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Selection of Materials and Surfaces for small volume parenteral primary packaging

Walter Schiess, Schott Pharmaceutical Packaging

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Requirements on primary packaging for injectables

- Permanent protection of the drug
- Clean primary packaging with a very low level of particles and no microbial contamination
- No loss of product during shelf-life
  = No chemical or physical interaction with the filled product

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Increased requirements by sensitive substances

- Liquids “ready-to-inject” preferred to lyophilized forms for cost and handling reasons
- Trend to lower concentrations of active species (adsorption phenomena ?)
- Trend to less additives (detergents, stabilizers, buffers, ...)

→ What material / coating is the most suitable ?

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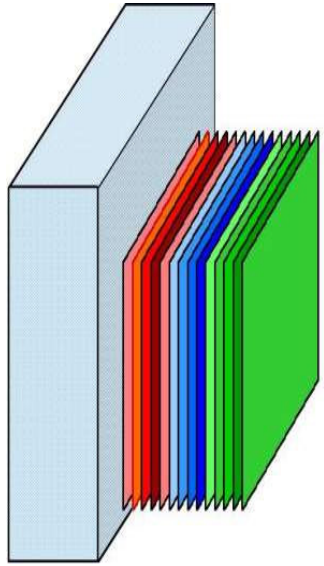
Materials and Surfaces

Borosilicate glass

Polymers
COC /COP



Specific coatings

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Borosilicate glass

Advantages	Limitations
Long term experience, reputation as high grade material	Danger of breakage
Excellent barrier properties	Partly free alkali oxides
High transparency, light protection with amber glass available	Traces of metal ions
High chemical resistance	Adsorption of proteins
High temperature resistance (e.g. heat tunnel sterilization)	Difficult manufacturing process Washing process

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Polymer
as primary packaging material

Central aspects

- Good barrier properties
- Inert product, very low amount of extractables and leachables
- Bio-compatible

COC (Cyclic-olefin copolymer) and COP (Cyclic-olefin polymer) fulfill those requirements

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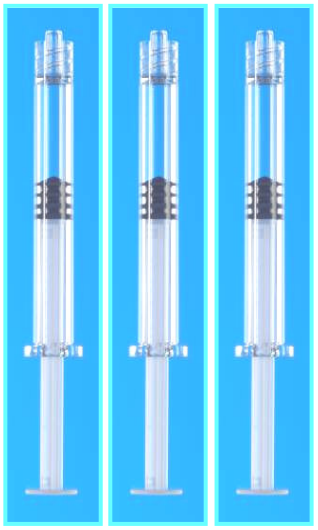
Advantages of COC/COP

- Straight-forward and clean manufacturing process
- Design flexibility
- Strict dimensional tolerances and well defined shapes
- Less defects due to homogenous material
- Break resistant



Schott TopPac®

- *The COP/COC polymers have a limited resistance to oily and fatty substances*

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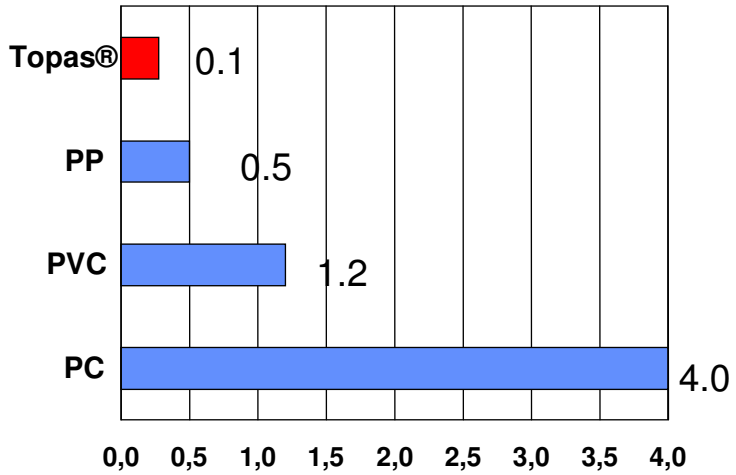
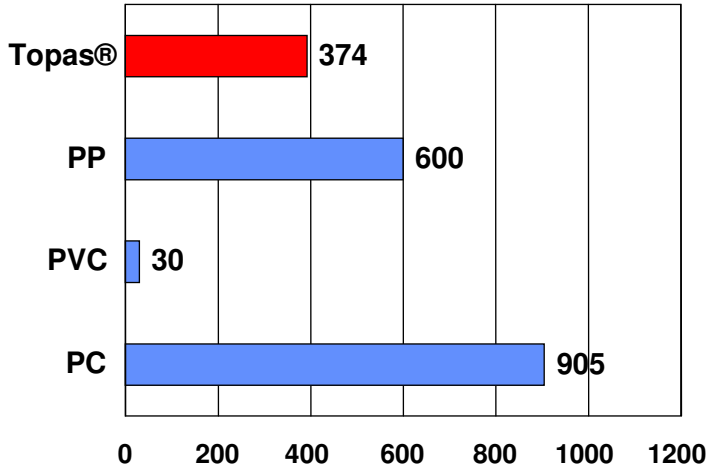
Barrier properties of COC / Topas®

Water vapor permeability



g x 1000 µm / m² x 24h
(40 °C, 90% r.h.)

