Best Practices for Glass Primary Containers

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Glass Science

Glass Types, Physical Properties, Chemical Properties

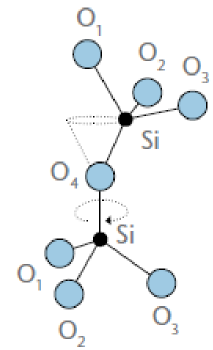
What is Glass?

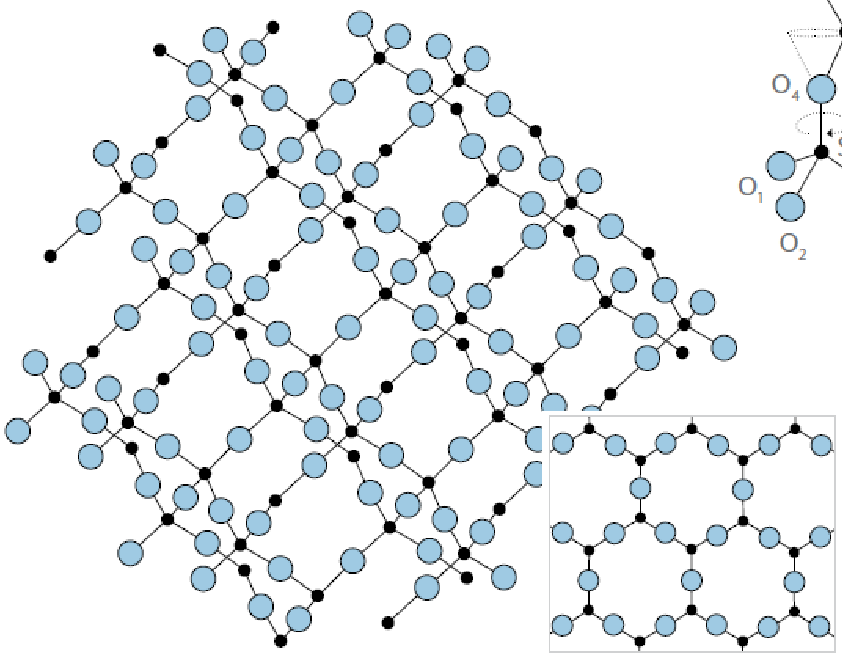
- Tamman (1932): Solid, non-crystalline materials are in the glass state
- Uhlmann (1972): Glasses are amorphous material with a crystalline fraction
- Scholze (1988): Glass is a frozen supercooled liquid

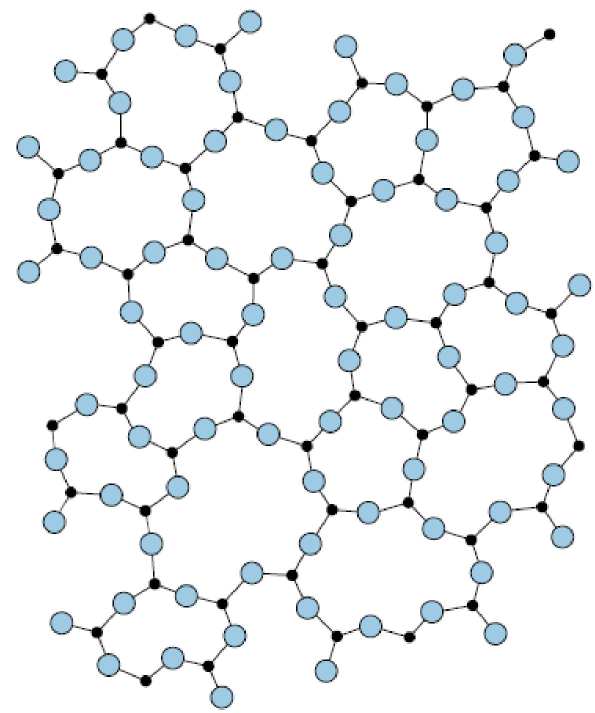
Quartz Glass

crystalline quartz
opaque crystal

amorphous quartz
transparent glass

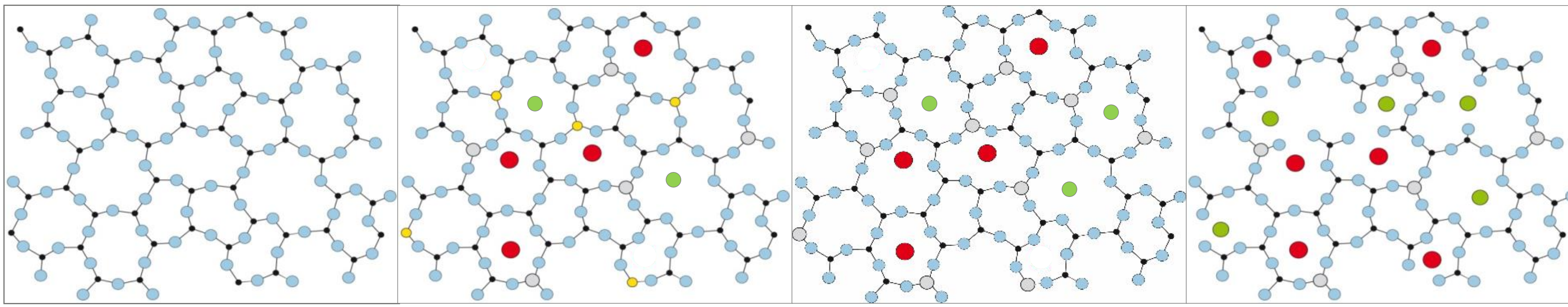






Glass Types

Quartz | Borosilicate | Aluminosilicate | Soda-lime



Quartz
- Oxygen
- Silicon

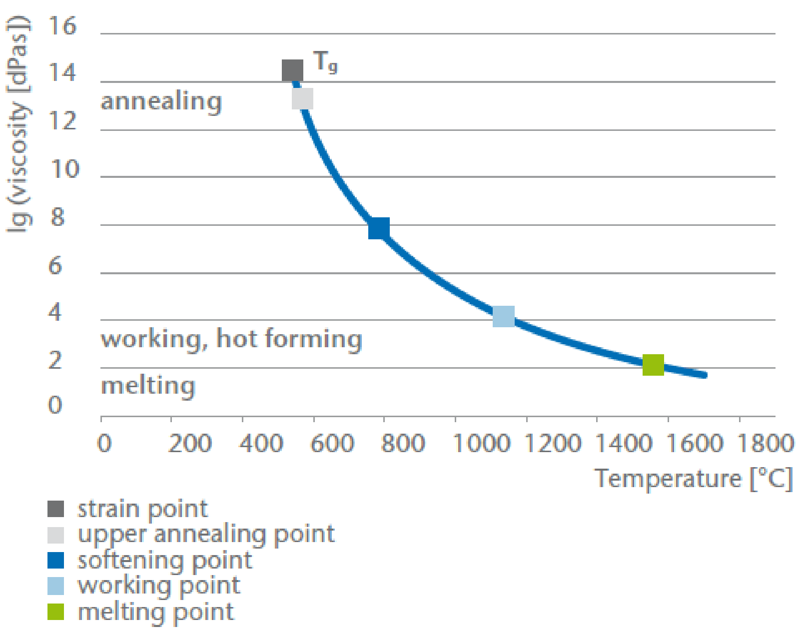
Borosilicate
- Oxygen
- Silicon
- Boron
- Sodium
- Calcium
- Aluminum

Aluminosilicate
- Oxygen
- Silicon
- Sodium
- Calcium
- Aluminum

Soda-lime
- Oxygen
- Silicon
- Sodium
- Calcium
- Aluminum

Physical Properties

Viscosity is the resistance to flow.
The higher the resistance to flow the higher the viscosity



	Viscosity η (dPas)
Water	10^{-2}
Olive oil	10^{0}
Honey	10^{2}
Glass melt (1600 °C)	10^{2}
Glass at T_g (565 °C)	$10^{13.5 - 14.5}$
Glass at RT (25 °C)	10^{19}

FIOLAX® clear

Technical Data

Glass Type/Application	Neutral glass tubing, chemically highly resistant Pharmaceutical primary packaging		
Physical Data	Coefficient of mean linear thermal expansion α (20°C;300°C) acc. to ISO 7991	4.9	$\cdot 10^{-6} K^{-1}$
	Transformation Temperature T_g	565	°C
	Glass temperature at viscosity η in dPa·s		
	10^{13} (annealing point)	565	°C
	$10^{7.6}$ (softening point)	785	°C
	10^{4} (working point)	1160	°C
	Density ρ at 25°C	2.34	$g \cdot cm^{-3}$

Physical Properties

The coefficient of thermal expansion (CTE or α) describes how much a material expands when it is heated. The smaller the CTE the less it expands.

