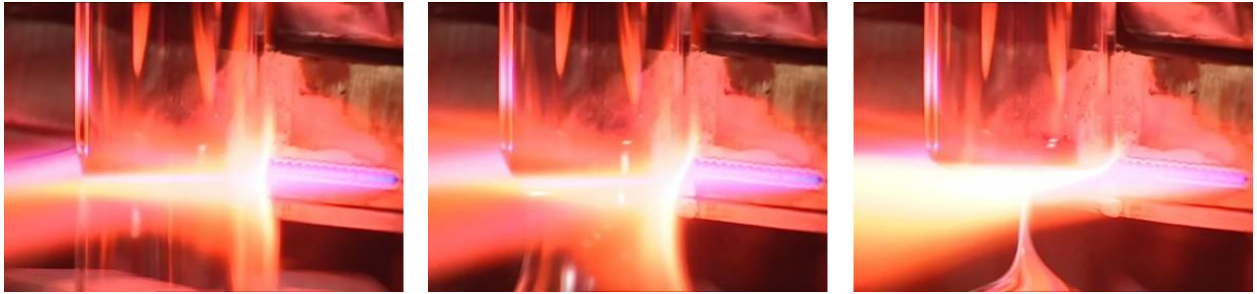
The conversion process parameters contribute to the establishment of a non-uniform composition on the glass surface, provoking phase separation region, a well-known phenomenon in alkali borosilicate glasses.



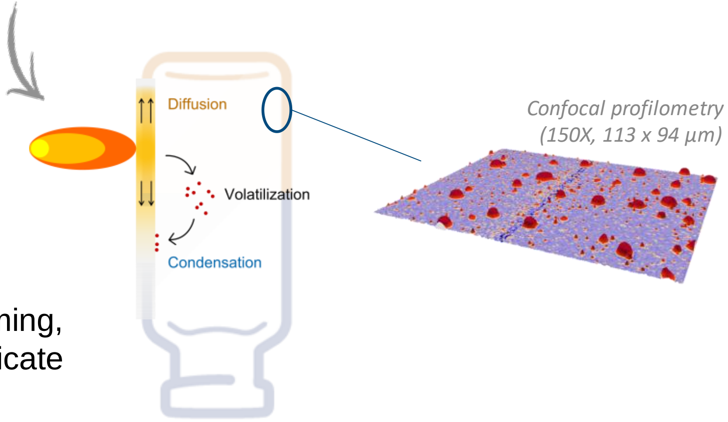
Physico-chemical properties of the glass container depend on a correct balance between former oxides and melting agents and on the thermal history of the glass.

