Primary Packaging Materials Part I: Glass, Polymers

Bernd Zeiß, Gerresheimer

Manufacturing Technologies

Tubular Glass Technology

Injection Molding and Assembly Technology

Moulded Glass Technology

Blow Molding, Injection Blow Molding, Injection Stretch Blow Molding Technology

Glass for Pharmaceutical Use

Composition influences

- Hydrolytic resistance
  - glass attack by water at (121 ± 1) °C for (60 ± 1) min (USP)
  - Further chemical resistance
- Low thermal expansion
  - Break resistance
  - Further physical resistance

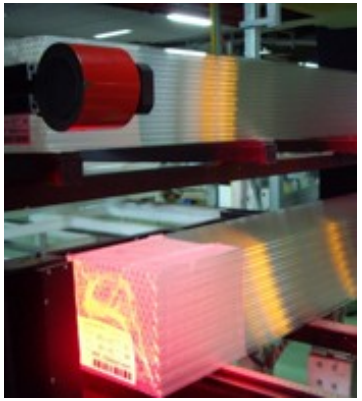
Pharma glass types	Type III	Type II	Type I
Typical composition	Drinkables, non treated low alkalinity glass	Injectable, surface treated NH_4SO_4	Injectable, Borosilciate melts at 1680°C
Sand SiO_2	70%	70%	65-80 %
Soda Na_2O	15%	15%	5-9 %
Limestone CaO	10%	10%	0-4 %
Borax B_2O_3	-	-	12-14%
Overige	5%	5%	8-13 %
Amber glass: iron oxide (Fe_2O_3)			

Glass Molding

Blow and Blow
- press into mold with compressed air

Press and Blow
- Press into mold with metal stamp

Tubing and Converting





Glass Challenges

Packaging development
- Dimensions/tolerances
- pH shift %
- Breakage

Market recall risk
- Particles incl. glass
- e.g. after crimping
- Delamination

Analysis of Safety Signals related to Glass Quality

The Agency evaluated surveillance data to determine whether there were any new or emerging safety signals related to quality issues associated with glass containers used in drug products on the market. FDA analyzed surveillance data from FY 2008 through FY2017. A new safety signal or change in frequency of reports of a known safety concern could reflect the emergence of an issue that would warrant a new or updated advisory by the Agency in order to inform manufacturers. However, FDA's analysis of available data did not identify any new or increasing safety signals since the advisory was issued in 2011. At a recent glass quality conference with presentations by FDA and industry experts, participants noted progress has been made in improving glass quality for pharmaceutical packaging.[2] Given this trend and the lack of any new safety signals related to glass quality issues, FDA will not update the 2011 advisory at this time.

FDA will continue to monitor drug quality, evaluate and assess incidents involving quality issues, and respond with appropriate actions when information suggests a need to correct an issue with drug safety or availability.

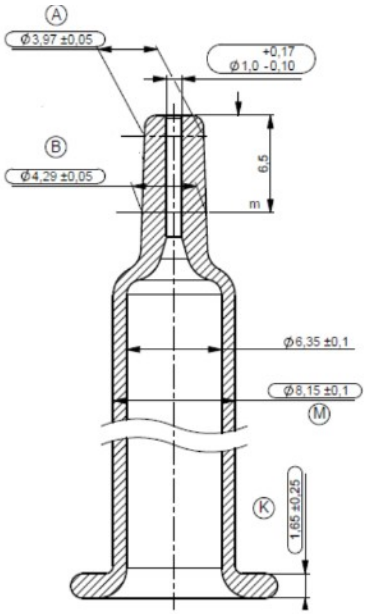
FDA 2019: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm607223.htm

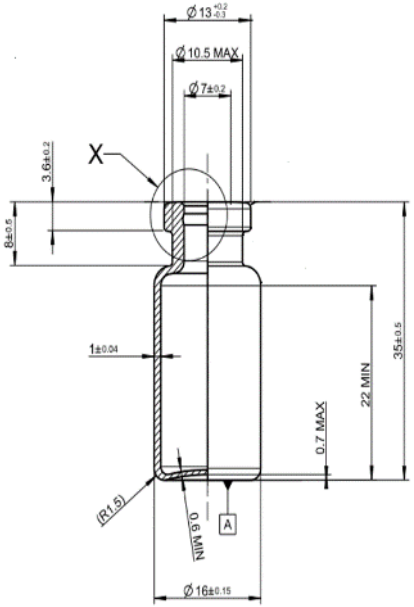
Hospira Issues A Voluntary Nationwide Recall For Labetalol Hydrochloride Injection, USP, Due To The Potential Of Cracked Glass At The Rim Surface Of The Vials