Glass sort	α [10^{-6}/°C]	Temperature range [°C]
Glass ceramic (ZERODUR®)	< 0.1	0….100
Glass ceramic (CERAN®)	< 1	20….700
Quartz glass	< 1	20….300
Borosilicate glass (BORO-8330™)	3.3	20….300
Borosilicate glass (FIOLAX® clear)	4.9	20….300
Soda lime glass	9…9.6	20….300
Alumina	≈ 20	0….50

$$\alpha = \frac{\Delta L}{L}\cdot\frac{1}{\Delta T} = \frac{1}{L}\cdot\frac{L' - L}{T' - T}$$

The thermal expansion is influenced by

- the composition
- the cooling conditions

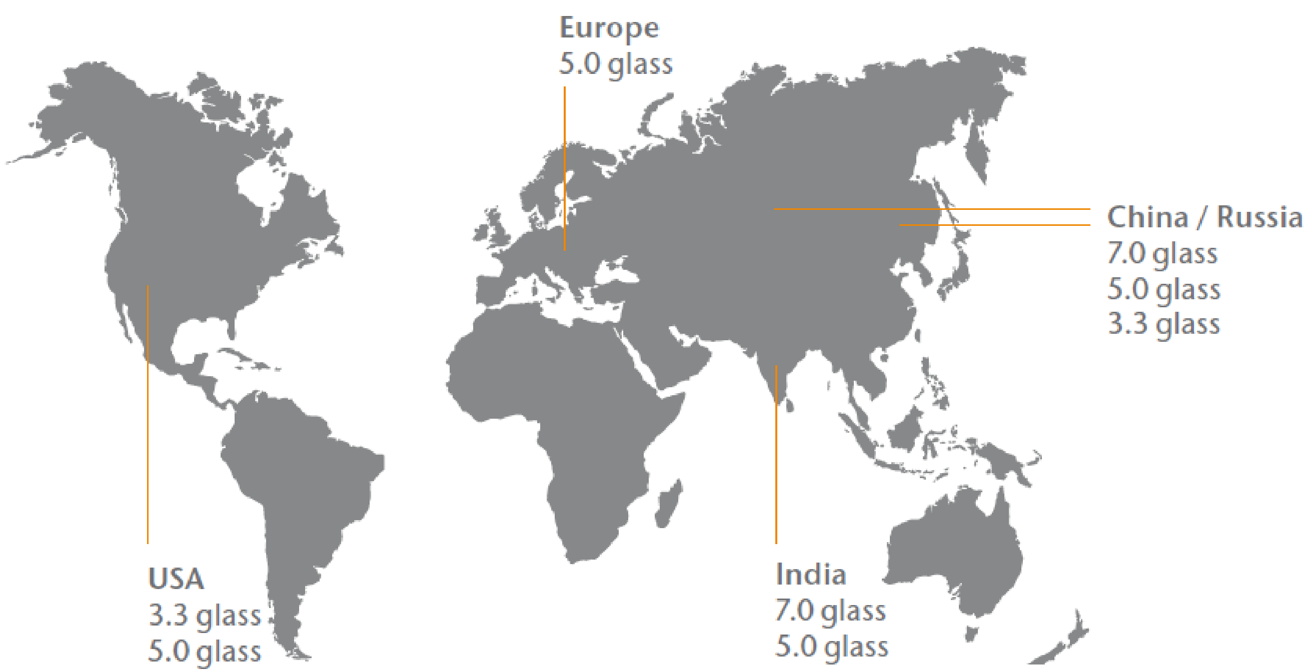
Physical Properties

Glass Type	Borosilicate 3.3	Borosilicate 5.0	Borosilicate 7.0
Composition			
SiO_2	80 - 82	72 - 75	70 - 74
B_2O_3	12 - 13	9 - 11	5 - 8
Al_2O_3	2	5 -7	4 - 6.5
Na_2O/K_2O	4	6 - 9	9 - 12
MgO/CaO/BaO	0	1 - 3	5 - 7
Physical Data			
Working Point	1,260 °C	1,145 - 1,170 °C	1,030 - 1,100 °C
Transformation Temperature (Tg)	525 °C	565 - 575 °C	550 - 580 °C
Mean Coefficient of Thermal Expansion (CTE)	3.3	4.9 - 5.5	6.3 - 7.5

Physical Properties

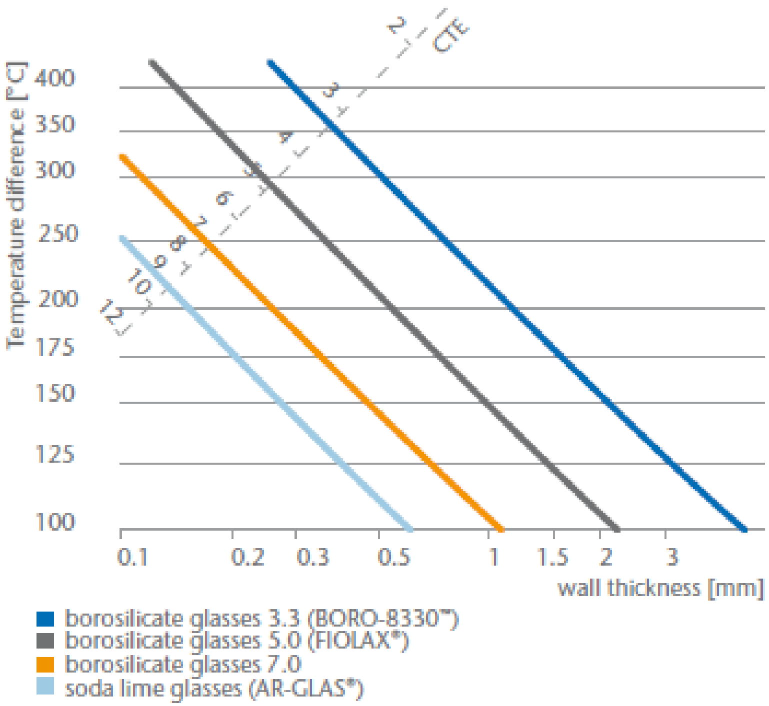
There are 3 groups of Type I glass tubing

- 3.3 glass is mainly used in the USA.
- 5.0 glass („FIOLAX® type", neutral glass) is the most widely used pharmaceutical glass worldwide.
- 7.0 glass is mainly used in India, China, Russia.



Physical Propertes

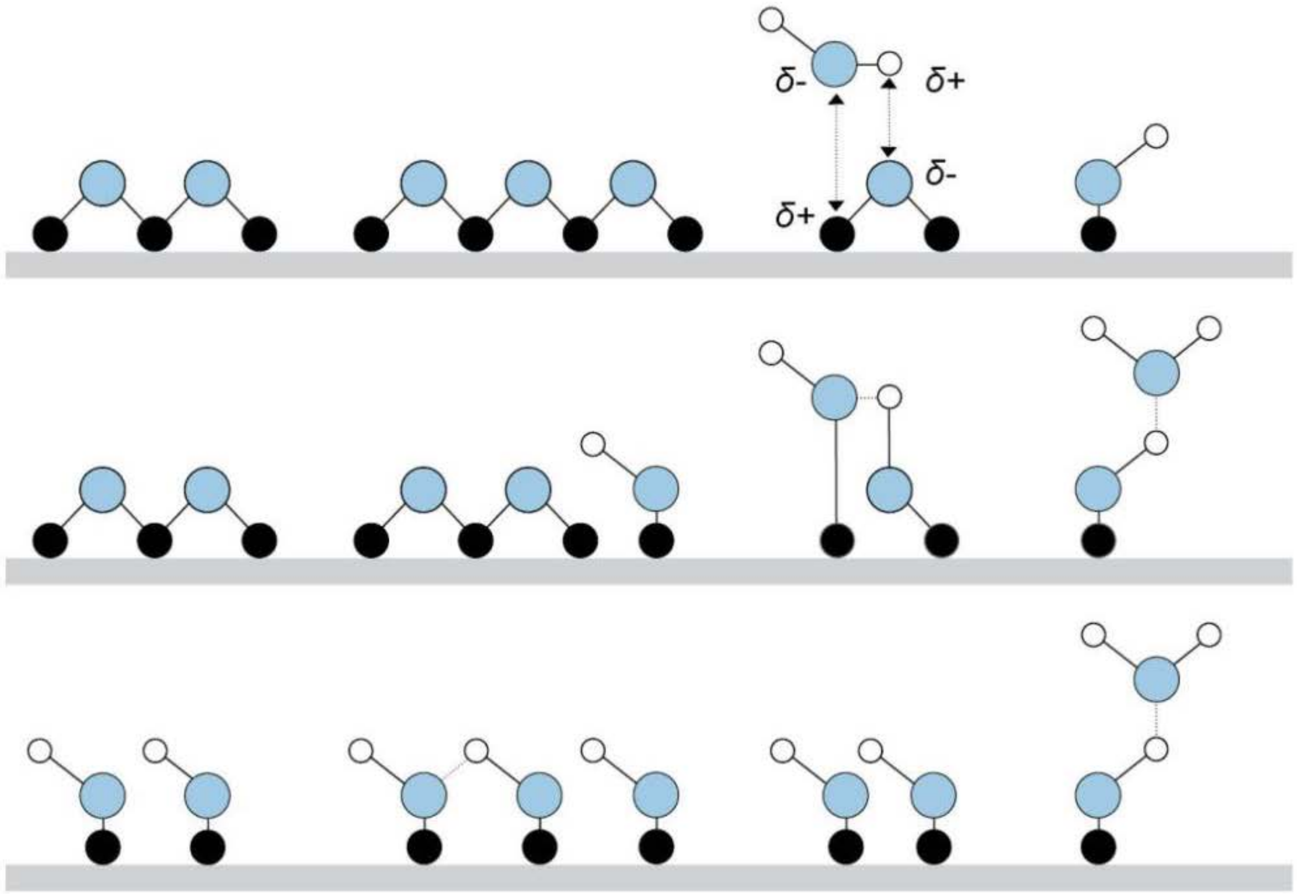
Glass has a very low thermal conductivity. The thermal shock resistance depends on both the CTE and the wall thickness.



