

# PDA Training Course Extractables & Leachables

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## Extractable & Leachable Considerations for Small Volume Parenteral Applications

Dries Cardoen



## Content

1. **Regulatory Expectations** for SVP – Brief Recap
2. **Rubbers** – an Introduction
3. **Rubber *Oligomers*** – Toxicity & Reactivity
4. **Glass** & Glass related Issues
5. **Other Materials** used in Small Volume Parenteral C/C Manufacturing
6. Main SVP containers: **E/L considerations**
  - Vials – Lyo vials
  - Prefilled syringes
  - Cartridges

# 1. Regulatory Expectations for Small Volume Parenterals – Brief Recap

# 1. Regulatory Expectations - US



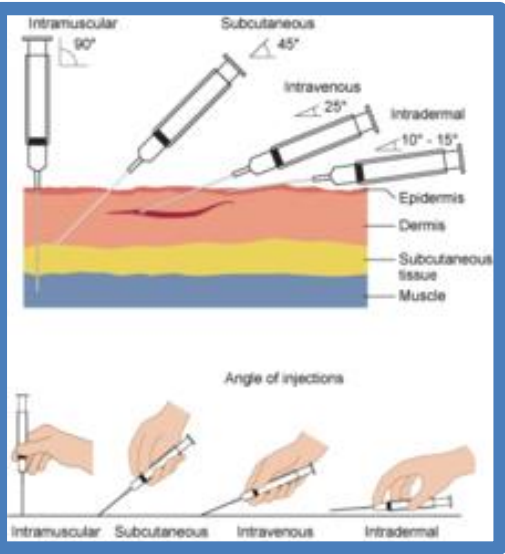
**LIQUID SVP's**

**Ranking the Packaging Concerns**

Examples of <b>PACKAGING CONCERNS</b> for Common Classes of Drug Products			
Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Components – Dosage Form Interactions		
	High	Medium	Low
Highest	Inhalation Aerosols and Sprays	<b>Injections and Injectable Suspensions;</b> Inhalation Solutions	<b>Sterile Powders and Powders for Injection;</b> Inhalation Powders
High	Transdermal Ointments and Patches	Ophthalmic Solutions and Suspensions; Nasal Aerosols and Sprays	-
Low	Topical Solutions and Suspensions, Topical and Lingual Aerosols, Oral Suspensions and Solutions	-	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules; Topical Powders; Oral Powders

LYO

**100% Absorption/Bioavailability in Human Body Distribution via Systemic Circulation.**



**Originally Included into the FDA (Draft) Guidance for Industry (1999): "Container/Closure systems for Packaging Human Drugs and Biologics"**

# 1. Regulatory Expectations - US

LIQUID SVP's

Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Components – Dosage Form Interactions		
	High	Medium	Low
Highest	Inhalation Aerosols and Sprays	Injections and Injectable Suspensions; Inhalation Solutions	Sterile Powders and Powders for Injection; Inhalation Powders
High	Transdermal Ointments and Patches	Ophthalmic Solutions and Suspensions; Nasal Aerosols and Sprays	-
Low	Topical Solutions and Suspensions, Topical and Lingual Aerosols, Oral Suspensions and Solutions	-	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules; Topical Powders; Oral Powders

## Remark:

1. the **“Medium”** Likelihood of Packaging - DP Interaction for **Liquid SVP's** is mainly based upon the **observation that most Parenteral DP are Aqueous Based**. For **Non-aqueous** based drug products: more **caution** is needed!
  
2. The **“Low”** Likelihood of Packaging - DP Interaction for **LYO SVP's** is mainly based upon the observation that:
  1. the *interaction* between a solid (Lyo cake) a material ( eg rubber) *is limited*
  2. AND, there is *limited direct contact* between Lyo cake and Rubber closure
    - However the Mechanism of interaction for a LYO Cake and its MoC may not need always a direct contact.
    - **BE CAREFUL when “rationalizing” a LYO application as being Non Critical!!!**

# 1. Regulatory Expectations - US

## Recent “Informal” Communications from the FDA



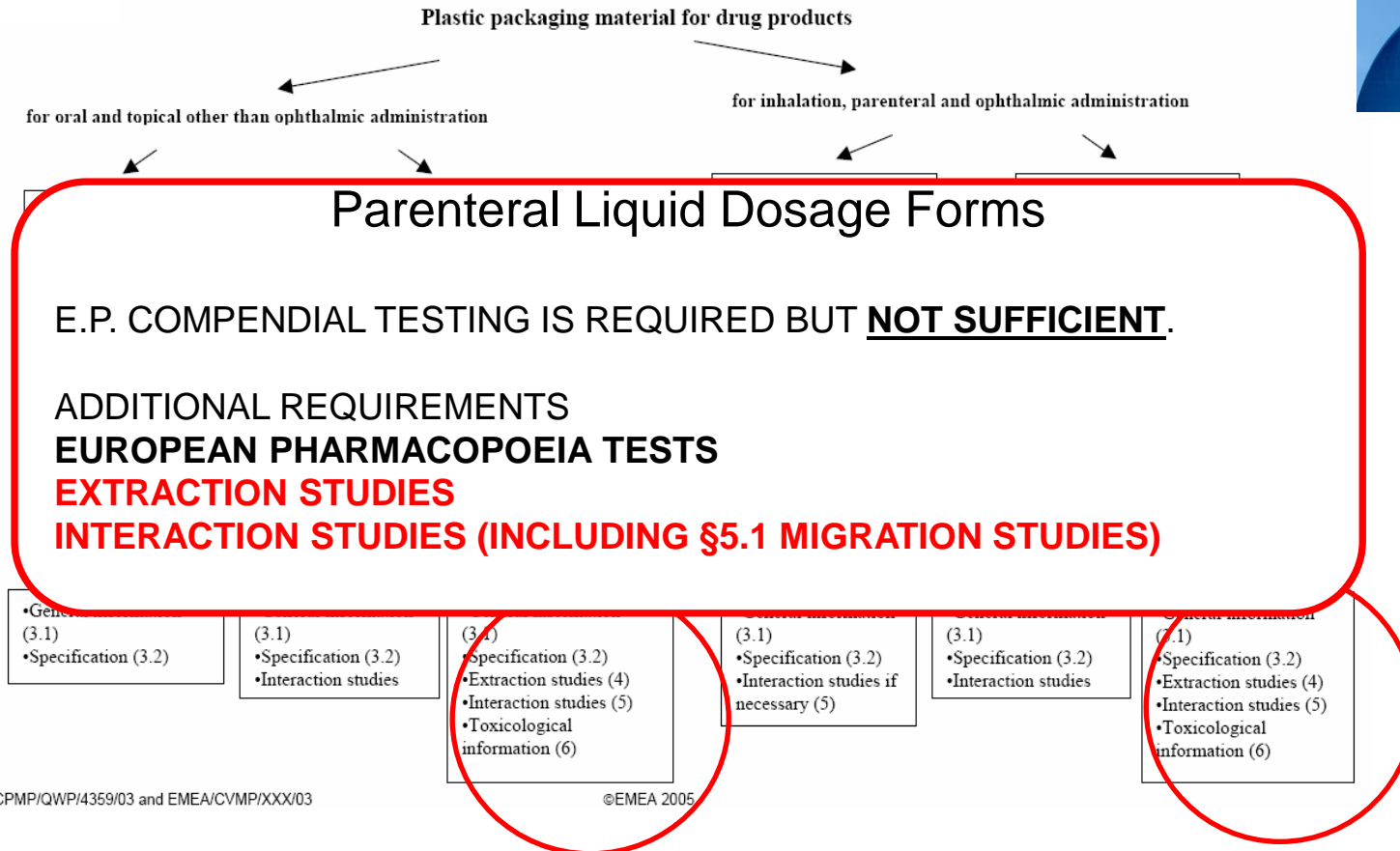
Video of **Dan Mellon** (FDA - CDER)

[https://www.youtube.com/watch?v=mol\\_X2zQeig](https://www.youtube.com/watch?v=mol_X2zQeig)