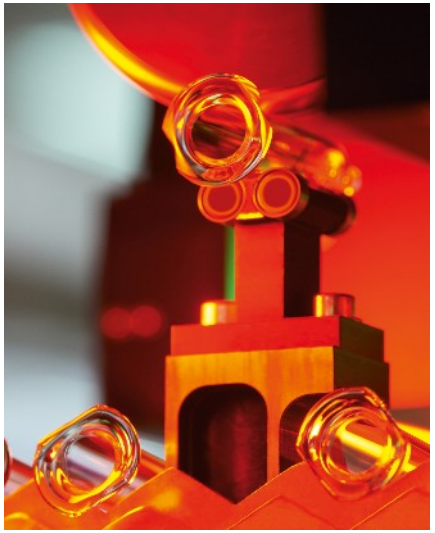
February 23, 2018

Glass Tolerances

- Free forming in tubular glass containers
- Outer dimensions of tubing
- 100% Camera controls – cosmetic and dimensional defects



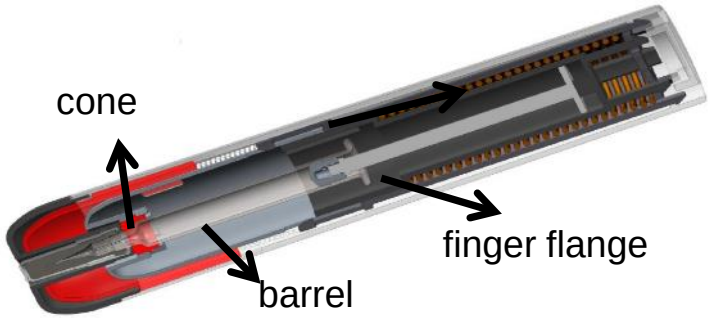




Glass Breakage

- On filling line – main issue line clearance!
- At end user – no major issues
- Syringe breakage in Auto-Injector
  - – syringe to be specified before (cone, finger flange)
- No market issue

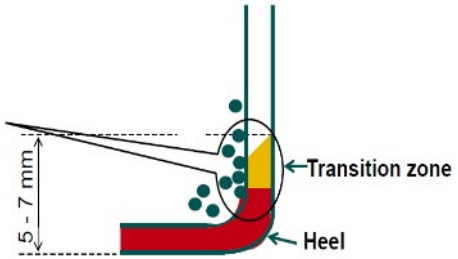
- Avoid glass to glass contact in production
- Strong Improvements over the years

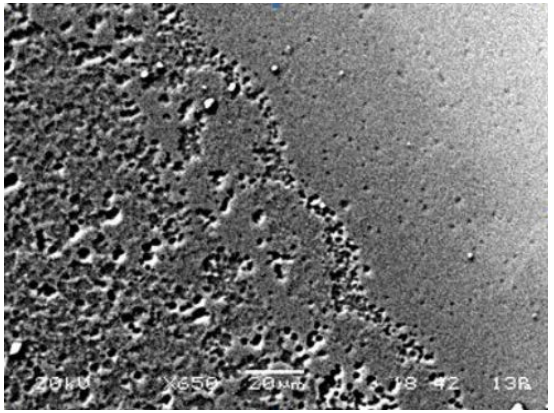


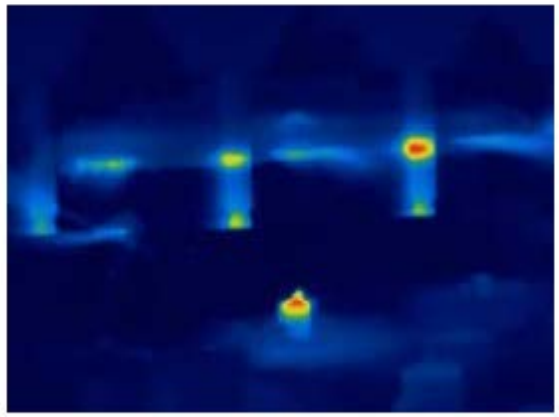
Glass Delamination

Caused by
- certain pH values
- certain buffers (citrate)
- cannot be deteced in empty containers

Delamination control by
- indicative lab testing USP 1660
- controlled temperature in glass container production
- KG33 better
- vial issue, no reports on syringes