Oxygen permeability



cm³ x 100 µm / m² x 24h x bar
(23 °C, 0% r.h.)

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Material and possible sterilization methods

Method	COC/COP	Glass
Autoclave 121 °C, 20 min	yes	yes
Gamma irradiation, 25 kGy	yes	*no*
Electron radiation	yes	*no*
Heat tunnel 280 °C, 5 min	*no*	yes
Ethylene oxide	yes	yes

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New drugs in stability studies…
>> packaging challenges with proteins

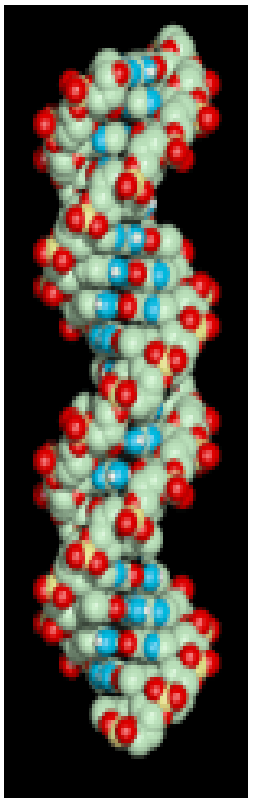
- Proteins are large complex molecules with many reactive sites

  >> various chemical (e.g. oxidation) and physical (e.g. aggregation, precipitation) degradation pathways possible

- Proteins are very sensitive to (glass) surfaces

  >> chemical reactions may be catalysed at surfaces

  >> tend to denature at interfaces between hydrophilic and hydrophobic surfaces



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Interaction Studies - Polymer

Adsorption of proteins -Test results 2003 (University of Munich)

- Bovine Serum Albumin (BSA) vs. Interferon α-2a

- Bulk solutions diluted with isotonic phosphate buffer (0.1 M, pH 7.4, 0.05% sodium azide) to 200 µg/ml

- Storage in vials of borosilicate, siliconized borosilicate and COC (Schott TopPac®)

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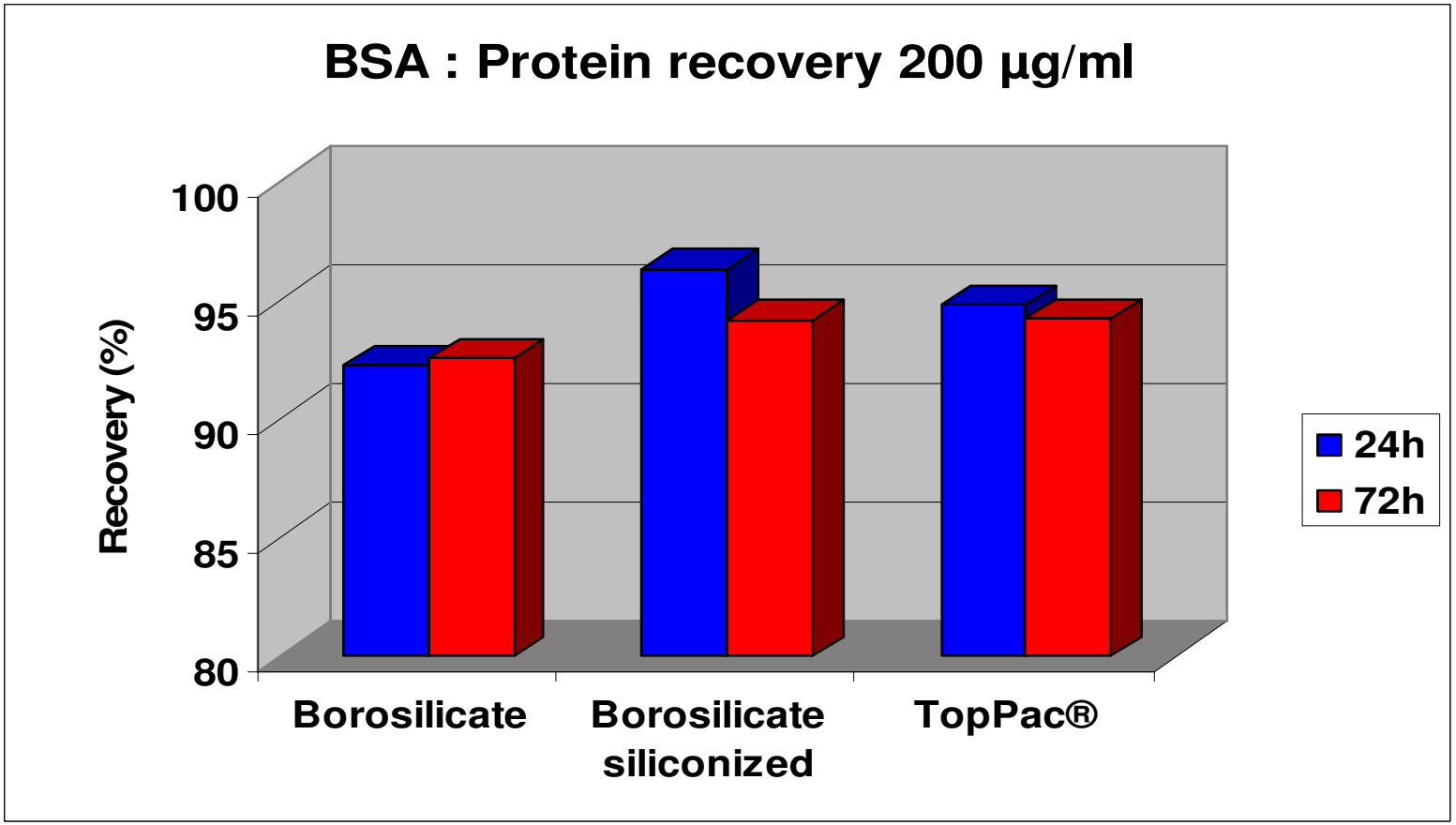
Interaction Studies - Polymer

