Primary containers and container closure systems
Part I: Bottles, vials, ampoules, cartridges, syringes

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Market share

Source: IQVIA Midas database, GX data
# Requirements towards Injections and Ophthalmics

**FDA Guidance Container Closure Systems for Packaging Human Drugs and Biologics**

- Packaging Description is part of the Registration Dossier
- Material in direct contact to the dosage form
- storage/stability - transport - functionality (device)

<table>
<thead>
<tr>
<th>Protection</th>
<th>Compatibility</th>
<th>Safety</th>
<th>Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>Adsorption</td>
<td>Leachables</td>
<td>CCI</td>
</tr>
<tr>
<td>Light</td>
<td>pH change</td>
<td>Extractables</td>
<td>Drug Delivery</td>
</tr>
<tr>
<td>Water loss</td>
<td>Precipitation</td>
<td>Toxicity</td>
<td>NS pull off</td>
</tr>
<tr>
<td>Loss of solvent</td>
<td>Colour change</td>
<td>Glue or ink migration</td>
<td>Break loose and Gliding</td>
</tr>
<tr>
<td>Oxygen</td>
<td>Packaging brittleness</td>
<td></td>
<td>Elderly people, children</td>
</tr>
<tr>
<td>Microbial ingress</td>
<td></td>
<td></td>
<td>Connections</td>
</tr>
</tbody>
</table>
Requirements

Primary Packaging Containers

Consider packaging from the beginning
Critical contact material
Device (functions) and container at the same time

Physical characteristics
• Standardized by ISO
• Material
• Design, size, wall thickness…
• Breakability

Chemical characteristics
• USP, EP, JP tests
• L&E
• Trace metals, impurities
Requirements
Primary Packaging Containers

Fill and Finish compatibility
• Standardization needed
• Transparency (visual inspection)
• Sterilization

System functionality
• Long term storage
• Opening forces
• Delivery forces
• Stability/interactions with drug substance
• Endotoxin level
• Biocompatibility
• Subvisible particles
• Closure integrity (CCI)
Requirements
Primary Packaging Containers

Patient /end user
- Volume
- Intended use
- Safety
- Market
- Pricing
## Available Systems

<table>
<thead>
<tr>
<th>Container</th>
<th>Advantage</th>
<th>Main application</th>
<th>Material</th>
<th>Alternative</th>
<th>Risk/Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bottles</td>
<td>Big Size</td>
<td>Infusion, oral</td>
<td>Glass and Polymer</td>
<td>Bags and Pouches</td>
<td>Breakage, CCI</td>
</tr>
<tr>
<td>Vials</td>
<td>Common, size range</td>
<td>Injectables</td>
<td>Glass</td>
<td>COP/COC, other polyolefins</td>
<td>Breakage, Delamination, pH shift, handling</td>
</tr>
<tr>
<td>Ampoules</td>
<td>Price, only glass</td>
<td>Injectables</td>
<td>Glass</td>
<td>BFS</td>
<td>Particles, breakage</td>
</tr>
<tr>
<td>Cartridges</td>
<td>standardized</td>
<td>Injectables</td>
<td>Glass</td>
<td>COP</td>
<td>Device needed, 2 closures</td>
</tr>
<tr>
<td>Syringe (PFS)</td>
<td>Packaging and device</td>
<td>Injectables</td>
<td>Glass</td>
<td>COP/COC</td>
<td>Silicone oil, tungsten, functionality</td>
</tr>
</tbody>
</table>
Bottles

Molded Glass Type II and III
- infusion, transfusion
- oral liquids, syrup, tablets etc.
- traditional, 50-1000 ml

- Polymer (oral liquids): PE, PET
- Flexible modern infusion bags and pouches: multilayer, PVC

- Long term storage
- Break resistant, tight (CCI)
- Barrier
- Easy filling
- Easy handling at hospital
- Connectivity
- Hospital use (infusion)

From Gx website
From B Braun website
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Vials

Glass
- Tubular Glass (glass type I, II, III; 2r - 50r), ISO
- Molded Glass (glass type II, III, often >50 mL)
- Screw head, serum, Lyo (blow back)
- Amber, clear
- Bulk or Nested RTF®
- Coated, siliconized, special treatments

Polymer
- COP, Multishell®, Sizes of 2-100 ml
- Bulk or RTU
Ampoules

- Tubular glass Type I
- Clear or amber
- 1 - 30 ml
- Form B, C, D ampoules
- One point cut most frequent
- Particles at opening
- Colour rings
- Siliconization

Figure 1 — Typical examples of OPC ampoules
Cartridges

- Tubular glass type I
- 1.8 ml (dental)
- 3 ml (insulin)
- Amber, clear
- ISO standard, customized
- Bulk, RTF in dev.
- Polymer (COP) in dev.
Prefillable Syringes

Tubular glass Type I
- 0.5 ml - 5 ml, up to 100 ml
- Luer cone, luer lock, staked-in needle
- Bulk, RTF
- Clear, (amber)
- Silicone free in dev.

