Primary Packaging For Biopharmaceuticals: Challenges & Options

MIBio 2014; Cambridge, UK; 30 Sep 2014

Horst Koller, SCHOTT Schweiz AG

Agenda

1. Glass and Plastics as Packaging Materials
2. Introduction to Extractable and Leachable (E&L)
3. Challenges of Primary Packaging
4. Options for Optimization
5. Summary

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Glass and Plastics as Packaging Materials

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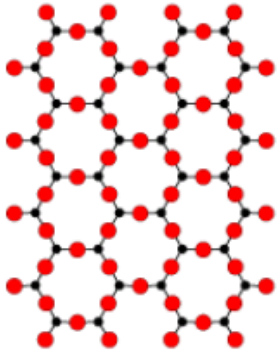
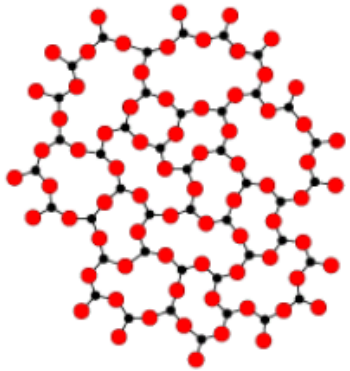
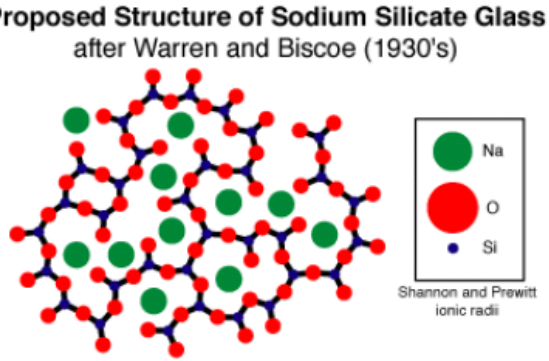
Chemical Composition of Glass



Quarz crystal
MP >2000°C



Quarz glass
MP ~1700°C



- Mixture of crystalline oxides, carbonates, etc.
- Glass is a “frozen super cooled liquid”
- Glass is an inorganic melt, cooled down and solidified without crystallization.
- Considered solid below ~500ºC, without defined melting point because of its amorphous structure.
- Composed of:
  - Network former : SiO_2 (SiO_4^{4-})
  - Network modifiers to lower melting point - Na_2O, B_2O_3, PbO
  - Stabilizers to improve durability - CaO, Al_2O_3
  - Colorants as needed - Fe_2O_3 - TiO_2

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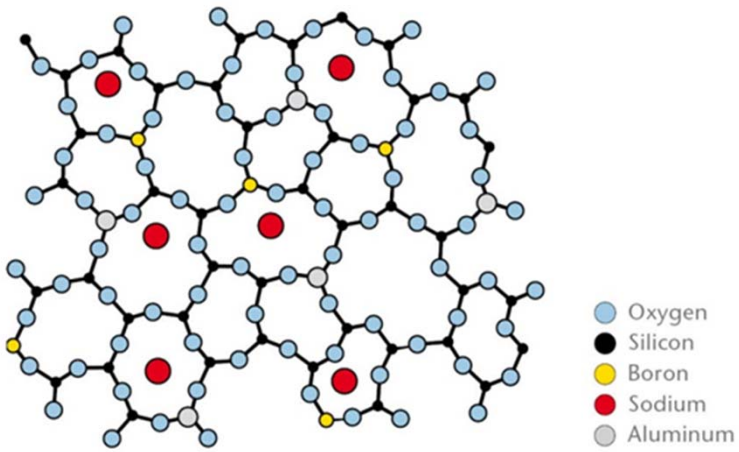
Chemical Composition of Glass



- → Potential E & L from glass:
- Silicon
- Oxygen
- Sodium, Potassium
- Aluminum
- Boron
- Calcium, Magnesium, Barium