The smaller the CTE the higher the thermal shock resistance.

The thinner the wall the higher the thermal shock resistance.

Physical Properties



Hot glass surface:
Scratch sensitive!

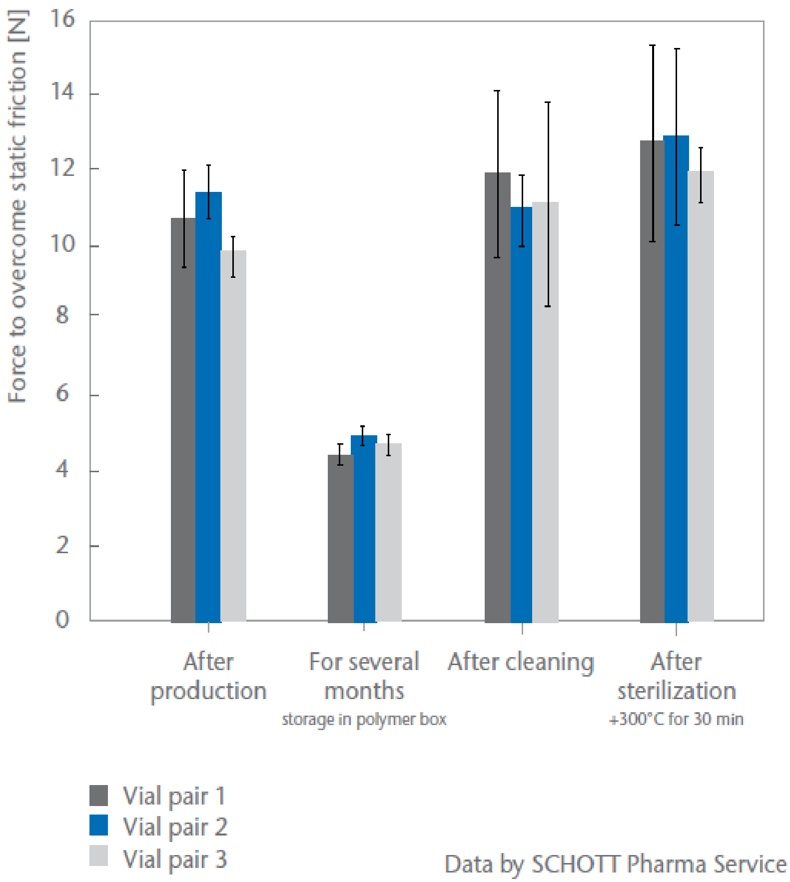
Adsorption of humidity
during cooling
(air contact, coating)

Saturated glass surface
„water skin“

- Better scratch resistance

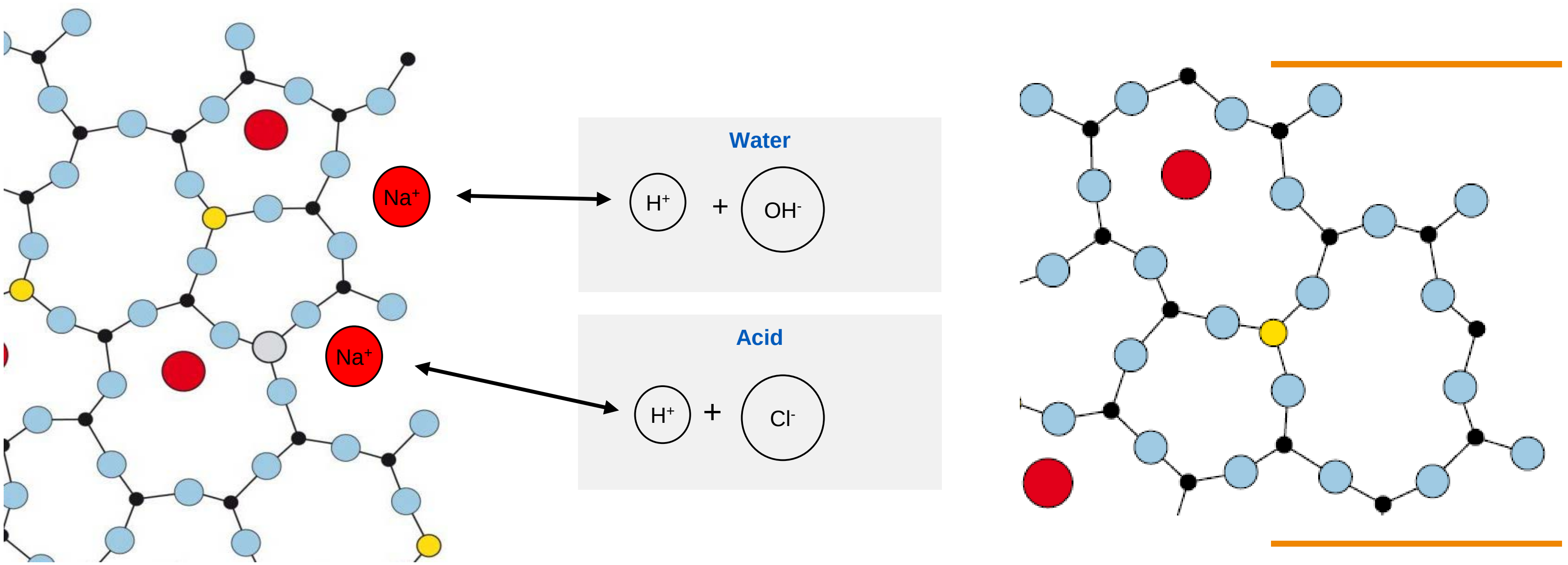
Physical Properties

Friction measurements prove the existence of the protection layer



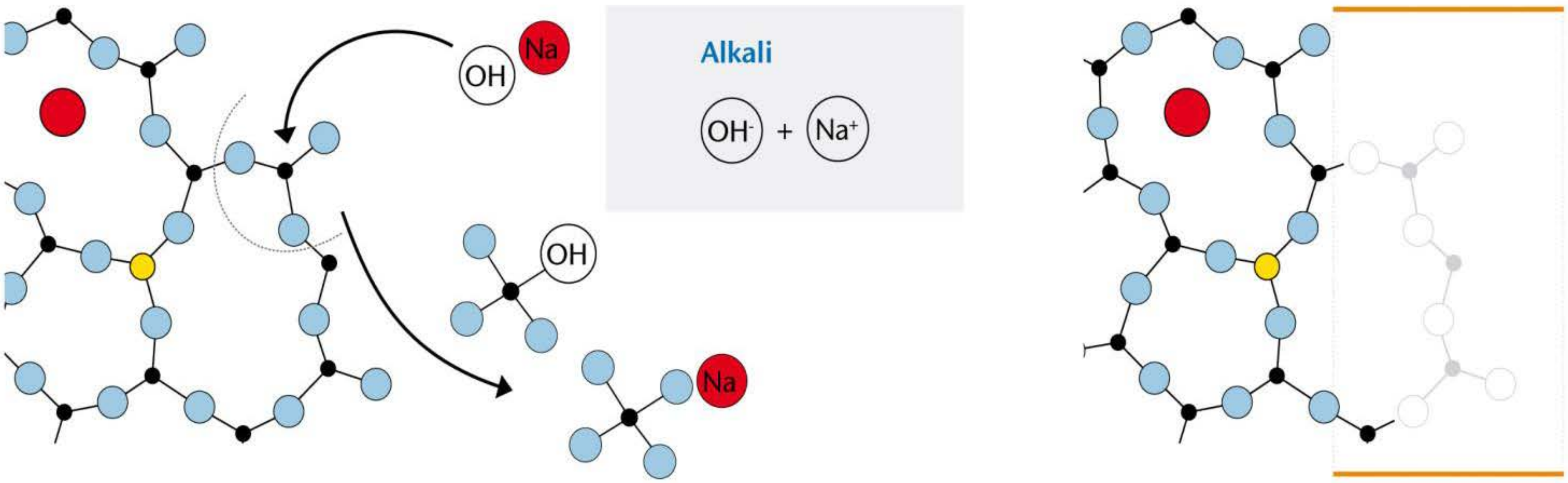
Chemical Properties

Chemical stability is the resistance of the glass to chemical attack by defined agents: Water and acid attack cause an ion exchange



Chemical Properties

Chemical stability is the resistance of the glass to chemical attack by defined agents: Alkali attack causes a dissolution of the network



