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Type I Glass for Pharmaceutical Containers: Technical Requirements and regulatory update

Daniele Zuccato, Core Team Leader

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Topics

Glass Containers for Pharmaceutical Use

Glass Containers Production

Delamination

Regulatory Updates

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Glass Containers for Pharmaceutical Use

This is the title of the Section 3.2.1 of the current edition of the European Pharmacopoeia, EP

Glass Containers for Pharmaceutical Use
Glasses According to the European Pharmacopoeia (EP)

The **EP** (and the **USP**) classifies **2 Types** of **Glasses** according to their **Hydrolytic Resistance** (TEST B)

Type of Glass	Identification Item (Glass Grain Test)
Neutral Glass	Limit Value ≤ 0,10ml HCl 0,02 M Per gram of glass
Soda – Lime – Silica Glass	Limit Value ≤ 0,85ml HCl 0,02 M Per gram of glass

Titration of the Extract Solution obtained from 10 g glass powder in 50 ml water at 121° C for 30 min.

Glass Containers for Pharmaceutical Use
Glass Containers According to the European Pharmacopoeia (EP)

The EP
(and the **USP**)
classifies **3 Types**
of **Glass Containers**
according to their
Hydrolytic
Resistance
(HR)

Glass Containers for Pharmaceutical Use

Glass Containers: Type I – According to the European Pharmacopoeia (EP)

Definition

"Neutral glass, with a high hydrolytic resistance due to the chemical composition of the glass itself".

Recommendation For Use

"Suitable for most preparations whether or not for parenteral use".

Glass Containers for Pharmaceutical Use
Glass Containers: Type II – According to the European Pharmacopoeia (EP)

Definition

"Usually of soda-lime-silica glass with a high hydrolytic resistance resulting from suitable treatment of the surface".

Recommendation For Use

"Suitable for most acidic and neutral, aqueous preparations whether or not for parenteral use".

Glass Containers for Pharmaceutical Use
Glass Containers: Type III – According to the European Pharmacopoeia (EP)

Definition

"Usually of soda-lime-silica glass with only moderate hydrolytic resistance".

Recommendation For Use

"In general suitable for non-aqueous preparations for parenteral use, for powders for parenteral use (except for freeze-dried preparations) and for preparations not for parenteral use".

Glass Containers According to the European Pharmacopoeia (EP)

Titration Limit Values in the test for **Surface Hydrolytic Resistance (TEST A)**

Maximum volume of HCl 0,01 M for 100 ml of extract solution after 1 h at 121°C

Filling Volume (mL)	Types I and II	Types III
≤1	2,0	20,0
1 ÷ 2	1,8	17,6
2 ÷ 3	1,6	16,1
3 ÷ 5	1,3	13,2
5 ÷ 10	1,0	10,2
10 ÷ 20	0,80	8,1
20 ÷ 50	0,60	6,1
50 ÷ 100	0,50	4,8

Glass Containers for Pharmaceutical Use
Glass Containers According to the European Pharmacopoeia (EP)

- Distinction between Type I and II glass containers

- Applied to glass containers for aqueous parenteral preparations.
- Limit Value ≤ 0,1 ppm of As

- For coloured glass containers
- UV-VIS sprectrometer with an integrating sphere

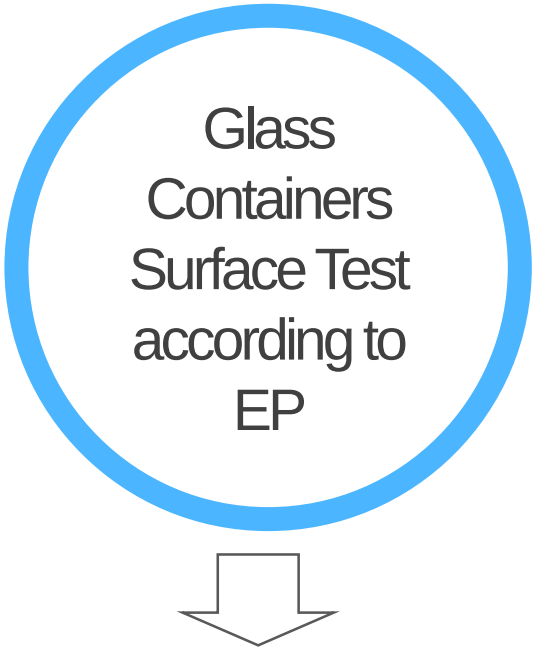
Glass Containers for Pharmaceutical Use
Glass Containers According to the Annex to the European Pharmacopoeia (EP)

Flame Spectrometry Limit Values in the test for surface hydrolytic resistance

Limit Values for the concentrations of oxides, expressed as sodium oxide mg/ml

Filling Volume (ml)	Types I and II
≤1	5,00
1 ÷ 2	4,50
2 ÷ 3	4,10
3 ÷ 5	3,20
5 ÷ 10	2,50
10 ÷ 20	2,00
20 ÷ 50	1,50
50 ÷ 100	1,20

Glass Containers for Pharmaceutical Use
Glass Containers According to the Attachment to the European Pharmacopoeia (EP)



No stoichiometric correspondance between them.

Titration test of the aqueous extract solution after 1 hour at 121° C

The test is compulsory

Individual alkali release by FAAS according to the EP Annex

The test is suggested as an additional tool for production quality control

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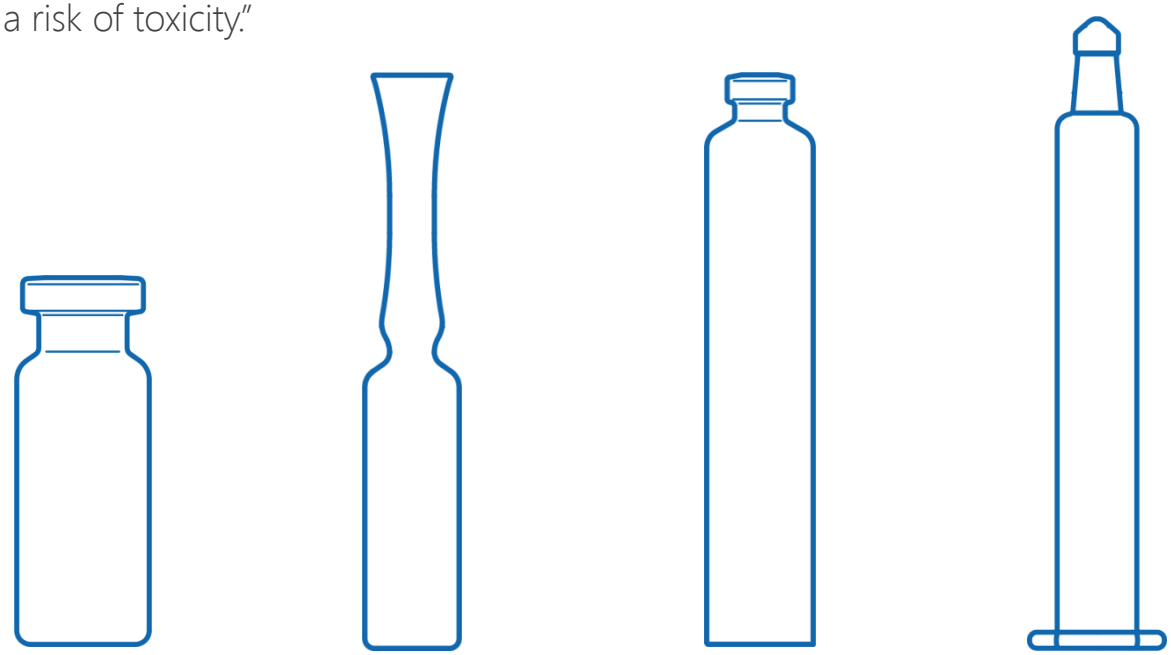
Glass Containers for Pharmaceutical Use
The Principle of the EP

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."



