Regulatory Demands

- European Pharmacopoeia (Ph. Eur.)
- US Pharmacopoeia (USP)
- Japanese Pharmacopoeia (JP)
- ISO 719, ISO 720 (Hydrolytic Resistance)
- ISO 9001
- ISO 15378
- ISO 14001
Glass Advanced Seminar

Training Module VI: Regulatory Demands for Special Glass Tubing
FIOLAX Academy: Training Module VI

Governmental Requirements in General

- Governmental Requirements for Pharmaceutical Primary Packaging
- International and National Standards
- Documents at SCHOTT Tubing
Governmental Requirements in General

European Packaging and Packaging Waste Directive 94/62/EC

Regulation (EC) No 1907/2006
- concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH)

Directive 2002/95/EC
- concerning the Restriction of the use of certain Hazardous Substances in electrical and electronic equipment (RoHS)

Environmental Protection Agency of the United States of America (EPA)
- concerning human health and environment
European Packaging and Packaging Waste Directive 94/62/EC

- aims to harmonize national measures in order to prevent or reduce the impact of packaging and packaging waste on the environment
- aims to ensure the functioning of the internal market
- contains provisions on the prevention of packaging waste, on the re-use of packaging and on the recovery and recycling of packaging waste
- Article 11: Heavy metal limits for packaging Pb, Hg, Cd, Cr (VI) in sum 100 ppm by weight

Glass tubing for pharmaceutical packaging is exempted from this regulation.

- is a regulation of the European Union
- concerns the Registration, Evaluation, Authorization and Restriction of Chemicals
- should ensure a high level of protection of human health and the environment
- should ensure the free movement of substances on their own, in preparations and in articles
- should promote the development of alternative methods for the assessment of hazard substances
- Companies have the responsibility to make an assessment of the hazards and potential risks by substances they manufacture or import (at/above 1 tonne per year). This information is communicated to ECHA.

**Hazard Substances = Substances of Very High Concern (SVHC)**
SVHC are listed in the Candidate List of the ECHA (European Chemicals Agency) which is updated regularly. The List contains 21 organic compounds, 3 organometallic compounds, 12 inorganic compounds (latest update 16 June 2014).

The REACH regulation imposes no duty to register articles made of glass.
SCHOTT REACH Certificate

REACH Declaration of Conformity

The new chemical policy of the European Union, the REACH regulation, entered into force on 1st June 2007. It regulates the manufacture, the import and the placing on the market of substances, substances in preparations and substances in articles.

The Special Glass tubing from SCHOTT are articles under the definitions within REACH, because their special shape, surface and design determines their function to a greater degree than does their chemical composition. The REACH regulation imposes no duty to register articles made of glass, as the included substances are not intended to be released under normal or reasonable foreseeable conditions of use.

We will fulfill our obligations from the REACH regulation. We have checked with our suppliers that all the necessary raw materials for the glass production are treated consistently within REACH.

The supplier of an article containing a substance from the so called "candidate list" of substances of very high concern published by EC, in a concentration above 0.1 % weight by weight shall provide the recipient of the article or the consumer with certain information (Art. 33 REACH).

Glass has been included in Annex V (11) REACH and is regarded as a substance under REACH. Our Special Glass Tubing consist of the substance glass only. Glass itself is not on the "candidate list" and is assumed to be not on it in the future. Thus, there is no duty to communicate information on substances in articles for our glass articles.

Yours sincerely

SCHOTT AG, Site Mittelrhein
Business Segment Tubing
Dr. Bettine Bolles
Product Manager
Pharmaceutical Tubing

SCHOTT AG, Site Mittelrhein
Business Segment Tubing
Dr. Kersten Herrig
Director Quality Management
Site Mittelrhein and
Business Segment Tubing
EU-RoHS / Directive 2002/95/EC

- concerns the Restriction of the use of certain Hazardous Substances in electrical and electronic equipment
- aims to approximate the laws of the member states on the restrictions of the use of hazardous substances in electrical and electronic equipment
- aims that new electrical and electronic equipment put on the market does not contain lead, mercury, cadmium, hexavalent chromium, polybrominated biphenyls (PBB) or polybrominated diphenyl ethers (PBDE)
- list of exemptions exists which is reviewed currently at least every four years