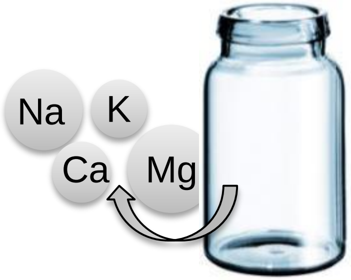
Chemical Properties

The quality of a glass is assessed by its hydrolytic stability

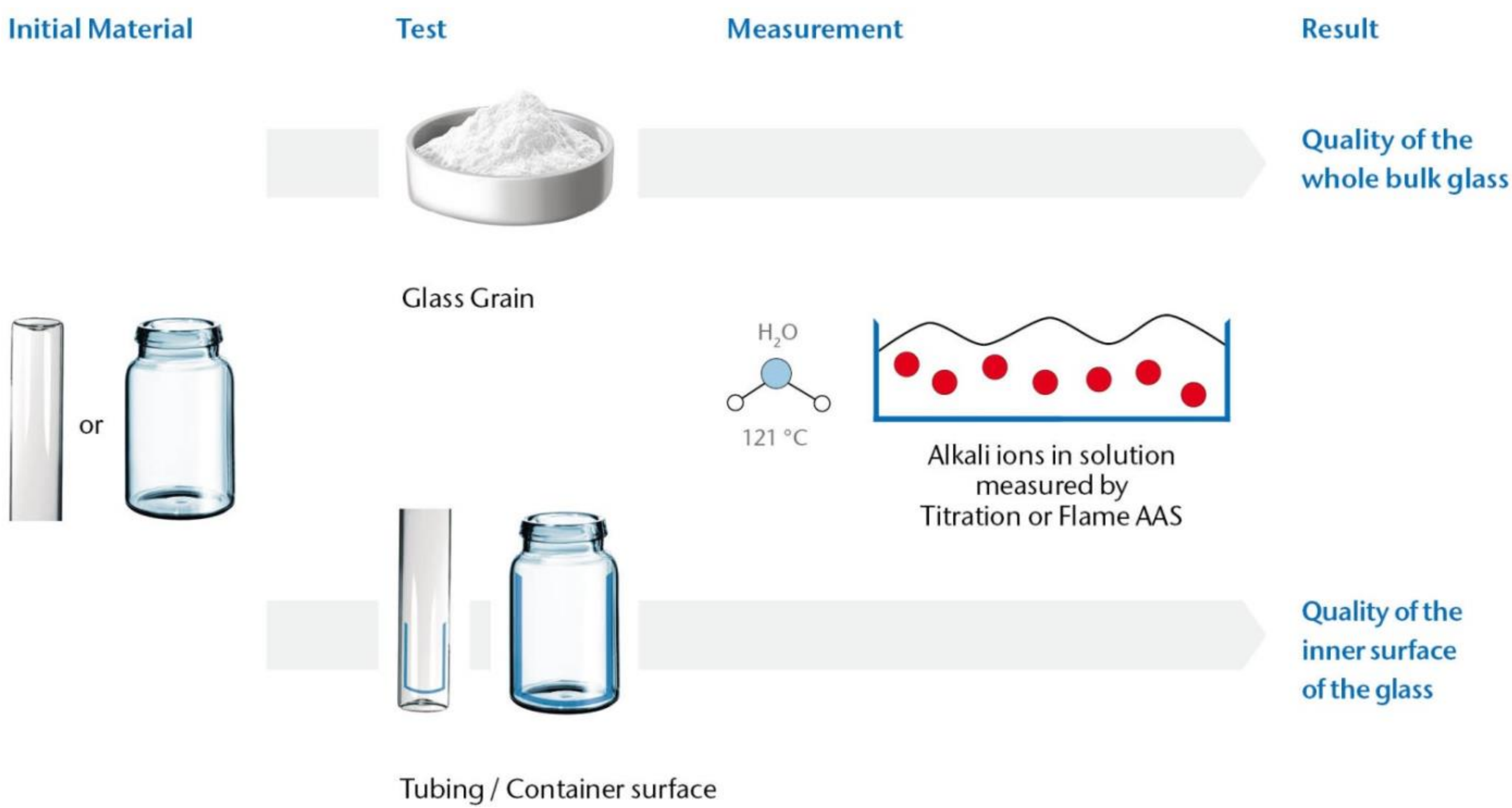
According to Ph. Eur. the hydrolytic stability is defined as follows:

The hydrolytic stability of glass containers for pharmaceutical use is 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 or **glass grains** and water.

Soluble mineral substances can be: Na, K, Ca, Ba, Mg



Chemical Properties



Take Away Messages

- Glass consists of network formers (Si, B, Al, O, …) as well as network modifiers (Na, K, Ca, Mg, …).
- Thermal expansion: Glasses can be categorized acc. to their CTE (e.g. 5.0 borosilicate glass). The lower the CTE the higher the thermal shock resistance.
- Chemical stability: the lower the amount of network modifiers the higher the chemical and hydrolytic resistance and the lower the interaction with the drug.
- Regulatory: The hydrolytic resistance is measured by the glass grains test and the inner surface test → borosilicate glass is type I, sodalime glass is type III.