1. **Identify Leachable Compounds above** the Qualification Threshold (**QT**)
2. The **use of Inappropriate Threshold Levels**
3. **Inadequate Sensitivity** of the Detection Methods for Leachables (AET>LOQ)
4. Inadequate Stability Data to **Examine Trends** in Leachables
5. **Inadequate toxicology justification** to support a Permitted Daily Exposure (PDE)
6. **Inadequate descriptions** of **how Extractables Data were used** to design Leachables assessments
7. Inadequate **correlations between Extractables & Leachables**

# 1. Regulatory – EU – Plastic Immediate Packaging Materials (2005)

- Going through the decision tree: **liquid dosage forms – high requirements**



## 2. Rubbers – An introduction

*Supported by Datwyler*

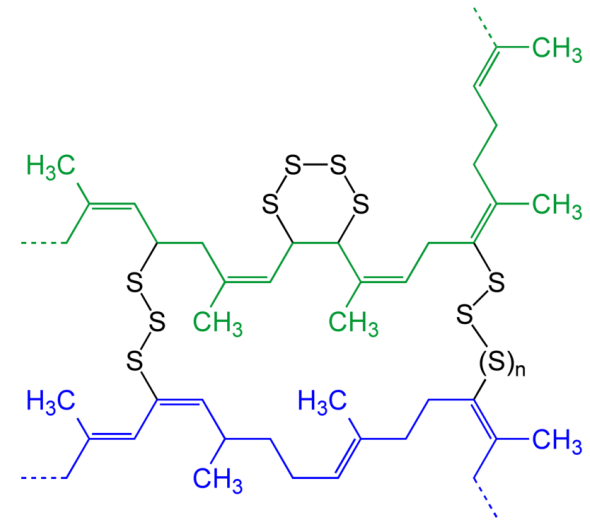


## 2. Rubbers – an Introduction

### What is rubber?

An **elastic** material

A **compounded** material



- *Basis of a rubber* → polymer → **elastomer**
- **Elasticity via crosslinking** (curing, vulcanising) the elastomer
- *Additional ingredients to “tune” the rubber*

## 2. Rubbers – an Introduction

**Rubber = Compounded Material of:**

1. Elastomer



2. Filler



3. Cure system

4. Pigment

5. Other ingredients



## 2. Rubbers – an Introduction

**BASE  
COMPOSITION**

e.g.  
Elastomer type  
Filler  
Additives

**LEADS TO  
PHYSICAL /  
CHEMICAL  
PROPERTIES**

e.g.  
E&L profile  
Hardness  
Compression set  
Tensile strength

**LEADS TO  
PRODUCT  
PERFORMANCE &  
APPLICATION**

e.g.  
Drug Compatibility  
Container Closure Integrity  
Gamma/Steam Resistance  
Fragmentation  
Gliding Curve

## 2. Rubbers – an Introduction

Rubber = Compounded material of:

**1. Elastomer**



2. Filler



3. Cure system

4. Pigment

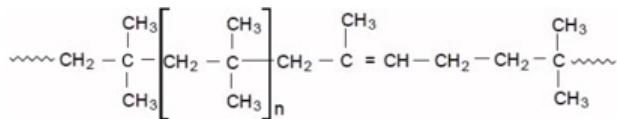
5. Other ingredients



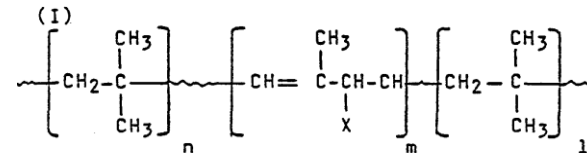
## 2. Rubbers – an Introduction

# Elastomer

- **Halobutyl (BromoButyl, ChloroButyl)**
  - Bromobutyl and Chlorobutyl Elastomers *predominantly used* in SVP rubber components
  - *Cleanest curing* system
  - *Lowest permeability*
  - *High resistance to ageing*



Butyl



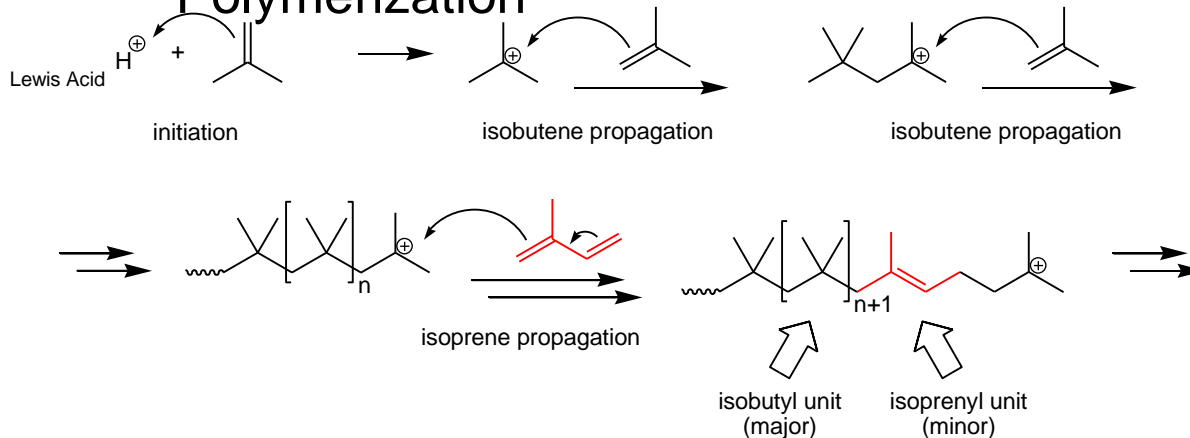
X = Cl or Br

Halobutyl

## 2. Rubbers – an Introduction

Elastomer

### Butyl Elastomer (IIR): Cationic Polymerization



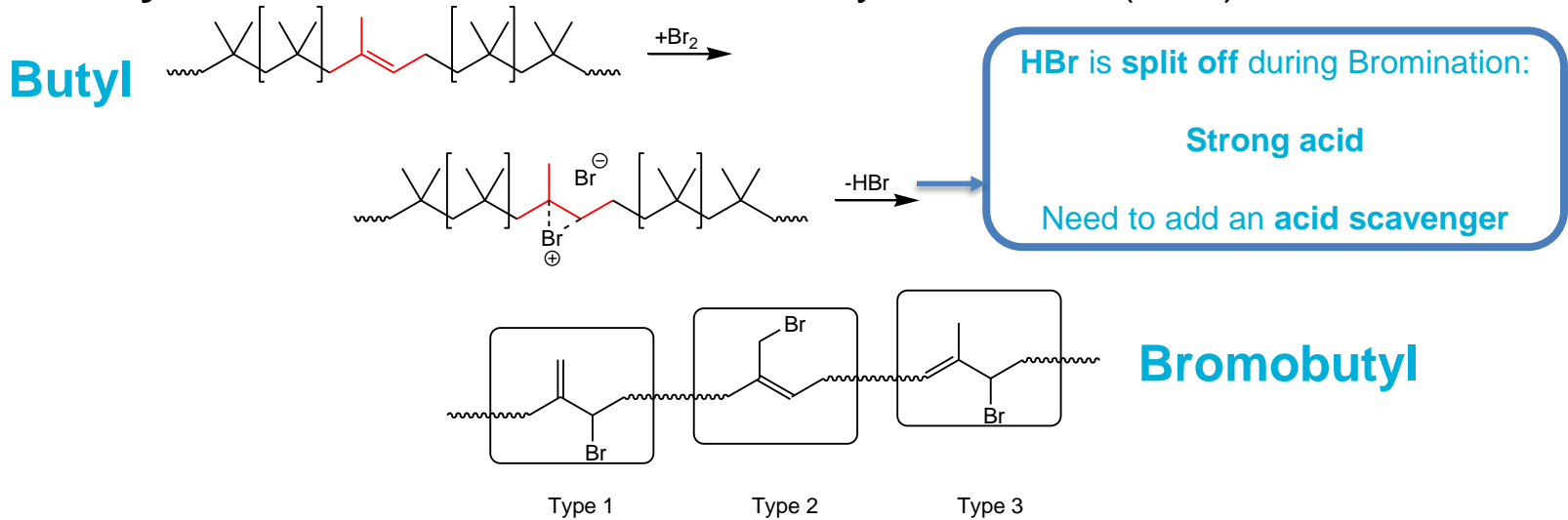
➤ Note: the Polymerization Starts with a Isobutene Unit (present in high excess!!)

