Why high quality containers pay off

Florence Buscke, SCHOTT Pharmaceutical Packaging

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Primary packaging is an integral part of the drug and needs careful consideration at an early development stage.

Primary packaging & drug delivery systems are the bridge between drug and patient.
Customer challenges require our solutions

- **Perfect fit for use**
  Stable solution of drug, container and closure system

- **Efficient processing**
  Efficient, fast and flexible processing

- **Safe & easy administration**
  Safe and easy drug delivery

**Customer challenges**

- Drug stability
- Particles & Contamination
- Delamination
- Breakage
- Fill & finish complexity & life cycle management

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Drug contact material – container type and resistance test according to ISO 4802-2

<table>
<thead>
<tr>
<th>Material</th>
<th>Glass</th>
<th>Rubber Stopper</th>
<th>Rubber closure</th>
<th>Lubricant</th>
<th>Glue</th>
<th>Needle</th>
<th>Tungsten</th>
</tr>
</thead>
<tbody>
<tr>
<td>Container Type</td>
<td>Ampoule</td>
<td>Vial</td>
<td>Cartridge</td>
<td>SN PFS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hydrolytic Resistance:**
1h 121°C in autoclave

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Key features of high quality containers

**Perfect fit for use**
Stable solution of drug, container and closure system

**Chemical durability**

**Efficient processing**
Efficient, fast and cost competitive fill & finish

**Functional surfaces**

Lyophilization in SCHOTT TopLyo®

**Safe & easy administration**
Safe and easy drug delivery

**Dimensional accuracy**

© SCHOTT
Key features of high quality containers

- Chemical durability
- Functional surfaces
- Dimensional accuracy

Lyophilization in SCHOTT TopLyo®

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Leachables level in a drug: dependent on contact surface e.g. vials: „Low-Fill“ challenge

Contact surface & filling volume are crucial factors for leachables level

**High filling volume**
Ratio of contact surface to filling volume = small

**Low filling volume**
Ratio of contact surface to filling volume = big
Leachables level in a drug:
ISO norm gives no indication – 8362-1 vs. SCHOTT Quicktest®

Hydrolytic Resistance:
90% of Brimful 1h 121°C in autoclave

Quicktest®: 1ml 121°C

Brimful volume: 4ml
90% brimful volume: 3,6ml
Nominal volume: 2ml
Low-Fill volumes: e.g. 1ml

Brimful calculated by all the geometric dimensions (no measure needed)
Mass: calculated by the geometric parameters and the table 1 has clarified also that the nominal for parameter “Mass”
can deviate about 10% and calculated for 5.1 expansion glass with a given density like FIOLAX® clear.
Both values are a result of the drawing of the ISO vials and the use of Type I Borosilicate glass with density of 2.34g/cm³.
Pre-requisite for superior container quality:
Measure the glass attack & the delamination propensity

Dissolution
Erosion
No risk for lamellae (maybe precipitations)
Example of Errosion: Citrate buffer pH6 24 weeks 40°C:
2R Vials for 24 weeks 40°C:

<table>
<thead>
<tr>
<th>Element</th>
<th>Citrate buffer pH 6.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>B [mg/L]</td>
<td>2.1</td>
</tr>
<tr>
<td>Al [mg/L]</td>
<td>3.0</td>
</tr>
<tr>
<td>Si [mg/L]</td>
<td>20.1</td>
</tr>
<tr>
<td>Si/B-ratio</td>
<td>10.1</td>
</tr>
</tbody>
</table>

Micro-roughness erosion

<table>
<thead>
<tr>
<th>Element</th>
<th>Citrate buffer pH 6.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>B [mg/L]</td>
<td>2.0</td>
</tr>
<tr>
<td>Al [mg/L]</td>
<td>3.0</td>
</tr>
<tr>
<td>Si [mg/L]</td>
<td>18.8</td>
</tr>
<tr>
<td>Si/B-ratio</td>
<td>9.4</td>
</tr>
</tbody>
</table>

No micro-roughness erosion

© SCHOTT
E.g. Selective Dissolution: Sodium bicarbonate buffer pH 8
2R Vials for 24 weeks 40°C:

<table>
<thead>
<tr>
<th>Element</th>
<th>Sodium bicarbonate pH 8.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>B [mg/L]</td>
<td>2.0</td>
</tr>
<tr>
<td>Al [mg/L]</td>
<td>0.045</td>
</tr>
<tr>
<td>Si [mg/L]</td>
<td>8.2</td>
</tr>
<tr>
<td>Si/B-ratio</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Weak porous layer medium erosion