Hydrolytic Resistance Class				
I	I	I	III	III
FIOLAX® clear	**FIOLAX® amber**	**BORO-8330™**	**ILLAX®**	**AR-GLAS®**
Si	Si	Si	Si	Si
O	O	O	O	O
Na	Na	Na	Na	Na
Al	Al	Al	Al	Al
B	B	B	B	B
Ca	Ca	K	Ca	Ca
	Fe		K	K
	Ti		Mn	Mg
	K		Fe	Ba
	Ba		Ba	

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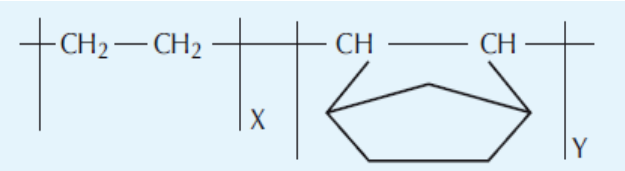
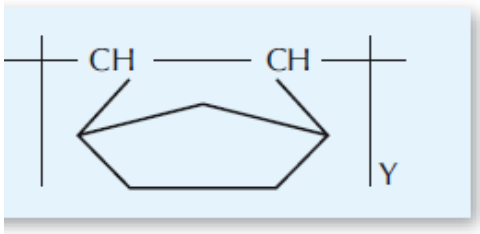
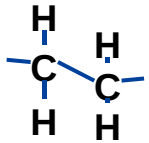
Chemical Composition of Plastics



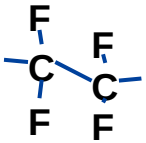
COC: Cyclic Olefin Copolymer



COP: Cyclic Olefin Polymers

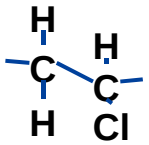


PE: Poly-Ethylene



PE: Poly-TetraFluor-Ethylene

PP: Poly-Propylene



PVC: Poly-Vinyl-Chlorid

- Polymerization of Monomers; cyclic and / or linear
- Amorphous and non-amorphous structures
- Different glass transition temperatures
- Composed of:
  - Antioxidants
  - Colorants
  - UV Stabilizers
  - Catalysts
  - Slip Additives

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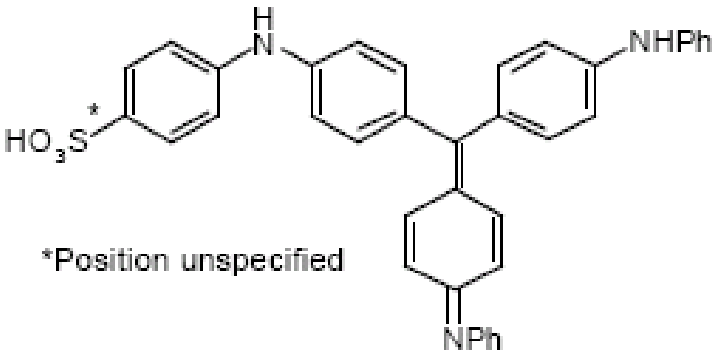
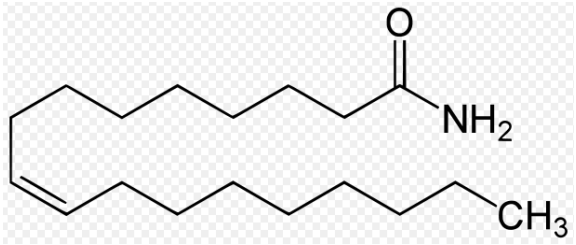
Chemical Composition of Plastics

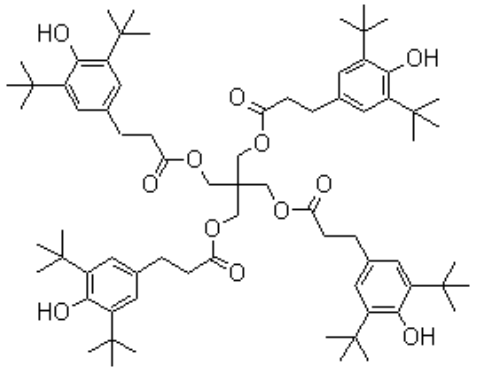
- → Potential E & L from plastics:
- Lubricants
- Monomers
- Oligomers
- Degradation products
- Solvents