Limits in general:
Cadmium 0.01 % (100 ppm)
All others 0.1 % (1000 ppm)

More information can be found on page www.element14.com/legislation
FIOlax Academy: Training Module VI

Governmental Requirements in General

Governmental Requirements for Pharmaceutical Primary Packaging

International and National Standards

Documents at SCHOTT Tubing
Governmental Requirements for Pharmaceutical Primary Packaging

**United States Pharmacopoeia (USP)**
- <660> Containers – Glass
- <232> Elemental Impurities – Limits
- <1660> Evaluation of the Inner Surface Durability of Glass Containers

**European Pharmacopoeia (Ph. Eur.)**
- 3.2.1. Glass containers for pharmaceutical use
- 5.20. Metal Catalysts or Metal Reagent Residues

**Japanese Pharmacopoeia (JP)**
- 7.01 Test for Glass Containers for Injections

**India IP**
- 6.1 Containers

**Russia GOST**

**China YBB and BP**

Most of other national Pharmacopoeia are aligned with the Ph. Eur. or USP.
Comparison of USP, Ph.Eur. and JP: Hydrolytic Resistance

<table>
<thead>
<tr>
<th></th>
<th>Europe Ph. Eur.</th>
<th>USA USP</th>
<th>Japan JP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glass grain test</strong></td>
<td>0.02 M HCl</td>
<td>0.02 M HCl</td>
<td>vials: 2 ml</td>
</tr>
<tr>
<td></td>
<td>50 ml test liquid</td>
<td>50 ml test liquid</td>
<td>0.01 M H₂SO₄ / 5 g glass</td>
</tr>
<tr>
<td><strong>Surface test</strong></td>
<td>0.01 M HCl</td>
<td>0.01 M HCl</td>
<td>not described</td>
</tr>
<tr>
<td></td>
<td>/ 100 ml test liquid</td>
<td>/ 100 ml test liquid</td>
<td></td>
</tr>
<tr>
<td><strong>Extraction method</strong></td>
<td>autoclaving</td>
<td>autoclaving</td>
<td>boiling 2 hours</td>
</tr>
<tr>
<td><strong>Measurement method</strong></td>
<td>glass grain: titration</td>
<td>titration</td>
<td>titration</td>
</tr>
<tr>
<td></td>
<td>surface: titration and flame AAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Limit Type I acc. surface test</strong></td>
<td>the same depending on the filling volume</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ISO 719 and ISO 720 describe the glass grain test
ISO 4802-1 and ISO 4802-2 describe the container surface test
Comparison of USP, Ph.Eur., JP and Russia GOST: Light Protection

<table>
<thead>
<tr>
<th></th>
<th>Europe / USA Ph. Eur. / USP</th>
<th>Japan JP</th>
<th>Russia GOST</th>
</tr>
</thead>
<tbody>
<tr>
<td>290 - 450 nm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ampoules</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>up to 1</td>
<td>50</td>
<td>For the whole range of wall thickness</td>
<td>50</td>
</tr>
<tr>
<td>&gt; 1 - 2</td>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 2 - 5</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 5 - 10</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10 - 20</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>more than 20</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>up to 1</td>
<td>25</td>
<td>For the whole range of wall thickness</td>
<td>50</td>
</tr>
<tr>
<td>&gt; 1 - 2</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 2 - 5</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 5 - 10</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10 - 20</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>more than 20</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>590 - 610 nm</td>
<td>not specified</td>
<td>not specified</td>
<td>WT ≤ 1.00 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WT &gt; 1.00 mm</td>
</tr>
</tbody>
</table>
Governmental Requirements for Pharmaceutical Primary Packaging

**Russian GOST**
- different glass types for different applications
- transmission dependent on wall thickness of container

**China YBB and BP**
- YBB is the States’ standard – official and important for pharmaceutical industry
- BP is the technical standard – use in other industry

Most of other national Pharmacopoeia are aligned with the Ph. Eur. or USP, e.g. the British Pharmacopeia, used in the former British Commonwealth
FIOLAX Academy: Training Module VI

Governmental Requirements in General
Governmental Requirements for Pharmaceutical Primary Packaging

International and National Standards

Documents at SCHOTT Tubing
Standards for Glass Tubing and Pharmaceutical Primary Packaging