Glass Quality: factors that affect surface chemistry in glass converting process



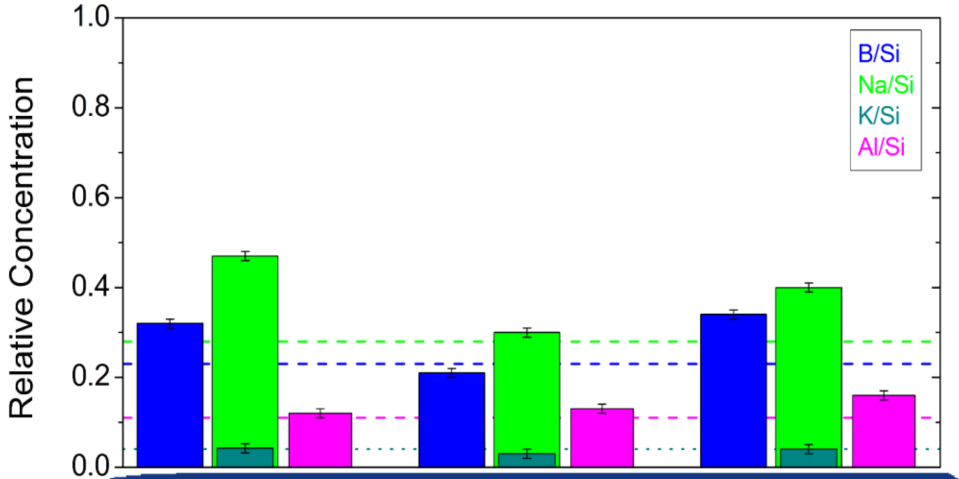


Glass elements volatilization and adhesion on the glass surface



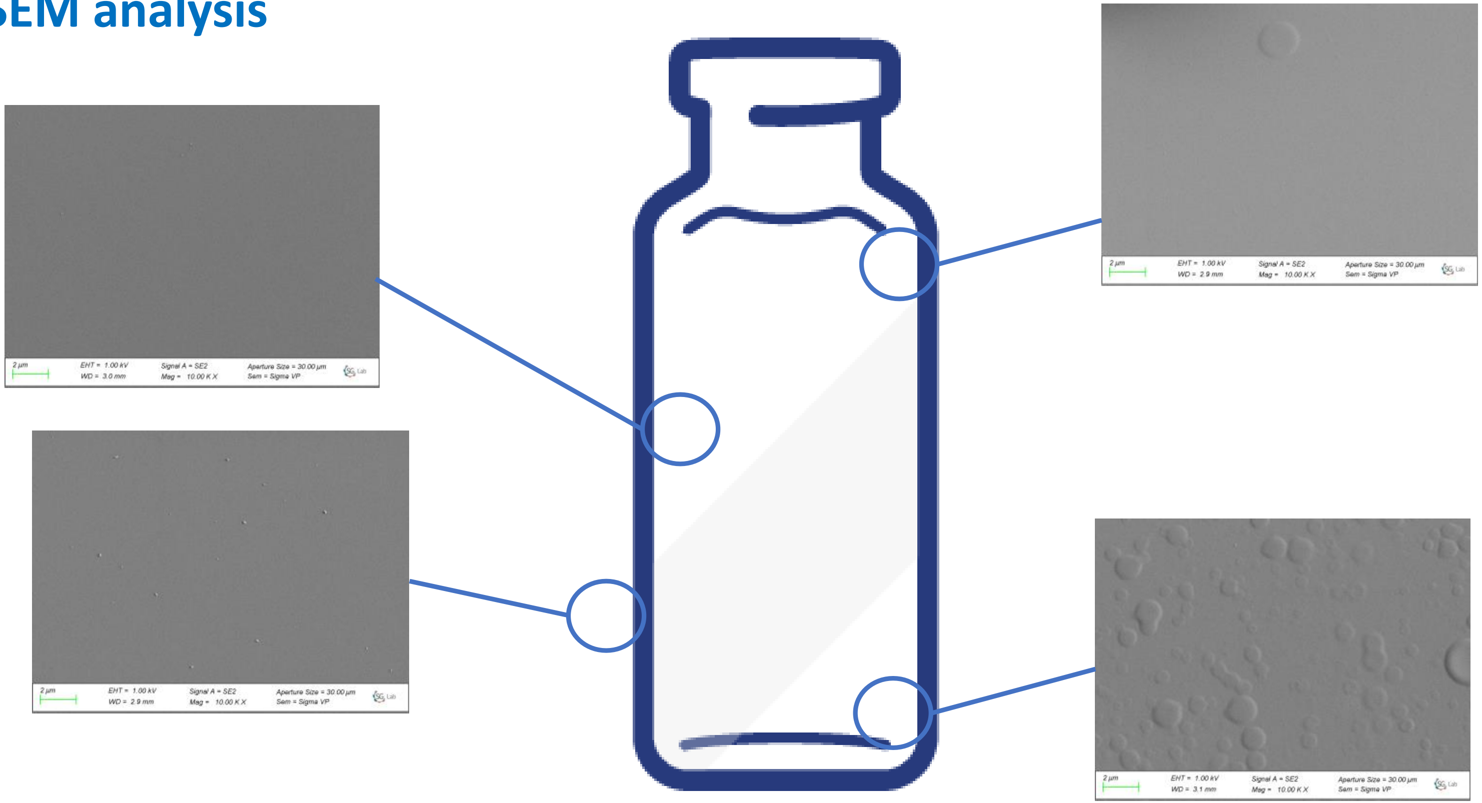
At temperatures above the working point e.g. during forming, compounds start to evaporate from the glass (for borosilicate glass are mainly sodium borates)

Alkali Borates from the Glass Composition

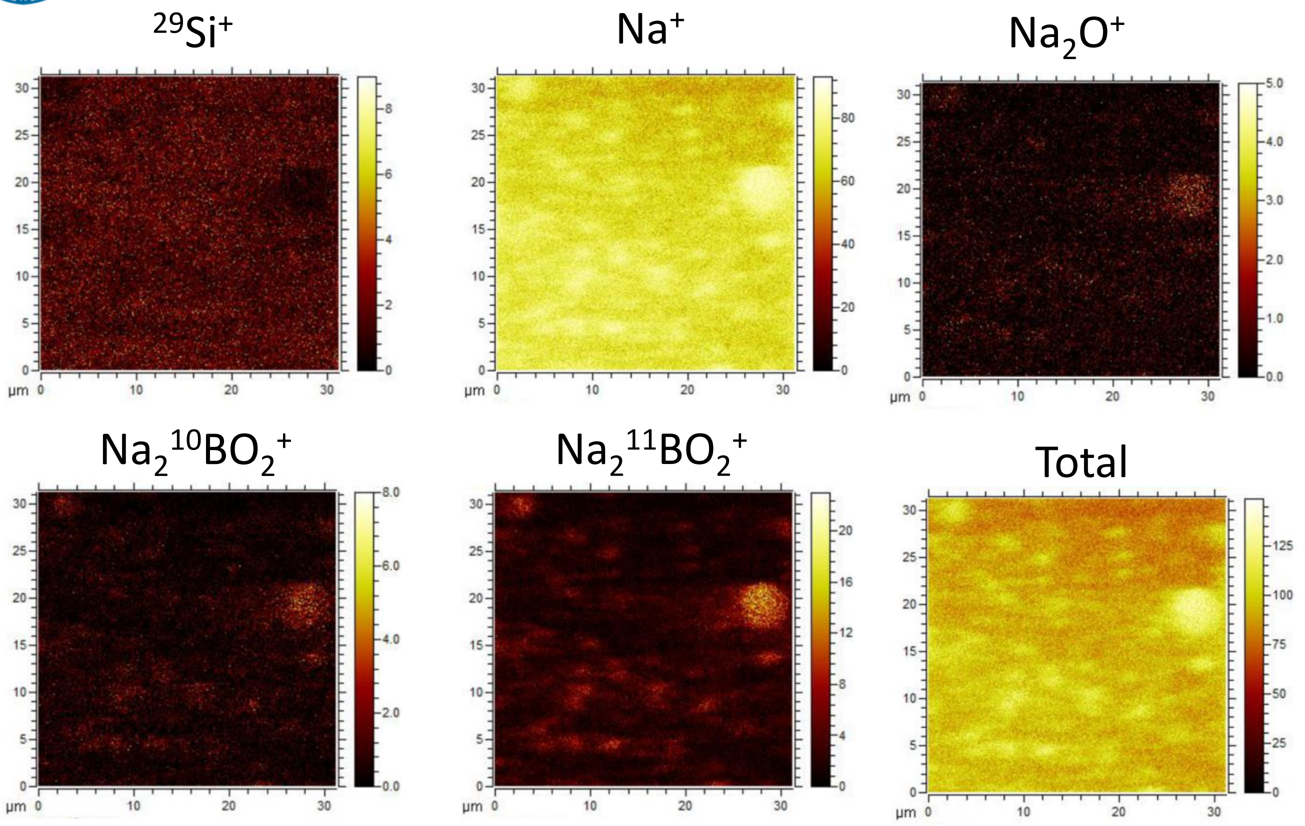


- XPS (X-ray Photoelectron Spectroscopy) analysis
- Sampling depth: 10 nm
- Dashed lines indicate values measured on glass tubes