Bovine Serum Albumin

Shows very similar behaviour of the recovery rate in COC (SchottTopPac®) compared to glass



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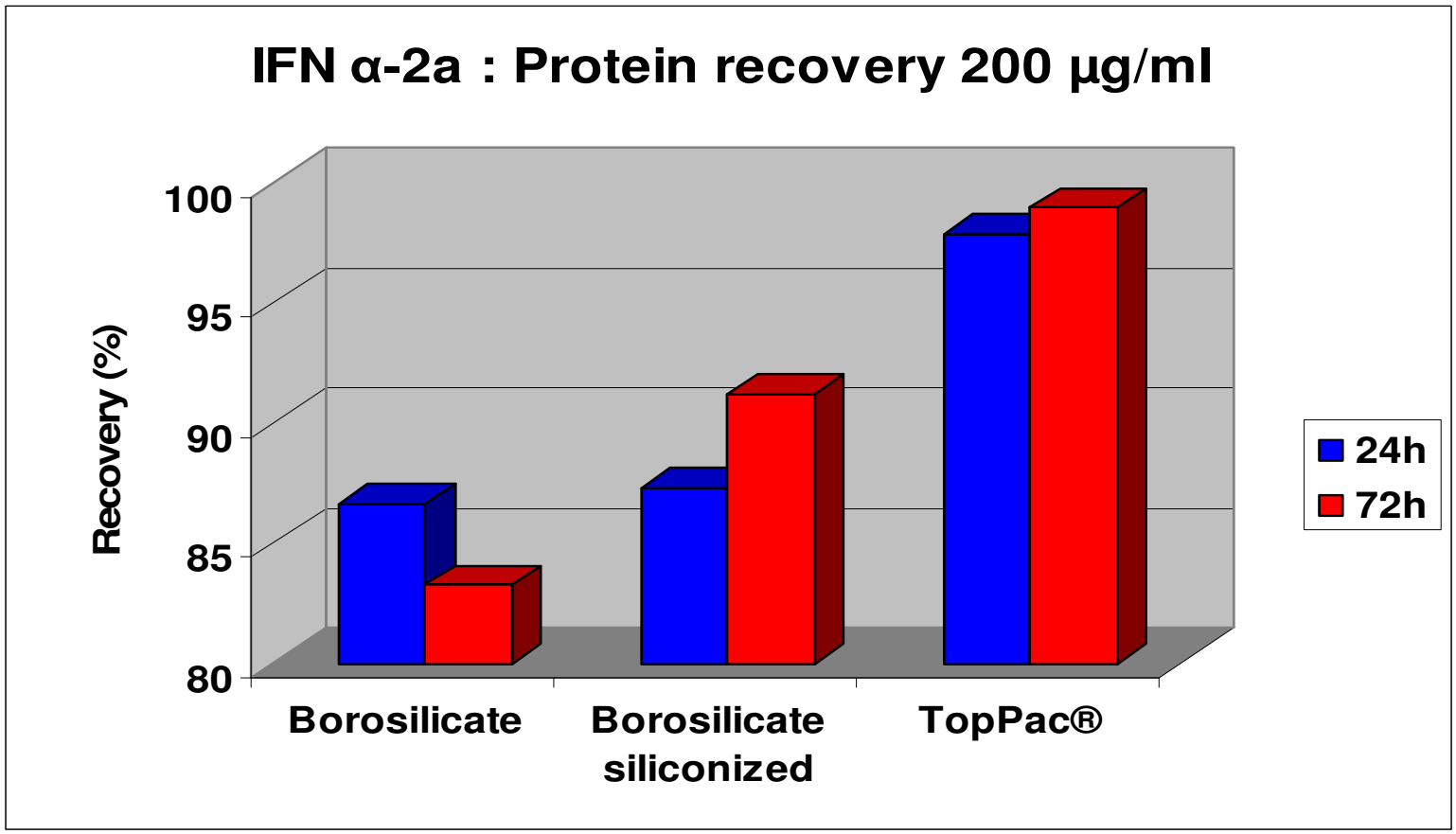
Interaction Studies - Polymer