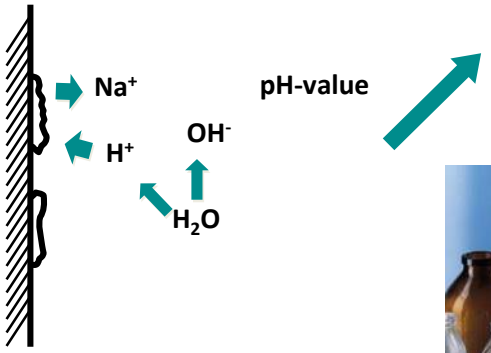


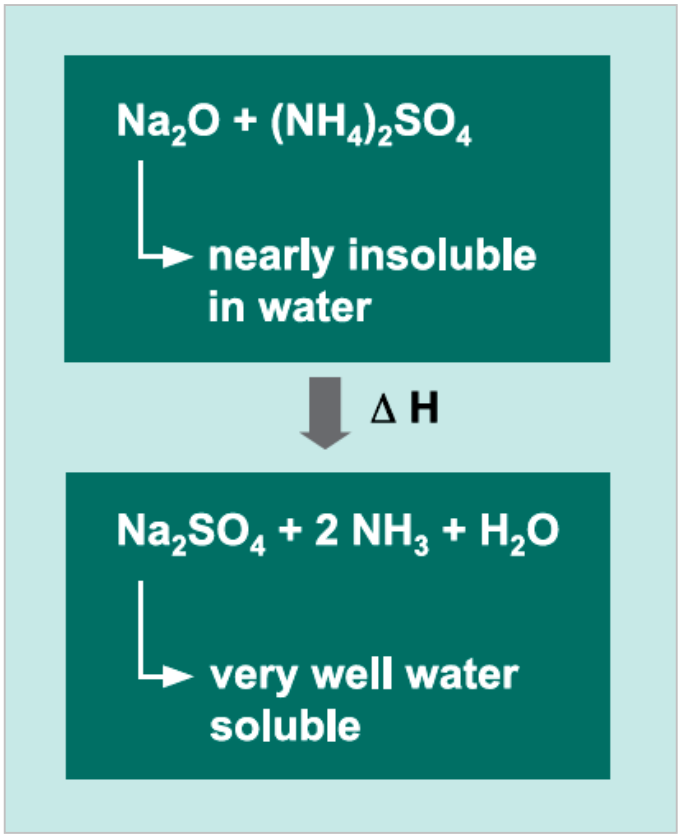
Glass pH shift

Caused by Alkalinity of glass (solving acids)
De-alkalization minimizes pH shift

In high pH environment:

- Sodium oxide from glass releases sodium ions in the liquid
- Ion exchange, pH rise





1. De-alkalize glass with ammonium sulphate at glass converter
2. Wash before filling, less alkalinity, less sodium on glass surface

Glass Trends

Limit Breakage
- Aluminium silicate glass (Corning…)
- Improve durability by process (Nipro…)
- Ion exchange (K+ replaces Na+)

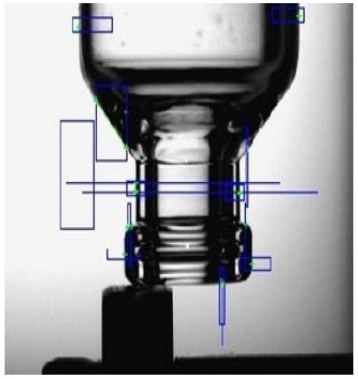
Limit delamination and ion shift
- SiO_2 coating in vials (Schott)
- Delamination proof test (Schott)
- Benign and controlled production (Gx…)

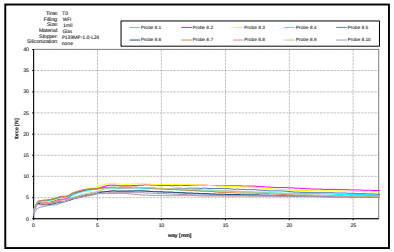
Tighten tolerances
- Tight tube tolerances (Schott,…)
- Sophisticated camera controls (Gx,…)

Others
- RTU vials and cartridges
- Silicone free syringes (new stoppers)

from Schott website

from Stevanato website





Silicone free syringe, Gliding force

Polymers

Thermoplasts:

- Polyethylene (PE), HDPE, LDPE
- Polyvinylchloride (PVC)
- Polypropylene (PP)
- Polyamide (PA, Nylon)
- Polycarbonate (PC)
- Ethylene vinyl acetate (EVA)
- Polyethylen terephthalate (PET)
- Cyclic Olefin Polymer (COP), -Copolymer (COC)
- Polystyrene (PS)

- Polyolefin (mixtures of LDPE, HDPE, PP, EVA)

Duroplasts
Thermoplastic elastomers
Elastomers

Additives in plastic (antioxidants, heat stabiliz, colorants)
Silicone oil, coatings, laquers

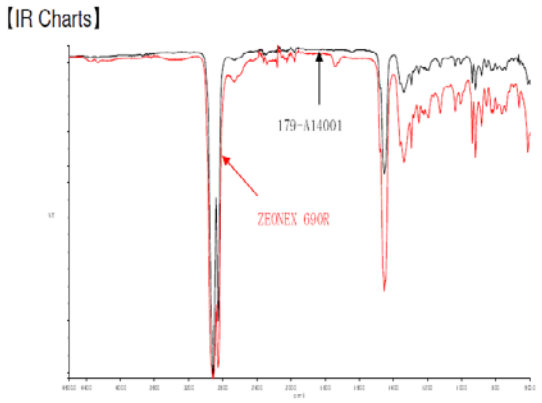
Polymers

USP <661.1> Materials of Construction
- Identification (IR)
- Physicochemical tests (absorbance, acidity/alk, TOC)
- Extractable metals
- Extraction, limit additives, colours
- Biological Reactivity Tests, In Vitro <87>
- Biological Reactivity Tests, In Vivo <88>