Ultramarine Blue



Oleamide



Pentaerythritol Tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate) [Ix1010]

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2. Introduction to Extractable and Leachable (E&L)
3. Challenges of Primary Packaging
4. Options for Optimization
5. Summary

Introduction to Extractable and Leachable (E&L)

- **Extractables:**

Components of a certain packaging material that are released during a certain **stress test procedure** (e.g. aggressive solvents, exaggerated conditions of time and temperature)

Extractables are determined by exposing components or systems to conditions that are more severe than normally found in a biopharmaceutical process, typically using a variety of solvents at high temperatures. The goal of an extractable study is to identify as many compounds as possible that have the potential to become leachables.

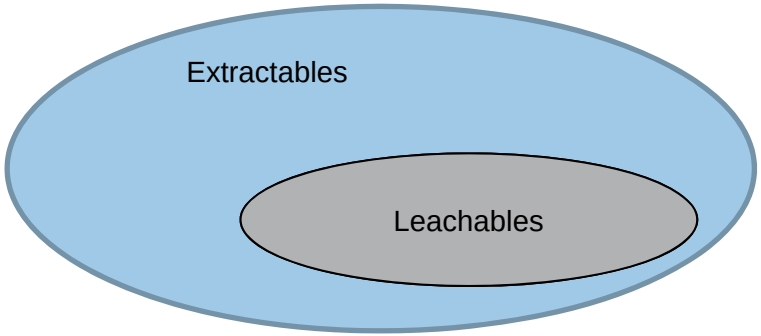
- **Leachables:**

Components of the container closure system that are migrating into the drug formulation during **usual production process and storage**

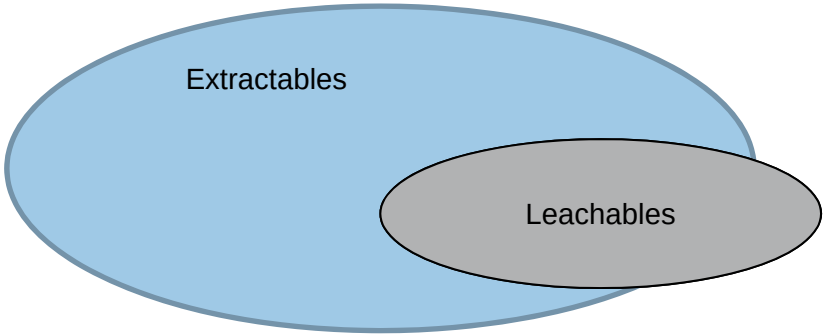
Up to now it was believed that leachables are a subset of extractables. Nowadays it has become more clearly that there is a possibility of the occurrence of leachables that are not detected by the usual extractables screenings e.g. because they form under special and different conditions between the drug formulation and some material components. It is thus not recommended to rely solely on Extractables data.

Introduction to Extractable and Leachable (E&L)

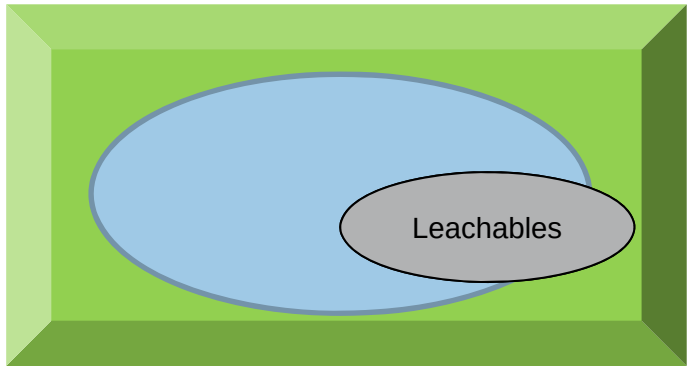
THEORY



PRACTICE



Closing the GAP



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Challenges of Primary Packaging (E&L)