- 98 – 99 mol% is isobutylene
- 1 – 2 mol% is isoprene

## 2. Rubbers – an Introduction

Elastomer

### Bromobutyl Rubber: Bromination of the Butyl Elastomer (BIIR)

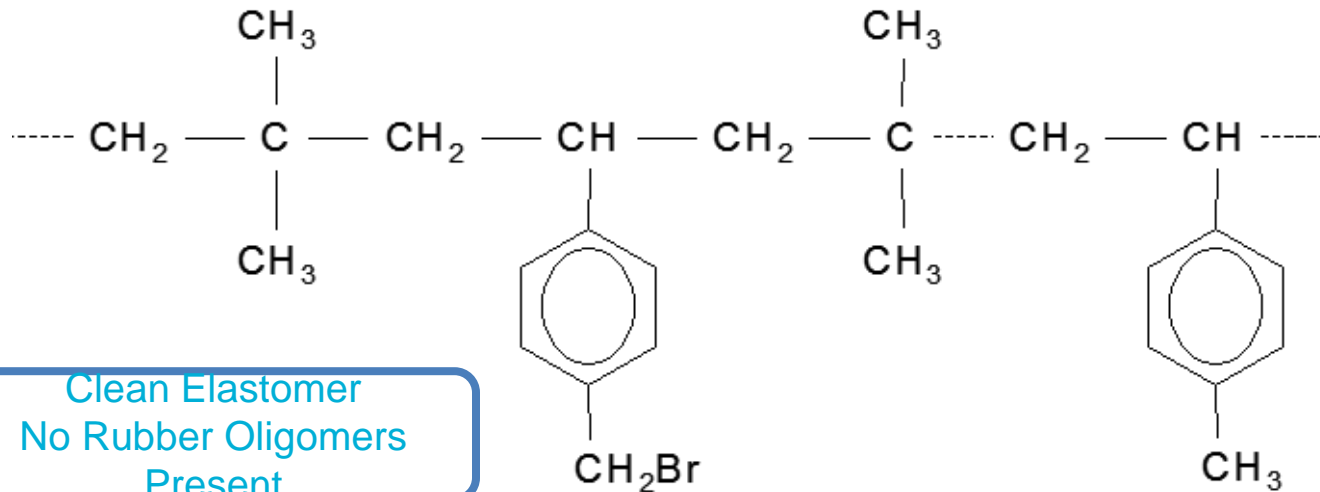


**Bromination of the Backbone makes Elastomer more reactive in vulcanization/cross linking**  
(BIIR has a relatively Low  $N^\circ$  of double bonds in backbone)

## 2. Rubbers – an Introduction

Elastomer

Regular **butyl** still on the market, and also newer types like **BIMS**  
(*Brominated isobutylene para-methylstyrene*)



Clean Elastomer  
No Rubber Oligomers  
Present

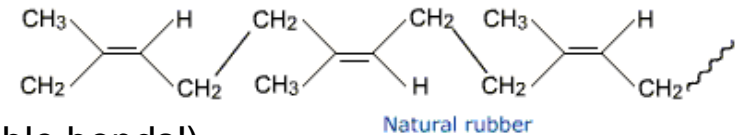


## 2. Rubbers – an Introduction

# Elastomer

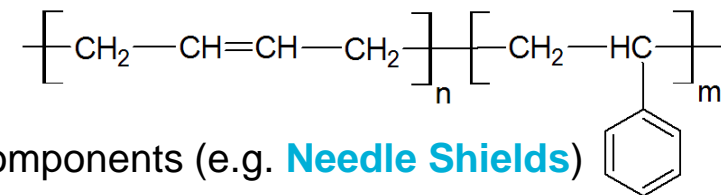
- **Natural rubber / Polyisoprene**

- Natural rubber: latex **allergy** discussions
- **Historically** the **oldest** elastomer type
- Need **complex curing** systems
- **Good elastic** properties
- More **affected by ageing/oxidation** (N° of Double bonds!)
- Polyisoprene (**Synthetic**) replaces **Natural** rubber



- **SBR** (styrene-butadiene rubber)

- Random Copolymer
- Intermediate **permeability**
- Typically used for pre-assembled **EtO** sterilized components (e.g. **Needle Shields**)

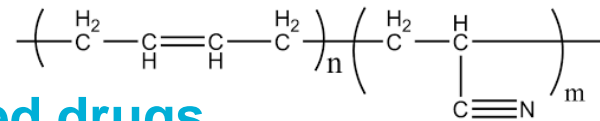


## 2. Rubbers – an Introduction

Elastomer

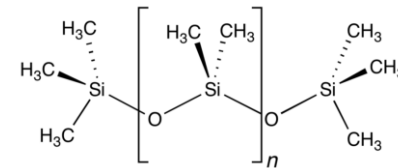
- **Nitrile** rubber

- Typically used for mineral **oil based drugs**



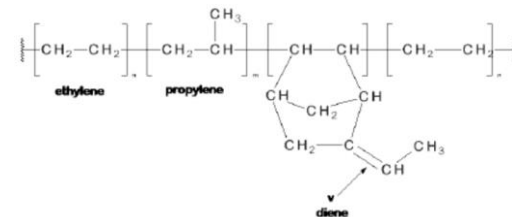
- **Silicone** rubber

- High **permeability**
- Typically **not used for parenteral** applications



- **EPDM** rubber

- For **niche** applications



## 2. Rubbers – an Introduction

Rubber = Compounded material of:

1. Elastomer



**2. Filler**



3. Cure system

4. Pigment

5. Other ingredients



## 2. Rubbers – an Introduction

### Filler

- Fillers give **mechanical strength (stiffness)** to a rubber
- Attributes **physical properties** to a rubber compound
  - **More filler = Harder compound**
    - Better for **gliding** profile plungers
    - **Worse for stopper piercing** (coring!)
- Inorganic fillers ('white compounds')
  - Aluminum silicate (clay)
  - Magnesium silicate (talc)
  - Silicate
  - [Calcium carbonate]
- Carbon black ('black compounds')
  - Undesired for cleanliness reasons
  - May be associated with PNA's



## 2. Rubbers – an Introduction

Rubber = Compounded material of:

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**3. Cure system**

4. Pigment

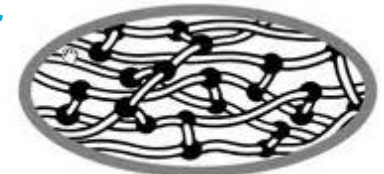
5. Other ingredients



## 2. Rubbers – an Introduction

### Curing System

- **Cure system:**
  - **Introducing Elasticity: from elastomer to rubber**
  - **Crosslinking** agent
  - **Activator:** gives the onset of vulcanization
  - **Accelerator:** speeds up the vulcanization
    - Easily extractable organic molecules such as thiurams, sulfonamides, thiazoles, ...
- **Modern cure systems**
  - Aim at giving **little extractables**
- **Historic cure systems**
  - Use **easily extractable organic accelerators**



THERMOSETTING

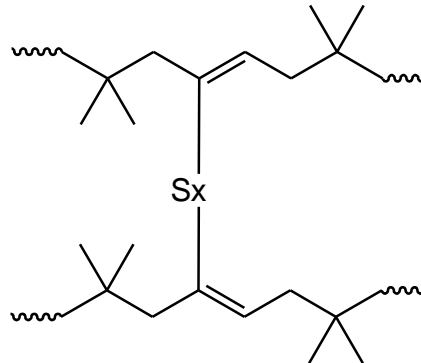
Crosslinked polymer chains

## 2. Rubbers – an Introduction

# Curing System

Rubber Curing / Vulcanization:

Oldest Curing  
Sulfur (S<sub>8</sub>) Vulcanization

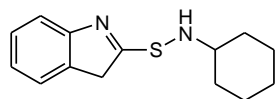


Rubber crosslinking requires S-Donors, activators, accelerators  
Activator: ZnO / Stearic acid

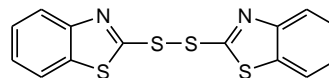
## 2. Rubbers – an Introduction

# Curing System

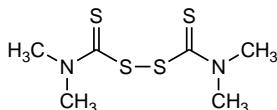
Rubber Curing – **Accelerators** used in **Older** Curing Systems:



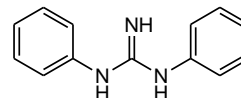
Cyclohexyl benzothiazole sulfenamide



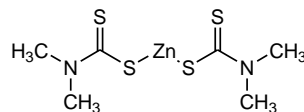
Mercaptobenzothiazole disulfide



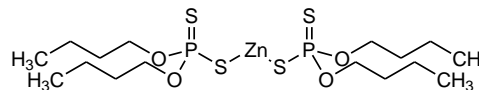
Tetramethylthiuram disulfide(TMTD)



Diphenyl guanidine



Zinc dimethyldithiocarbamate



Zinc dibutylphosphorodithiate

*accelerators: known  
to lead to  
n-Nitrosamine*

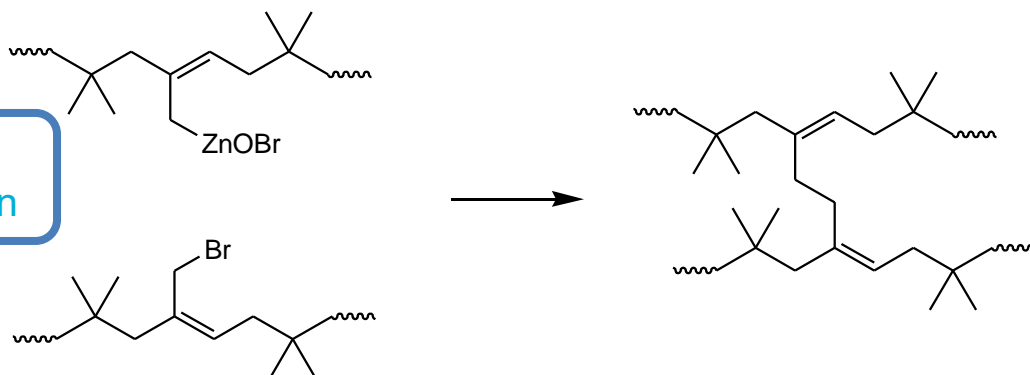


## 2. Rubbers – an Introduction

# Curing System

**ZnO** as Activator Compound in Halobutyl-Rubbers:

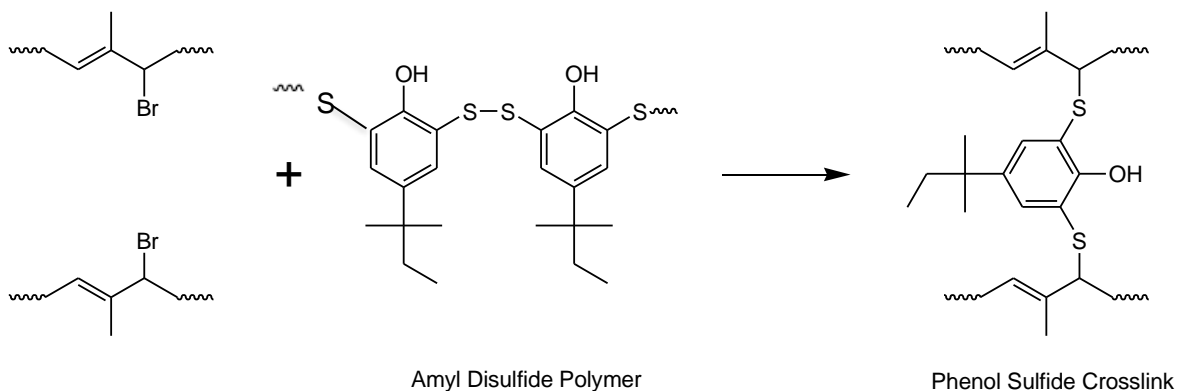
ZnO shows  
“catalyst” action



## 2. Rubbers – an Introduction

# Curing System

### Vultac Vulcanizing Agent for (Halobutyl) Elastomers



Bromide: good leaving group!

*Bond Energy C-H 413 J/mol ⇌ C-Br 209 J/mol*

Explains Br<sup>-</sup> release from bromobutyl rubbers

## 2. Rubbers – an Introduction

Rubber = Compounded material of:

1. Elastomer



2. Filler



3. Cure system



**4. Pigment**

5. Other ingredients

## 2. Rubbers – an Introduction

# Pigments

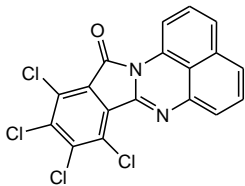
- **Inorganic pigments**

- Titanium dioxide
- Traces of carbon black
- Oxides of iron

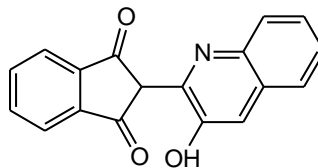
- **Organic pigments**

- Avoided in modern compounds

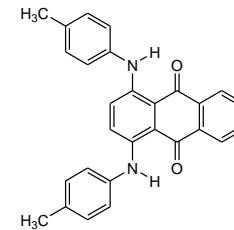
Cosmetic reasons – or-  
Differentiate different  
Strengths & Presentations



Solvent Red



Solvent yellow 114



Solvent Green 03

## 2. Rubbers – an Introduction

Rubber = Compounded material of:

1. Elastomer



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3. Cure system

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**5. Other ingredients**



## 2. Rubbers – an Introduction

### Other Ingredients

- **Halobutyl polymer stabilizers**  
*(neutralize HBr/HCl after halogenation & to prevent dehydrohalogenation during processing)*
  - Calcium stearate
  - Epoxydized soybean oil
- **Anti-oxidants**
  - Already present in halobutyl elastomer
  - Hindered phenol type anti-oxidants
  - Additionally added to improve environmental stability (ageing)
- **Plasticizer, Waxes, Oil**  
*(introduce softness, anti-“coring”)*
  - High polymeric weight plasticizers, Paraffinic oil
  - To tune a formulation (e.g. reduce coring)
- **Processing aids**

## 2. Rubbers – an Introduction

**THE COMPOSITION OF RUBBERS  
CAN BE VERY COMPLEX!!**

**RUBBER EXTRACTABLES: SUM OF**

1. Initial Ingredients of the Rubber Formulation
2. Impurities of these Ingredients  
(e.g. Residual Solvents, **Oligomers in Elastomer**, Halides in Halobutyl Rubber...)
3. Reaction/Degradation Products During the rubber Production (Milling, Calendaring, Molding)

Mixing of Blend



Milling

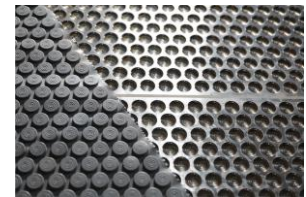


Calendar

Molding (Curing)