USP <661.2> Packaging Systems
- Materials may change during production
- all packaging types: inhalation, nasal, parenteral, oral, topical…
- Leachables and Extractables

EP harmonized with USP

Consider
Technical quality
Microbial limits
Sterilization



EXTRACTABLES STUDY:

DETERMINATION OF THE EXTRACTABLE AMOUNT OF CHEMICAL COMPOUNDS, PRESENT IN AND ON A

COP (CYCLO OLEFIN POLYMER) SYRINGE BARREL AFTER 2 DIFFERENT STERILIZATION PROCEDURES

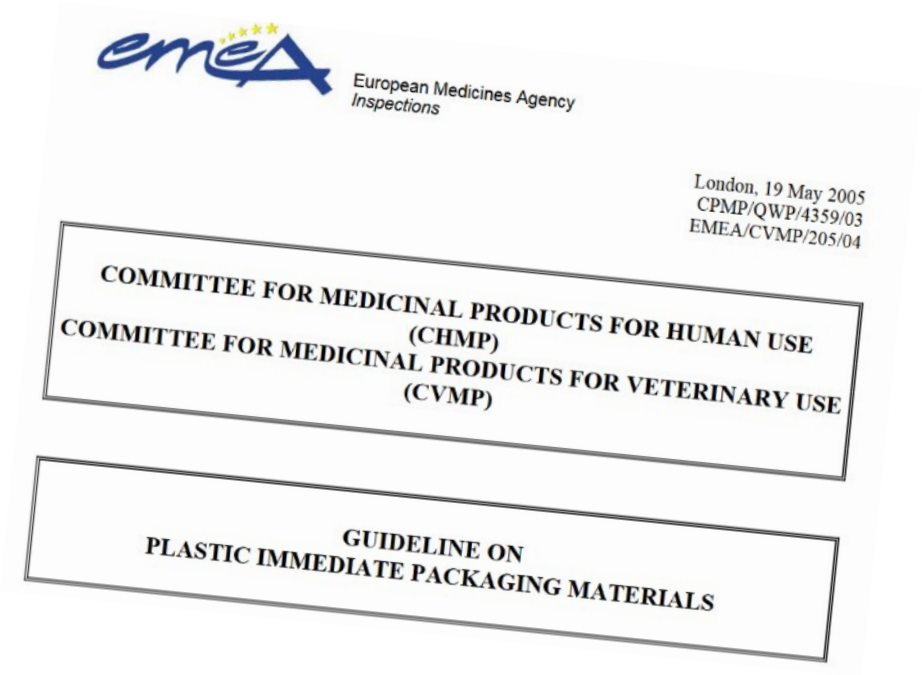
Stability Studies with Polymers

Guideline on Plastic Immediate Packaging Materials –EMEA

- For new registrations
- Not covering elastomers
- Describes developmet data to be handed in
- Decision trees
- Lechables and Extractables

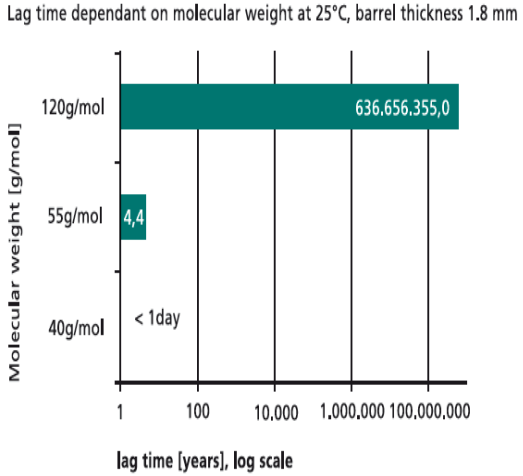
Needed for *non* solids:

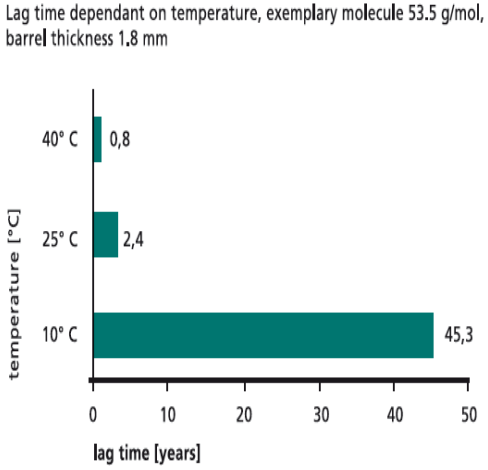
- General information
- Specifications
- Migration studies
- If not in Ph. Eur., additionally:
  - Tox. documentation
  - Extraction studies