**International**
- ISO (International Organization for Standardization)

**European**
- European Committee for Standardization (CEN)

**National**
- CEN/CENELEC (Comité Européen de Normalisation) (EN)
- ASTM International (American Society for Testing and Materials)
- AFNOR (Association française de Normalisation)
- ANSI (American National Standards Institute)
- BSI (The British Standards Institution)
- DIN (Deutsches Institut für Normung)
- UNI (Ente Nazionale Italiano di Unificazione)
- GOST (Gosudarstvennye Standarty) / Russian Standard
- JSA (Japanese Standards Association)
Standard Procedure for the Development of an ISO Standard

1. A Standard is created by a national Standard Institute – e.g. DIN xyz.
2. This Standard is passed to ISO and circulated as a “New Work Item Proposal”.
3. If there are other national Standard Institutes interested the detailed work starts with one of them as the “Secretariat”.
4. The Standard is published as a draft “ISO DIS”.
5. After “voting” the discussion/correction starts in a meeting.
6. If the new standard is accepted by a majority the “Final Draft” is published as ISO FDIS. Only editorial changes are allowed.
7. The standard is published bilingual (English, French) as a ISO Standard.
8. The ISO Standard is translated into the different languages. If the translation is identical with the ISO Standard the national Standard is published as e.g. DIN ISO.
List of some Standards for Glass Tubing

ISO 695  Glass – Resistance to attack by a boiling aqueous solution of mixed alkali – Method of test and classification
ISO 719  Glass – Hydrolytic resistance of glass grains at 98 °C
ISO 720  Glass – Hydrolytic resistance of glass grains at 121 °C
ISO 1776  Glass – Resistance to attack by hydrochloric acid at 100 °C – Flame emission or flame atomic absorption spectrometric method
ISO 3585  Borosilicate glass 3.3 – Properties
ISO 7884-1/-8  Glass – Viscosity and viscometric fixed points
ISO 7991  Glass – Determination of coefficient of mean linear thermal expansion
ASTM E 438  Standard Specifications for glasses in laboratory apparatus
DIN 12116  Testing of glass resistance to attack by a boiling aqueous solution of hydrochloric acid – Method of test and classification
GIT 8  Annealing of Glass (only in German)
List of some Standards for Containers made of Glass Tubing

ISO 718  Laboratory glassware – Thermal shock and thermal shock endurance
ISO 7459  Glass containers – Thermal shock resistance and thermal shock endurance
ISO 4802-1  Glassware – Hydrolytic resistance of the interior surfaces of glass containers –
           Part 1: Determination by titration method and classification
ISO 4802-2  Glassware – Hydrolytic resistance of the interior surfaces of glass containers –
           Part 2: Determination by flame spectrometry and classification
ISO 7068-2  Glass hollowware in contact with food –
           Release of lead and cadmium – Part 2: Permissible limits
ISO 8113  Glass containers – Resistance to vertical load
ISO 10993-1/-20  Biological evaluation of medical devices

Collection of Standards for Primary Packaging Material for Pharmaceutical use in:
DIN Taschenbuch 231, ISBN 10: 3-410-15464-7
## Comparison of Glass Grain Tests – ISO Standards and Pharmacopeia