Molded Rubber stoppers



## 2. Rubbers – an Introduction

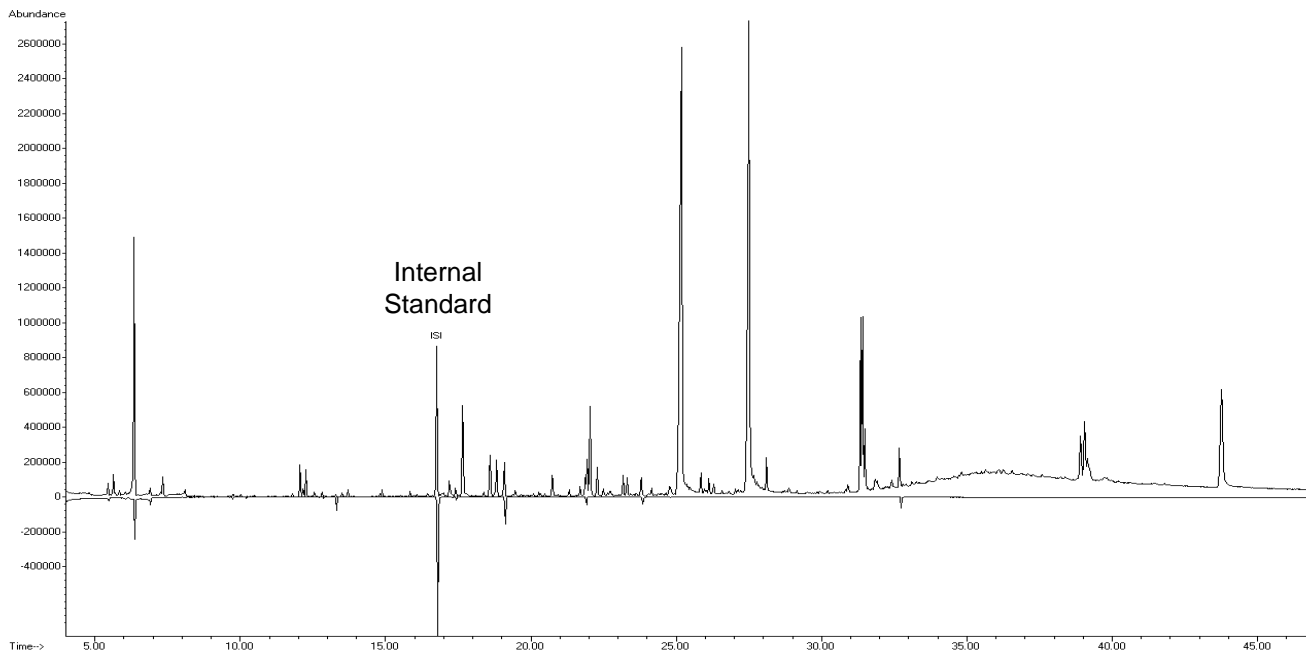
In general too many ingredients should be avoided: negative impact on E-profile

→ *“what you don’t put in, can’t come out”*



## 2. Rubbers – an Introduction

Difference in Extractable Results for an **OLD** vs **NEW** rubber  
(IPA Extract; GC/MS analysis)



“OLD” RUBBER

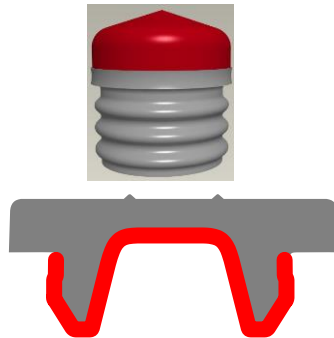
“NEW” RUBBER

## 2. Rubbers – an Introduction

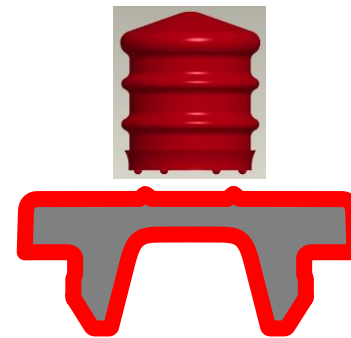
### COATED RUBBERS

- Coated closures: significant improvement in E&L terms
- Key attribute: barrier effect from the fluoropolymer!
  - *Simplified extractables profile*
  - *Improved Drug Compatibility*

Film coating technology

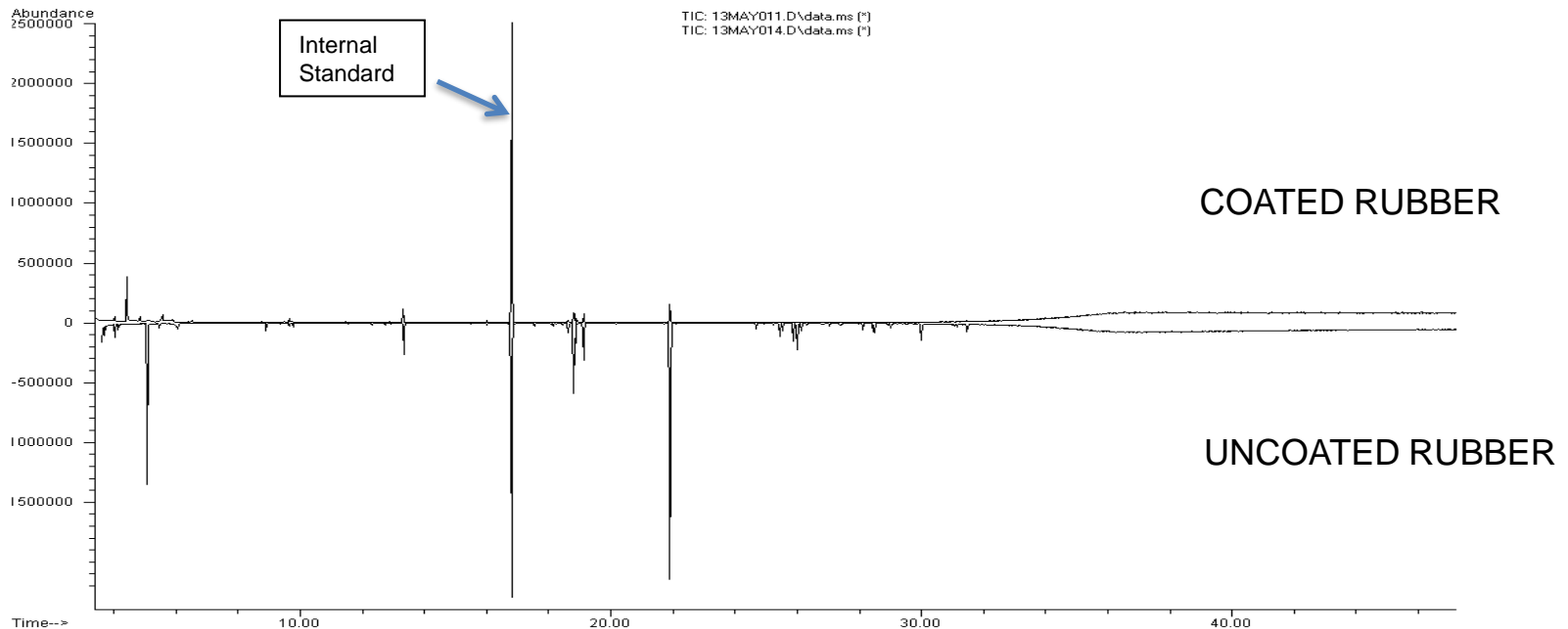


Spray coating technology



## 2. Rubbers – an Introduction

Difference in Extractable Results for a **Coated vs Uncoated rubber**,  
for the same rubber grade (*IPA Extract; GC/MS analysis*)



## 2. Rubbers – an Introduction

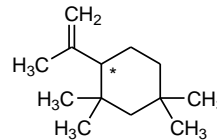
**Number of Leachables from rubbers in SVPs is determined by:**

- The Type of **Rubber Formulation**
- The **Number of Ingredients** in the Rubber
- **Type** of Ingredients (type of vulcanisation, type of AO, stabilizer....)
- **Coated/Non-coated** rubbers
- The **Composition of the Medicinal Product** (MP)
- The **Type of Contact** between the rubber and the MP (*e.g. exposed surface area*)
- The **Storage Temperature**
- The **Storage Time** (Expiration Date)

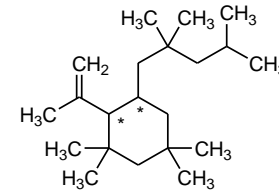
## 3. Rubber Oligomers: Toxicity & Reactivity

### 3. Rubber Oligomers: Toxicity & Reactivity

#### $C_{13}H_{24}$ and $C_{21}H_{40}$ Oligomers



C13 oligomer



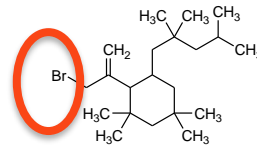
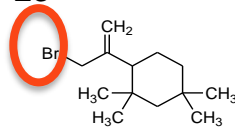
C21 oligomer

- **Formed** both **during the Polymerization** and the **rubber curing** at high temperatures
- Considered as
  - **Cyclic aliphatic hydrocarbon** compounds
  - **One double bond**
- **No experimental data / Literature** data is known about **toxicity of these compounds**
- **Structure Activity Relationship Assessment (SAR)**: compound of **low toxicity risk**.