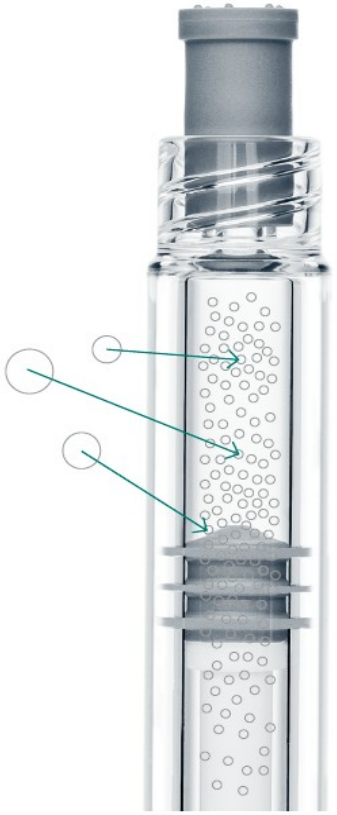


Polymers challenges

- Permeation of vapors and other molecules in either direction
- Leaching of constituents from the plastic
- Sorption (absorption and/or adsorption)
- Many different polmers







Gerresheimer COP migration study

Manufacturing technologies

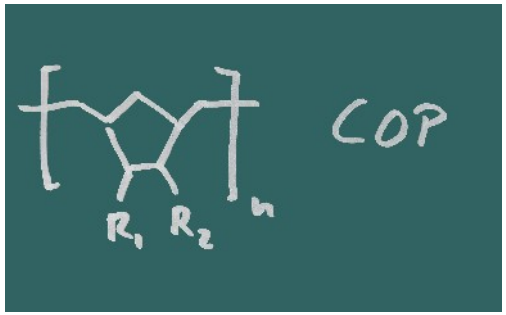
Tubular Glass Technology

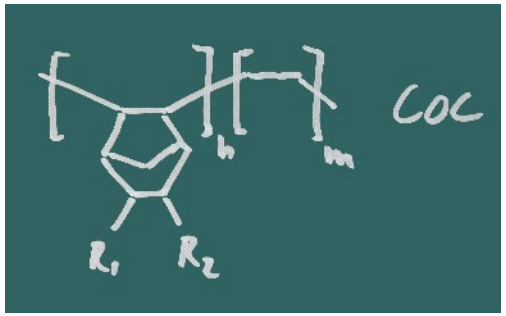
Injection Molding and Assembly Technology

Moulded Glass Technology

Blow Molding, Injection Blow Molding, Injection Stretch Blow Molding Technology

COP/COP





COP and COC

- Glass like transparency
- No pH shift
- No delamination
- Suited for long term storage of drugs

- Not fully gas tight (to be tested with drug)

Gx Multishell vials

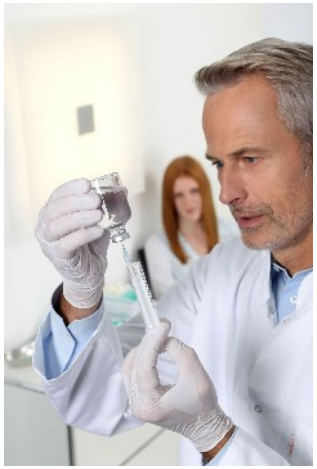
From Gx website

From Schott website

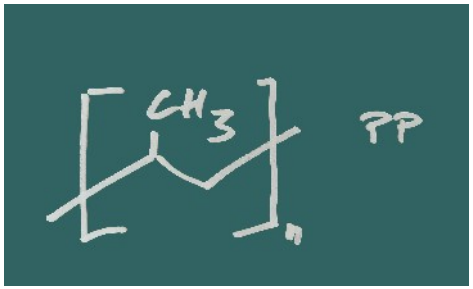
Polypropylene

- Suited for
- Disposable syringes (not PFS!)
- Saline in PFS flush syringes (cleaning IV catheders from blood, hospital use)
- not core PFS market
- Caps made of PP

- Limited transparency
- Brittle below 0° C
- No pH shift
- No delamination
- Not fully gas tight (to be tested with drug)