Interferon α-2a:

Significantly higher recovery rate in COC (Schott TopPac®) compared to glass



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Systemic toxicity after gamma sterilization and autoclaving

EN/ISO 10993-11 "Biological Evaluation of Medical Devices - Part 11: Tests for Systemic Toxicity"

Material	Sterilization Method	Results
TopPac Syringe 6013B-51	Gamma & 121 °C	passed
Topas 8007B-52	Gamma	passed
Topas 6013B-51	Gamma & 121 °C	passed
Topas 6015S-04	Gamma & 121 °C	passed

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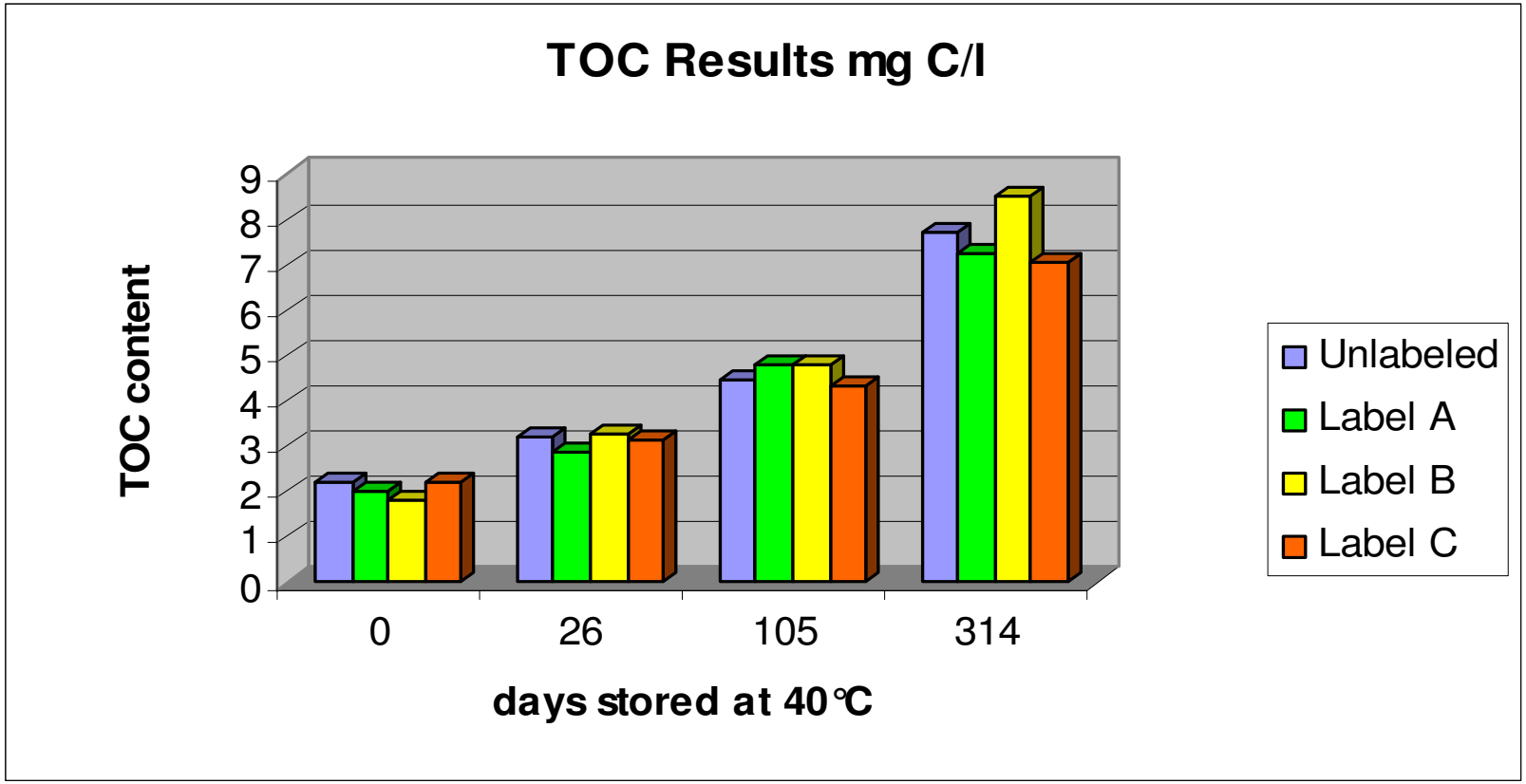
Migration Studies on COC syringes