### 3. Rubber Oligomers: Toxicity & Reactivity

#### Halogenated Rubber Oligomers – Compounds of high concern

$C_{13}H_{23}Br$  /  $C_{13}H_{23}Cl$  and  $C_{21}H_{39}Br$  /  $C_{21}H_{39}Cl$  Oligomers



- Considered as
  - **HALOGENATED** Cyclic Aliphatic Hydrocarbon compounds (**Allyl Halide**)
  - **Alkylating Agents**
  - One double bond
- Structure Activity Relationship (SAR) Assessment:

**CARCINOGENICITY IN HUMANS IS PLAUSIBLE**

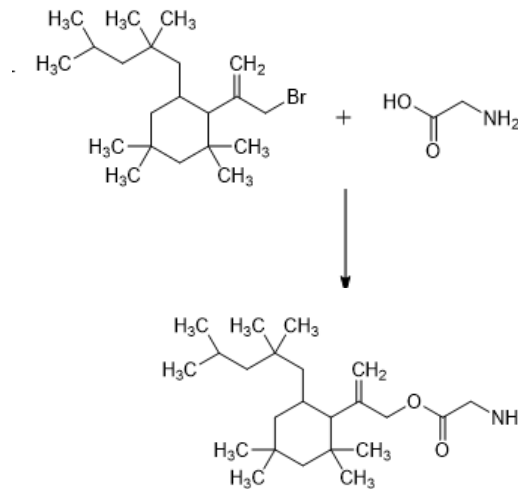
- As no experimental data / Literature data is known about the toxicity of these compounds, a lot of Pharma companies:
  - » **Rely on the result of a SAR assessment** to perform a tox evaluation
  - » **Conclude** that these compounds are of **High Concern**

### 3. Rubber Oligomers: Toxicity & Reactivity

**Lyophilized Drug Product B in a glass vial with a rubber stopper (without coating):**

Excipients a.o.: Glycine

C<sub>21</sub>H<sub>39</sub>Br rubber oligomer source -  
leachable from a rubber stopper



Glycine (excipient, bulking agent)

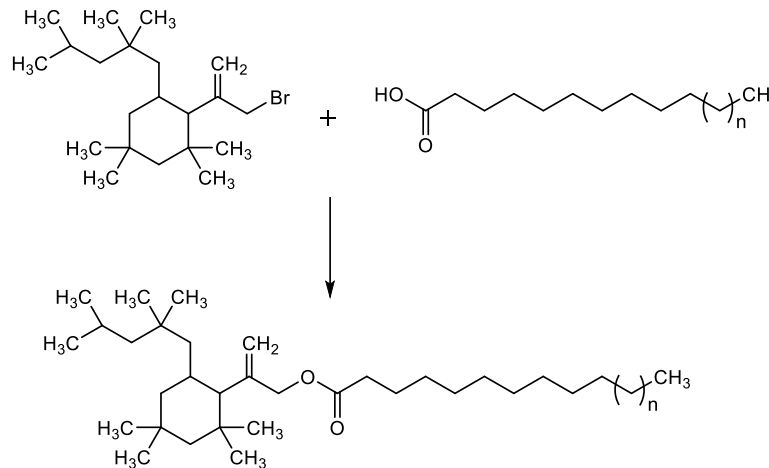


### 3. Rubber Oligomers: Toxicity & Reactivity

**Lyophilized Drug Product A in a glass vial with a rubber stopper (without coating):**

*Excipients a.o.: Polysorbate 20*

C21H39Br rubber oligomer source  
- leachable from a rubber stopper



Fatty acids source –  
Polysorbate 20

### 3. Rubber Oligomers: Toxicity & Reactivity

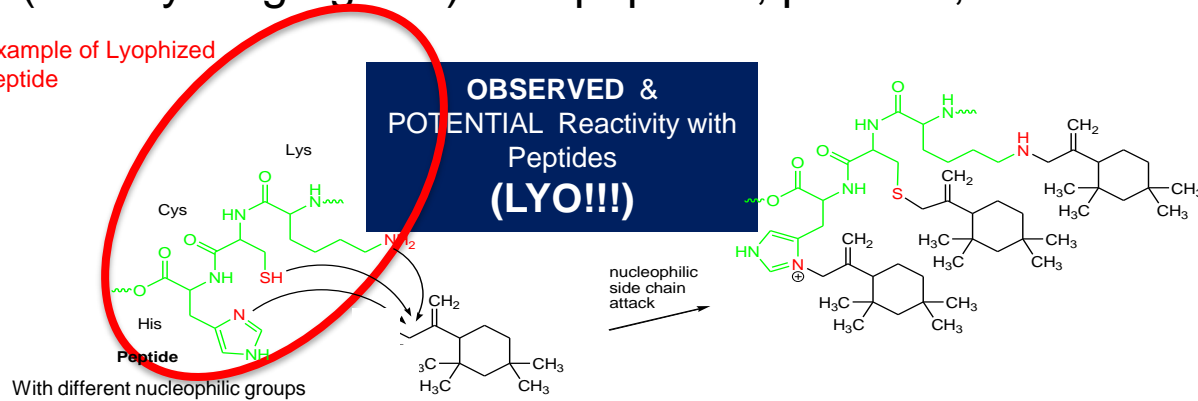
Adduct Formation of an Small Molecule API with  
the  $C_{13}H_{23}Br$  and  $C_{21}H_{39}Br$  oligomers



### 3. Rubber Oligomers: Toxicity & Reactivity

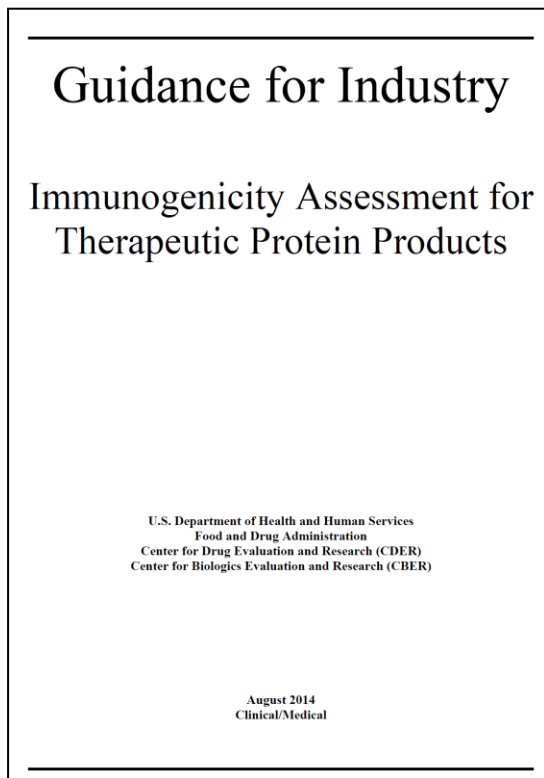
**Observed Reactivity** of  $C_{13}H_{23}Br$  and  $C_{21}H_{39}Br$   
(as alkylating agents) with peptides, proteins, and nucleic acids

Example of Lyophilized peptide



Fictitious Example of a Peptide with different nucleophilic functional groups

### 3. Rubber Oligomers: Toxicity & Reactivity



Interactions between therapeutic protein products and the container closure may negatively affect product quality and immunogenicity. These interactions are more likely with prefilled syringes of therapeutic protein products. These syringes are composed of multiple surfaces and materials that interact with the therapeutic protein product over a prolonged time period and thus have the potential to alter product quality and immunogenicity. The following are other container closure considerations pertinent to immunogenicity:

***“... Interactions are more likely with prefilled syringes of therapeutic protein products...”***

***“... Materials that interact with the therapeutic protein product over a prolonged time and thus have the potential to alter product quality and immunogenicity...”***

FDA Guidance for Industry,  
2014

## 4. Glass & Glass Related Issues *Vials, Prefilled Syringes, Cartridges*

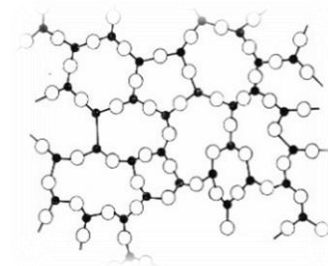
## 4. Glass & Glass Related Issues

### What is Glass?

An **inorganic fused substance** that has been **cooled to a rigid condition without crystallization** (e.g. Supercooled amorphous substance)

### Why Glass as Packaging Material?

- **Well-known** material
- **Transparent**
- **Heat resistant**
- Good **barrier** properties: gas & vapour tight
- Chemically and physically (quite) **inert**.