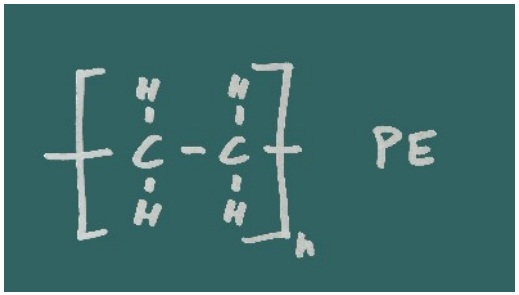


BBraun Flush Syringe



Polyethylene

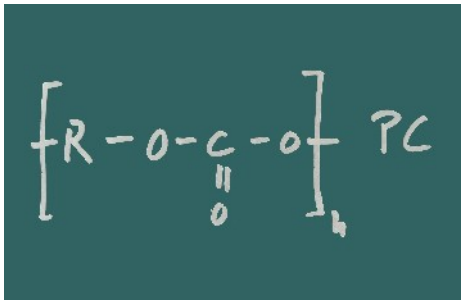
- High Density PE – e.g. HDPE caps
- Low Density e.g. LDPE dropper bottles
- Parenterals and Ophthalmics
- Limited transparency
- No pH shift
- No delamination
- Not fully gas tight (to be tested with drug)

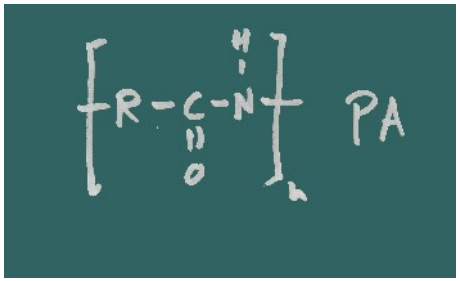


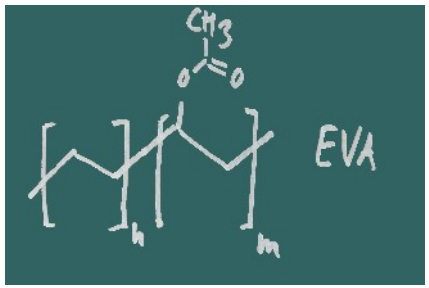
From Gx website

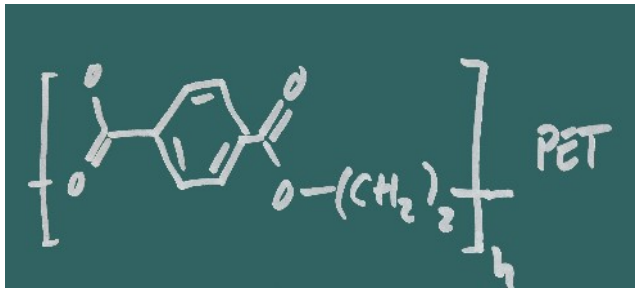
Other Polymers

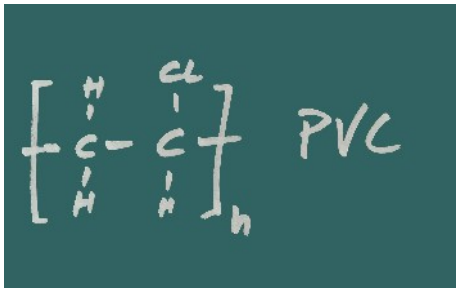
- Polycarbonate (PC)
  - may contain BPA, not primary packaging
  - Luer lock adapter, plunger rods (autoclavable)
- Polyamide (PA)
  - gas barrier layer in Multishell vials, not primary cont. mat.
- Ethylene vinyl acetate (EVA)
  - hoses and infusion containers
- Polyvinylchlorid (PVC)
  - blood and blood products in hoses and bags
- Polyethylen terephthalate (PET)
  - non parenterals
- Silicone
  - hoses and closures





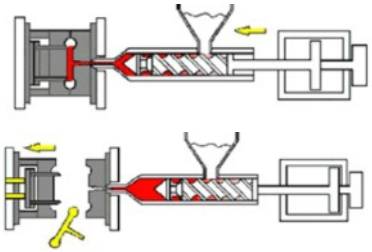






Molding

- Injection molding
- Extrusion Blow molding
- Injection Blow Molding
- Injection Stretch Blow Molding
- Co-injection blow molding
- 2k Molding
- …



Injection moldng, Taisei-kako

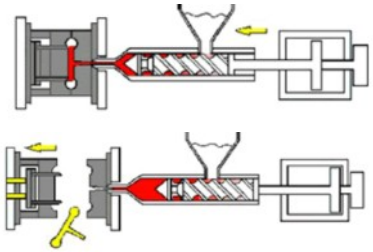
Polymer → Plastify (heat, pressure) → Inject into cavity → Hardening → Take from mold → packaging

Molding

- Tight dimensions
- No washing, clean afterwards
- Complex designs possible

- Shrinkage
- Mold needed
  - Mold making time
  - Cost
  - Surface treatment
  - Injection point/mark

- Cavity number layout



Injection moldng, Taisei-kako

Comparing Polymers 1

Properties	Glass	COP	COC	PP	PE	PA	PET
Break resistance	-	+	+	+	+	++	++
O_2-barrier	++	o	o	-	-	+	-
CO_2-barrier	++	o	o	-	-	+	-
Transparency	++	++	++	+	o	++	++
Steam sterilizable	++	+	+	+	-	+	-
Sterilisable by X-ray	-	+	+	+	+	+	o
Sterilisable by heat	++	-	-	-	-	-	-

