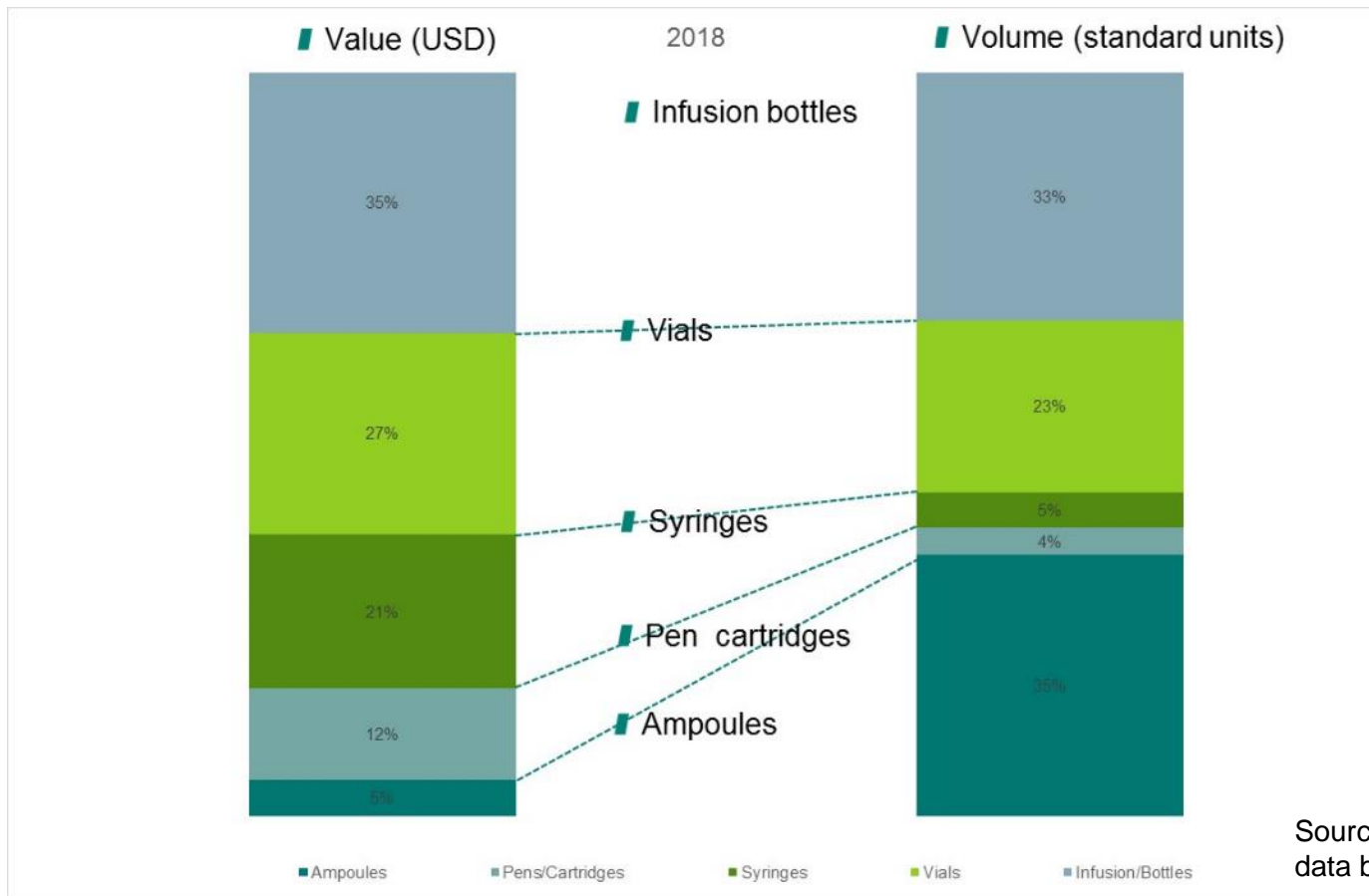


Primary containers and container closure systems Part I: Bottles, vials, ampoules, cartridges, syringes