*J. Zuercher, ECA Course E/L, Prague 2010*

## 4. Glass & Glass Related Issues

### Composition of Glass – Function of Ingredients

- **SiO<sub>2</sub>** : Backbone structure
- **CaO** : Increasing hardness & Chemical resistance
- **Al<sub>2</sub>O<sub>3</sub>** : Increasing Chemical Resistance
- **Na<sub>2</sub>O & B<sub>2</sub>O<sub>3</sub>** : Lowering the melting point
- **Fe<sub>2</sub>O<sub>3</sub>, TiO<sub>2</sub>** : Amber Glass
- **CuO** : Blue Glass
- **Mn<sup>3+</sup>** : Violet Glass

*J. Zuercher, ECA Course E/L, Prague 2010*

## 4. Glass & Glass Related Issues

### Glass Types

Glass Type	General Description	Uses
I	High resistant Borosilicate	Parenteral Preparations
II	Treated Soda-Lime	Acidic and Neutral Parenteral Preparations
III	Soda Lime	Not for Parenteral Preparations
NP	Soda-Lime	Oral / Topical



## 4. Glass & Glass Related Issues

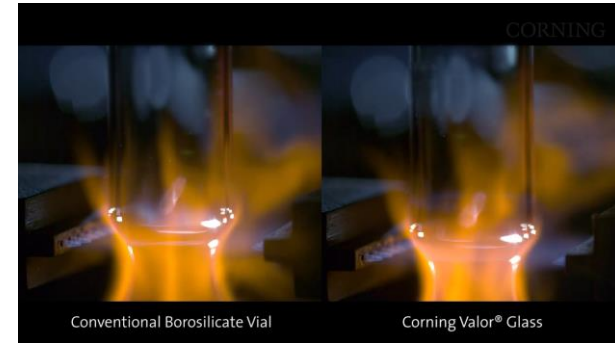
### Glass Composition for different Glass Types:

Component	Type I (Borosilicate)	Type II, III, NP (Soda-Lime)
SiO <sub>2</sub>	70 - 73%	69 - 73%
B <sub>2</sub> O <sub>3</sub>	10%	0 - 1%
Na <sub>2</sub> O	2 - 9%	13 - 14%
Al <sub>2</sub> O <sub>3</sub>	6 - 7%	2 - 4%
BaO	0,1 - 2,0%	0 - 2%
K <sub>2</sub> O	1 - 2%	0 - 3%
CaO	0,7 - 1,0%	5 - 7%
MgO	0 - 0,5%	3 - 4%
ZnO	0 - 0,5%	-

“Soda – Lime”

## 4. Glass & Glass Related Issues

### Examples for Extractables / Leachables



- **High heating** during molding process leads to an **increasing release of alkali ions** from the glass surface => **Delamination**
- **Heating promotes migration of alkali oxides** within the silica matrix to the glass surface
- During the process, **components of the heated glass vaporize and deposit** on the surface
- Relevant for **glass containers** made from **tubular glass** (vials)
- **Small volume** containers are **more impacted** than larger containers

## 4. Glass & Glass Related Issues

### Parameters, impacting the Glass Leachables

- **Filling Volume:** *smaller filling volumes show higher leachable concentrations*
- **Storage time:** *leachable concentrations increase over time*
- **Sterilization / Sterilization time:** *longer autoclaving cycles, higher concentrations*
- **Sterilization Temperature:** *higher temperatures, higher concentrations*
- **Type of contact solution:**

*[Si]: Lactic acid < acetic acid < ascorbic acid < malic acid < tartaric acid < oxalic acid < citric acid*  
**Complexing agents**, such as EDTA may also impact the metal release from Glass
- **Impact of pH:** *higher pH, higher [Si] release.*  
*In general, more metals are leaching out of glass at pH>9*

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## 4. Glass & Glass Related Issues

### Risk of Glass Leachables

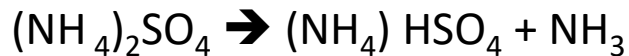
- **Most observed Metal Leachables from Glass:**  
**Si** and **Na** as MAJOR leachables, **K, B, Ca & Al** as MINOR LEA, **Fe**: traces
- **Alkali release:** pH shift of unbuffered solutions
- **Silicon (Si) release:** increased particle load, delamination!
- **Aluminum release:**  
*Aluminum can accumulate in patients with reduced renal function, causing e.g. neurological diseases*
- Potential **Arsenic (As) release:**  
*glass can contain arsenic oxide (III) as a **fining agent to improve glass transparency**. Arsenic is toxic!*
- **Release of metals**, causing **precipitation** with some salts, present in the DP  
*Ba => BaSO<sub>4</sub>, Al => Al(OH)<sub>3</sub>*

## 4. Glass & Glass Related Issues

### How to (try to) prevent Glass Leaching

#### 1. Chemical surface treatment

$(\text{NH}_4)_2\text{SO}_4$  is injected before annealing



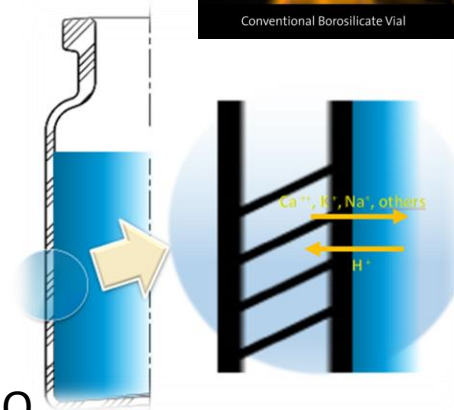
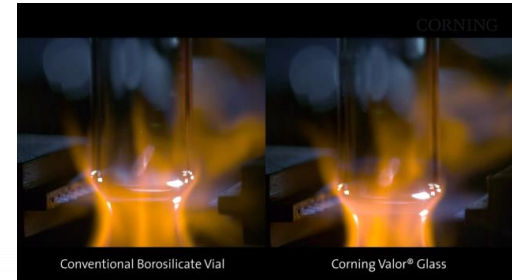
Afterwards, rinsing with Water to remove soluble  $\text{NaSO}_4$

**Result: lower pH shift because lower amounts of Na will leach**

#### 2. Coating on Glass (SiOx): Schott Type I plus

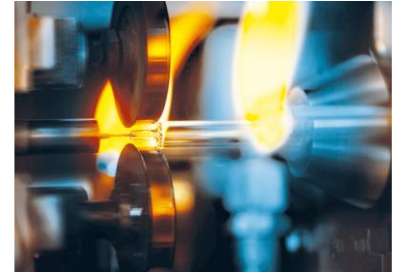
#### 3. Siliconisation will reduce interaction between glass and DP

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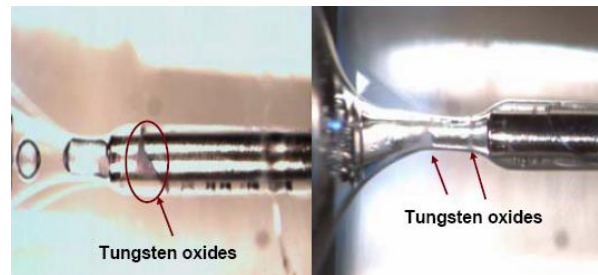
## 4. Glass & Glass Related Issues