Glass Containers for Pharmaceutical Use
Chemical Composition of Type I Glasses

Representative chemical composition of Type I glass tubing containers

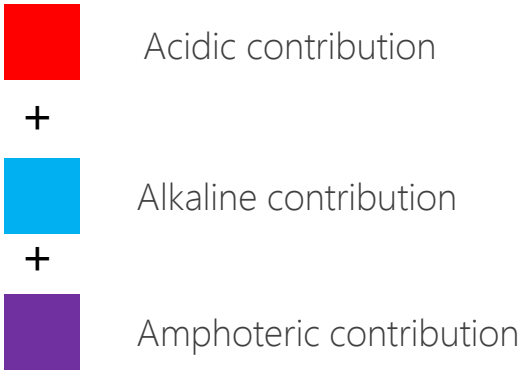
Oxides	Weight %
SiO_2	73,0
B_2O_3	11,0
Al_2O_3	6,0
$Na_2O + K_2O$	8,0
$CaO + BaO$	2,0

Glass Containers for Pharmaceutical Use
Hydrolytic Resistance

Elements present in the extract solution

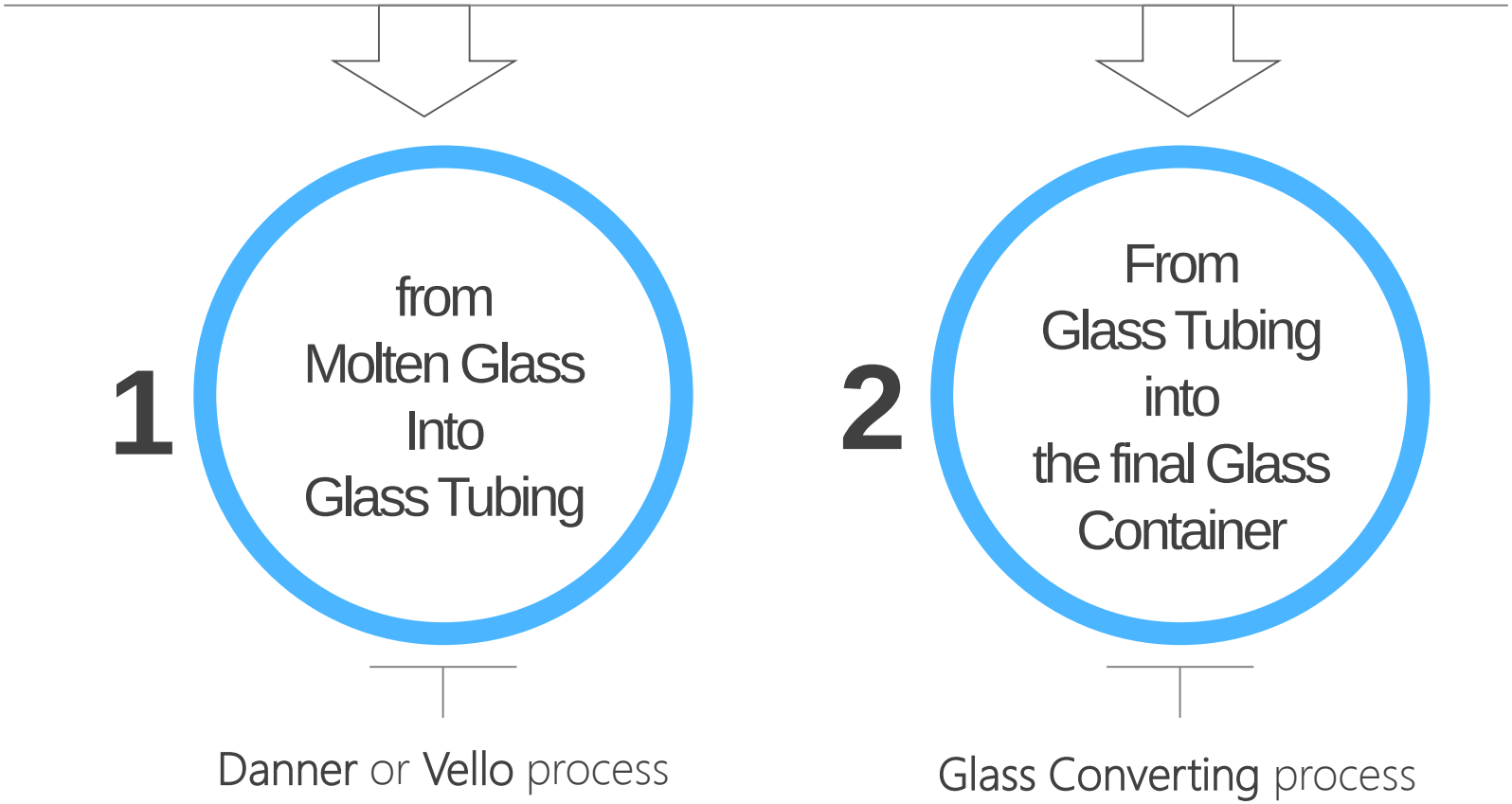
SiO_2 > Na_2O+K_2O > B_2O_3 > $CaO+BaO$ > Al_2O_3

Final pH

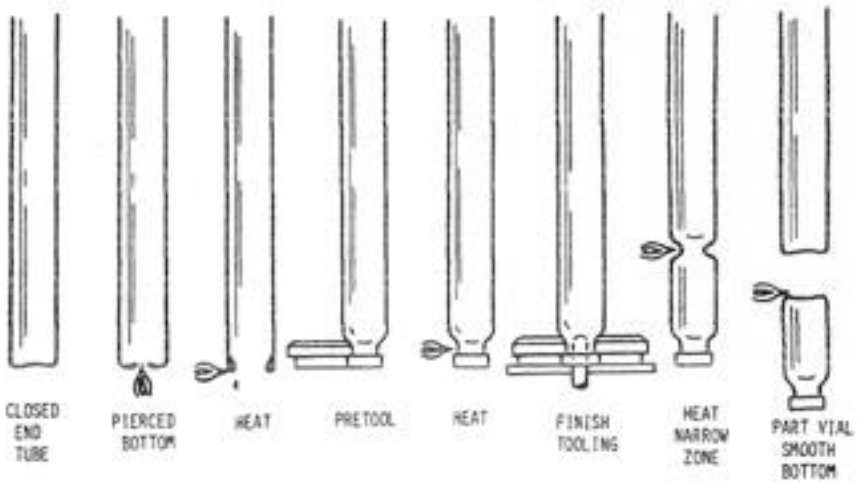


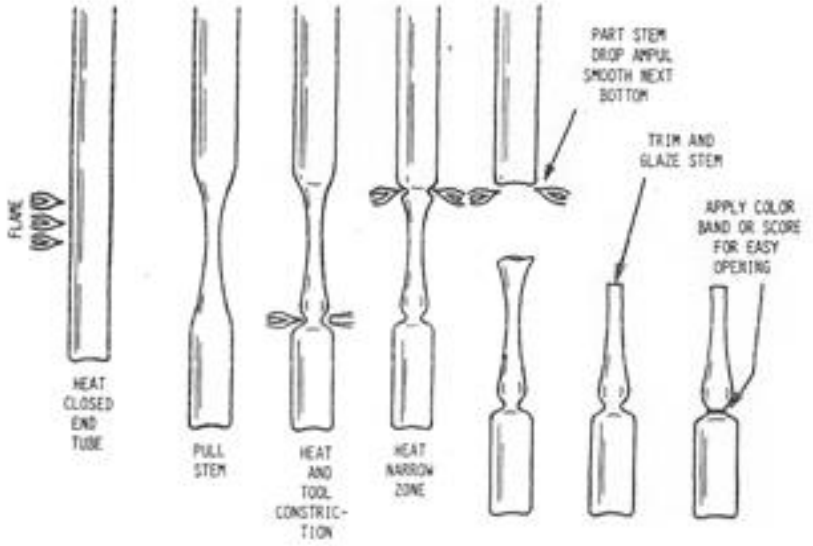
Glass Containers for Pharmaceutical Use
Glass Tubing Production