Bernd Zeiß, Gerresheimer

Market share



Source: IQVIA Midas data base, 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)

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

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

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

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

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

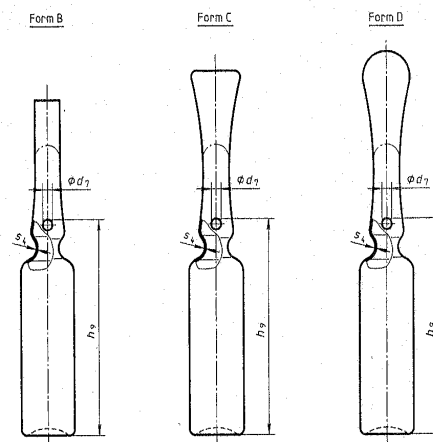
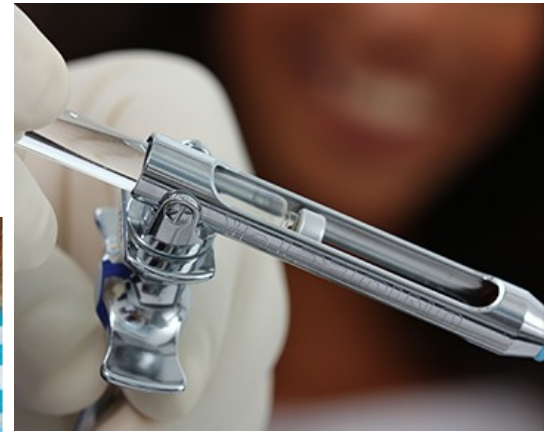