<table>
<thead>
<tr>
<th></th>
<th>ISO 719</th>
<th>ISO 720</th>
<th>Ph. Eur.</th>
<th>USP</th>
<th>JP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grain Size min - max</strong></td>
<td>500 µm</td>
<td>425 µm</td>
<td>425 µm</td>
<td>425 µm</td>
<td>850 µm</td>
</tr>
<tr>
<td></td>
<td>300 µm</td>
<td>300 µm</td>
<td>300 µm</td>
<td>300 µm</td>
<td>300 µm</td>
</tr>
<tr>
<td><strong>Purification</strong></td>
<td>Magnet</td>
<td>Magnet</td>
<td>Magnet</td>
<td>Magnet</td>
<td>Water</td>
</tr>
<tr>
<td></td>
<td>Acetone</td>
<td>Acetone</td>
<td>Acetone</td>
<td>Acetone</td>
<td>Ethanol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ultrasonic</td>
<td>Ultrasonic</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Extraction</strong></td>
<td>2 g/50 ml</td>
<td>10 g/50 ml</td>
<td>10 g/50 ml</td>
<td>10 g/50 ml</td>
<td>5 g/50 ml</td>
</tr>
<tr>
<td></td>
<td>98 °C/60 min</td>
<td>121 °C/30 min</td>
<td>121 °C/30 min</td>
<td>121 °C/30 min</td>
<td>100 °C/120 min</td>
</tr>
<tr>
<td><strong>Titration</strong></td>
<td>25 ml</td>
<td>50 ml</td>
<td>50 ml</td>
<td>50 ml</td>
<td>50 ml</td>
</tr>
<tr>
<td></td>
<td>0.01 NHCl</td>
<td>0.02 M HCl</td>
<td>0.02 M HCl</td>
<td>0.02 M HCl</td>
<td>0.02 NH₄SO₄</td>
</tr>
<tr>
<td><strong>Limit Type I</strong></td>
<td>0.1 ml per 1 g Glass</td>
<td>0.1 ml per 1 g Glass</td>
<td>0.1 ml per 1 g Glass</td>
<td>0.1 ml per 1 g Glass</td>
<td>0.3 ml/2.0 ml per 5 g Glass</td>
</tr>
</tbody>
</table>
## ISO Standards for Primary Packaging

<table>
<thead>
<tr>
<th>Product</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vials for injectables</td>
<td>ISO 8362-1 (Blow-back was added)</td>
</tr>
<tr>
<td>Screw-neck vials</td>
<td>ISO 11418-7</td>
</tr>
<tr>
<td>Ampoules with breakring</td>
<td>ISO 9187-1</td>
</tr>
<tr>
<td>Ampoules with OPC</td>
<td>ISO 9187-2</td>
</tr>
<tr>
<td>Prefillable syringes</td>
<td>ISO 11040-4</td>
</tr>
<tr>
<td>Cartridges</td>
<td>ISO 13926-1</td>
</tr>
<tr>
<td>Syringes with luer-slip cone</td>
<td>ISO 594-1</td>
</tr>
<tr>
<td>Syringes with luer-lock cone</td>
<td>ISO 595-1</td>
</tr>
</tbody>
</table>
Some test results of Glass and Glass Containers

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Boro-8330™</td>
<td>Type I</td>
<td>Type I</td>
<td>Type I</td>
<td>HGA 1</td>
<td>HGB 1</td>
<td>Type I, Class A</td>
</tr>
<tr>
<td>NGC</td>
<td>Type I</td>
<td>Type I</td>
<td>Type I</td>
<td>HGA 1</td>
<td>HGB 1</td>
<td>not specified</td>
</tr>
<tr>
<td>NGA</td>
<td>Type I</td>
<td>Type I</td>
<td>Type I</td>
<td>HGA 1</td>
<td>HGB 1</td>
<td>not specified</td>
</tr>
<tr>
<td>ILLAX®</td>
<td>Type III</td>
<td>Type III</td>
<td>not specified</td>
<td>HGA 2</td>
<td>HGB 2</td>
<td>not specified</td>
</tr>
<tr>
<td>AR-GLAS®</td>
<td>Type III</td>
<td>Type III</td>
<td>not specified</td>
<td>HGA 2</td>
<td>HGB 3</td>
<td>Type II</td>
</tr>
</tbody>
</table>

Note: A type I glass tubing does not necessarily result in a type I container!
FIOLEX Academy: Training Module VI

Governmental Requirements in General
Governmental Requirements for Pharmaceutical Primary Packaging
International and National Standards

Documents at SCHOTT Tubing
FIOLAX® Certificate of Conformity

SCHOTT

Mitterteich, 2013-01-01

CERTIFICATE

We hereby certify that the neutral glass tubing of FIOLAX® has been produced by consistently using a Quality Management System according to ISO 9001:2008 and
ISO 15376:2011 as well as in accordance with our Technical Terms of Supply TLB 2009.
The alkali release measured as per the powdered glass test specified for type I glass
according to current US Pharmacopeia typically ranges within the following values:
0.038 ± 0.005 ml 0.02 M HCl / 1 g glass
With a upper limit for the first hydrolytic class (comparable; water resistance class 1 resp.
HGB 1 according to ISO 719 and HGA 1 according to ISO 720) of
0.1 ml 0.02 M HCl / 1 g glass

Our neutral glass tubing of FIOLAX® clear and FIOLAX® amber conforms to the
requirements of the current US Pharmacopeia for type I glass as well as to the stipulations
of all other known pharmacopeias (e.g. current Ph. Eur. and JP). Various tests on containers
made from FIOLAX® tubing have shown that the arsenic release is well below the limit value
of 0.1 ppm As.
The composition of FIOLAX® amber fulfills the requirements for guaranteeing protection
against light, e.g. occ. to current Ph. Eur. and USP for containers with wall thicknesses
according to ISO 9187 and ISO 8362 resp., and after correct thermal treatment of the
containers made of tubular glass.
The content of Barium in FIOLAX® clear is less than 250 ppm.