Production of Glass Tubing Containers

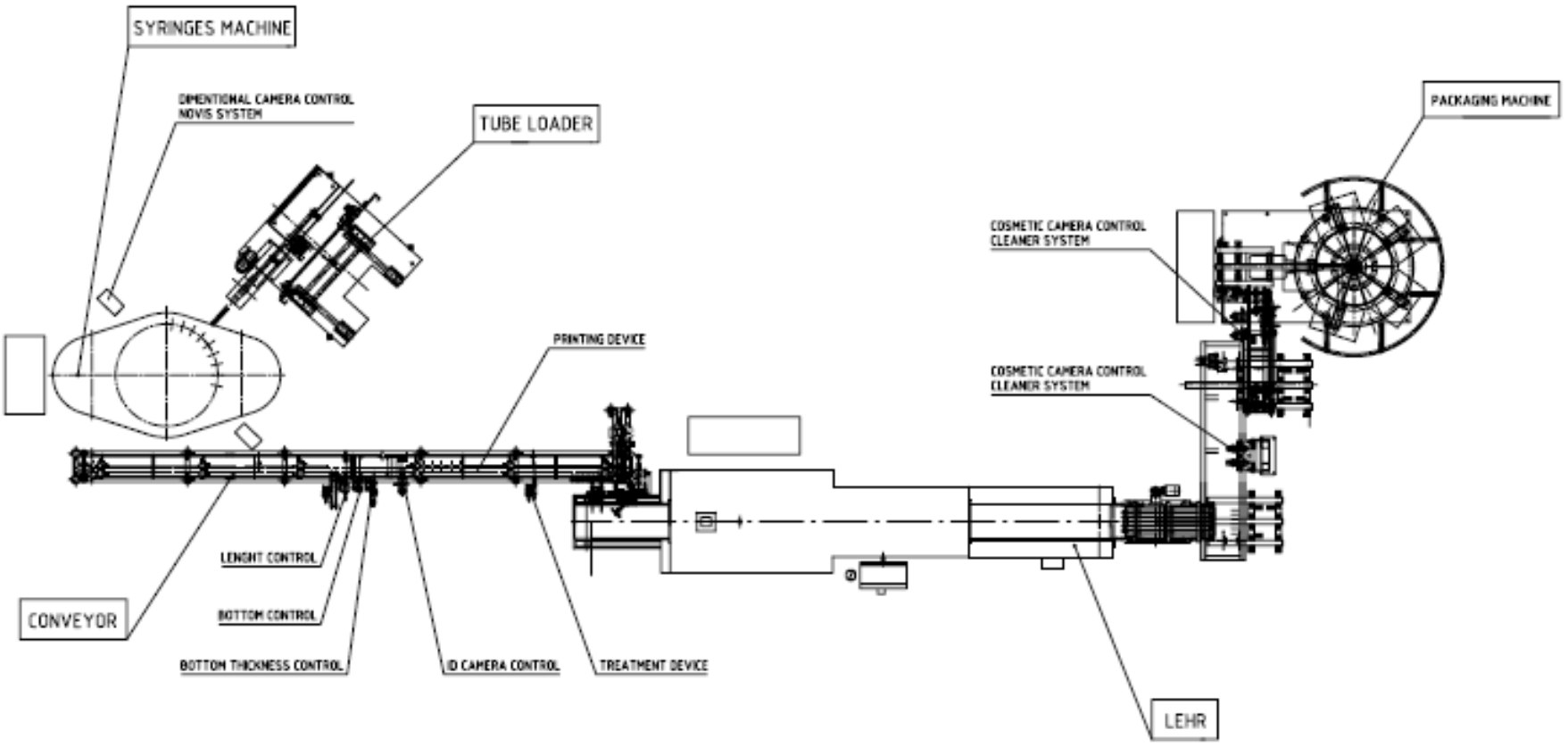


Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers



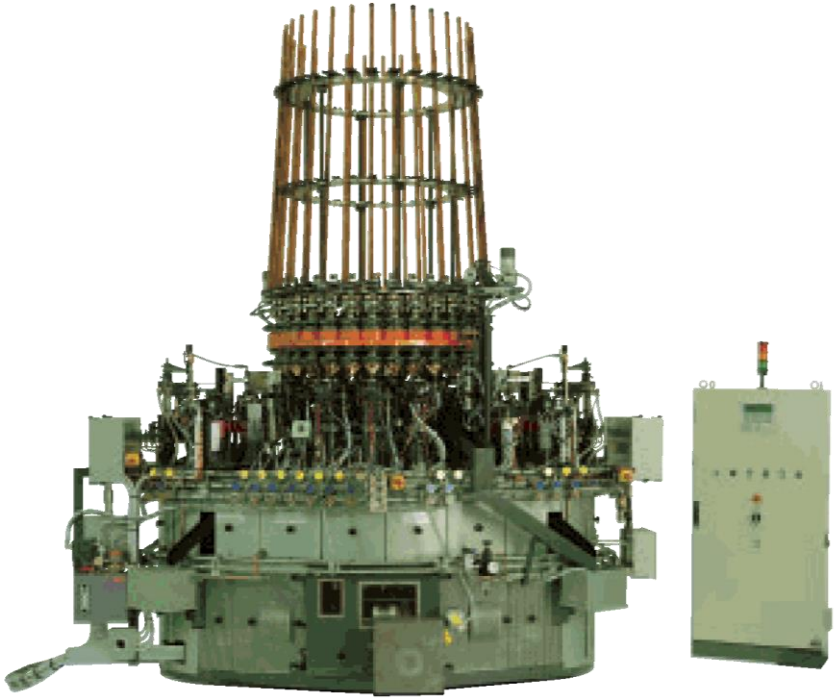


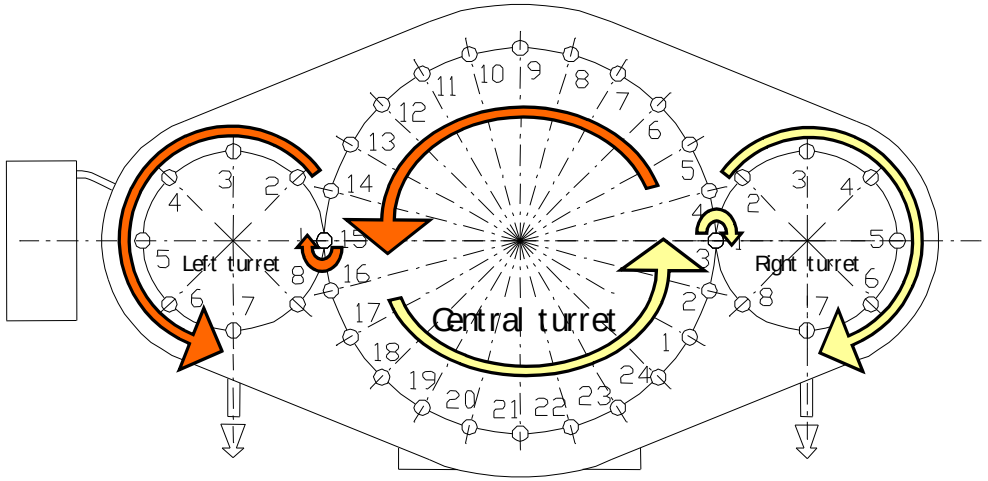
Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers



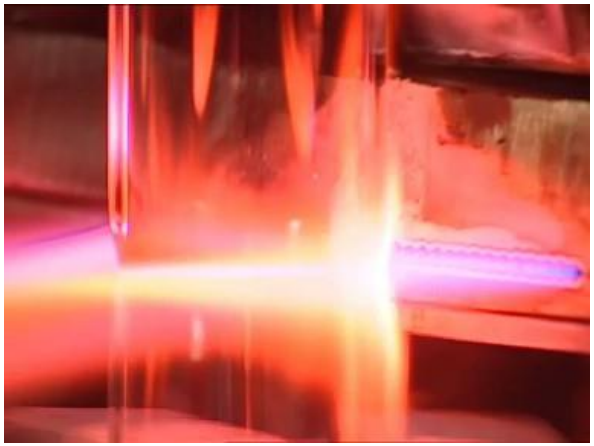
Glass Containers for Pharmaceutical Use

Production of Glass Tubing Containers

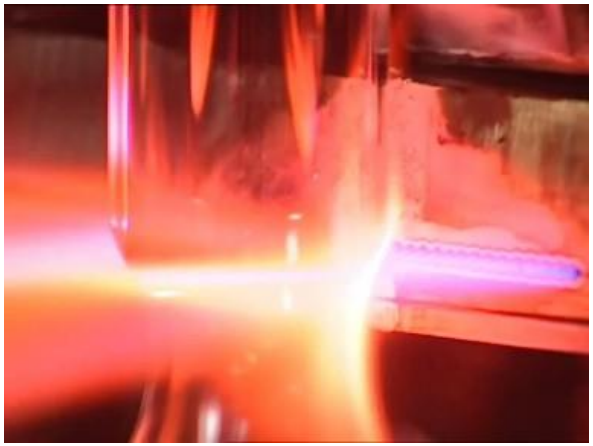




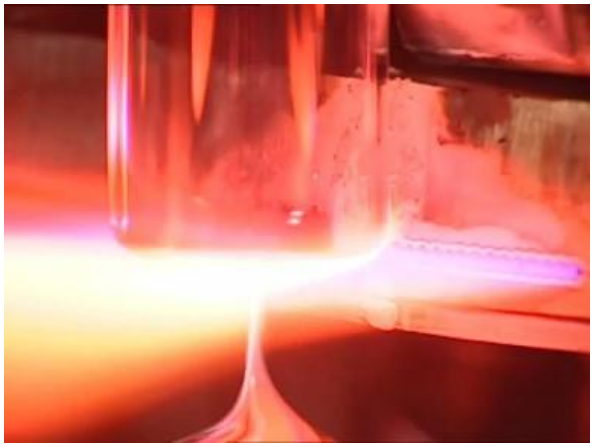
Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers



Pre-heating

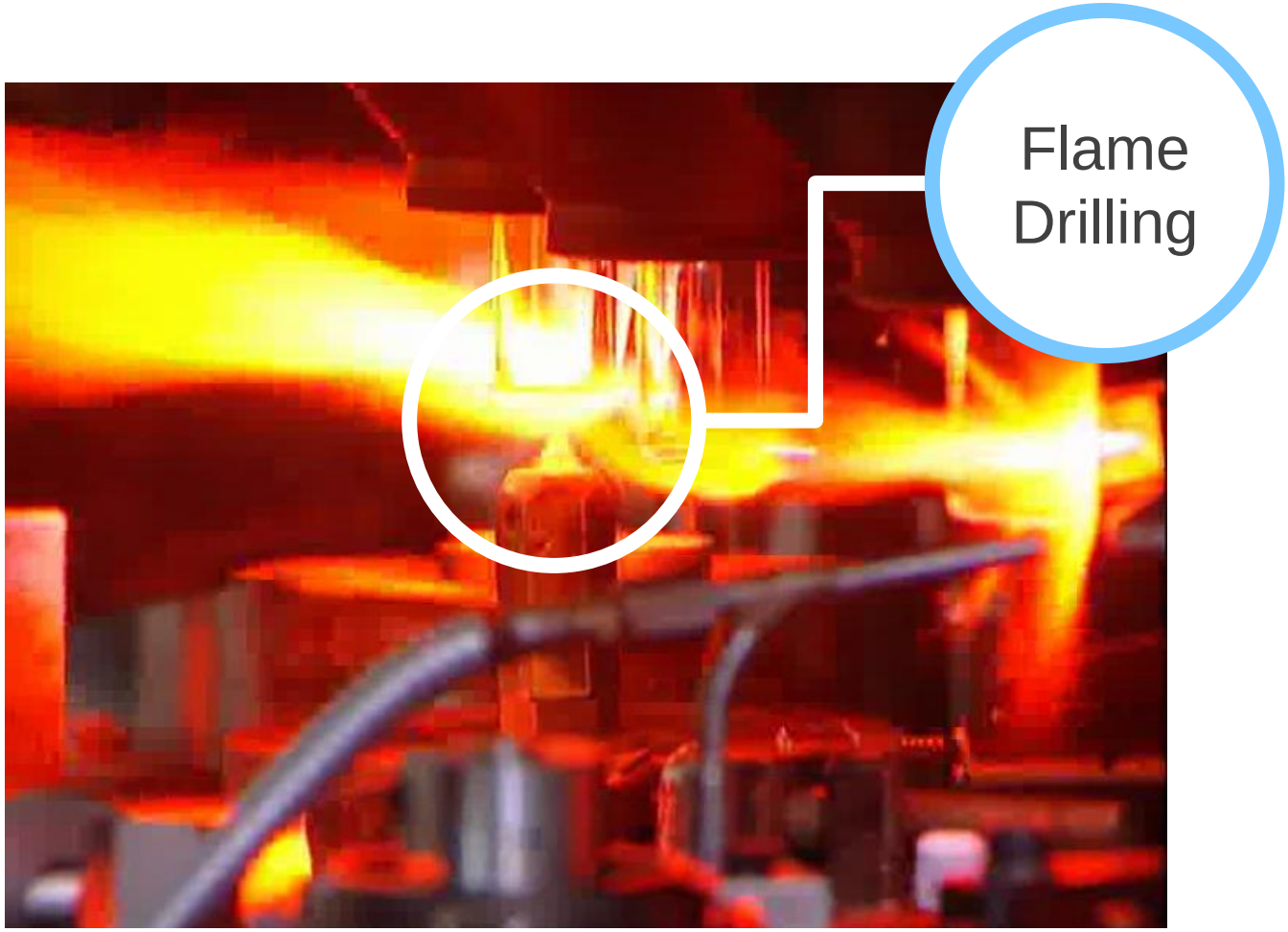


Pre-heating

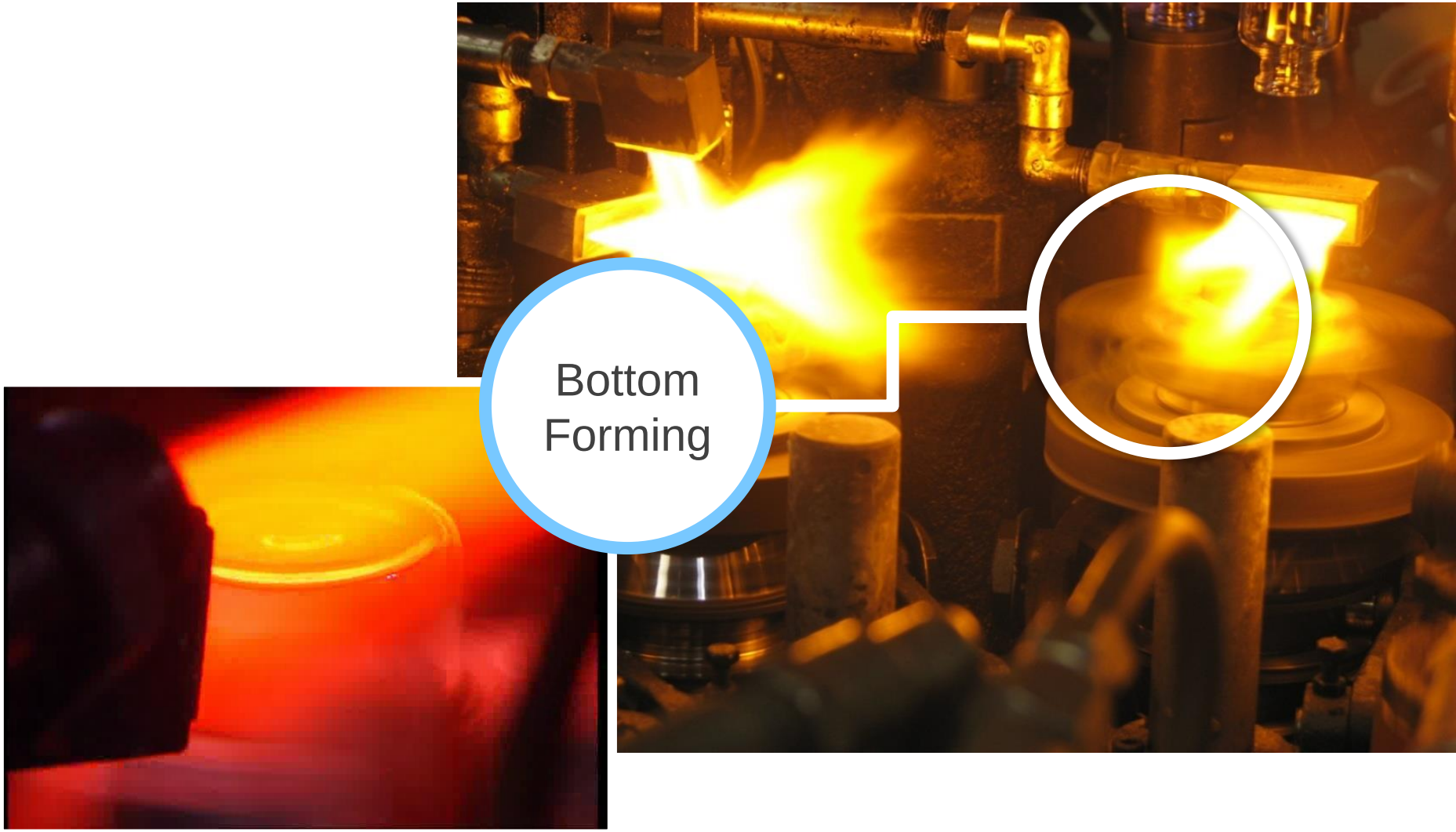


Cutting

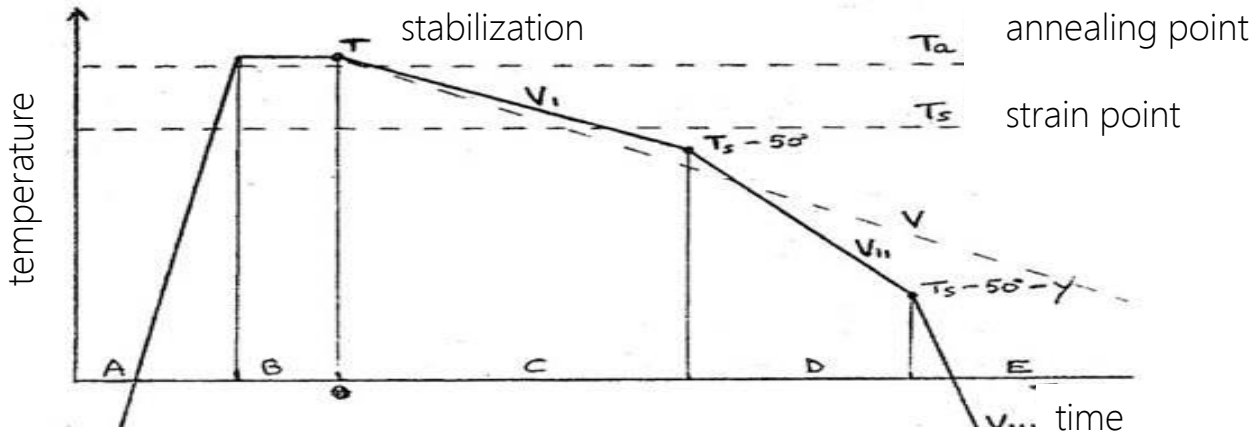
Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers

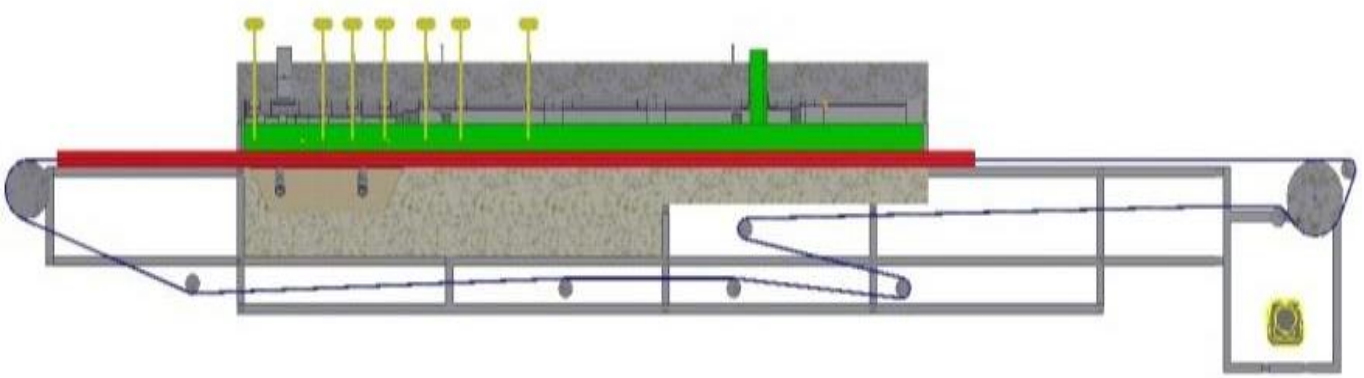


Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers



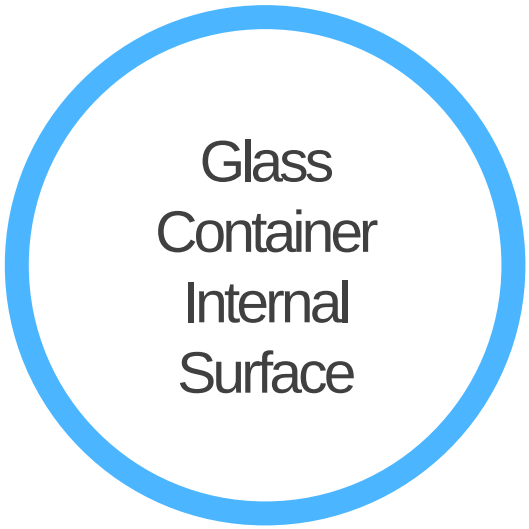
Annealing process





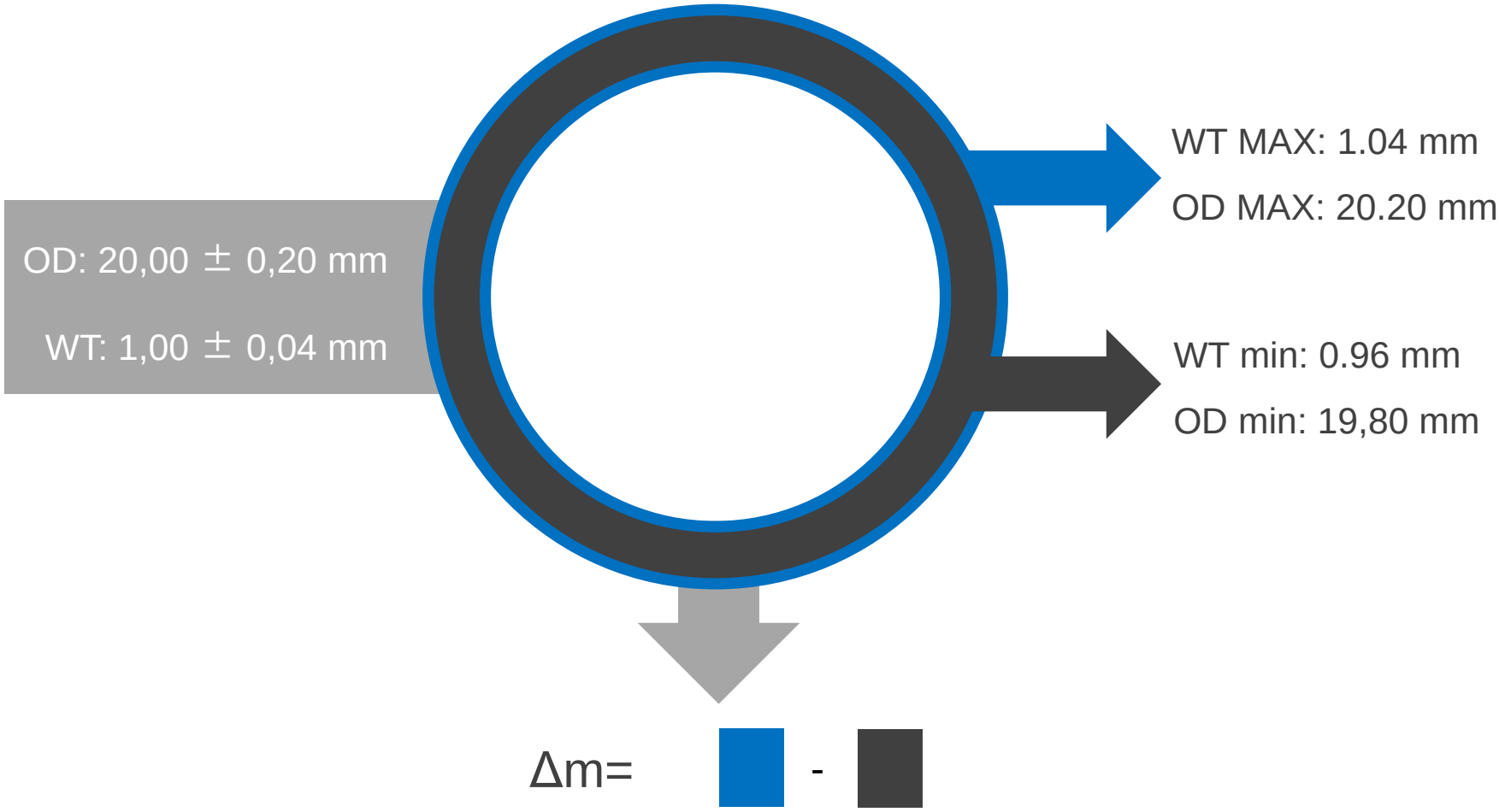
Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers

Factors Affecting the Chemical Release of the Internal Surface of Glass Tubing Containers



- Tubing Size
  (Dimensional tolerances)
- State of Internal
  Surface of Tubing
- Forming Stages
  (Temperatures and times)
- Annealing
  (Temperatures and times)

Dimensional Tolerances of Glass Tubing



Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers

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

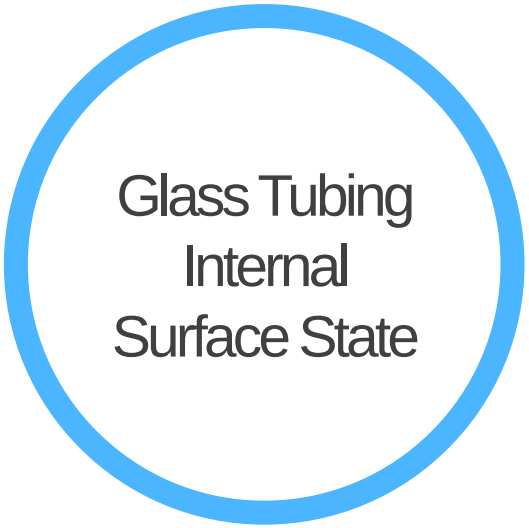
$\Delta m = \pm 4\ \%$ (generally ≤ 2%)

m=mass

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

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

Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers



Roughness:

Increase of the surface area

Size of the elemental structure units:

Higher cooling rates generate larger structural units with lower chemical resistance

Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers

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

Phase separation and sublimation of alkali borates

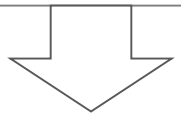
Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers

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

Increased alkali extractability

Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers

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



- Sulphur treatment;
- Siliconisation;
- Ion Exchange;
- PECVD;
- Others

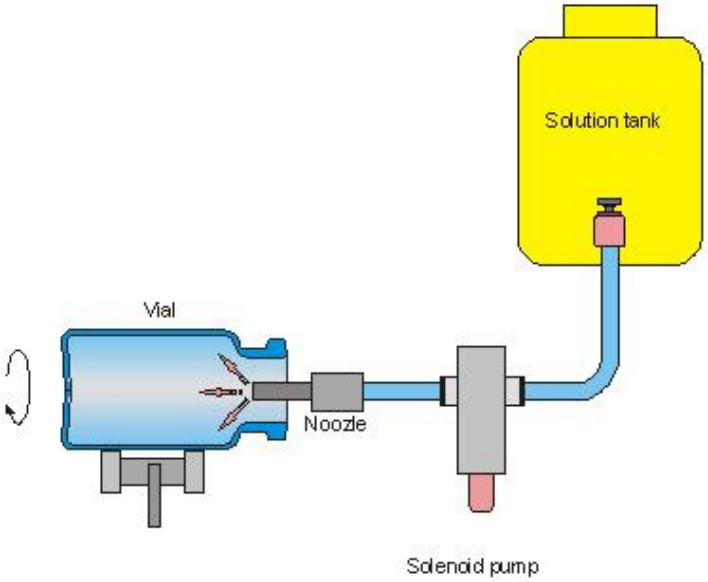
Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers

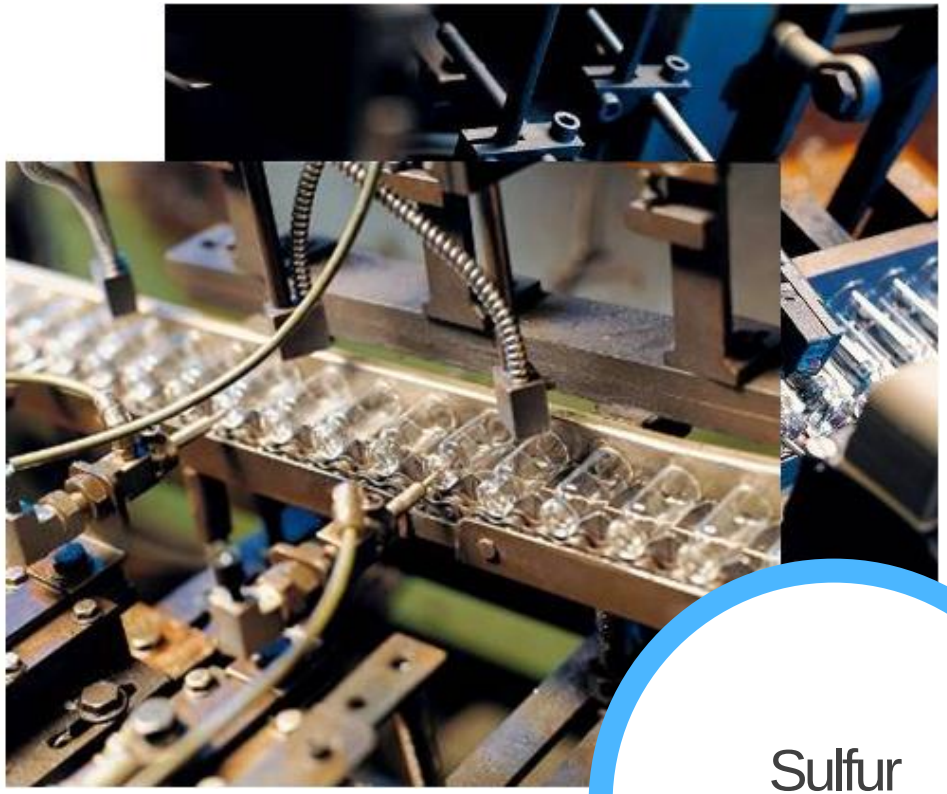
At high temperature ammonium sulphate decomposes and reacts with surface alkalies **forming water soluble sulphate salts.**

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.**

Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers





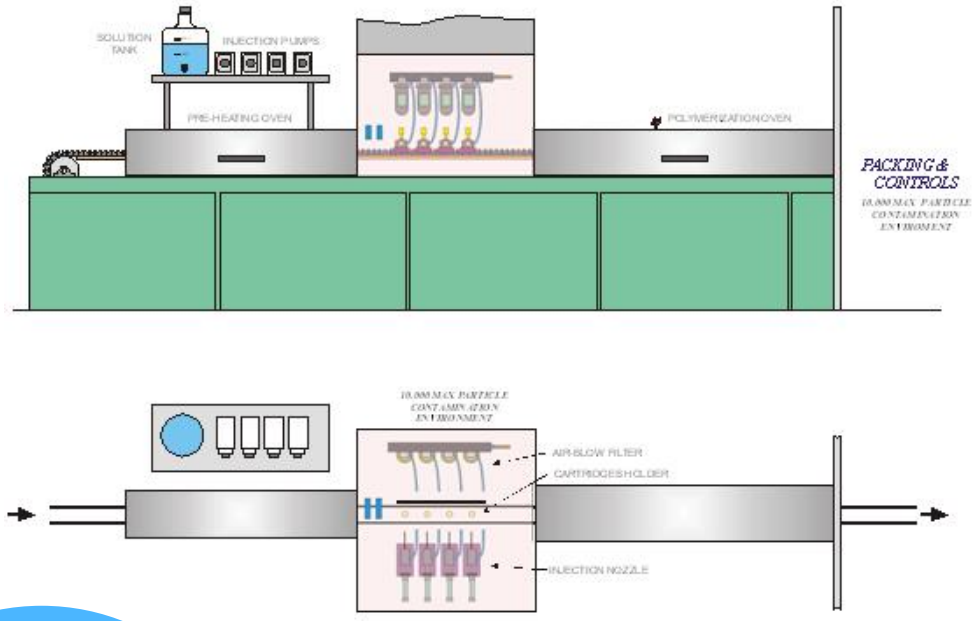
Sulfur Treatment

Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers

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**

Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers



Siliconization

- Direct connection to the forming line
- Servomotor movements with adjustable speed for nozzles
- Volumetric pumps for silicone emulsion

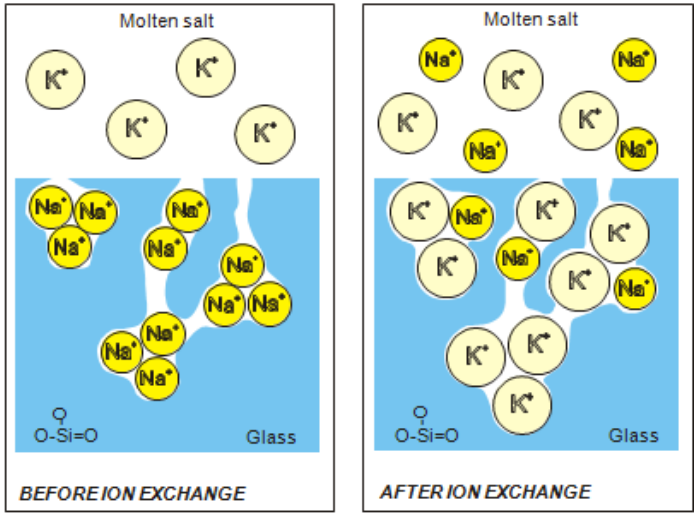
- Multiple injection
- Air flow control for spraying system
- Suction system to prevent external contamination

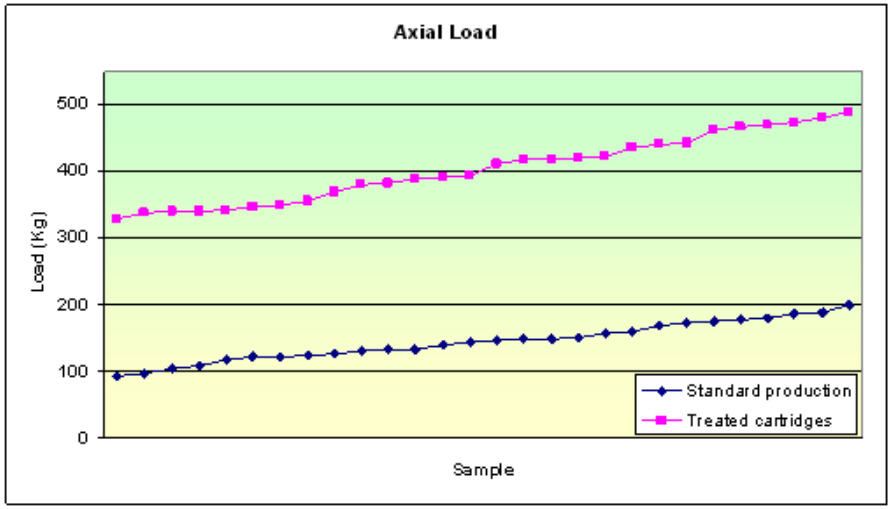
Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers

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**

Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers





Ion Exchange

Mechanical Resistance Increase

Glass Containers for Pharmaceutical Use
Glass Tubing Containers vs Molded containers