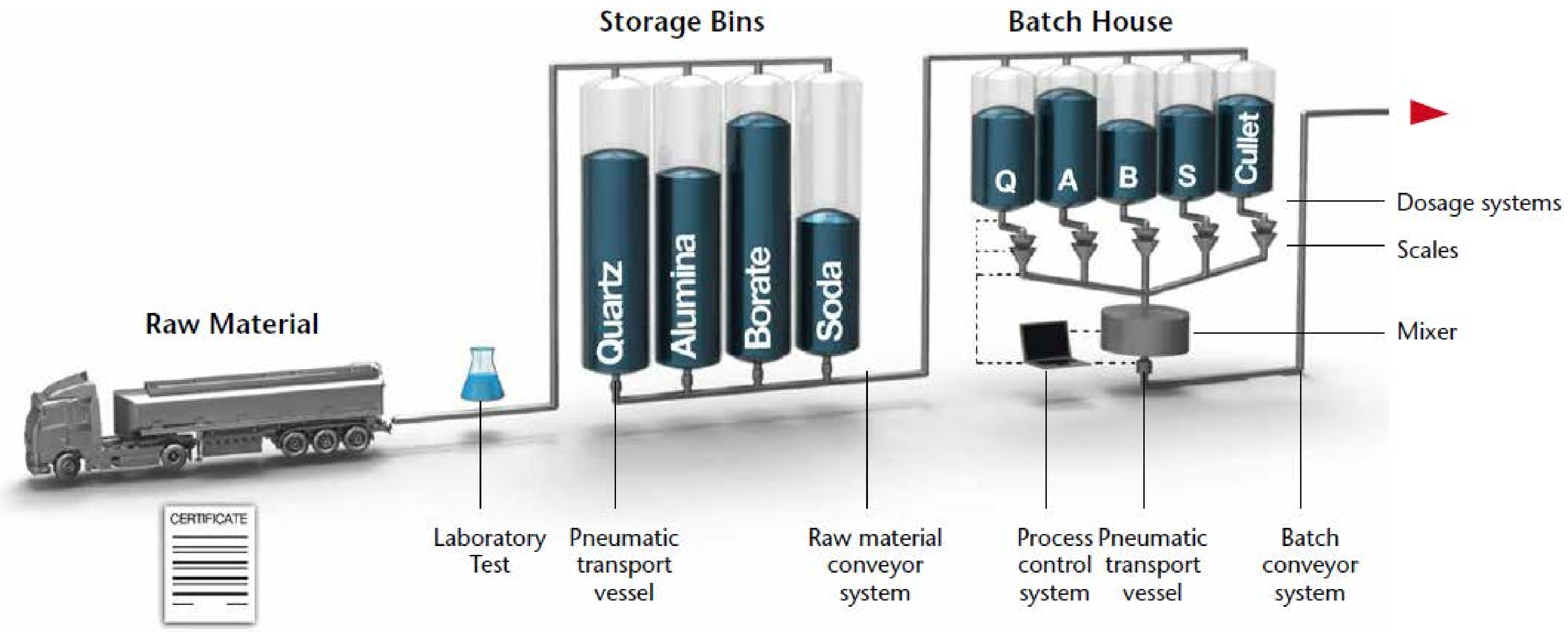
Glass Making

Glass Melting, Tubing Production, Container Production

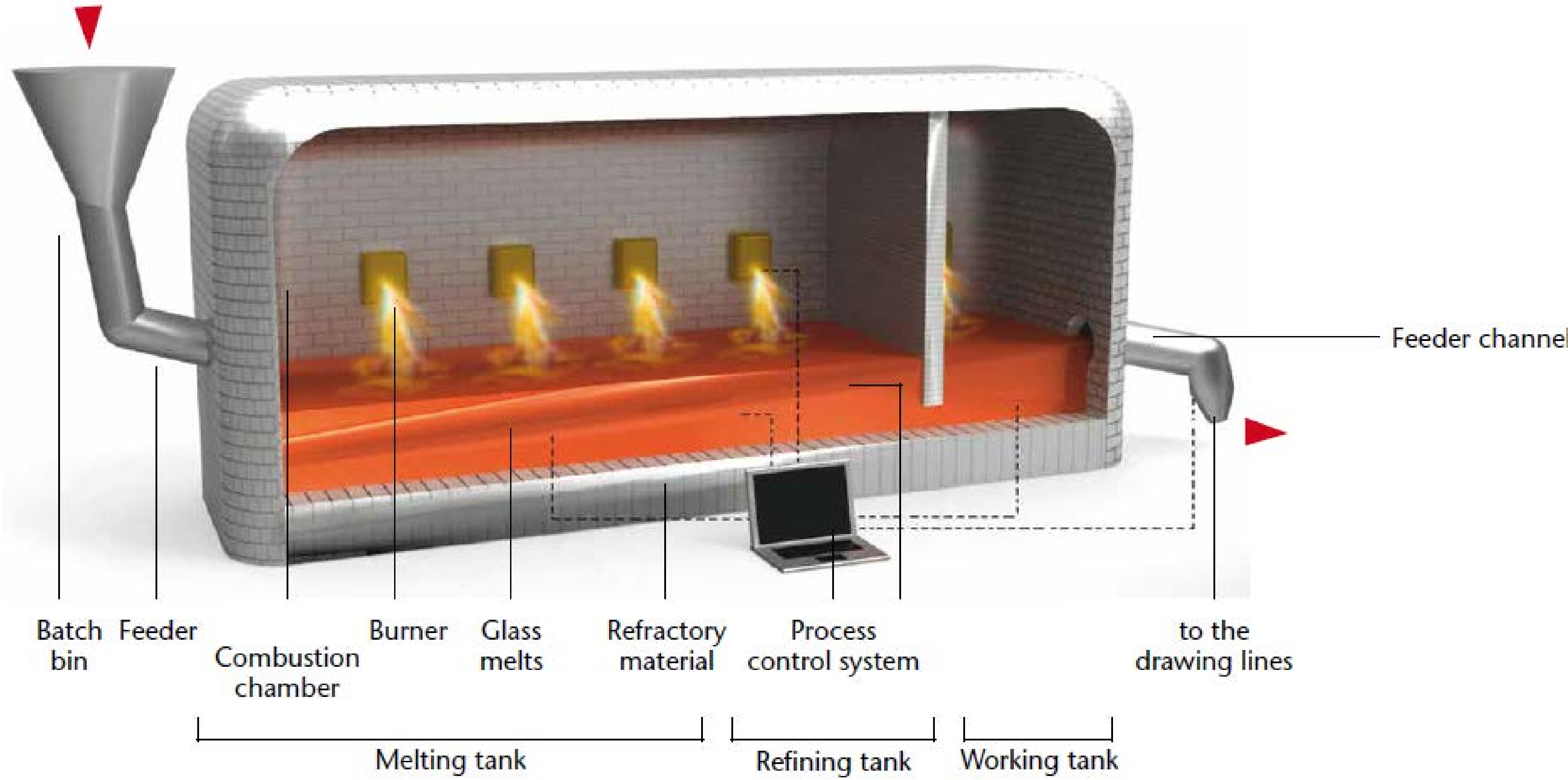
Raw Materials

Element	Raw material as found in nature	
Network formers		
Silicon (Si)	SiO_2	sand
Boron (B)	$Na_2B_4O_7$	borax
Network intermediates		
Aluminum (Al)	Al_2O_3	alumina
Network modifiers		
Sodium (Na)	Na_2CO_3	soda
Potassium (K)	K_2CO_3	potash
Calcium (Ca)	$CaCO_3$ $CaMg(CO_3)_2$	chalk, marble, limestone dolomit
Magnesium (Mg)	$MgCO_3$ $CaMg(CO_3)_2$	magnesia dolomit