++ very good, o neutral -- not acceptable

Comparing Polymers 2

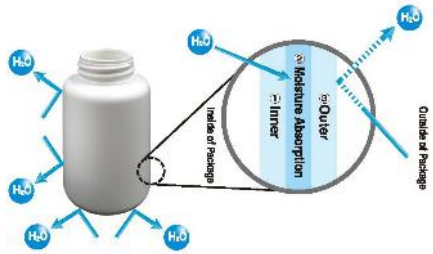
Properties	Glass	COP	COC	PP	PE	PA	PET
Compatibility with drug products	++	+	+	+	+	--	--
Water vapour barrier	++	+	+	+	o	o	+
Chemical resistance	+	+	+	+	+	o	+
pH-resistance	-	++	++	+	+	o	++
Extractables	+	++	++	+	+	+	o
Disposability	+	o	o	+	+	o	o

++ very good, o neutral -- not acceptable

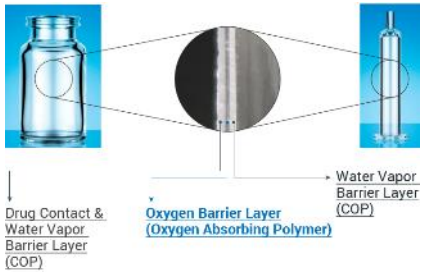
Trends in Pharma Polymers

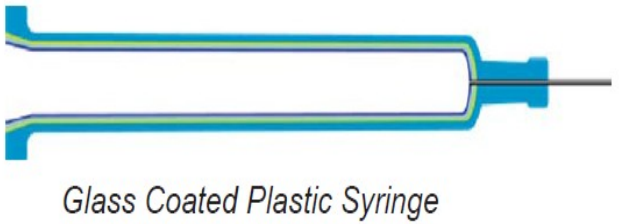
- Improve barrier
- Improve cleanliness (L&E)
- Lubrication

- Blow Fill Seal
- Multilayer
- Coating
- Blends
- Oxygen and moisture scavengers
- 3d Printing?



Mitsubishi Gas Chemical





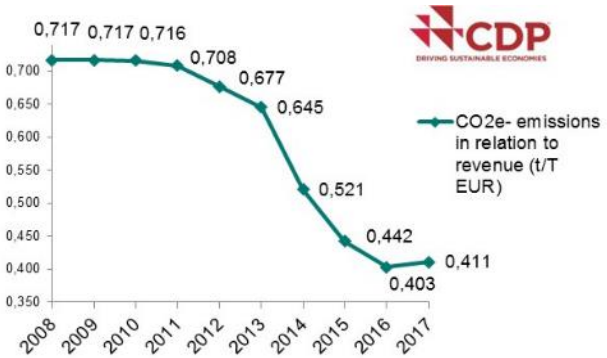
SiO2 Medical

General Trends in Pharma Packaging

Packaging itself
- Child resistant packaging
- Easy opening
- Sustainability
  - CO_2 reduction
  - Biomaterials - bio PE, PET

Devices
- Connected Devices
- Combination Products
  - defined in 21 CFR 3.2(e)

Pharma
- Boost in Biotech
  - sensitve drug compatability
- New trends in lyophilisation
  - more lyo applications



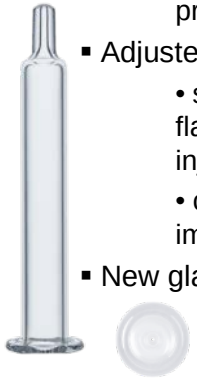
Material Competition - COP vs. Glass syringes

Breakage risk

Addressed by Glass industry

Break resistance improved:

- New production lines
  - No glass to glass contact
  - High end camera inspection (crack prevention)
- Adjusted designs
  - small round finger flange for auto-injector use
  - cone breakage improvement
- New glass types



Wide tolerances

Addressed by Glass industry

Tighter tolerances achieved:

- Improved production technology
- High end camera inspection

Tungsten issue

Addressed by Glass industry

Many approaches to solve tungsten problem:

- Lower, specified tungsten levels possible (<<500 ng/sy)
  - Improvements in production
  - Washing
- Tungsten free production with alloy pins
- Metal free syringes available using ceramic pins

Lubricant free system

Under investigation

- Silicone reduced syringes are available, e.g. baked-on siliconized RTF syringes (90% particle reduction)
- Silicone free glass syringes are possible:

Dedicated rubber stoppers needed

Alternative lubricants (e.g. PFPE)

- new material added

Thank you!