SEM analysis



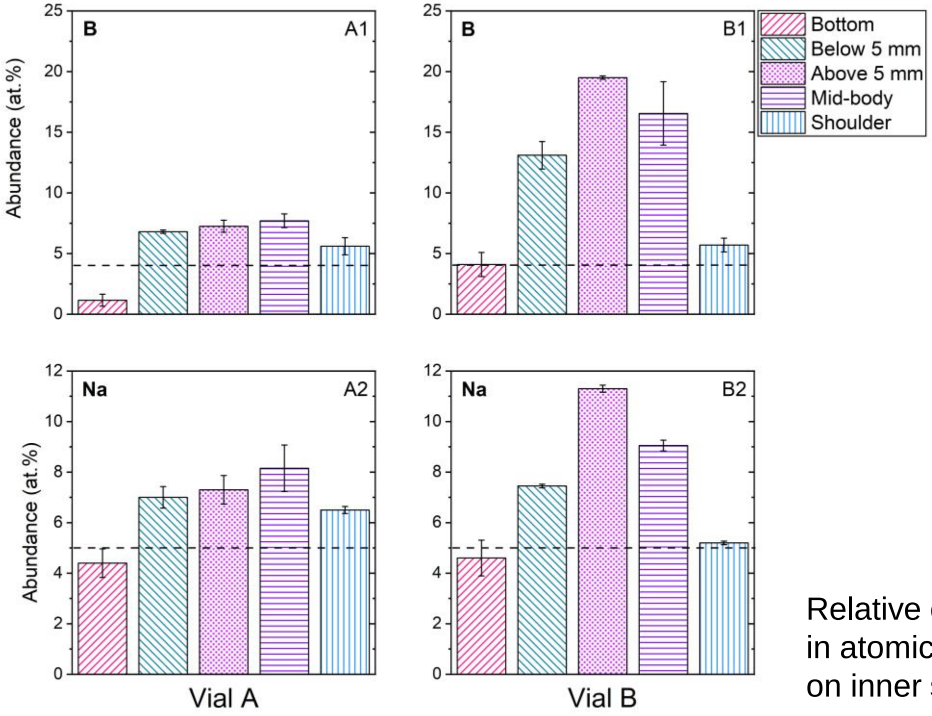
Glass Quality: factors that affect surface chemistry in glass converting process



ToF-SIMS images of inner surface of wall near bottom of the vial after the forming process (field of view: 30×30 µm^2). The lateral resolution is about 1 µm.

Glass Quality: factors that affect surface chemistry in glass converting process

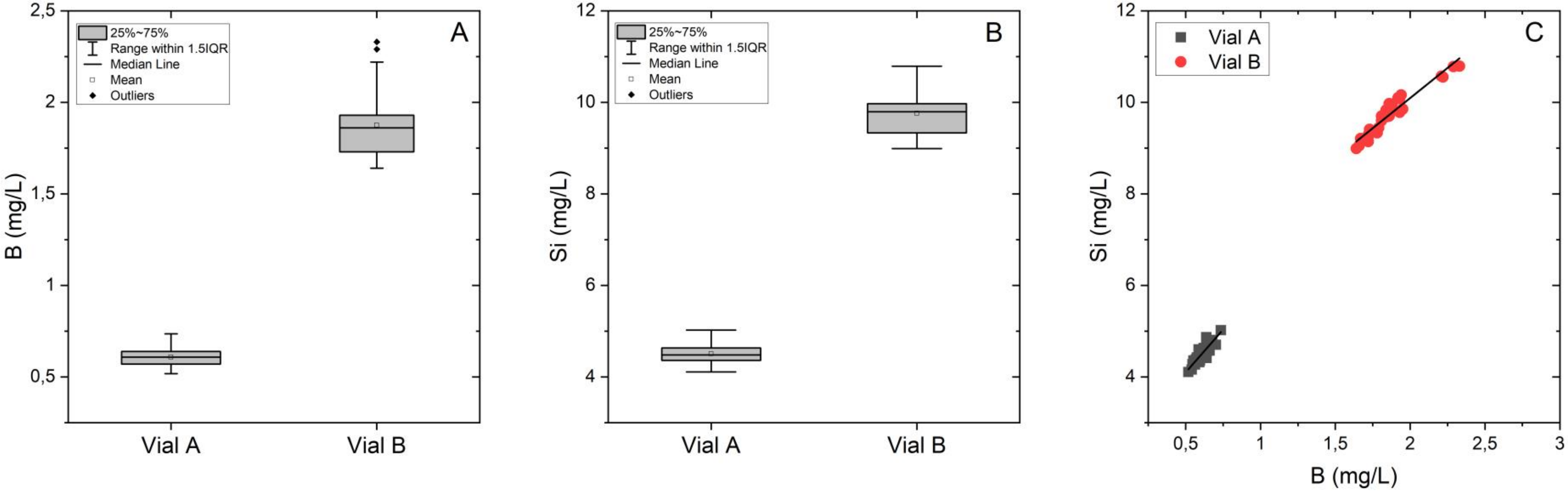
Improved manufacturing process can reduce glass surface physico-chemical structural changes



Vial B was created using a non-optimized converting process, whereas Vial A was obtained following the expected standard converting technique (i.e. improved forming and optimized annealing)

Relative concentration of boron (first row) and sodium (second row) in atomic percent, determined by XPS at 10 nm of sampling depth on inner surface of Vial A and Vial B. Dashed line indicates the ratio measured on inner surface of corresponding glass tube.

Evaluation of inner surface durability



ICP-OES values of Si and B (mg/L) after extraction in 0.9% KCl adjusted to pH 8 and subject to autoclave cycle at 121 °C for 1 h (as per USP <1660>), for Vial A and B.