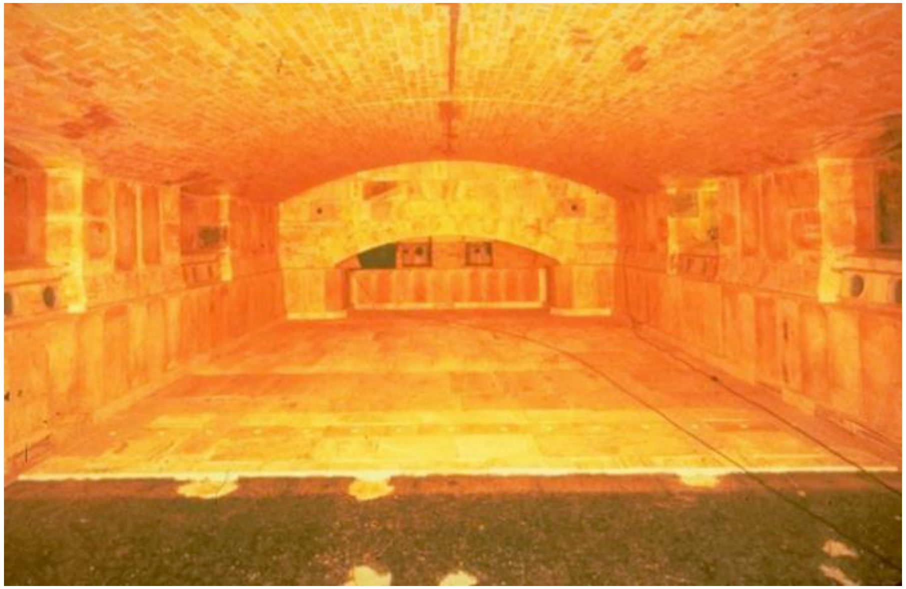
Raw Material Management



Glass Melting



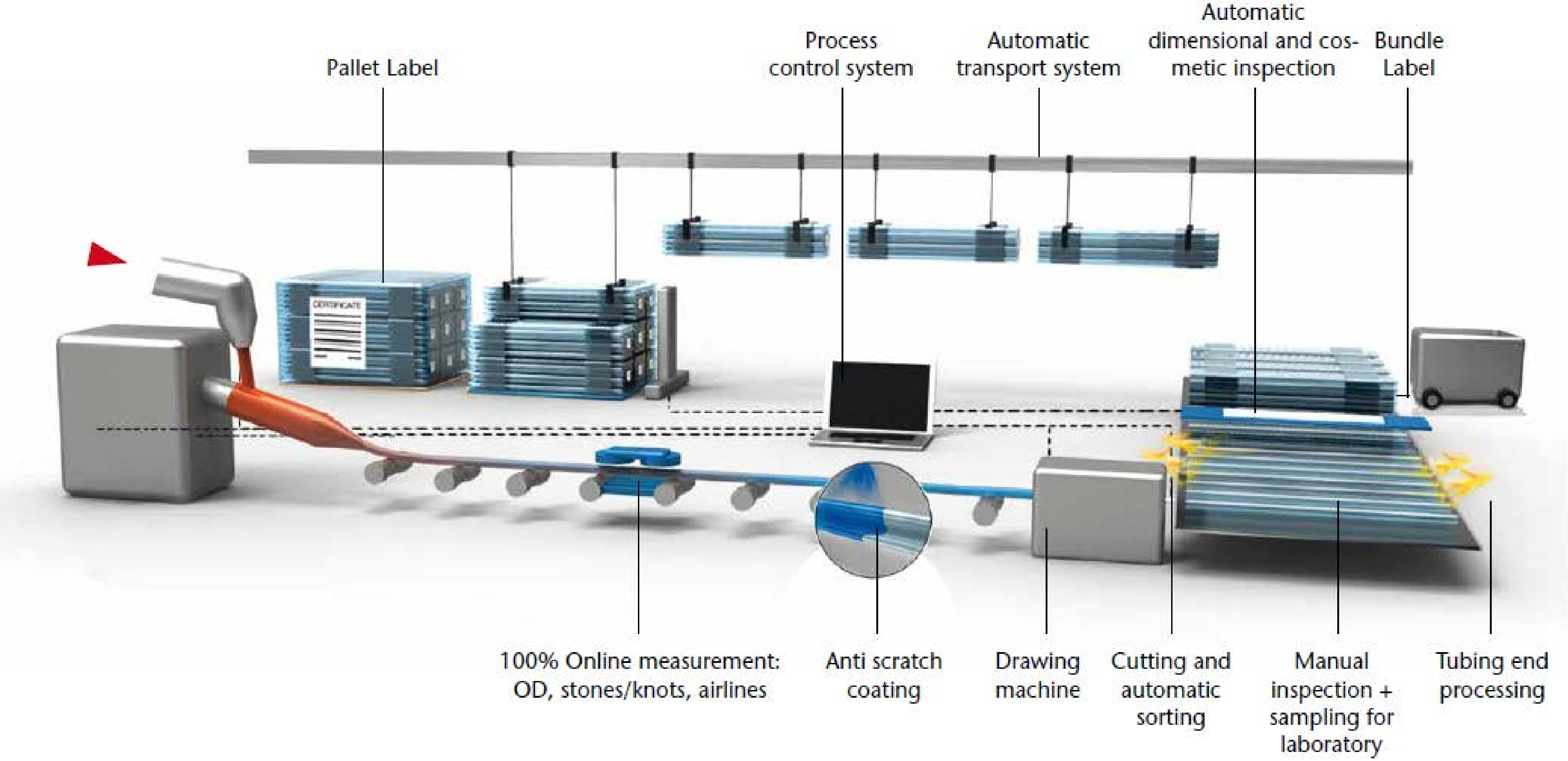
Glass Melting



Melting tank

Danner mandrel

Tube Drawing & Packaging



Tubular Glass Defects

Surface Defects from Tubing:
Stones and Knots

Stones: opaque inclusions

Knots: transparent inclusions

Source: Material that is not melted properly in the melting procedure

Stones

Knots

Tubular Glass Defects

Surface Defects from Tubing:
Airlines

Closed: elongated gaseous inclusion within the glass

Open: elongated gaseous inclusion on the glass surface

Source: Gas created during the melting process and not removed properly

Tubular Glass Defects

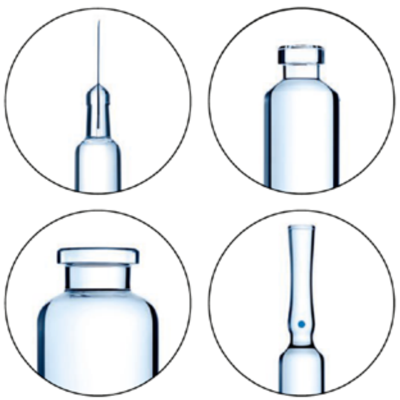
Surface Defects from Tubing:
Scratches

Scratch: constitutes a slight damage to the outer surface of the glass but it does not penetrate the glass wall

Source: A scratch can be created along the whole value chain

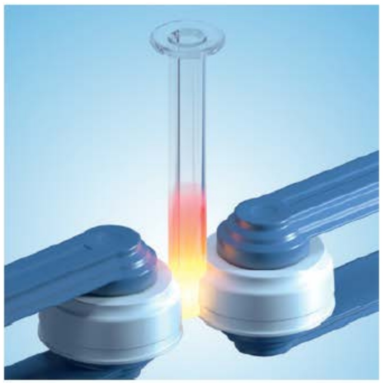
Tubular Container Value Chain

Glass Tubing → Container Manufacturing → Fill & Finish



Vial Production

Syringe Production



Forming

Needle assembly

WFI washing

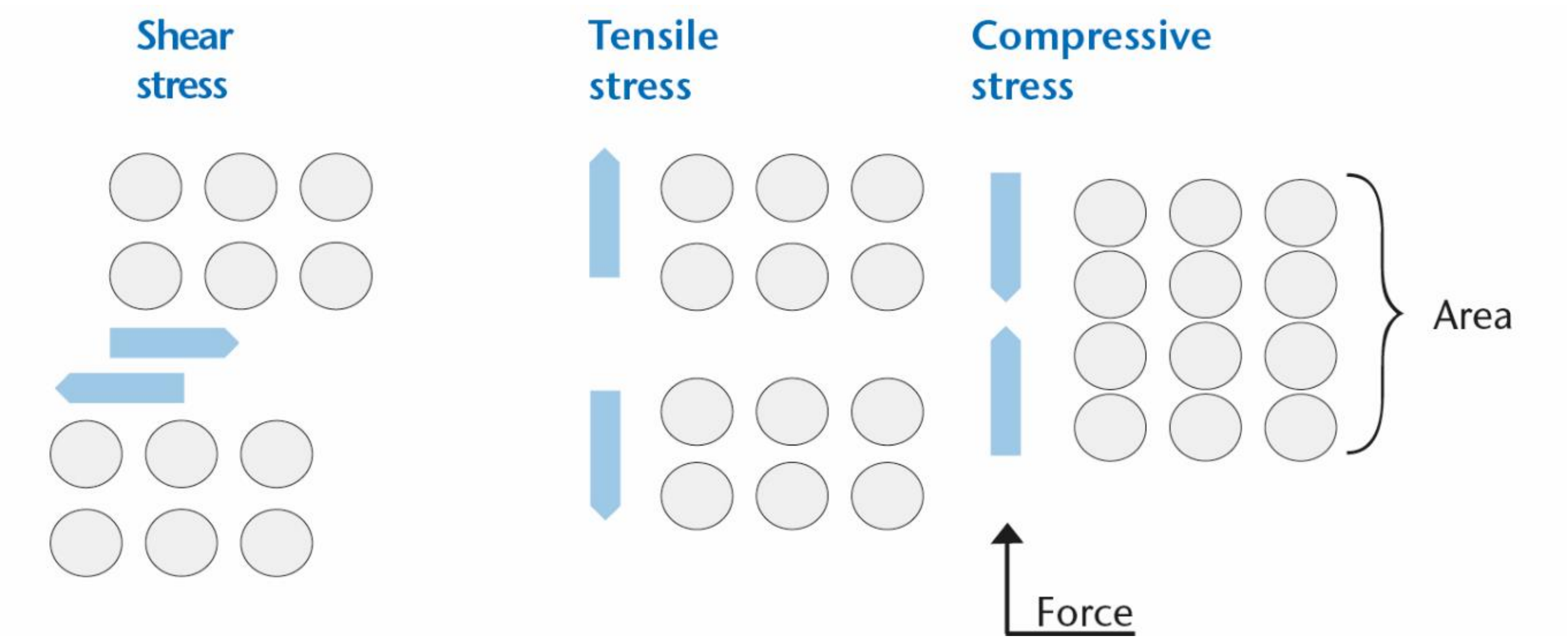
Siliconization

Closure setting

Packaging

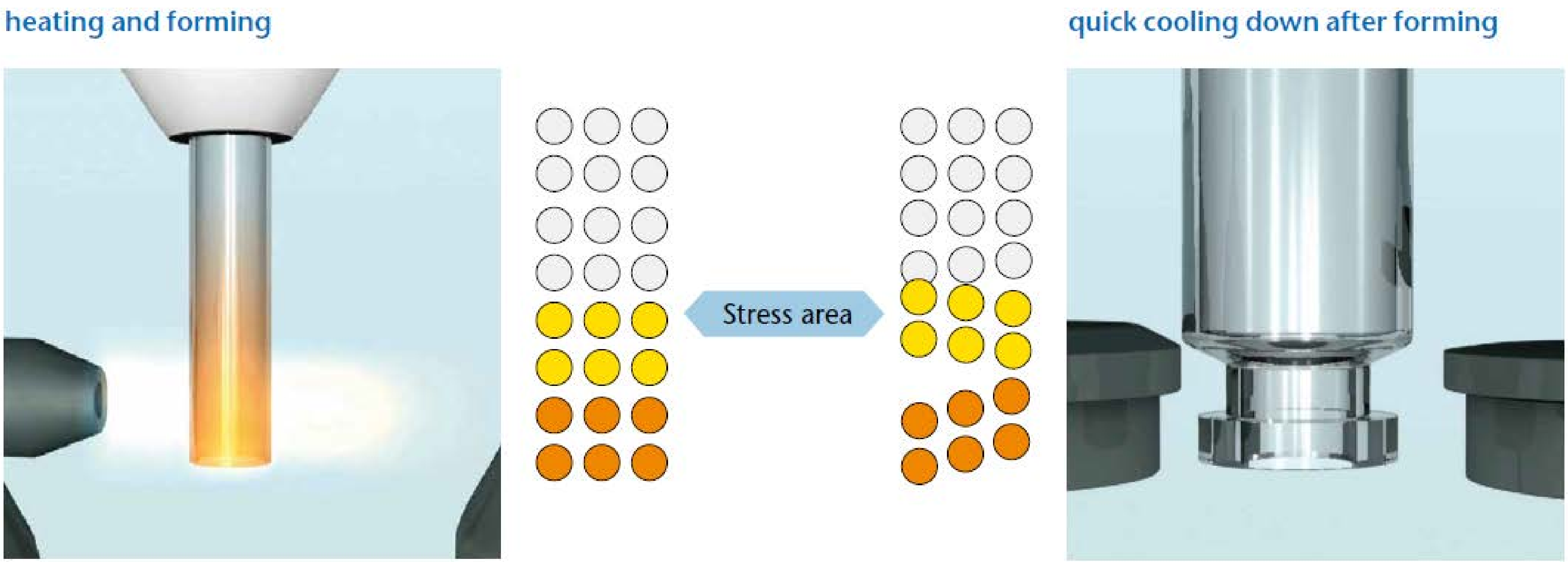
Container Production

Stress is defined as force per area.
There are three kinds of stresses described for glass:



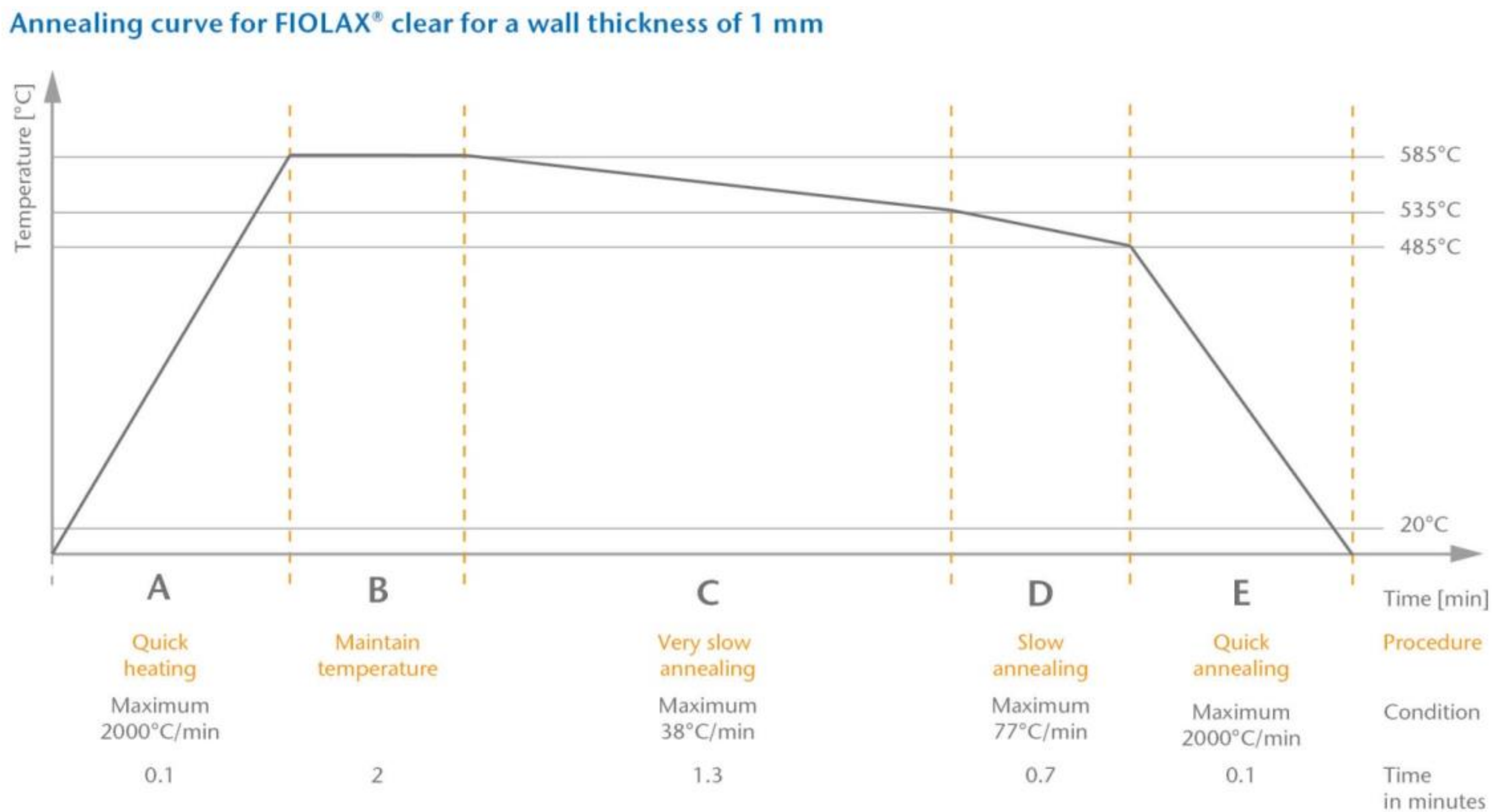
Container Production

Stress is created by partial quick cooling from temperatures above T_g.
It can only be released when heating again above T_g and cooling down slowly.