TOC Analysis of Label Migration Study



No significant difference in TOC between unlabeled and labelled syringes

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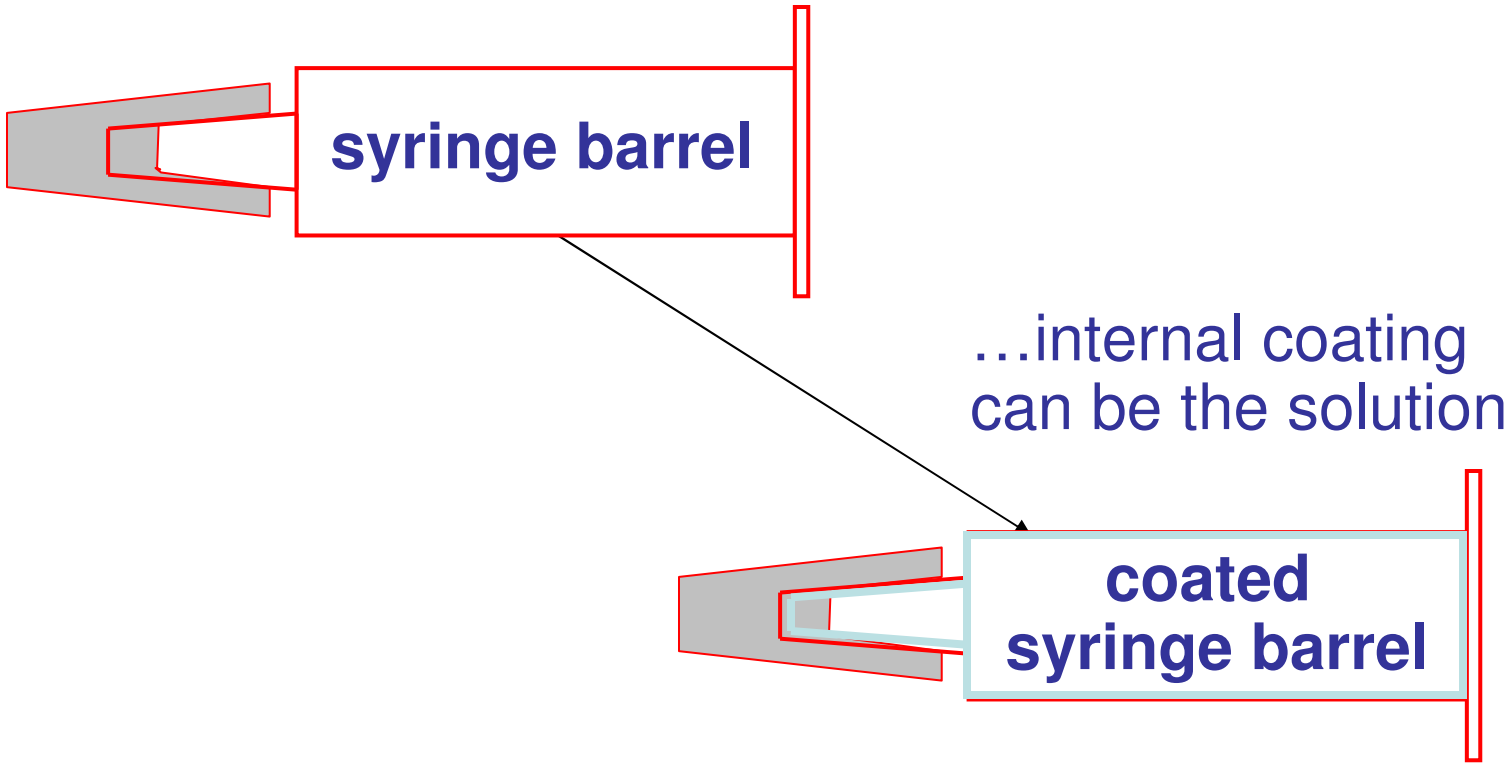
In case a type I glass surface or a COC surface
cannot guarantee the stability of a protein based drug …



PICVD coating (on glass or polymer)