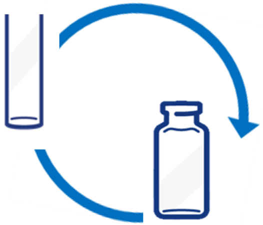
Case Studies

Choosing the “Right Glass”

PURPOSE

Investigation over the glass tubes for new Drug Product application

Simulation Study → Drug Product formulation → Stability study



GOAL

Identify the glass tube that fits the Drug Product needs to support the selection rationale of the glass container system

Choosing the "Right Glass"

Simulation conditions

- Depyrogenation
- Filling with a high ionic strength solution
- Low filling volume (high SA/V)
- Terminal sterilization
- Accelerated and real time stability

Surface evaluation and morphological analysis

- Light Microscopy DIC (Differential Interference Contrast)
- High resolution inspection of inner surface morphology by SEM (Scanning Electron Microscopy)

Chemical Analysis

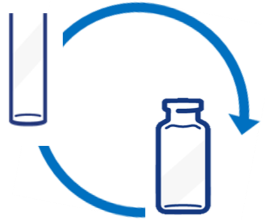
- ICP-OES (Al, B, Si, Ca quantitative analysis)

Visual Inspection

- Visual Inspection (EP 2.9.20 Particulate contamination: Visible Particles)

Samples

2 TYPES OF GLASS TUBE



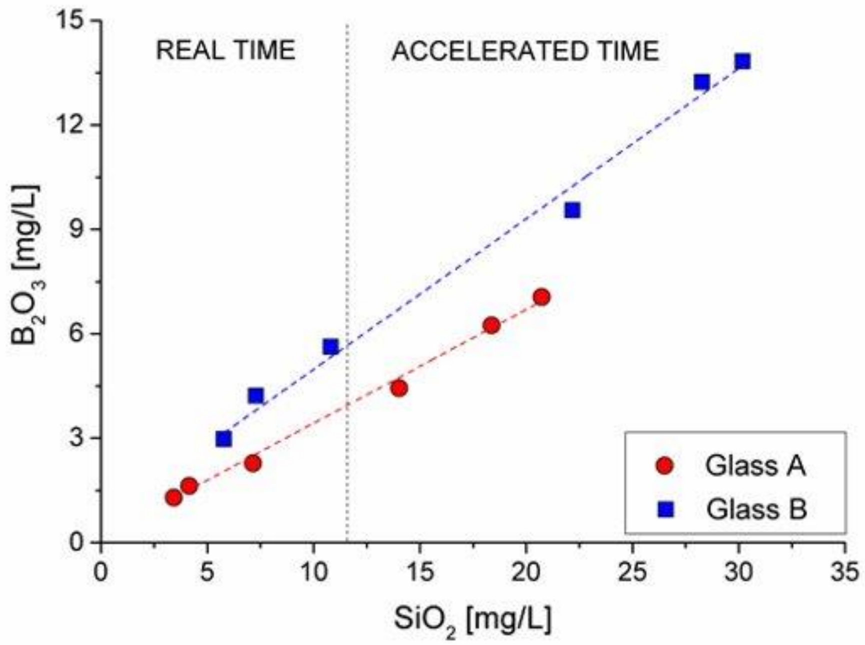
2R VIALS

	SiO_2	B_2O_3	Al_2O_3	Na_2O	K_2O	CaO+ BaO	Other	HR
GLASS A	>70	8-10	6-8	7.8	<0.1	1-2	0.7	0.79
GLASS B	>70	8-10	6-8	6.0	1.9	1-2	0.6	0.56

Glass chemical composition and vial hydrolytic resistance (HR)

Aging and Chemical Analysis

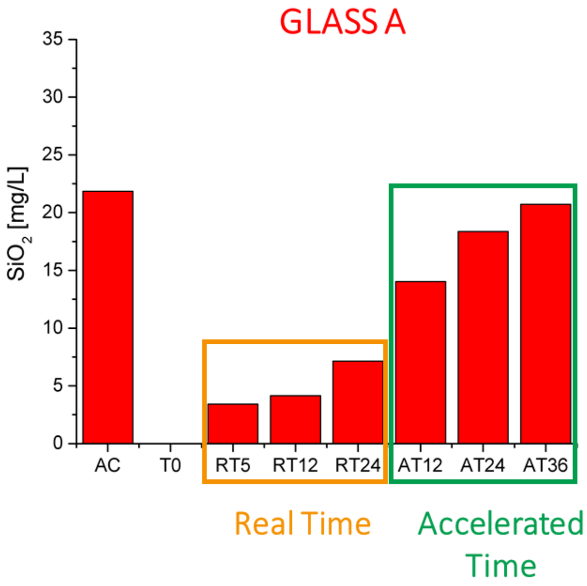
ID	Actual Duration	Conditions	Simulated or Equivalent Time(months)
T0	Freshly filled	-	0
RT5	5 months	25 °C± 2°C; 40%HR	5
RT12	12 months		12
RT24	24 months		24
AT12	5 weeks	60 °C ± 2°C; 40%HR	12
AT24	10 weeks		24
AT36	15 weeks		36
AC	60 minutes	121 °C	24

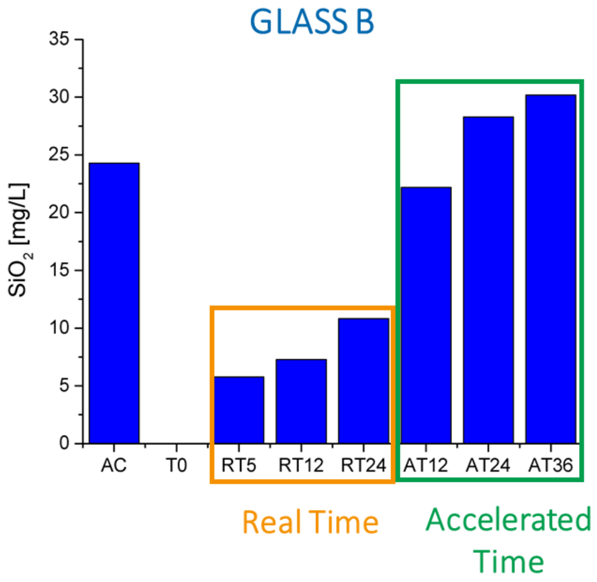


Storage conditions description: RT=Real-time; AT=Accelerated Time; AC=Autoclave Cycle