Bernd Zeiß, Head of Technical Support
Gerresheimer Bünde GmbH

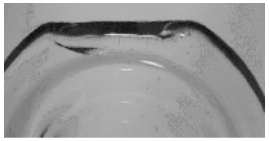
Backup

Polymer Containers for Parenterals

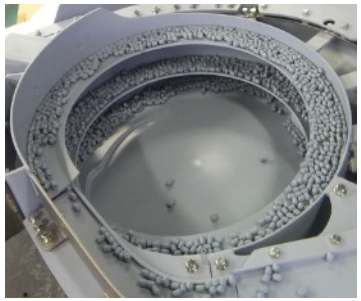
Processing and Quality

Generally all existing filling lines can be used to process COP syringes - Some special requirements:

- Scratch prevention
  - Single transport
  - Soft transport chucks - “Pick and place” preferred
  - Touch syringe outside the main barrel body - gripping the luer lock or finger flange
  - Avoid contact of metal parts (filling needles, pipes, grippers)



Glass defects



- Antistatics, lightweight
  - Slower transport speed compared to glass syringe filling
  - Antistatic prevention to avoid attraction of charged dirt particles

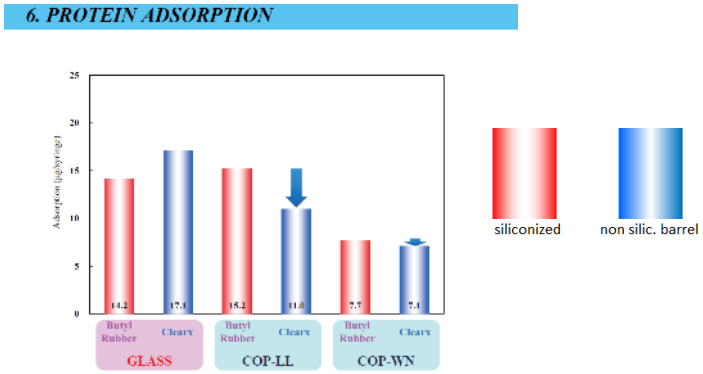
- Adapt visual inspection (“a scratch is not a crack”)
- Adapt benign autoclaving to avoid tip cap pop off and side effects on barrel (whitening of barrel)

Regulations COP and COC

- DMF Type III
- Major chapters of ISO 10993 “Biocompatibility” fulfilled
- USP 661.1 Approvals
- EP , USP, JP Pharmacopoeia approvals
- Chapter 3.1.16 in EP (draft under evaluation at EDQM)
- ISO 11040-6 Prefilled syringes - Part 6: Plastic barrels for injectables

Comprehensive investigations COP/COC

- Materials
- Sterilization (γ, E-beam, steam, EtO)
- Colour change (γ, E-beam)
- Leachables & Extractables
- Protein adsorption
- Break loose and gliding forces
- Gas permeation
- Particles (SVP)
- Auto-injector use
- CCI testing
- Labeling
- Adhesives migration
- Long-term experience



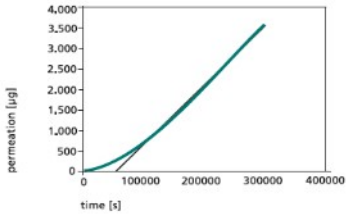
Barrier Properties and Migration of Molecules through COP

Migration depends on
- Barrel material (COP)
- Barrel thickness
- Temperature
- Molecule weight (g/mol) or size (Å3) of migrant

- *Lag time = delay effect of material on permeation*

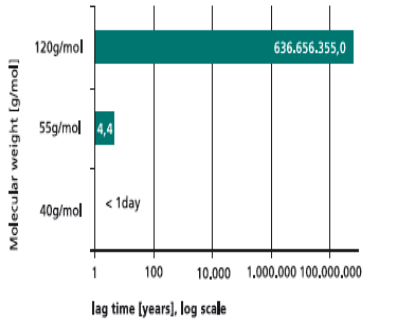
Lag time for COP syringes can be calculated for any known molecule
- Migration into and out of container
- No migration of large molecules
- Can be calculated to save laboratory cost and -time

Exact lag time calculations can be carried out with a calculation tool – the lag time calculator

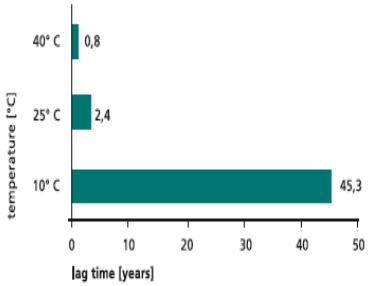


Lag time concept: 2 steps of permeation (migration):
1. Dynamic process: time lag is the difference between the time at which the migrant enters the barrier and time at which a steady state is reached
2. Steady state of permeation (migration)

Lag time dependant on molecular weight at 25°C, barrel thickness 1,8 mm



Lag time dependant on temperature, exemplary molecule 53.5 g/mol, barrel thickness 1.8 mm



Thank you!

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