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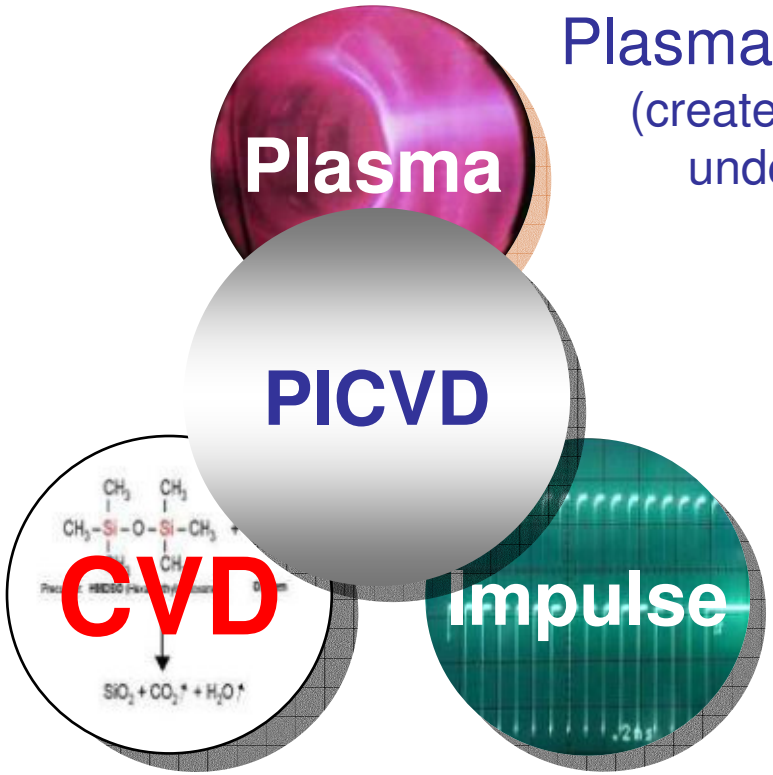
What is PICVD?



Plasma: 4th state of matter
(created at low pressure and under supply of energy)

Chemical Vapour Deposition
(gaseous reactants are deposited onto a substrate e.g. syringe)

Energy supply
(pulsed energy from a microwave source)

= Plasma Impulse Chemical Vapor Deposition
= Schott PI Coating®

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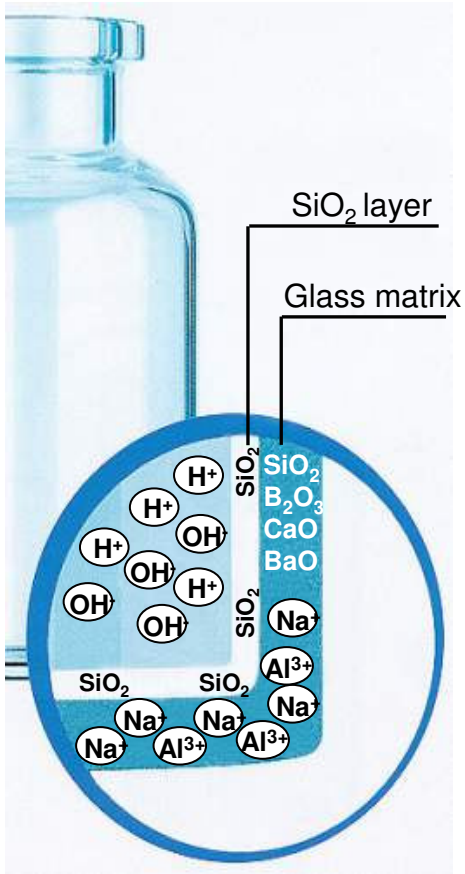
Schott Type I plus®: Pure silica surface



- Quartz-like internal surface
- Covalent bonds to the material
- Chemically uniform
- Density coating (i. e. non-porous)
- No significant dimensional changes: Layer thickness: 0,1 - 0,2 µm
- Available for multiple container formats