The occurence of potential extractables and leachables from the container material are influenced by multiple factors:

- Glass Composition / Plastic Composition
- Converting Process: Hot Forming / Injection Molding
- Container Size / Volume Ratio
- Container Lubrification: Silicone Oil in Syringes / Vials
- Drug Product: pH-Value, Complexing Agents, Buffers, Solvents
- Storage Conditions

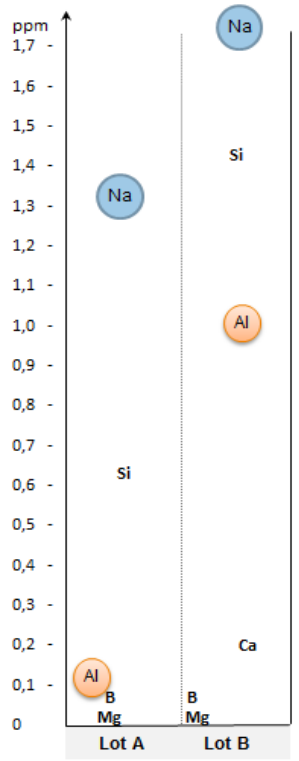

Figure 1

Figure 1 shows the difference in extractables concentration depending on the temperature during converting. 2ml ampoules from Lot A were converted with high temperature and Lot B with low temperature. An extraction according to ISO 4802-2 showed higher values for Sodium and Aluminum in case of Lot B.

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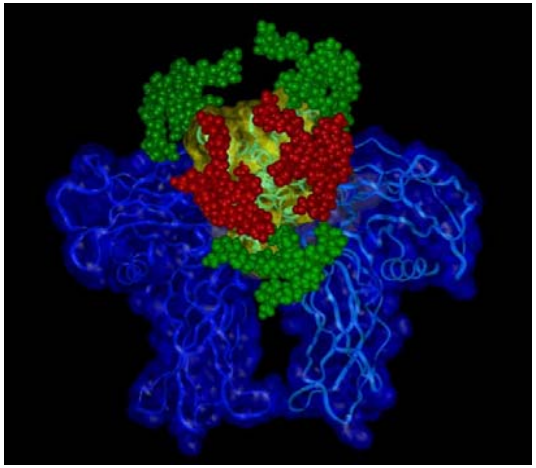
Challenges of Primary Packaging (E&L)

Extractable Metal ions from the hot forming process can trigger:

- Precipitation
- Aggregation
- Degradation
- Inactivation of active sites

Channel Forming of Staked Needle Syringe with Tungsten Pin



Tungsten-Oxide

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Challenges of Primary Packaging (Delamination)

Delamination is a glass wall morphology phenomena:

- Can be seen as flakes (Fig 1a / 1b)
- It is most pronounced in the transition zone between the wall and bottom (Fig 2)
- It is linked with a porous reaction layer (Fig 3)