Aging and Chemical Analysis

Autoclave Ageing **VS** Stability Testing



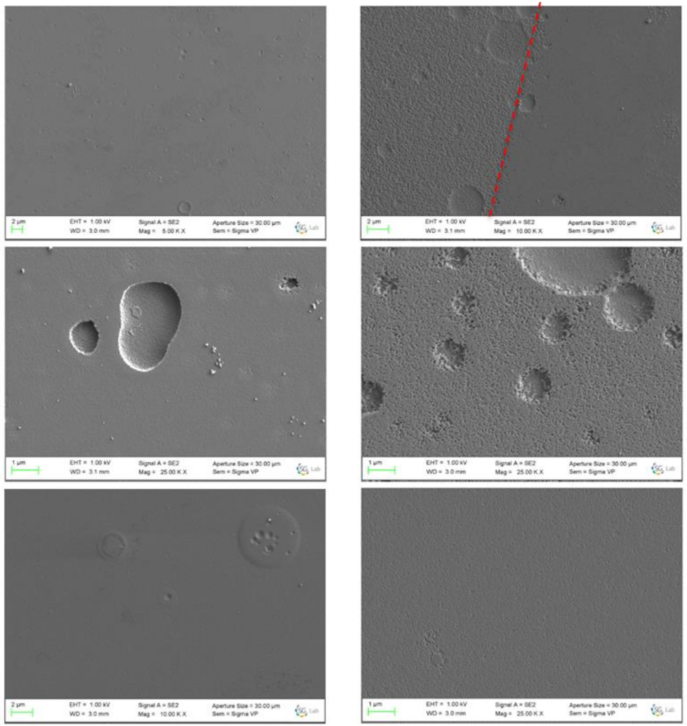


RT=Real-time; AT=Accelerated Time; AC=Autoclave Cycle

Choosing the "Right Glass"

Morphological analysis

GLASS A | GLASS B



Filling volume AT12

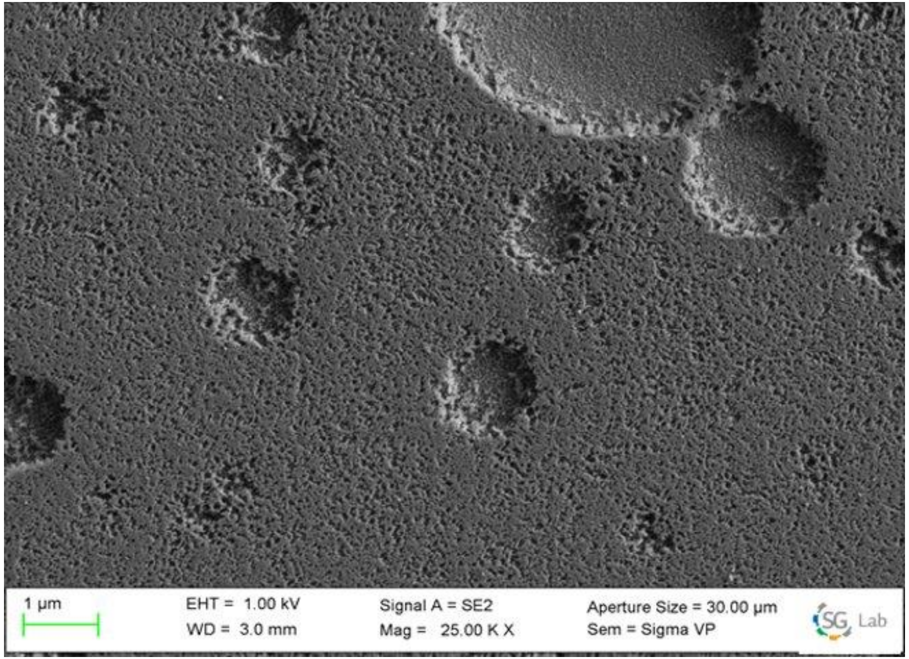
Wall near bottom area AT24

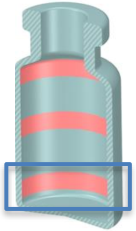
Shoulder area AT24

Morphological analysis

SEM

GLASS B





Goal achieved

Identify the glass tube that fits the Drug Product needs to support the selection rationale of the glass container system

Take home messages

- **Hydrolytic Resistance** value is not a reliable indicator of corrosion/delamination propensity
- **Real time stability** testing provides the most reliable data related to glass corrosion
- Acceleration of glass durability test by **autoclave** does not accurately predict and simulate the surface changes for low temperature glass storage (e.g. 25°C)

PURPOSE

Investigate the impact of processes and treatments on glass container durability

Screening Study → USP <1660>

USP <1660> provides advice on the *evaluation of the inner surface durability* for glass containers in direct contact with different pharmaceutical products

GOAL

Changes in process parameters do not affect glass durability → improvement of the risk assessment rationale

Case Study: impact of processes and treatments

Screening Conditions

- Different Depyrogenation parameters
- Filling with 0.9% KCl pH 8.0 at 90% of brimful capacity
- Autoclave cycle (1h, 121 °C)
- Accelerated stability (40 °C ± 2 °C / 75% RH ± 5% RH)