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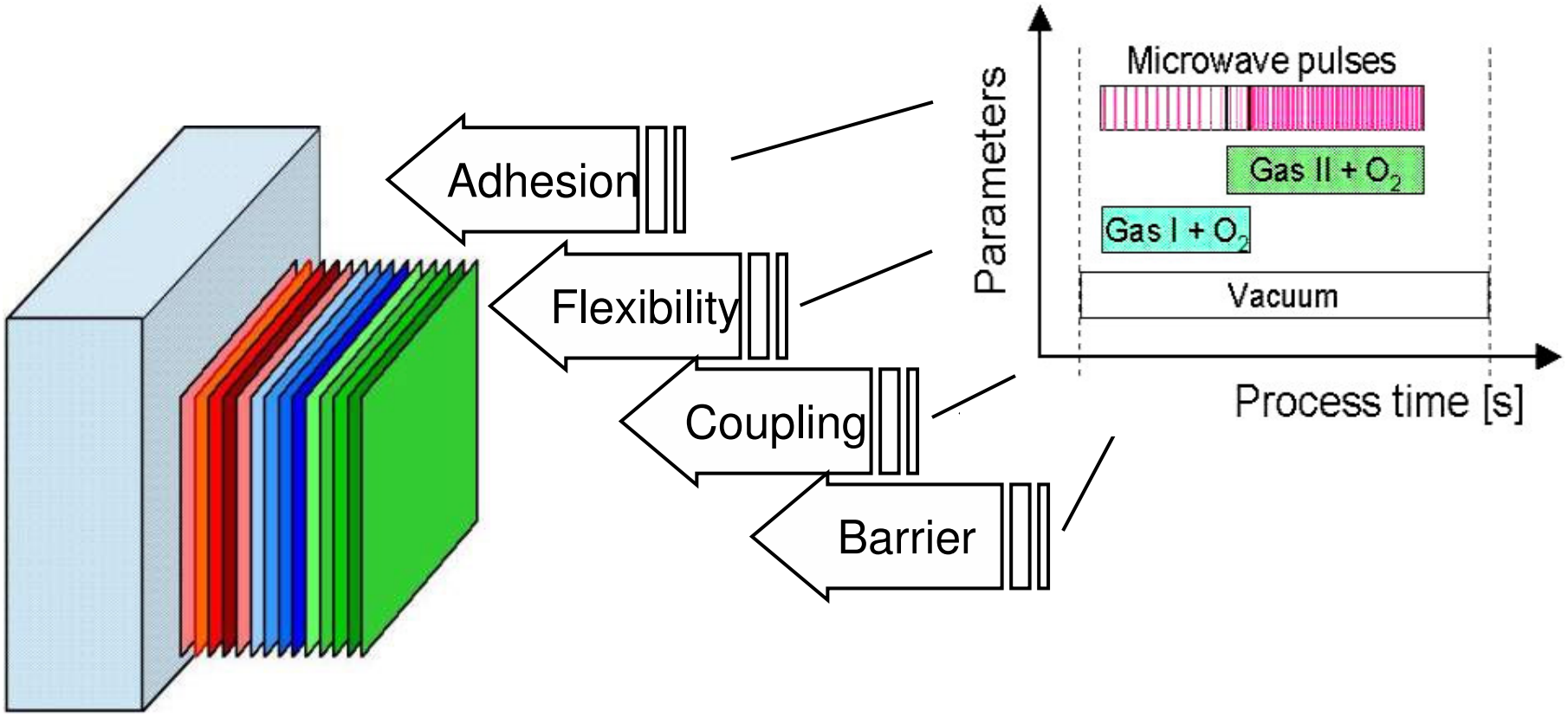
Customized tailoring of the coated layers



Layer designs for glass and polymer available

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Change of properties with specific coatings

Schott PI coating® technology is a powerful tool:

✓ Schott Type I plus®	➔ barrier improvement: reduced ion leaching
✓ hydrophobic Schott Type I plus®	➔ easy emptying of glass vials and improved cosmetics of lyo cake
✓ Polymer materials	➔ barrier improvement: reduced gas and water vapour permeation

Schott PI coating® technology is highly flexible:

- ✓ Coating possible on all pharma packaging formats: vials, cartridges, syringes
- ✓ Adaptation to glass and plastic materials: COC, PET, PP …
- ✓ Customized coatings with layer properties adapted to the active ingredient: hydrophobic coating, protein deterrent coating …

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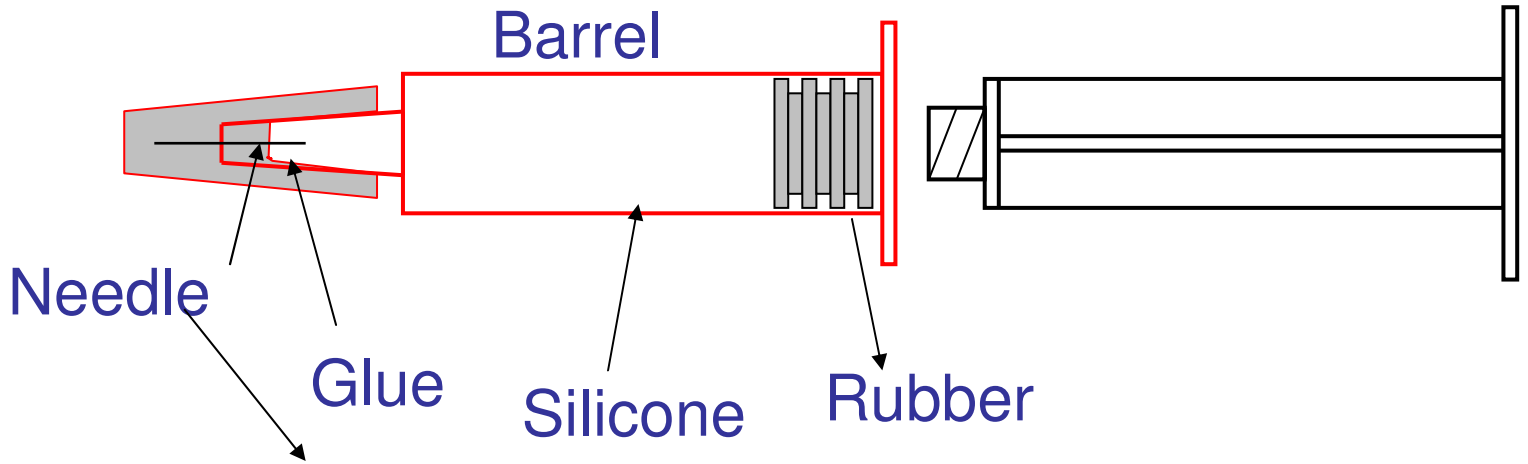
Materials in contact with the drug



Materials which can influence the stability of the drug.