Container Production

Typical annealing curve for release of residual stress

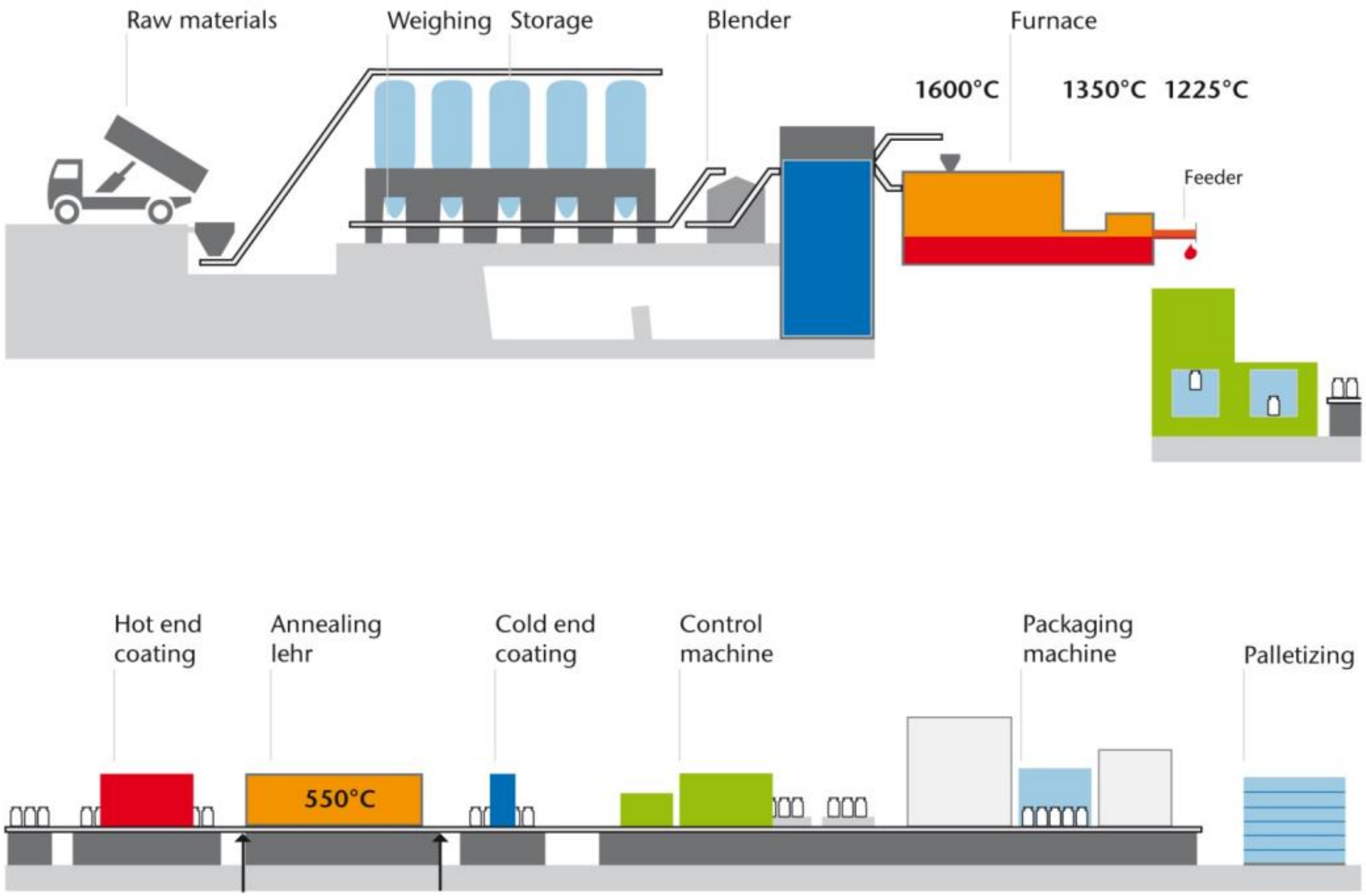


Molded Container Value Chain

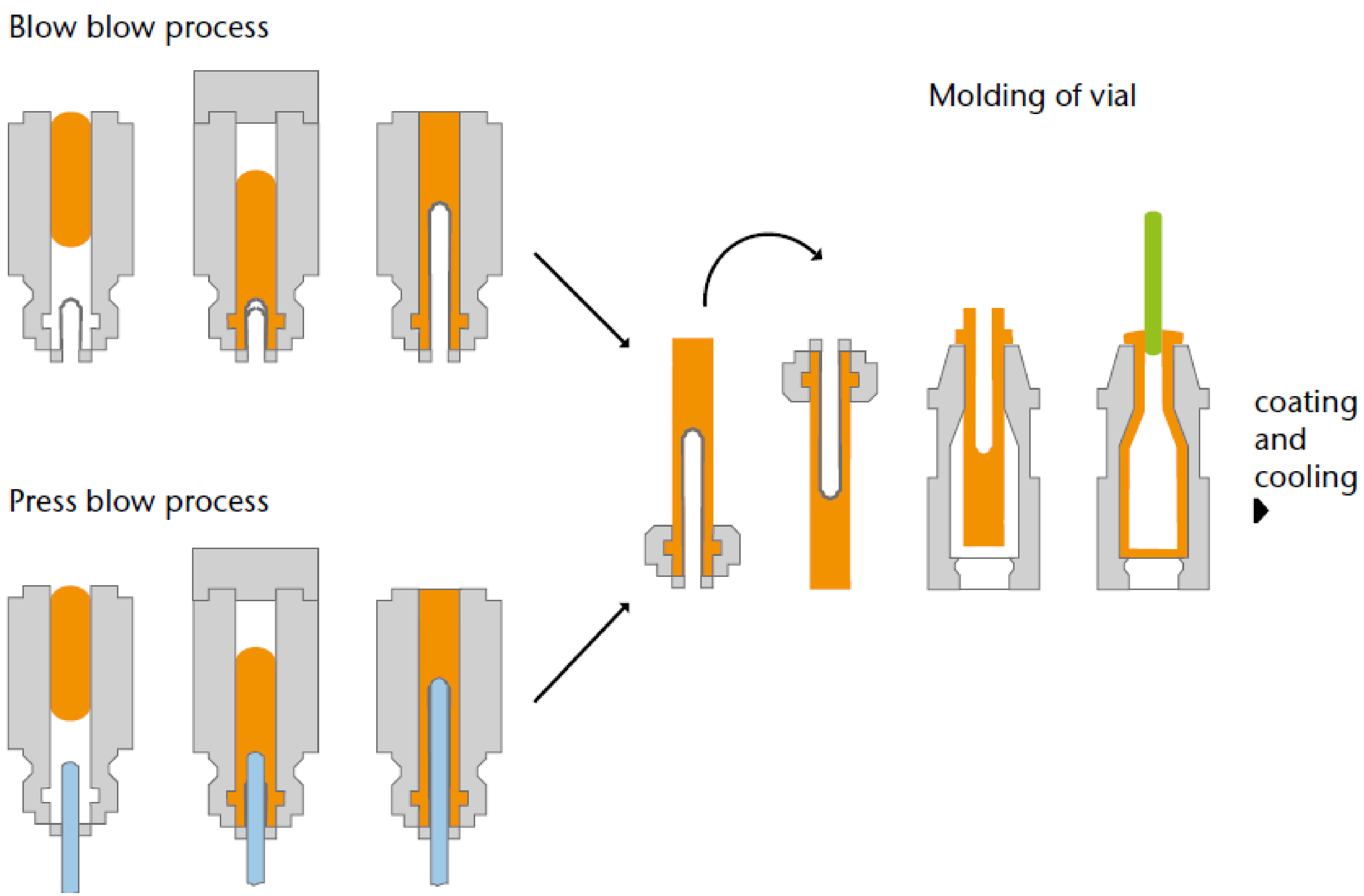
Container Manufacturing

Fill & Finish

Molded Containers



Molded Containers



Molded Containers

Molded | Tubing

52 gramm | 40 gramm

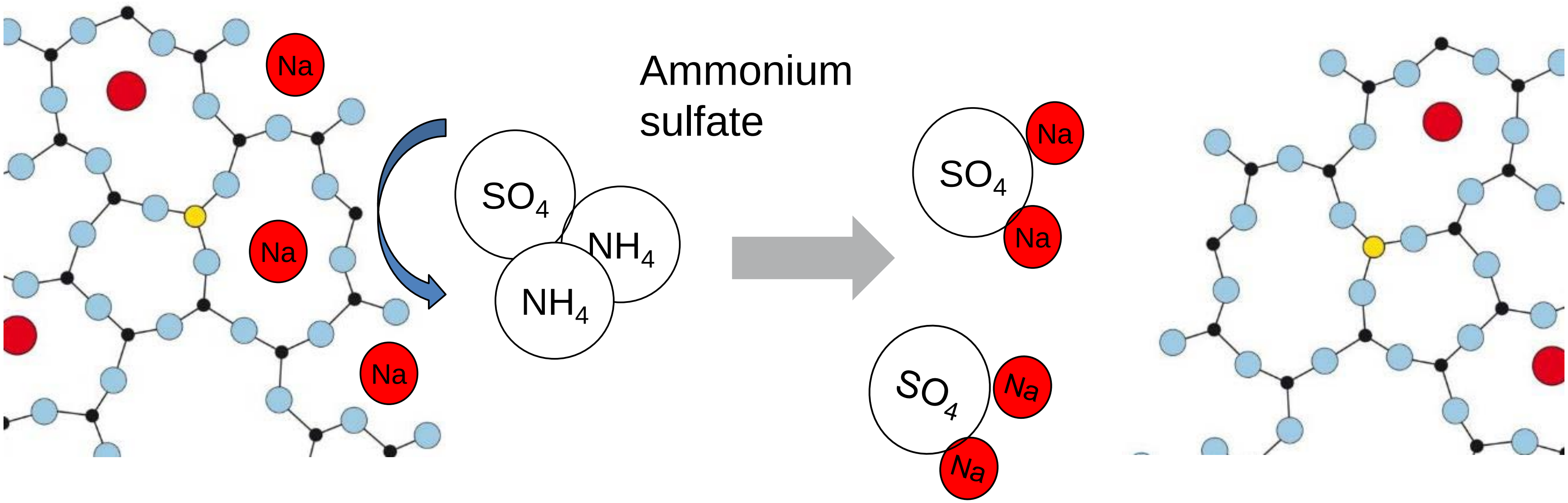
Molded

Tubing

Molded Containers

	Borosilicate 3.3 group tubing	Borosilicate 5.0 group tubing	Borosilicate 7.0 group tubing	Borosilicate Type I group molded	Soda lime glass
Composition					
SiO_2	80 - 82	72 - 75	70 - 74	65 - 70	70-75
B_2O_3	12 - 13	9 - 11	5 - 8	9 - 11	0 - 1
Al_2O_3	2	5 - 7	4 - 6,5	3 - 7	2 - 4
Na_2O/K_2O	4	6 - 9	9 - 12	9 - 10	12 - 16
MgO/CaO/BaO	0	1 - 3	5 - 7	4 - 5	10 - 15
Physical Data					
Working Point	1260°C	1145 - 1170°C	1030 - 1100°C	1050 - 1080°C	1015 - 1045°C
CTE	3.3	4.9 - 5.5	6.3 - 7.5	6.0 - 6.5	9 - 9.5

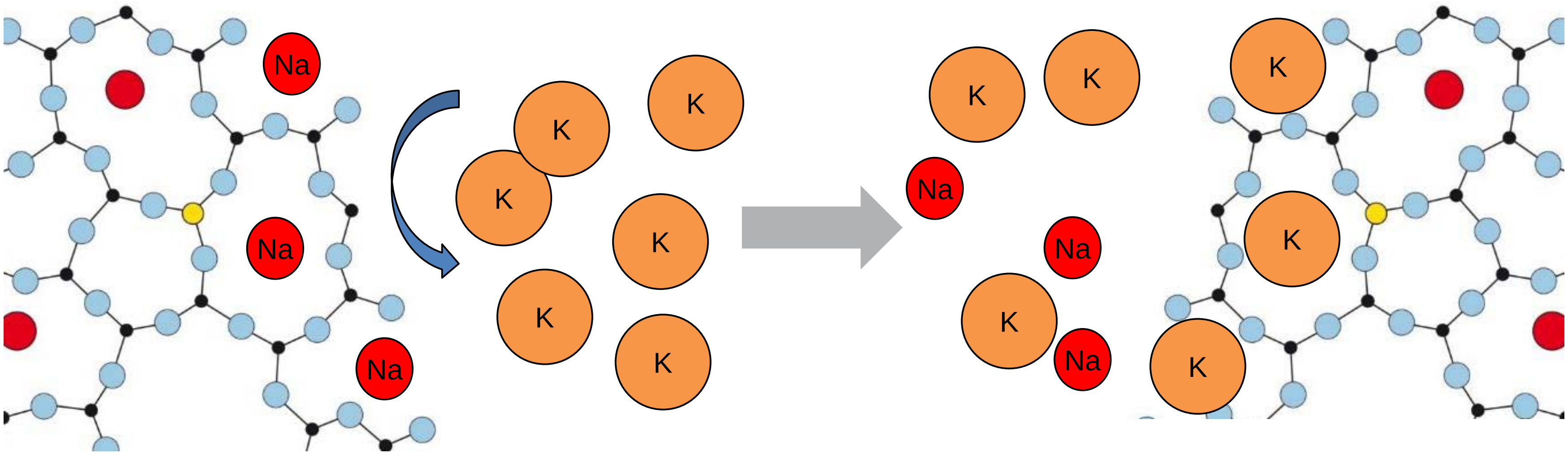
Further Treatments



Increasing the hydrolytic resistance of the surface

BUT: compromising the surface integrity and increasing the risk of flake creation (Delamination)

Further Treatments



Exchange of sodium by potassium ions creates compressive stress on the surface

Requires subsequent chemical treatment (leaching process) before use

Take Away Messages

- Tubing Production: Glass tubing is produced in a continuous process.
- Container Production: Vials can either be produced directly from the glass melt (molded vials) or formed starting with glass tubing (tubular vials). Ampoules, cartridges and syringes are always produced starting from glass tubing.
- Stress: Local melting leads to internal stress and requires an annealing step.
- Further Treatments: Containers can be further treated to better fit special requirements, but all influences of additional treatments should be considered.