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

>100mL

<20mL

<1mL*

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Topics

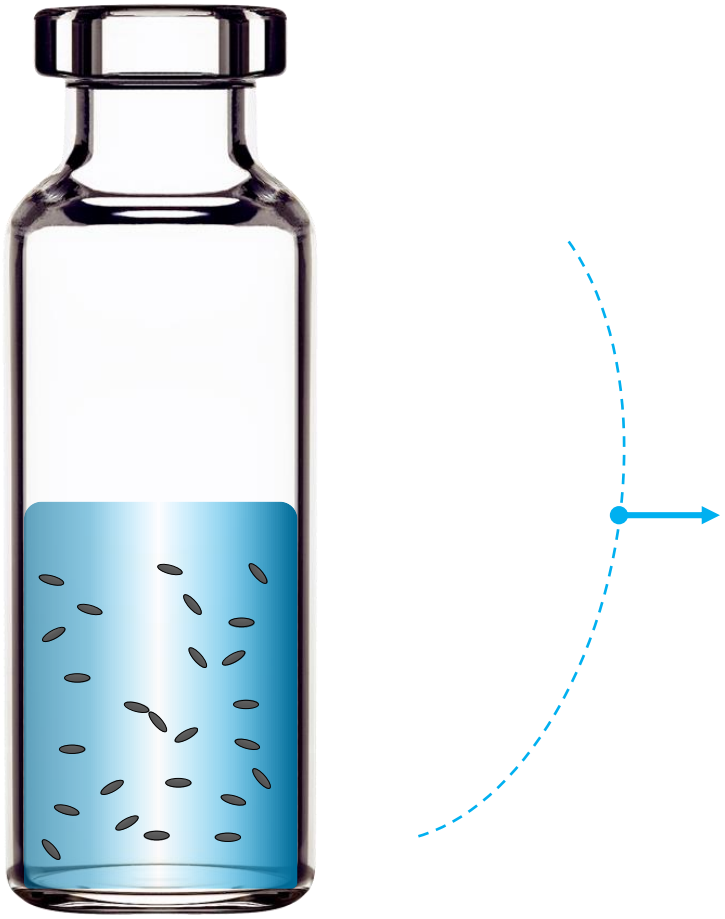
Glass Containers for Pharmaceutical Use

Glass Containers Production

Delamination

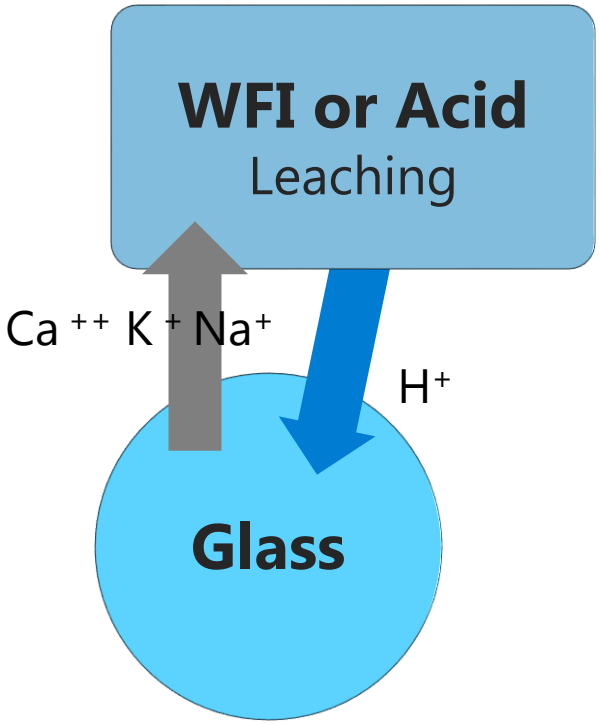
Regulatory Updates

Glass Containers for Pharmaceutical Use
Delamination



- Separation of thin glass layers (lamellae) that appear as shiny, needle shaped particles floating in the contact liquid
- The formation of a silica-rich layer poorly bonded to the substrate is the first stage of an extended delamination
- Glass-liquid interactions are responsible for the formation of an altered layer

Glass Containers for Pharmaceutical Use
Delamination – Glass liquid interactions



Formation of a alkali depleted layer

Increasing of the layer thickness

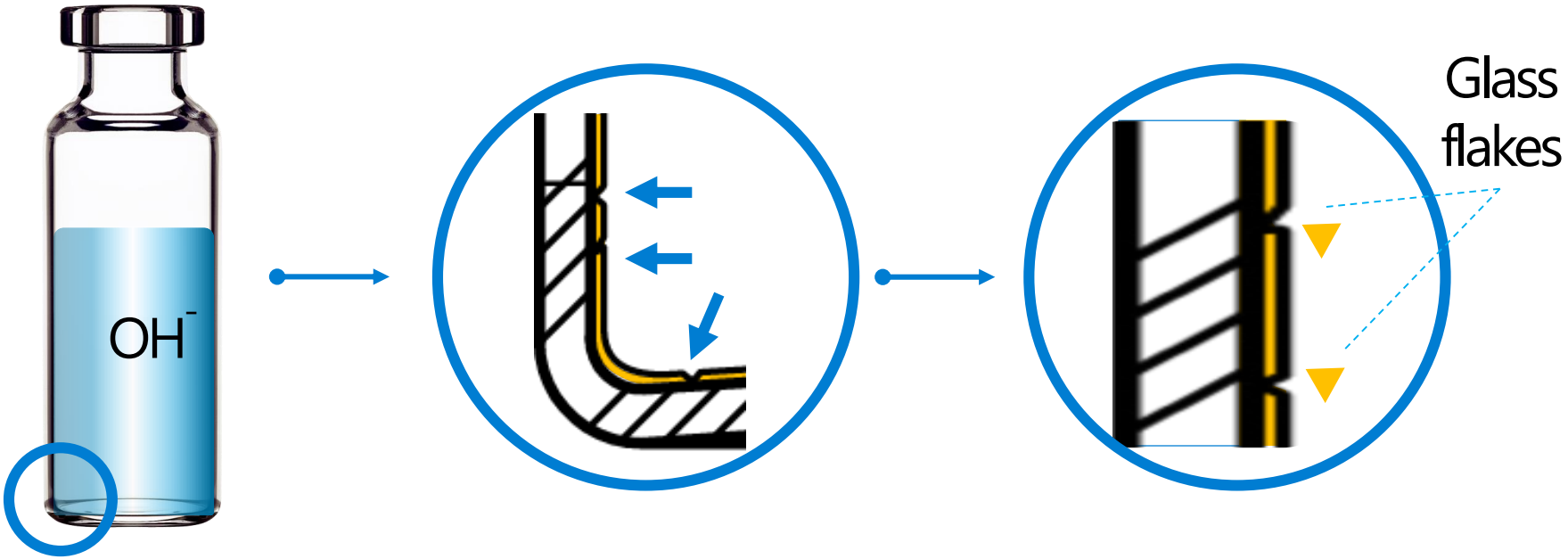
Cracking

Detachment of scales

Glass Containers for Pharmaceutical Use
Delamination of Pharmaceutical Glass

- The first stage is always the formation of an altered layer
- When vials are filled with the liquid preparation, this layer is subject to a strong re-hydration and swelling

Glass Containers for Pharmaceutical Use
Delamination of Pharmaceutical Glass



- Some preparations may favour delamination
- Alkaline solutions strongly affect the dissolution of the silica layer. SiO_2 concentration in the extraction liquid increases steeply
- Flakes appearance

Glass Containers for Pharmaceutical Use
Factors affecting delamination of Pharmaceutical Glass

- Sulfur treatment
- coating

→ **Surface treatments**

- Speed of the transformation process
- burners flame temperature
- improper annealing stage, tensile stresses
- type of glass

→ **Conversion process**

- Formulation chemical composition
- pH & ionic strength of the drug formulation
- Depyro and sterilization processes
- Storage conditions

→ **Drug formulation & post-treatments**

Glass Containers for Pharmaceutical Use
Test protocol for Delamination propensity measurement

Vial as received

Colorimetric test

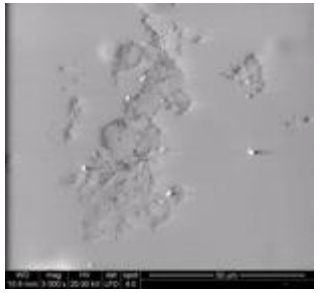
Vial filled with the intended preparation 1h autoclave 121 ° C

ICP-OES ppm SiO_2 in the extract	Visual inspection for particles presence	Colorimetric test

SEM of selected vials

Confirmation of the results

Fully aligned with USP <1660> guidelines



Glass Containers for Pharmaceutical Use
Test protocol for Delamination propensity measurement

SG Studies and Scientific publications

Delamination Propensity of Pharmaceutical Glass Containers by Accelerated Testing with Different Extraction Media

Emanuel Guadagnino (ret.) and Daniele Zuccato, PhD, Stevanto Group

How can injectable drug manufacturers prevent glass delamination? The issue of delamination is a serious one as it can cause glass particles to appear in vials, a problem that has forced a number of drug product recalls in recent years. To combat this, pharmaceutical and biopharmaceutical manufacturers need to understand the underlying reasons for glass delamination.