Polymer
- COP and COC
- 0.5 ml - 50 ml
- RTF
- Infusion pump syringes
Prefillable Syringes

**Glass Barrel** - all syringes are made from borosilicate glass tubes Type 1

**Plunger Stopper** - made from pharmaceutical elastomers, serves as primary seal

**Plunger Rod** – available in appropriate sizes, different materials and in a variety of colours

**Backstop** - enlarges the fingerflange for improved handling and serves as safeguard for the plunger stopper

**Silicone Oil** - acts as a lubricant as it enables plunger stoppers to move easily inside the barrel, ensures long term functionality

**UV Glue** - UV light cures glue to hold cannula in place

**Needle Shield** – sustains sterility, protects needle against damage and user against needle injuries

**Cannula** - made from high quality steel, available in different lengths, diameters and grindings

**Print** - customized ceramic based printing
Market Players

Glass Primary Packaging
- Becton Dickinson
- Stevanato Group (Nuova Ompi)
- Schott
- Gerresheimer
- Nipro
- Bormioli
- SGD
- Wego
- Stölzle
- …

Tubing
- Schott
- Nipro
- Corning
- NEC

COP/COC containers
- Daikyo
- West
- Taisei Kako
- Gerresheimer
- Terumo
- SiO₂
- Schott
- …

- COP: Zeon
- COC: Topas
- Other polymers: diverse
References

Relevant norms and regulations
• ISO 11040-4: Glass syringes ready for filling
• ISO 11040-5: Plunger stoppers
• ISO 11040-6: Plastic syringes ready for filling
• ISO 11040-7: Nest & tub
• ISO 11040-8: Test methods for finished prefilled syringes
• ISO 13926-1: Pen cartridges
• ISO 9187-1 and 2: Ampoules
• ISO 8362-1: Vials from tubular glass
• ISO 8362 and 8536 Infusion and Injection Bottles
• ISO 9001: Quality management
• ISO 15378: GMP Primary packaging
• Ph. Eur. 2.6.14 Bacterial Endotoxins, USP <85> Bacterial Endotoxins Test
• Defect Evaluation Lists Glass, Defect Evaluation Lists Plastic
• Ph. Eur. 3.2.1 Glass Containers for Pharmaceutical Use
• USP <660> Chemical Resistance – Glass Containers; USP <1660> Delamination
• JP 7.01 Test for Glass Containers for Injection

• 4802-2 Hydrolytic Resistance, Container Class HC1

• ISO 80369-7 Small-bore connectors for liquids and gases in healthcare applications (former 594-1 and 2)
More References

- 21 CFR 211, Subpart E “Current Good Manufacturing Practice for Finished Pharmaceuticals”
- 21 CFR 820 „Quality System Regulation – Medical Devices“
- ISO 13485 „Medical Devices – Quality Management Systems”
- ISO 15378 cGMP for Primary packaging Materials
- Ph. Eur. 2.6.1 Sterility, USP <71> Sterility Tests
- ISO 10993-7 Ethylene Oxide Sterilization Residuals DIN EN ISO 11135 Bacterial
- Ph. Eur. 2.4.20 Arsenic, USP <211> Arsenic
- Cannula: ISO 9626 “Stainless steel needle tubing medical dev”
- Rubber: Ph. Eur. 3.2.9 “Rubber Closures for Containers”
- USP <381> “Elastomeric closures for injections”
- ISO 8871 “Elastomeric parts for aqueous par. prep.
- USP <87> or equivalent, USP <88> : Biological Reactivity Tests
- Lubricant: Conformity to applicable Monographs of EP and USP,
- Adhesive: USP <88> “Biological Reactivity Tests, in Vivo”
- BSE/TSE
- Toxic Packaging legislation EC-directives 94/62/EC, 2004/12/EC
- 2005/20/EC directive on packaging and packaging waste
- CONEG Toxic Packaging legislation

Drug master File type III…
Thank you!

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