<table>
<thead>
<tr>
<th>Element</th>
<th>Sodium bicarbonate pH 8.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>B [mg/L]</td>
<td>0.75</td>
</tr>
<tr>
<td>Al [mg/L]</td>
<td>0.16</td>
</tr>
<tr>
<td>Si [mg/L]</td>
<td>3.9</td>
</tr>
<tr>
<td>Si/B-ratio</td>
<td>5.2</td>
</tr>
</tbody>
</table>

No porous layer small erosion
E.g. Selective Dissolution and reaction: Phosphate buffer pH7

2R Vials for 24 weeks 40°C:

<table>
<thead>
<tr>
<th>Element</th>
<th>Phosphate buffer pH 7.0</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>B [mg/L]</td>
<td>1.1</td>
<td>0.48</td>
</tr>
<tr>
<td>Al [mg/L]</td>
<td>0.058</td>
<td>0.056</td>
</tr>
<tr>
<td>Si [mg/L]</td>
<td>9.2</td>
<td>4.8</td>
</tr>
<tr>
<td>Si/B-ratio</td>
<td>8.4</td>
<td>10</td>
</tr>
</tbody>
</table>

Compound layer medium erosion

<table>
<thead>
<tr>
<th>Element</th>
<th>Phosphate buffer pH 7.0</th>
<th>Next Generation of Vials</th>
</tr>
</thead>
<tbody>
<tr>
<td>B [mg/L]</td>
<td>0.48</td>
<td>0.48</td>
</tr>
<tr>
<td>Al [mg/L]</td>
<td>0.056</td>
<td>0.056</td>
</tr>
<tr>
<td>Si [mg/L]</td>
<td>4.8</td>
<td>4.8</td>
</tr>
<tr>
<td>Si/B-ratio</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

No compound layer small erosion

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EVERIC® pure

designed for drugs of the 21st century

- Perfect fit for use
  - Stable solution of drug, container and closure system

1. Improved Type I FIOLAX® borosilicate glass

2. Unmatched drug stability

3. Delamination under full control

No need to change registration files

Quicktest® the release criteria

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Pre-requisites for low leachables level in a container: FIOŁAX® CHR

**Feature**
- Reduced hydrolytic resistance for FIOŁAX® limited to 20-30% of the regulatory value
- Supplied with certificate of compliance (COC)
- Produced according to SCHOTT’s current technical performance specification with integrated perfeXion™ technology
- Diameter range from 6.85 up to 30.0 mm; >30.0 mm in development

**Advantage**
Stability for sensitive drugs due to reduced level of leachables and minimized pH-shift
Pre-requisites for low leachables level in a container:
Superior container quality for biologics with low-filling volumes

**Feature**
- Dedicated production line: with much tighter in-process control ensuring a homogeneous wall near bottom area (heel zone)
- Patented SCHOTT manufacturing technology
- Quicktest® for validation & product release
- Supplied with certificate of compliance (COC)
- No re-registration required
- Portfolio Range 2R-30R – 50R in development
- Minimized amount of leached “glass” elements

**Advantage**
Drug stability for low filling
Key features of high quality containers

Chemical durability

Functional surfaces

Lyophilization in SCHOTT TopLyo®

Dimensional accuracy

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Cosmetic/ Functional interactions between glass and drug

<table>
<thead>
<tr>
<th>Fogging</th>
<th>Lyo cake disruption</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Fogging Image" /></td>
<td><img src="image2" alt="Lyo cake disruption Images" /></td>
</tr>
</tbody>
</table>

…Could impact the cosmetic appearance
Standard silicone treatment – silicones adhere to the glass surface, but adhesion is reversible leading to free silicone

Free silicone particles can interact, e.g. with protein based drug formulations* (risk depends on solvent, API, temperature…). It can increase the severity of immune responses and reduce the drug’s tolerability

In this case, hydrogen bonding is the predominant interaction force between silicones and glass


http://www.ondrugdelivery.com: injectable drug delivery 2013 Formulations Focus

© SCHOTT
Baked-on silicone treatment – silicones are administered and adhere to the glass surface by heat treatment

The measurable quantity of free silicone oil is reduced to approx. 10% of the value compared to a non-heat treated siliconisation.