Declaration of Conformity

The heavy metal contents, e.g. lead, cadmium, mercury and hexavalent chromium of our
FIOLAX® tubing and our packing are below 100 ppm, i.e. considerably below the limit values
of the US and EC regulations (article 11 of stipulations 94/62/CE).

SCHOTT guarantees:

- Constant Type I glass composition (glass grain tests: Type I)
- Constant light protection
- Heavy metal impurities comply with all relevant regulators

© SCHOTT AG
ISO 9001 for all SCHOTT Tubing Production Plants
ISO 15378 and ISO 14001 SCHOTT AG
Global Quality Management
Pallet Label as Conformity Assessment – Supplier’s Declaration of Conformity

**FIOGLAX Academy Module VI: Regulatory Demands**

© SCHOTT AG

---

**FIOGLAX® amber**

**SCHOTT**

- **mean value and standard deviation of OD**
  - OD: 23.499 mm
  - std. dev.: 0.066 mm

- **mean value and standard deviation of WT**
  - wall: 1.097 mm
  - std. dev.: 0.007 mm

- **outside diameter**
  - 23.50 ± 0.19 mm

- **wall thickness**
  - 1.10 ± 0.05 mm

- **tubing length**
  - 1500 mm

- **pallet weight**
  - 955.8 kg

- **production date**
  - MAR / 12

- **SAP material number**
  - 00102831

- **transmission**
  - Glass, hydrolytic resistance grain class ISO 719 - HGB 1 / light transmission (450 nm , 1.00 mm )
  - 14,10 %

- **pallet number contained in code 128**
  - 00102831

- **control number of the tubing lot**
  - 1134345

- **RS article number code EAN 13**
  - 8712404338839

- **containment**
  - see bundle

- **CERT. No.:**
  - 864642

- **ART. No.:**
  - 864642

- **BATCH No. GLASS:**
  - 8414D012

- **15 ug Na2O/g glass**

---

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FIOLAX® – Other available documents

CONFIRMATION OF CONFLICT-FREE MATERIAL SUPPLY

With respect to the Dodd-Frank Wall Street Reform and Consumer Protection Act, we hereby confirm that our Special Glass tubing, which we deliver to you, does not contain any of the so-called Conflict Minerals as defined in Sec. 1502 of said Act.

Nadira Yousuf
Consultant Scientific Services and Compliance
Pharmaceutical Systems / Tubing
SCHOTT AG, site Mitterteich

Organic Contamination in SCHOTT Glass Tubing

We hereby certify that all raw materials used for the production of our glass tubing are of mineral origin.

The melting temperature for the production of our glass tubing is approx. 1600 °C. At this temperature organic compounds do not exist.

Therefore, a contamination of the glass with any organic substance like i.e.

- Aflatoxins
- 2,4-Dichlorophenoxyacetic acid (2,4-D)
- Monuron
- Any benzoates
- Saccharate
- BSF/BSE relevant contamination
- Di(2-ethylhexyl)phthalate (DEHP) or any other Phthalates
- Gluten
- Oils
- Lactose
- Melamine
- PFOS (Perfluorooctanesulfonic acid)
- Solvents
- Polyvinylchloride (PVC)
- Bisphenol A (BPA)

is not possible during melting and production. Moreover, the glass is free of 2-MCP and of any related substances, of nitrosamine-additives and of known nitrosamine precursors. Furthermore the applied coating agent does not contain any of such substances.

SCHOTT
Mitterteich, 2014-02-26

Dr. Bettina Bottres
Director Quality Management
Site Mitterteich and Business Segment Tubing

B. Holler

Dr. Karsten Henning

SCHOTT AG
Tubing

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