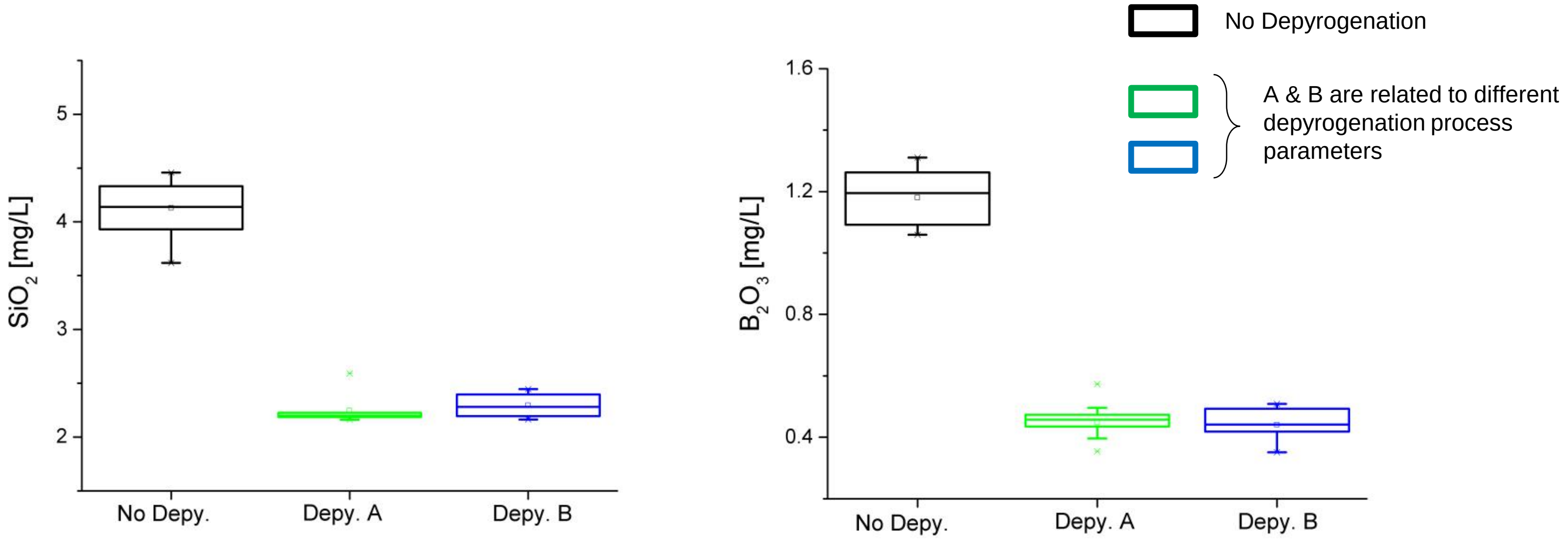
Surface evaluation and morphological analysis

- Light Microscopy DIC (Differential Interference Contrast)
- High resolution inspection of inner surface morphology by SEM (Scanning Electron Microscopy)

- ICP-OES (Al, B, Si, Ca quantitative analysis)
- pH measurements

- Visual Inspection (EP 2.9.20 Particulate contamination: Visible Particles)

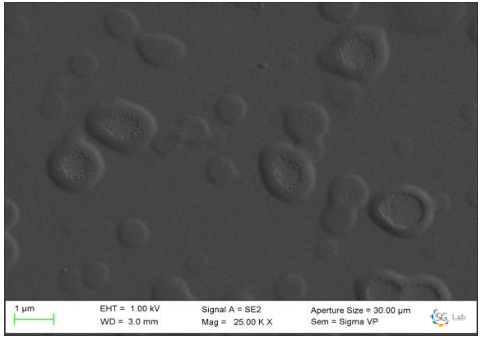
Case Study: impact of processes and treatments



SiO_2 and B_2O_3 extracted after 6 months of accelerated stability [40 ˚C ± 2 ˚C and 75% RH ± 5% RH]

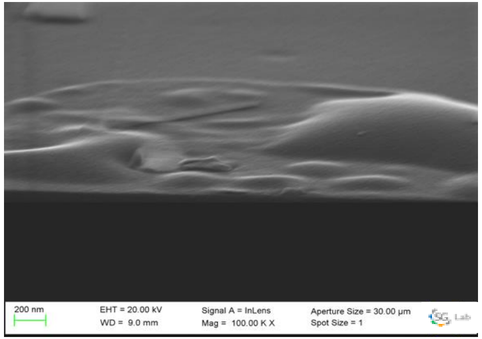
pH MEASUREMENT

	No Depy.	Depy A	Depy B
Autoclave	8.4	7.8	8.0
T1	8.2	7.8	7.8
T3	8.0	7.7	7.8
T6	8.2	7.9	7.9



Elements present in the extract solution: SiO_2 > Na_2O+K_2O > B_2O_3 > $CaO+BaO$ > Al_2O_3

SEM CROSS-SECTION



Final pH:

Acidic contribution
+
Basic contribution
+
Amphoteric contribution

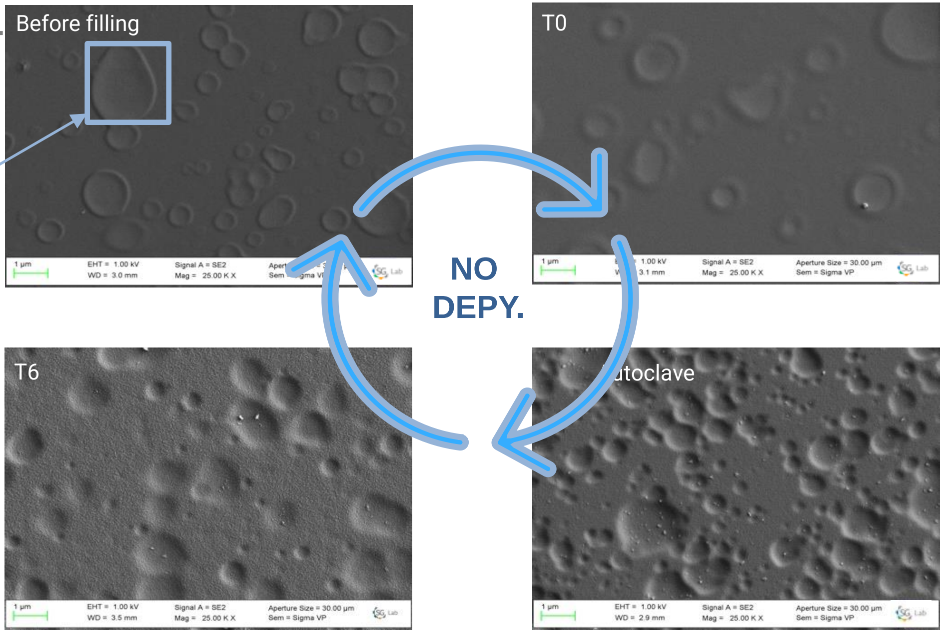
Morphological analysis

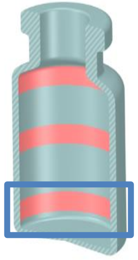
SEM

$NaBO_2$

$Na_2B_4O_7$

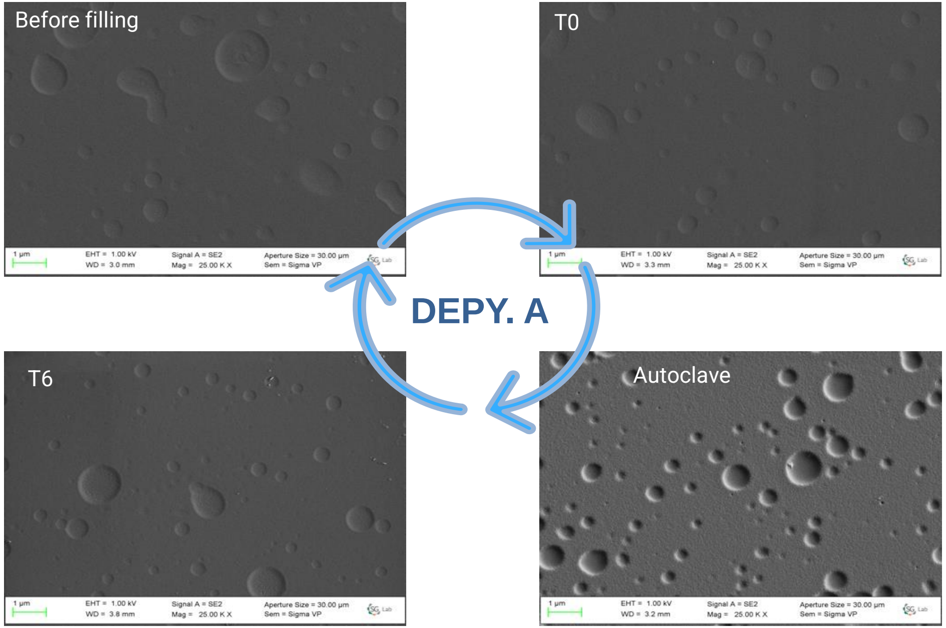
Alkali borates, highly water soluble

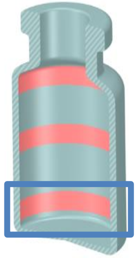




Morphological analysis

SEM





Goal achieved

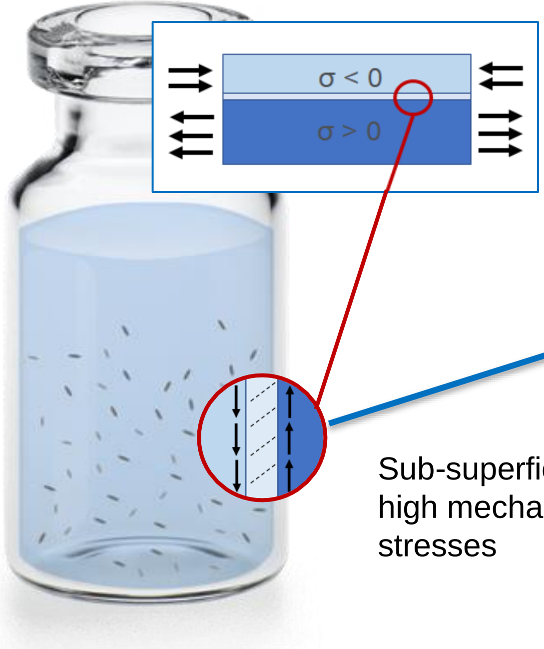
Changes in process parameters do not affect glass durability

Take home messages

- **Screening method can help to evaluate the impact of processes (e.g. sterilization, depyrogenation) on glass durability**
- **For this specific case, washing and depyrogenation do not directly affect glass durability**
- **Risk assessment process can be improved including glass durability attributes**

Glass Delamination

Delamination is the term used to define the detachment of glass flakes (lamellae) from the inner surface of containers, and their macroscopic appearance as a suspension in the contained solution.



Sub-superficial high mechanical stresses

- High temperature burners flames may cause strong evaporation of alkaline and borate species, exposing areas with a silica-rich surface (i.e. bottom, shoulder).
- Alkaline solutions strongly affect the dissolution of the silica layer. SiO_2 in the extraction liquid increases steeply.
- When SiO_2 solubility limits are exceeded, suspended particles shall appear.
- Depyrogenation seems to have no effect on the generation of flakes.
- The presence of silica complexing agents (i.e. glutaric acid, citric acid EDTA, phosphates,…) favor delamination.
- pH is a key factor: alkaline solutions increases the risk of delamination but the relationship is not completely clear.

Additional proprieties with internal and/or external treatment/coating

Additional proprieties with internal and/or external treatment/coating

Tubular glass containers can properly be internally and/or externally treated or coated to give additional properties:

- Sulphur treatment;
- Siliconization;
- Ion Exchange;
- CVD, PECVD, PICVD

Additional proprieties with internal and/or external treatment/coating

Sulphur Treatment

$$(NH_4)_2SO_4 \rightarrow NH_4HSO_4 + NH_3$$

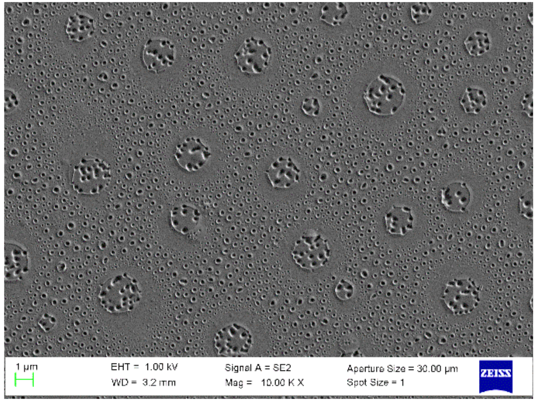
$$NH_4HSO_4 + 2\ Si\text{-}ONa \rightarrow Si\text{-}OH + Na_2SO_4 + NH_3$$

$$2\ SiOH \rightarrow Si\text{-}O\text{-}Si + H_2O$$

At high temperature ammonium sulphate decompones and reacts with surface alkalies forming water soluble sulphate salts.
A diffused opalescence gives visual evidence of the treatment.