The delamination of glass when it is exposed to certain environments is a very well-known phenomenon. For instance, the occurrence of flakes in soda-lime glass bottles intended to get into contact with food and beverages has been documented since the early forties. In that case, storage of the empty bottles under uncontrolled conditions of humidity and temperature showed to be a key factor. Along the production line, the packing stage is located at the exit of the annealing lehr, where bottles have a temperature of about 60°C. Then, bottles are placed on a pallet and covered with a polyethylene foil shrink wrap that can trap humid air within. The consequence is an early interaction with the inner glass surface, which is still sufficiently hot to react vigorously, giving rise to extensive weathering. This results in the formation of an altered alkali-depleted and silica-rich layer that has an expansion coefficient which is fairly different from the glass substrate underneath. When bottles are filled with any kind

to strong re-hydration,

PDA letter #July/August 2011

Delamination Propensity of Pharmaceutical Glass Containers by Accelerated Testing with Different Extraction Media

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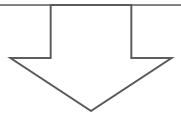
ABSTRACT: The delamination of pharmaceutical glass is a serious issue, as it can cause glass particles to appear in vials, a problem that has forced a number of drug product recalls in recent years. In Type I pharmaceutical glass vials, delamination occurs generally at the bottom and shoulder, where extensive flaming during the conversion process can favor a strong evaporation of alkali and borate species and the formation of heavily enriched silica layers. The contact with parenteral preparations dissolved in an alkaline medium increases the rate of glass corrosion, while the differential hydration of these layers can cause the detachment of flakes. The purpose of this study was to investigate the effect of the pH and the composition of the extraction solutions on the propensity of different glass types to delaminate. Repeated autoclave extractions at 121 °C were carried out on different glass types with different extraction media, including organic extractants like citric and glutaric acid. When vials were in contact with alkaline solutions and similarly aggressive media, an increase in silica extraction values indicated glass corrosion and an increasing risk for further delamination. Under such conditions expansion 33 glass is extensively corroded, showing high silica concentration and heavy flaking as compared to other glass types. Sulfur-treated glass also showed early flaking, even if SiO_2 concentration was very low. A similar ranking was observed with extractions carried out with glutaric and citric acids, but at far much higher SiO_2 concentration levels. Extractions with 0.9% KCl solution can be used as an accelerated test to highlight the propensity of a glass to delaminate, but in no case it can be taken as a guarantee that the glass will not delaminate when exposed to the pharmaceutical drug, whose extraction ability requires case-by-case study.

KEYWORDS: Hydrolytic resistance, Delamination, Glass

PDA J Pharm Sci and Tech , 2012 , 66 116-125

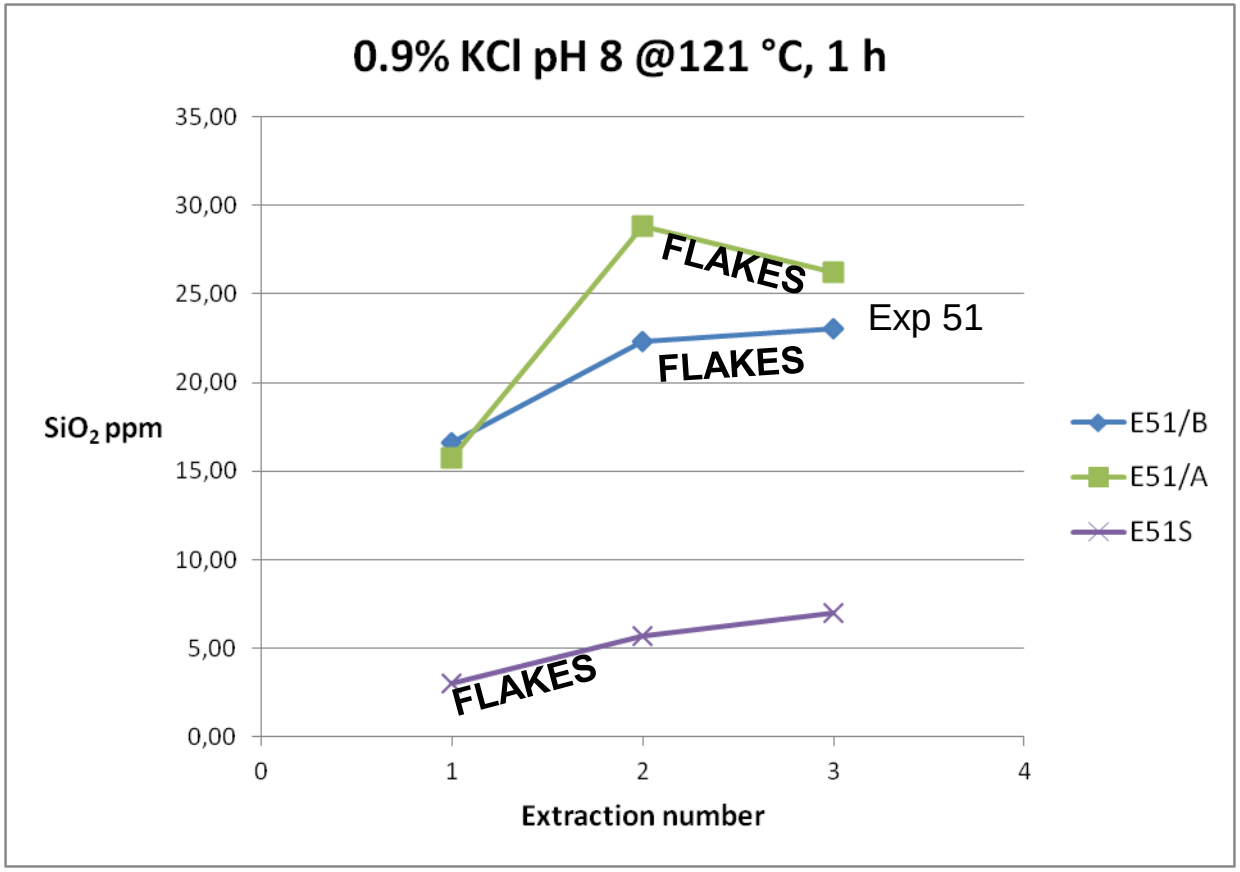
Glass Containers for Pharmaceutical Use
Delamination Studies Takeaways

Delamination Risk



- EP Titration values are not reliable indicators of delamination risk
- SiO_2 in solution increases with increasing appearance of flakes
- Sulfur treated glasses show strong propensity to delaminate vs alkaline solutions even at low SiO_2 values (but increasing SiO_2 / B_2O_3 ratio)
- Exp. 33 glass is the most extensively corroded
- Reducing tensile stressed minimizes the delamination risk

Glass Containers for Pharmaceutical Use
Sulfur treatment



Glass Type	E.P. titration values
Exp51/b	0.92
Exp51/a	0.63
Exp 51 Sulfur treated	0.51

Glass Containers for Pharmaceutical Use
Delamination: ICG - TC 12 “Glasses for Pharma”

New Technical Committee of the ICG - TC 12 *“Glasses for Pharma”*

- is considering the chemical (delamination) and the mechanical (micro-cracks/fragility) issues of glass containers for Pharmaceutics.

Membership:

- University of Padova – SSV
- Roche – Novo – Lilly
- SGD – Bormioli Rocco – Schott – Gerresheimer – NEG – Nipro – Nuova Ompi

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Topics

Glass Containers for Pharmaceutical Use

Glass Containers Production

Delamination

Regulatory Updates

Glass Containers for Pharmaceutical Use
Delamination of Pharmaceutical Glass – EP approach

European Pharmacopoeia

EP Version 8.3 - § Production

"When glass containers for pharmaceutical use are manufactured under stressed conditions (e.g. temperature time profile) and/or are placed in contact with particularly aggressive pharmaceutical preparations, they may give rise to delamination, i.e. the separation of the inner glass surface into layers, called lammellae or flakes. [...]

The process of interaction between the glass surface and the pharmaceutical preparation requires a long incubation time and flaking may need months after filling to become visible. [...]

It is recommended that the pharmaceutical user assess the compatibility of the glass container and the pharmaceutical **on a case-by-case basis**. [...]

Accelerated degradation testing can be used as a predictive tool to select the most appropriate container for the intended preparation, but the full compatibility of the active principle with the glass leachate can only be assessed by a stability test under normal condition of use."

Glass Containers for Pharmaceutical Use
Delamination of Pharmaceutical Glass – USP approach

New Guideline <1660>

- General Information Chapter <1660> = Guidance
- Published in USP's Pharmacopeial Forum Volume 38 (4), July-August, 2012
- Comment period ended September 31, 2012
- Comments received from glass industry and pharmaceutical companies
- USP's Expert Committee is revising again the chapter taking into account the comments received
- It is estimated that the revised chapter will be published in the Pharmacopeial Forum (PF) 43 (3), May-June, 2017

Glass Containers for Pharmaceutical Use
Delamination of Pharmaceutical Glass – USP <1660> Chapter Structure

- Glass Container Manufacture & Processing
  - Molded and Tubing containers
- Glass Surface Chemistry
- Factors Influencing Glass Inner Surface Durability
  - Container manufacture, processing & storage
  - Drug Product formulation, processing & storage
- Screening Analytical Techniques
  - Techniques to examine inner glass surface, extracted elements, lamellae and sub-visible and visible glass particles
- Screening Strategies
  - Use of aggressive model systems, drug product and water control to assess the chemical durability of the inner surface using screening analytical techniques

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Thank you for your attention !

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