- Glass / Polymer used to manufacture the container
- Closure components as rubber materials
- Silicone
- Metal from the needle
- Extractable out of the adhesive
- Heavy metal ions (Tungsten)

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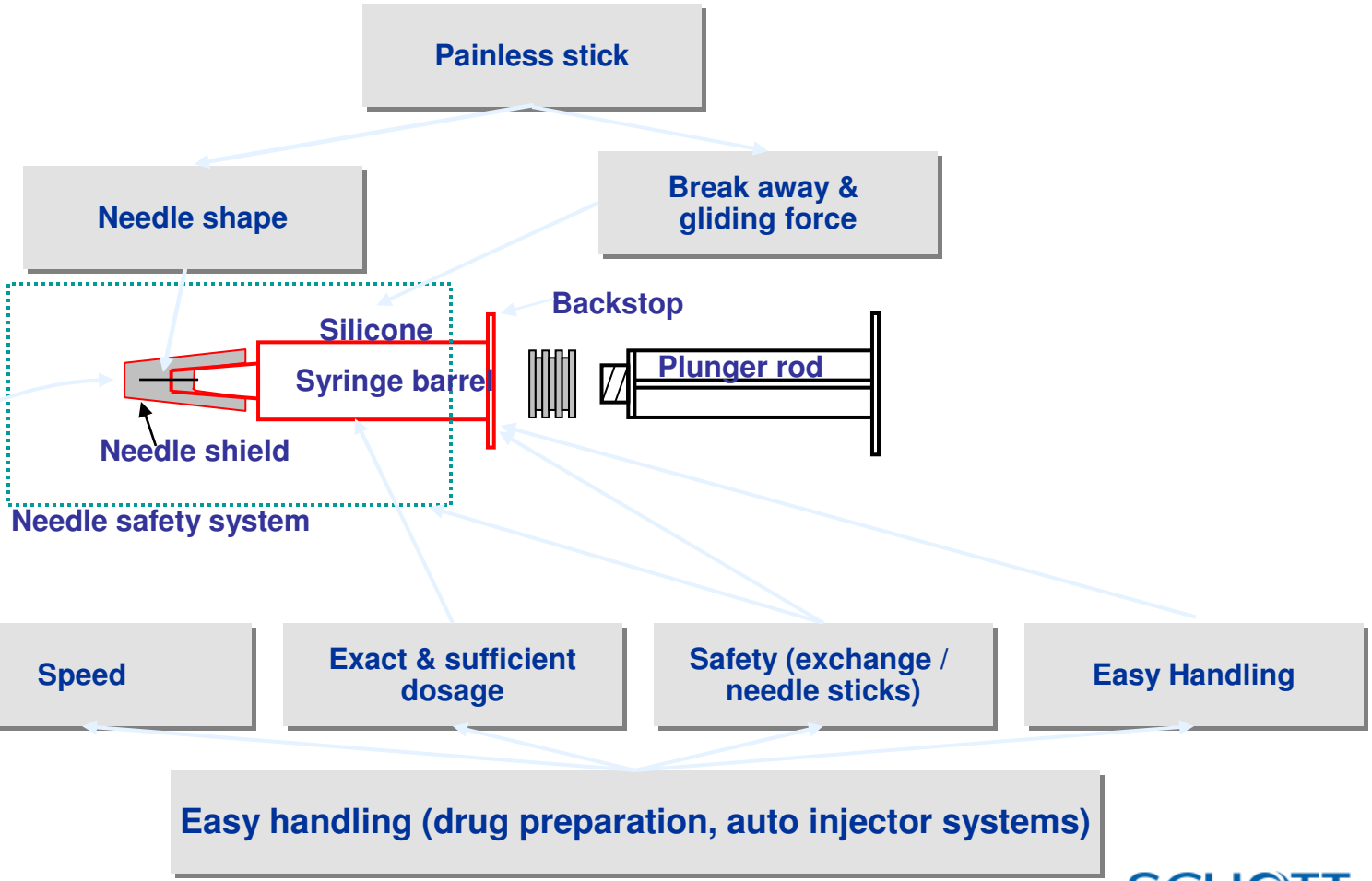
Complexity of Pre-Filled Syringes



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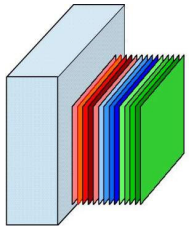
What materials and surfaces will be the best solution in the future

Glass

- Existing products
- Package change from vial to syringe
- High temperature resistance required
- Oxygen sensitive products

COC/COP

- Products sensitive to alkali (wfi, pH shift) and/or metal ions
- Adsorption problems
- Robust container required
- Specific design (big syringes) or integrated functions (e.g. luer lock adapter)



+ Coatings

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