After washing, a silica enriched layer is formed which acts as a barrier to further alkali extraction.

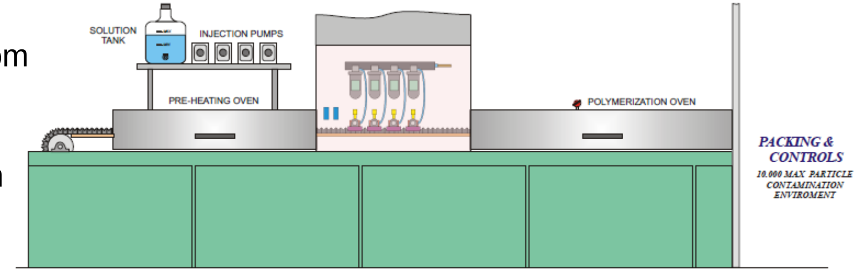
Applicable to both Type I and Type III glass. The thickness of the modified layer depends on process conditions. The glass cannot be reused.



Siliconization

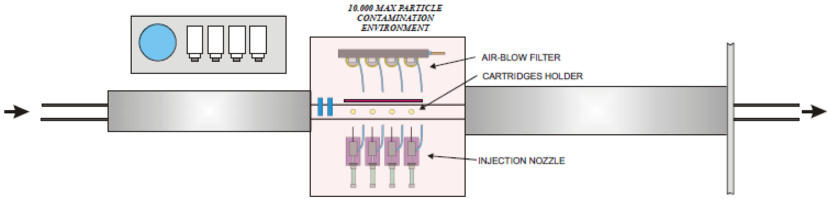
Is usually made to favor the complete extraction of the drug from the container and the plunger gliding in syringes.

Silicone coating contributes to reduce the alkali extraction from glass and to confer a strong hydrophobic effect.



Clean siliconized cartridges and syringes with cured silicone can be produced by using two different technologies:

- Siliconization by immersion
- Internal siliconization by spraying system



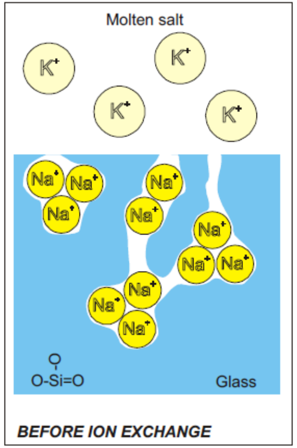
Internal siliconization by spray technology

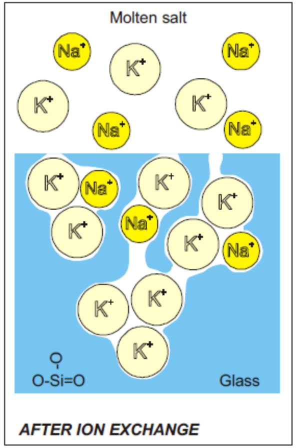
Additional proprieties with internal and/or external treatment/coating

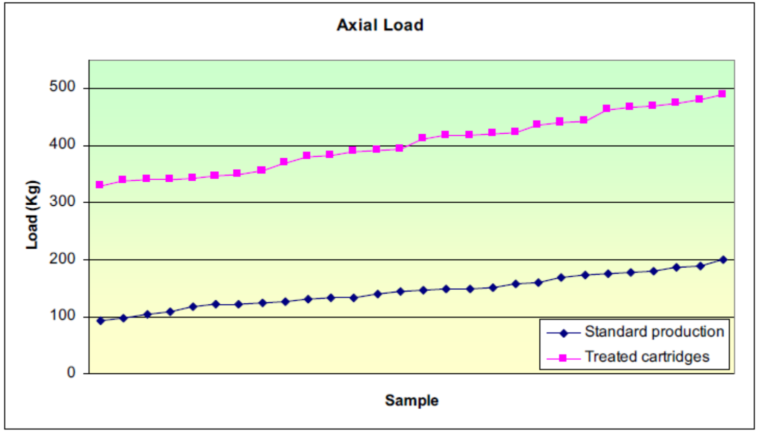
Chemical Strengthening - Ion Exchange

Is obtained by a particular process that helps the substitution of Na^+ ions present on the glass surface with K^+ ions.

This exchange put in compression the glass surface so increasing the overall mechanical resistance of the container.







Deposition Processes: CVD - PECVD - PICVD

The chemical vapor deposition (CVD) refers to a gas decomposition process born in Germany in 1938 for the production of thin SiO_2 anti-reflective coatings for optics.
Gaseous silicon tetrachloride $SiCl_4$ fired in a flame of hydrogen and oxygen forms quartz glass SiO_2 to be deposited in thin layers onto the glass substrate.

$$SiCl_4 + 2H_2 + O_2 = SiO_2 + 4HCl$$

The same process allows also the production of the preforms (rods) of synthetic quartz glass for optical glass fibers for telecommunication.

When the hydrogen-oxygen flame is replaced with a plasma source, we obtain the Plasma Enhanced Chemical Vapor Deposition (PECVD) and the Plasma Impulse Chemical Vapor Deposition (PICVD). Both processes are used for coating the internal surface of glass vials with a thin layer of SiO_2.

Molded Vials

Molded vials

Molded

- Mechanically stronger
- Better for large vials (>100 ml)

PRO's

PRO's

Tubular

- Better Walls and Finish dimensional consistency
- Cosmetically superior
- No Seams
- Facilitates inspection
- Weighs less
- Easier to label
- Lower tooling costs
- Better for Lyophilization

>100 mL

< 20 mL

< 1 mL*

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THANK YOU FOR YOUR ATTENTION!

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