Figure 1a

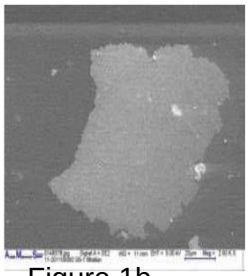

Figure 1b

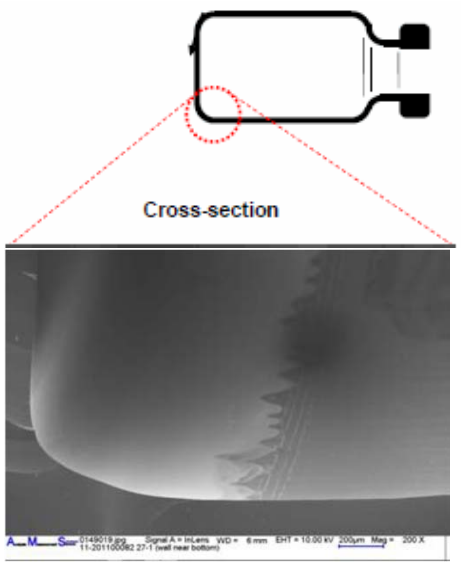

Figure 2

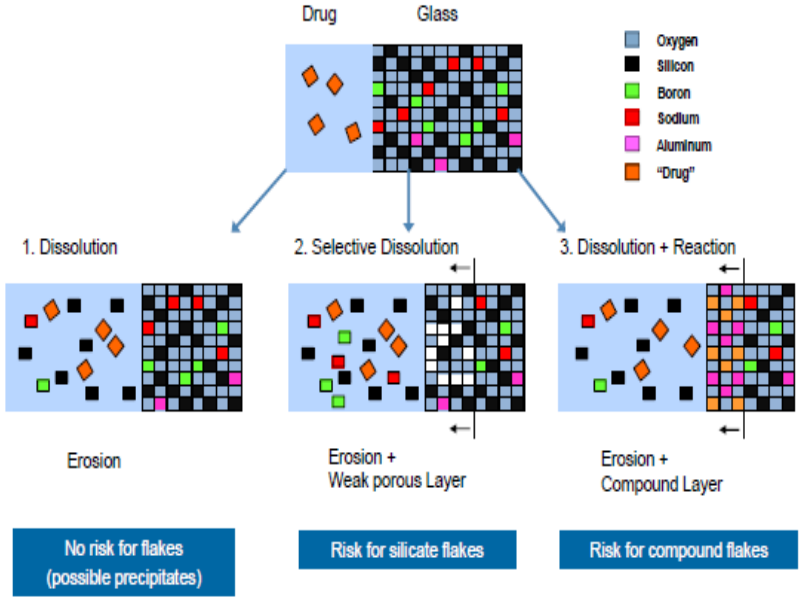

Figure 3

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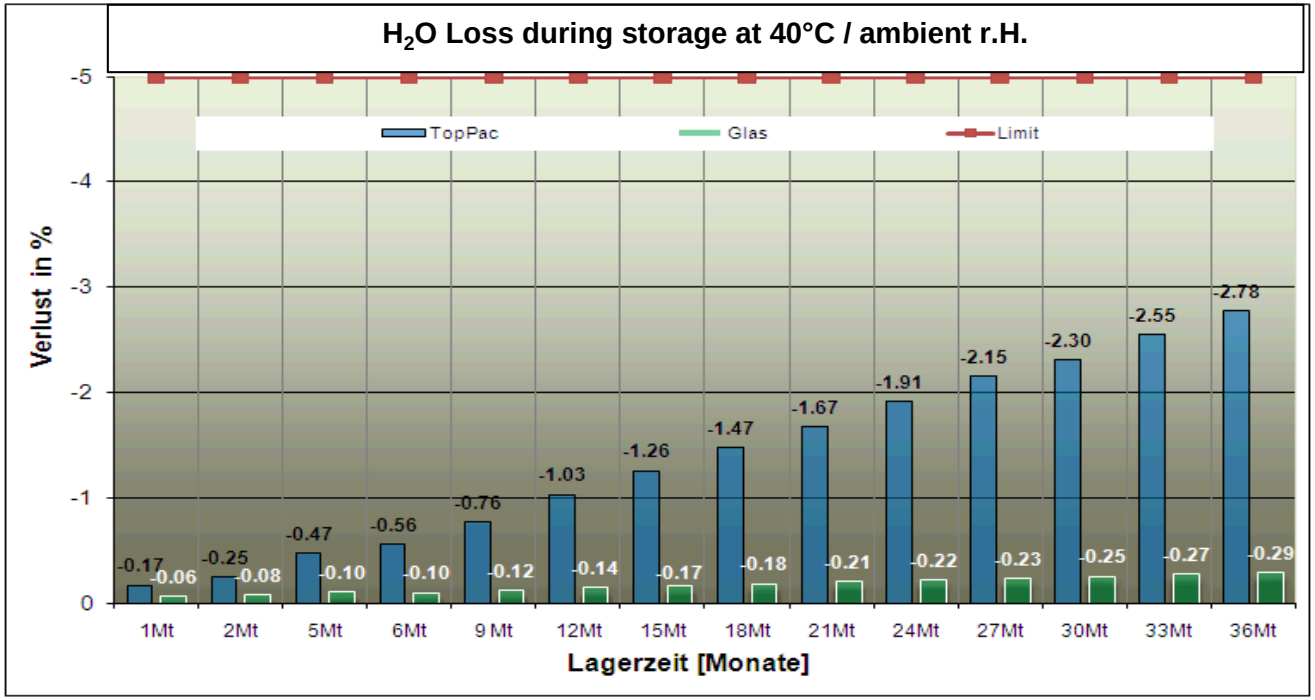
Challenges of Primary Packaging (Permeation)

