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

Daniele Zuccato, Core Team Leader
Glass Containers for Pharmaceutical Use

Glass Containers Production

Delamination

Regulatory Updates
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)

<table>
<thead>
<tr>
<th>Type of Glass</th>
<th>Identification Item (Glass Grain Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral Glass</td>
<td>Limit Value ≤ 0,10ml HCl 0,02 M Per gram of glass</td>
</tr>
<tr>
<td>Soda – Lime – Silica Glass</td>
<td>Limit Value ≤ 0,85ml HCl 0,02 M Per gram of glass</td>
</tr>
</tbody>
</table>

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):

- **Type I**: High HR
- **Type II**: High HR
- **Type III**: Moderate 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”.

Type I
High HR
**Glass Containers for Pharmaceutical Use**

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

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**Definition**

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

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**Recommendation For Use**

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

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Type II
High HR
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”.

Type III
Moderate
HR
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

<table>
<thead>
<tr>
<th>Filling Volume (mL)</th>
<th>Types I and II</th>
<th>Types III</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1</td>
<td>2,0</td>
<td>20,0</td>
</tr>
<tr>
<td>1 ÷ 2</td>
<td>1,8</td>
<td>17,6</td>
</tr>
<tr>
<td>2 ÷ 3</td>
<td>1,6</td>
<td>16,1</td>
</tr>
<tr>
<td>3 ÷ 5</td>
<td>1,3</td>
<td>13,2</td>
</tr>
<tr>
<td>5 ÷ 10</td>
<td>1,0</td>
<td>10,2</td>
</tr>
<tr>
<td>10 ÷ 20</td>
<td>0,80</td>
<td>8,1</td>
</tr>
<tr>
<td>20 ÷ 50</td>
<td>0,60</td>
<td>6,1</td>
</tr>
<tr>
<td>50 ÷ 100</td>
<td>0,50</td>
<td>4,8</td>
</tr>
</tbody>
</table>
Glass Containers for Pharmaceutical Use

Glass Containers According to the European Pharmacopoeia (EP)

- **Etching Test**
  - Distinction between Type I and II glass containers

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

- **Spectral Transmission**
  - For coloured glass containers
  - UV-VIS spectrometer 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

<table>
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<tr>
<th>Filling Volume (ml)</th>
<th>Types I and II</th>
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<tbody>
<tr>
<td>≤1</td>
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</tr>
<tr>
<td>3 ÷ 5</td>
<td>3,20</td>
</tr>
<tr>
<td>5 ÷ 10</td>
<td>2,50</td>
</tr>
<tr>
<td>10 ÷ 20</td>
<td>2,00</td>
</tr>
<tr>
<td>20 ÷ 50</td>
<td>1,50</td>
</tr>
<tr>
<td>50 ÷ 100</td>
<td>1,20</td>
</tr>
</tbody>
</table>
Glass Containers for Pharmaceutical Use
Glass Containers According to the Attachment to the European Pharmacopoeia (EP)

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

Glass Containers Surface Test according to EP

No stoichiometric correspondance between them.
Glass Containers for Pharmaceutical Use

Glass Containers Production

Topics

Delamination

Regulatory Updates
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

<table>
<thead>
<tr>
<th>Oxides</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>SiO$_2$</td>
<td>73,0</td>
</tr>
<tr>
<td>B$_2$O$_3$</td>
<td>11,0</td>
</tr>
<tr>
<td>Al$_2$O$_3$</td>
<td>6,0</td>
</tr>
<tr>
<td>Na$_2$O + K$_2$O</td>
<td>8,0</td>
</tr>
<tr>
<td>CaO + BaO</td>
<td>2,0</td>
</tr>
</tbody>
</table>

**Representative chemical composition of Type I glass tubing containers**
Glass Containers for Pharmaceutical Use
Hydrolytic Resistance

Elements present in the extract solution

\[ \text{SiO}_2 > \text{Na}_2\text{O} + \text{K}_2\text{O} > \text{B}_2\text{O}_3 > \text{CaO} + \text{BaO} > \text{Al}_2\text{O}_3 \]

Final pH

- Acidic contribution
- Alkaline contribution
- Amphoteric contribution
Glass Containers for Pharmaceutical Use
Glass Tubing Production

Production of Glass Tubing Containers

1. From Molten Glass Into Glass Tubing
   - Danner or Vello process

2. From Glass Tubing into the final Glass Container
   - Glass Converting process
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

Flame Drilling
Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers
Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers

Annealing process

- Stabilization
- Annealing point
- Strain point

Diagram showing the annealing process with temperature and time as variables.
Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers

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

- Glass Container Internal Surface
  - Tubing Size (Dimensional tolerances)
  - State of Internal Surface of Tubing
  - Forming Stages (Temperatures and times)
  - Annealing (Temperatures and times)
Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers

**Dimensional Tolerances of Glass Tubing**

- OD: 20.00 ± 0.20 mm
- WT: 1.00 ± 0.04 mm

- WT MAX: 1.04 mm
- OD MAX: 20.20 mm
- WT min: 0.96 mm
- OD min: 19.80 mm

Δm = -
Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers

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

Δm = ± 4 % (generally ≤ 2%)
m = mass

Q = m c ΔT

Q = Calories
m = glass mass
C = glass specific heat
T = temperature
Glass Tubing for Pharmaceutical Use

Production of Glass Tubing Containers

Glass Tubing Internal Surface State

Roughness:
Increase of the surface area

Size of the elemental structure units:
Higher cooling rates generate larger structural units with lower chemical resistance
The migration of elements from bulk to the surface increases with increasing temperature and time.

Phase separation and sublimation of alkali borates.
Annealing

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
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
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.
Glass Containers for Pharmaceutical Use
Production of Glass Tubing Containers

- 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

Chemical Strengthening

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

**Before Ion Exchange**

- Molten salt
- Ion exchange process
- Glass

**After Ion Exchange**

- Molten salt
- Ion exchange process
- Glass

**Graph:**

- **Axial Load**
- **Load (kg)**
- **Sample**
- **Standard production**
- **Treated cartridges**

**Processes:**

- 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)

**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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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

- **WFI or Acid Leaching**
  - Ca $^{++}$, K $^{+}$, Na $^{+}$
  - H $^{+}$

Glass

- Formation of an 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
• Some preparations may favour delamination
• Alkaline solutions strongly affect the dissolution of the silica layer. SiO₂ concentration in the extraction liquid increases steeply
• Flakes appearance
Glass Containers for Pharmaceutical Use
Factors affecting delamination of Pharmaceutical Glass

- Sulfur treatment
- coating

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

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

Surface treatments
Conversion process
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 SiO₂ 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
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$_2$O$_3$ ratio)
- Exp. 33 glass is the most extensively corroded
- Reducing tensile stressed minimizes the delamination risk
Glass Containers for Pharmaceutical Use
Sulfur treatment

<table>
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<tr>
<th>Glass Type</th>
<th>E.P. titration values</th>
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<tbody>
<tr>
<td>Exp51/b</td>
<td>0.92</td>
</tr>
<tr>
<td>Exp51/a</td>
<td>0.63</td>
</tr>
<tr>
<td>Exp 51 Sulfur treated</td>
<td>0.51</td>
</tr>
</tbody>
</table>

0.9% KCl pH 8 @121 °C, 1 h

Graph showing the extraction number and SiO₂ ppm for different glass types.

FLAKES
Exp 51
ES1/B
ES1/A
ES1S
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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“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
Thank you for your attention!