Figure 1 — Typical examples of OPC ampoules



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.*



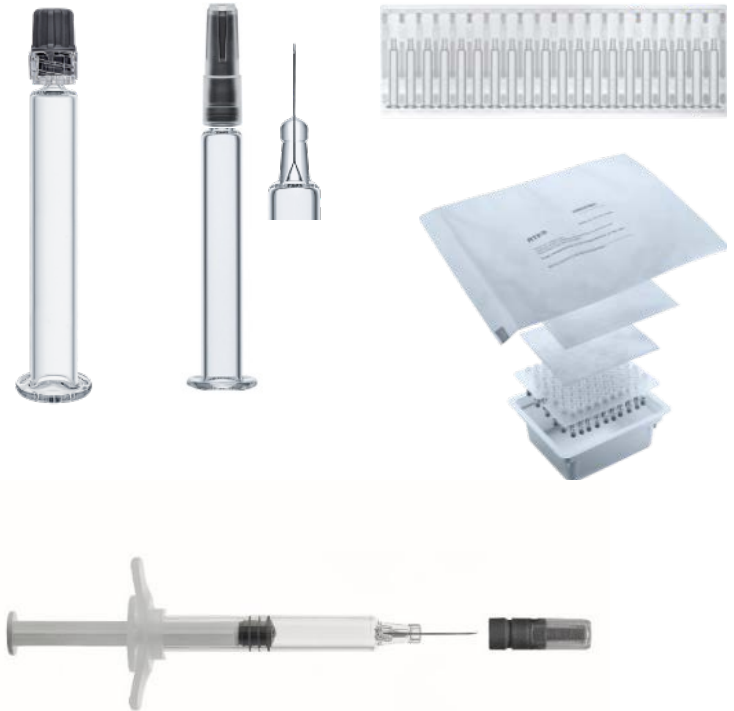
Prefillable Syringes

Tubular glass Type I

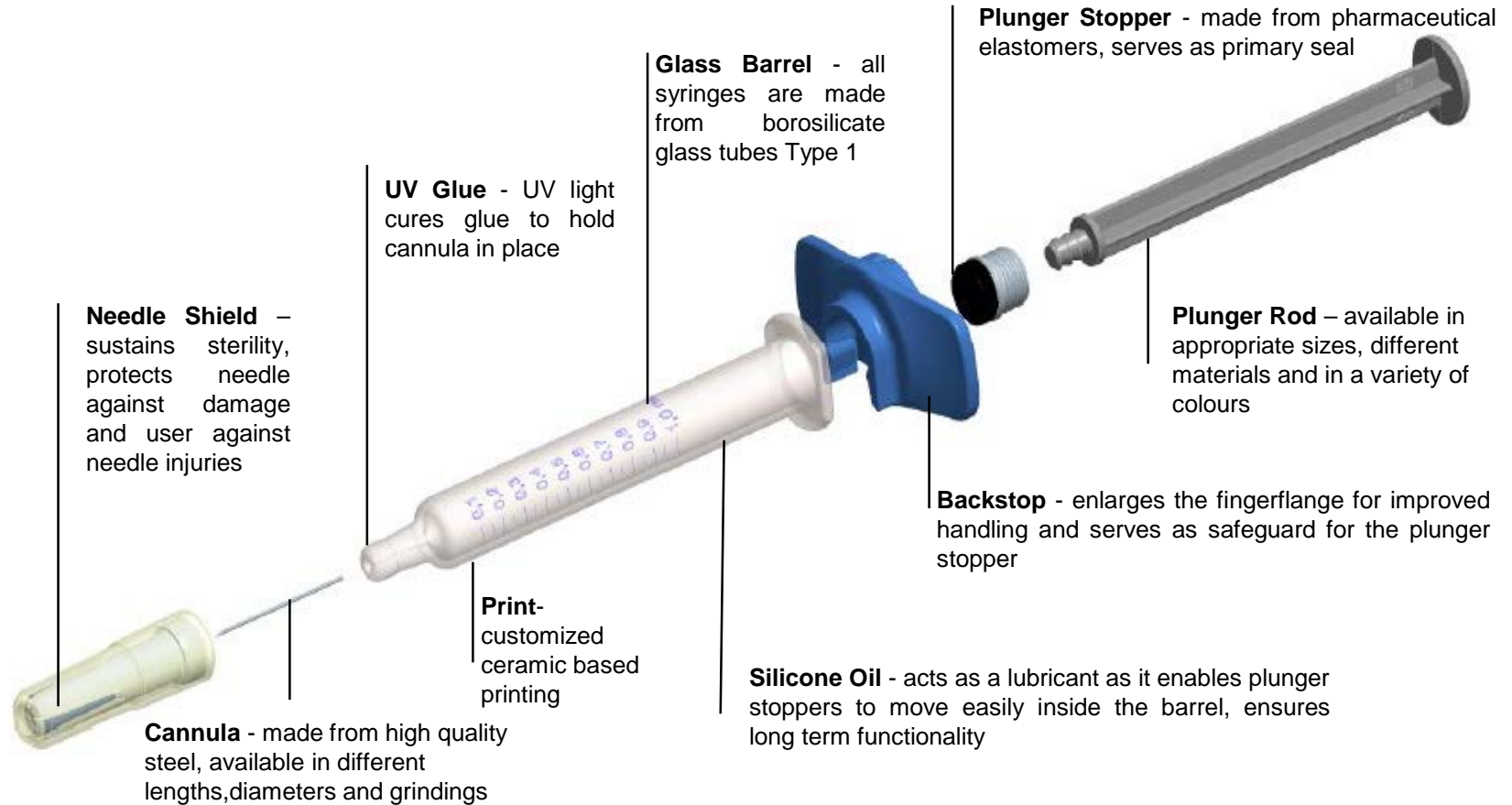
- 0.5 ml - 5 ml, up to 100 ml
- Luer cone, luer lock, staked-in needle
- Bulk, RTF
- Clear, (amber)
- Silicone free *in dev.*

Polymer

- COP and COC
- 0.5 ml - 50 ml
- RTF
- Infusion pump syringes



Prefillable Syringes



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!

Bernd Zeiß, Head of Technical Support
Gerresheimer Bünde GmbH