3ml Glass Syringe vs. 3ml Plastic Syringe



Syringe System Glass vs. Polymer → BIF = 9,6 related to H_2O Permeation

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Options for Optimizations

- Functional Coatings to optimize
  - Surface properties

SCHOTT Vials Delamination Controlled

SCHOTT TopLyo® vials

SCHOTT TopYield™ vials

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Options for Optimizations

- Barrier Coatings to optimize
  - Barrier Improvement factor (BIF)

- Definition:

$$BIF = \frac{\text{(Permeation)-Value of uncoated container}}{\text{(Permeation)-Value of coated container}}$$

extractable	glass non coated	glass coated	BIF
Sodium	3.5	<0.01	350
Calcium	1.1	<0.05	22
Bor	3.5	<0.1	35
Silicium	5.0	<0.3	15
Aluminum	2.3	<0.05	45

Leached Ions in µg/ml by AAS; after autoclaving at 1h/121°C, filled with 0,4m HCL

SCHOTT Type I Plus® vials

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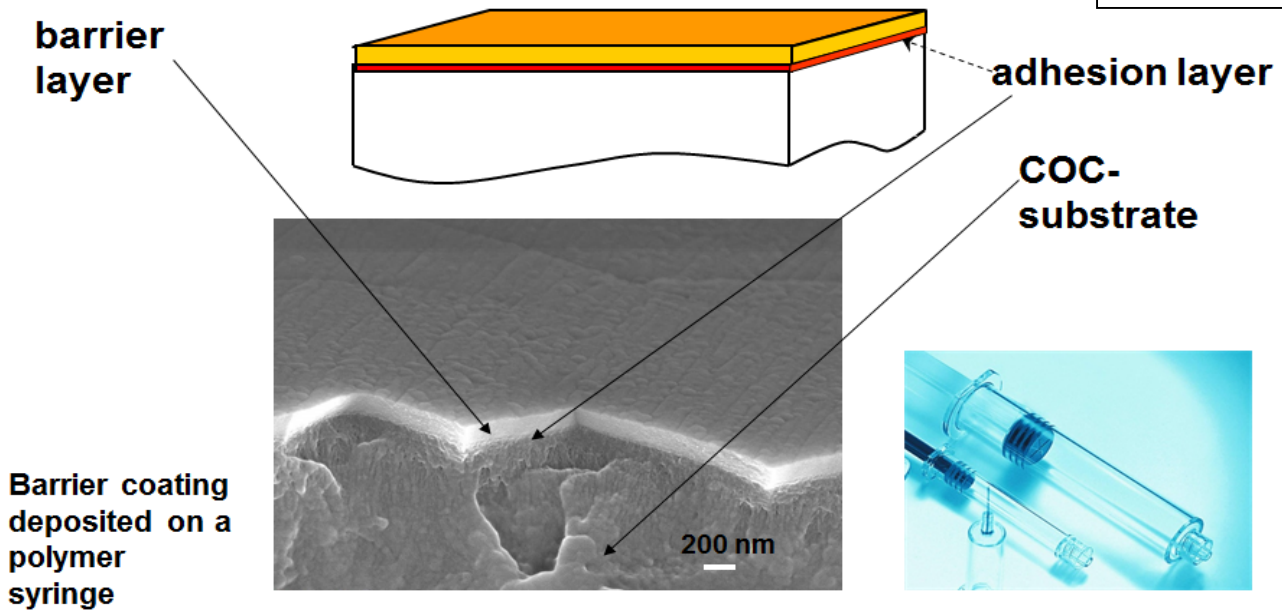
Options for Optimizations