- Additionally to hydrogen bonding, **covalent bonds** are partially established due to the heat process.
- The covalent bond is ~20 times more stable than the hydrogen bond. (~444 kJ/mol O-Si compared to ~21 kJ/mol O-H...O)

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SCHOTT TopLyo® doesn’t use large silicone molecules but a small precursor molecule (HMDSO) leading to stable coating.

Stable, uniform coating, higher density of anchor sites ( ) to substrate compared to baked-on silicon.

Stable, highly crosslinked layer network ( ).

There are no free silicone particles interacting with the drug (e.g. proteins).

This arises from avoiding silicones in the process, the strong layer adhesion to the substrate and the highly stable layer network.

polydimethylsiloxanes PDMS(silicones)
Hydrogen bonding
Covalent bond, attaches layer to glass substrate
Covalent bond, cross-linking the layer

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Improved Lyo-cake aesthetics

**Method:**
The formulation of 0.15 mg/ml human growth hormone, 40 mg/ml mannitol and 10 mg/ml sucrose in a phosphate/glycine buffer pH 7.0 was sterile filtered using 0.2 µm PES filter. 5.0 ml formulation was dried in 6R vials with different surfaces.

- **Lyophilization in Type I glass vials:**
  - Distinct circular disruption
  - Material pulled up before freeze drying

- **Lyophilization in SCHOTT TopLyo®:**
  - Less disruption
  - Less dry material pulling up from the edge
TopLyo® - Improved lyophilization

- Efficient processing
- Elegant lyo cake cosmetics
- Reduced fogging
- Cosmetically perfect lyophilization products

TopLyo® test release criteria:
Key features of high quality containers

- **Perfect fit for use**
  Stable solution of drug, container and closure system

- **Efficient processing**
  Efficient, fast and cost competitive fill & finish

- **Chemical durability**

- **Functional surfaces**
  Lyophilization in SCHOTT TopLyo®

- **Dimensional accuracy**
  Ampoule easyOFC
  Chocolate bar

© SCHOTT
Container dimensions impact functionality and processing

Ampoules  
Vials  
Cartridges  
Pre-filled Syringes

...focus on the system and NOT on individual components

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The Case 2015 – the probability of Japanese market loss

Market Situation:

2015: Appearance of hard to open Ampoules in Japan

Risk: Loosing market due to non-acceptance

Customer does not accept unbreakable or hard to open Ampoules anymore

Business ad risk ~ 1 bn $

2017: customer switched all Ampoules to easyOPC

Breakage fact:

89% of healthcare professionals struggle to open Ampoules

200 mio EUR annual costs of complaint management

ISO Range of breakage is not enough

Market defect rate of AQL 0.4 is not acceptable anymore
The easyOPC solves an industry issue at two key areas

1. Less incoming inspection
2. Less market complaints
3. Unmatched opening performance
4. Reduction of injuries at point of use
5. Reduction of unbreakable ampoules

- Efficient processing: Efficient, fast and cost competitive fill & finish
- Safe & easy administration: Safe and easy drug delivery
- Less quality costs, improved TCO
- No need to change registration files
- Less market and brand reputation risk
Unique position for easyOPC with controlled glass breakage

1. Narrower specification
   e.g. 1-3ml

2. Tightened Specification

<table>
<thead>
<tr>
<th></th>
<th>ISO</th>
<th>easyOPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1ml</td>
<td>25-65N</td>
<td>25-45N</td>
</tr>
<tr>
<td>2ml</td>
<td>25-65N</td>
<td>25-45N</td>
</tr>
<tr>
<td>3ml</td>
<td>30-70N</td>
<td>30-60N</td>
</tr>
<tr>
<td>5ml</td>
<td>30-70N</td>
<td>30-60N</td>
</tr>
<tr>
<td>20ml</td>
<td>30-80N</td>
<td>30-65N</td>
</tr>
</tbody>
</table>

SL or TL easyOPC

AQL 0.4

50ppm in lot

© SCHOTT
Primary packaging has direct impact on patient safety

1. Management of drug container interaction
2. Improved filling-line yield
3. Avoidance of complaints of administration failures

High quality containers pay off!
## Take home messages – High quality containers pay off

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No compromises on tubing: Borosilicate Type I glass tubing is the unmet quality basis for high-end containers</td>
</tr>
<tr>
<td>2</td>
<td>No compromises on container: Converting is integral part of medication due to influence on drug-container-interaction, processing &amp; patient safety</td>
</tr>
</tbody>
</table>
Thank you for your attention