- Barrier Coatings to optimize
  - Oxygen (O_2) Barrier

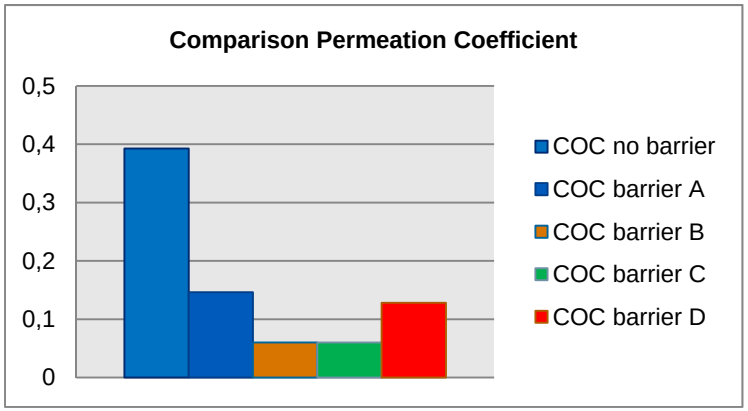
- Definition:

$$BIF = \frac{\text{(Permeation)-Value of uncoated container}}{\text{(Permeation)-Value of coated container}}$$

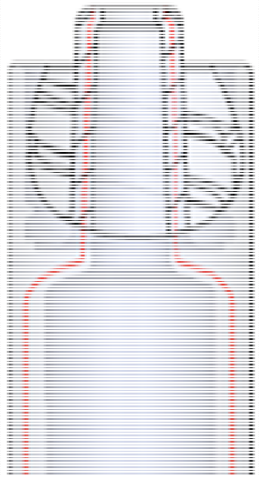


Options for Optimizations

- Barrier Improvements through
  - Molding Technologies

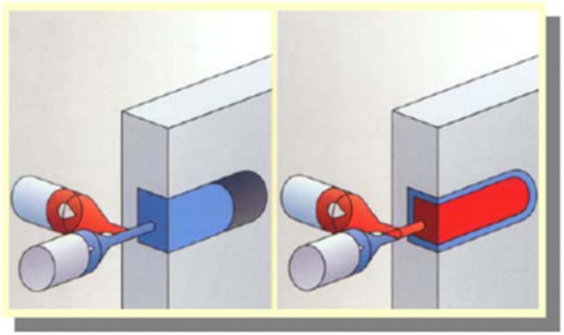


Barrier	BIF
A	2.7
B	6.5
C	6.5
D	3.2



Multilayer System

Reference : TechniCAL Brochure Co-Injection; Windsor Polymertechnology/ Germany



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Advantages / Disadvantages of Material

Vs.

Polymer	Vs.	Glass

Feature	Polymer	Glass
Absence of Heavy Metal‘s	better	
Breakage Resistance	better	
Design Space / Customizing / Tolerances	better	
Discoloration by radiation		better
Handling in Standard Filling Lines		better
Temperature Resistance	better	

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Advantages / Disadvantages of Material

Vs.

Polymer	Vs.	Glass

Feature	Polymer	Glass
Low E & L Profile	better	
„long term“ experience		better
Multiple Supply Source		better
Permeability (gases)		better
Delamination	better	
Sterilization Possibilities	better	

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Summary

- Glass packaging is still the `state of the art` packaging for biopharmaceuticals
- Container materials are always multi-ingredient compositions
- Leachable is time depending (Mind the gap)
- Surface optimization is possible but often costly
- Each and all container materials have their individual advantages and disadvantages
- There is no “one container fits all type and surface”

Thank you for your attention!
Questions?

Horst Koller, SCHOTT Schweiz AG