### Glass as Barrel Material



#### TUNGSTEN RESIDUES – PREFILLED SYRINGES

- Tungsten pin used in the production of glass pre-filled syringes to **open the syringe hub** (cavity where staked needle is glued in)
- Tungsten Oxide Residues are known to cause **protein degradation** (protein oxidation causing aggregation)



## 4. Glass & Glass Related Issues

### Glass as Barrel Material

#### GLUE RESIDUES – PREFILLED SYRINGES

- Glue is used to glue in the staked needle into the PFS-system
- Prolonged contact with a drug product may release glue components
- Target compounds may depend upon the glue used (through UV Curing)

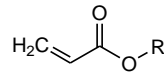


## 4. Glass & Glass Related Issues

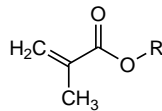
### Glass as Barrel Material – Related Compounds

#### GLUE RESIDUES

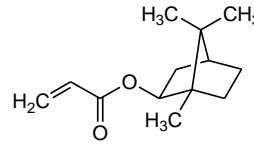
##### Base Polymer



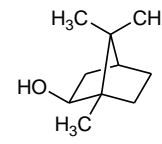
Acrylate



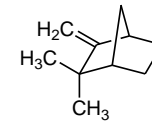
Methacrylate



Isobornyl acrylate

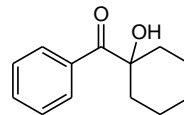


Isoborneol

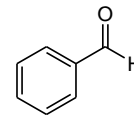


Camphene

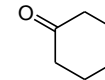
##### UV curing / activation



Irgacure 184



Benzaldehyde



Cyclohexanone



## 4. Glass & Glass Related Issues

### Glass as Barrel Material – Related Compounds

#### SILICONE OIL RESIDUES (strictly speaking: No Leachable)

- *Silicone oil residues may **denature proteins** or form **aggregates***
- *Glass surfaces are siliconized a.o. to reduce potential interactions with aqueous contact solutions*
- *Hydrophobic surface / reduced wettability*
- *Reduced alkali release*
- *Silicone oil remainders become leachables*

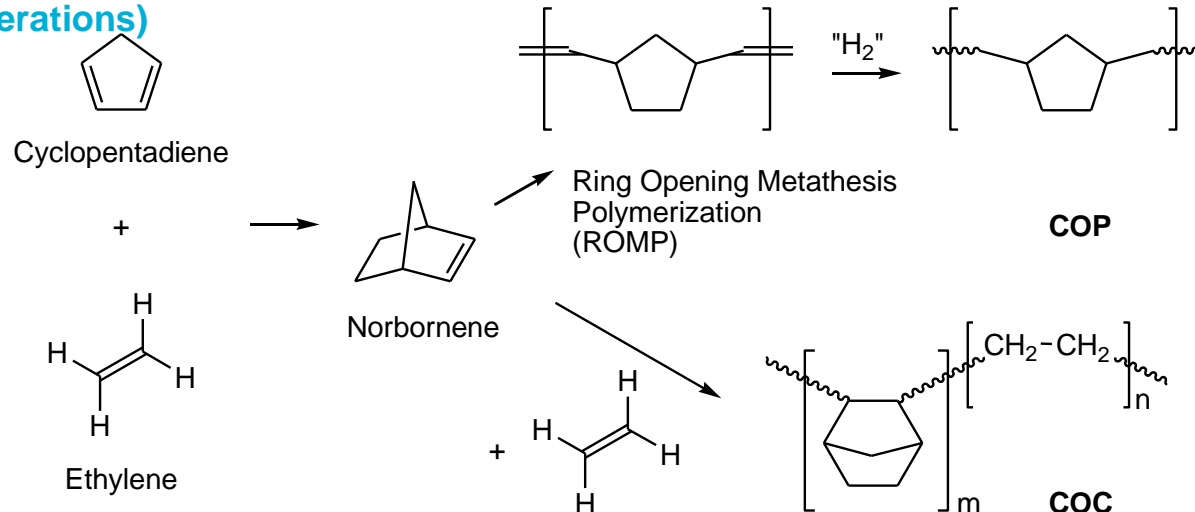
Less of an issue with  
Baked Silicone

## 5. Other Materials used in Small Volume Parenteral C/C Manufacturing

## 5. Other Materials used in Small Volume Parenteral C/C Mfng

### COP: Cyclic Olefin Polymers COC: Cyclic Olefin Copolymers

- Relatively **Clean** Materials
- **High Tg, rigid** materials
- However, **low gas barrier** (O<sub>2</sub>) properties
- **Risk for diffusion**: potential (regulatory) risk for **label migration (secondary packaging considerations)**



## 5. Other Materials used in Small Volume Parenteral C/C Mfng

### CRITICAL PARTS OF A POLYMER SYRINGE WRT E/L

#### PRIMARY PACKAGING (Direct Contact between DP and Material):

- The Barrel: COC, COP, PP
- The Piston: Rubber
- The Tip Cap: Rubber
- The Needle

Same Concern as for Glass PFS

#### SECONDARY PACKAGING (No Direct Contact between DP and Material):

- *The Needle Shield (should it be considered as primary or secondary?):* Rubber
- **The Label:** Adhesive, Ink, other Label Components
- In some Cases: The Lacker
- In some Cases: The Packaging of the Syringe (Overwrap, Tubs,...)

Specific for  
Polymer PFS!

## 5. Other Materials used in Small Volume Parenteral C/C Mfng

### TYPICAL COMPOSITION OF **COMMERCIAL POLYMERS**,

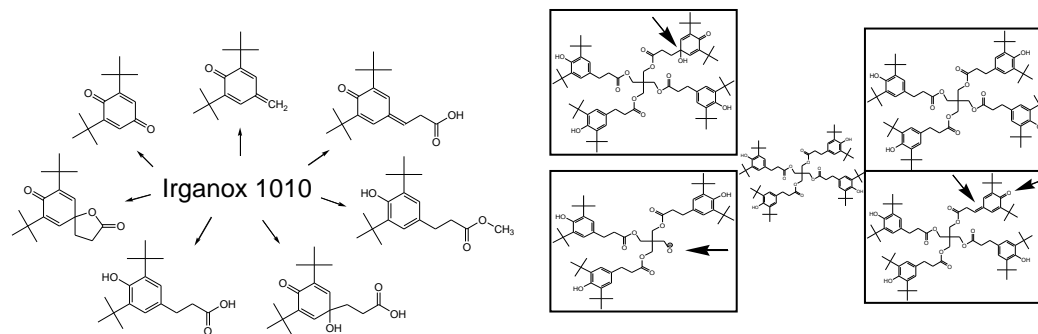
e.g. For Barrel Manufacture

- Additives (*BHT, Irganox 1010, Stearates, Pigments, Clarifiers...*)
- Residues (*Monomers, Solvent Residues, Processing Residues..*)
- Oligomers (*Mainly for PP*)
- Potential Degradation Compounds from Polymers
  - *Organic Acids, Aldehydes, Ketones, Alcohols, Chain Scission Fragments...*
- Degradation Compounds from Polymer Additives
- ...

Intentionally Added  
Substances

Non-Intentionally  
Added Substances

Example:



## 5. Other Materials used in Small Volume Parenteral C/C Mfng

### Regulatory Requirements for Secondary Packaging

- FDA guidance document: ‘Container Closure systems for Packaging Human Drugs and Biologics’, 1999:  
*“if the packaging system is relatively permeable, the possibility increases that the dosage form could be contaminated by the migration of an ink or adhesive component...In such case the secondary packaging component should be considered a potential source of contamination and the safety of its materials of construction should be taken into consideration...”*
- EMA: ‘Guideline on Plastic Immediate Packaging Materials’, 2005:  
*“it should be scientifically demonstrated that no components of ink or adhesives, applied to the outer surface of the container closure system, will migrate into the medicinal product.”*

## 5. Other Materials used in Small Volume Parenteral C/C Mfng

### Secondary Packaging

#### ➤ Label

- Adhesive
- Paper
- Ink
- Varnish

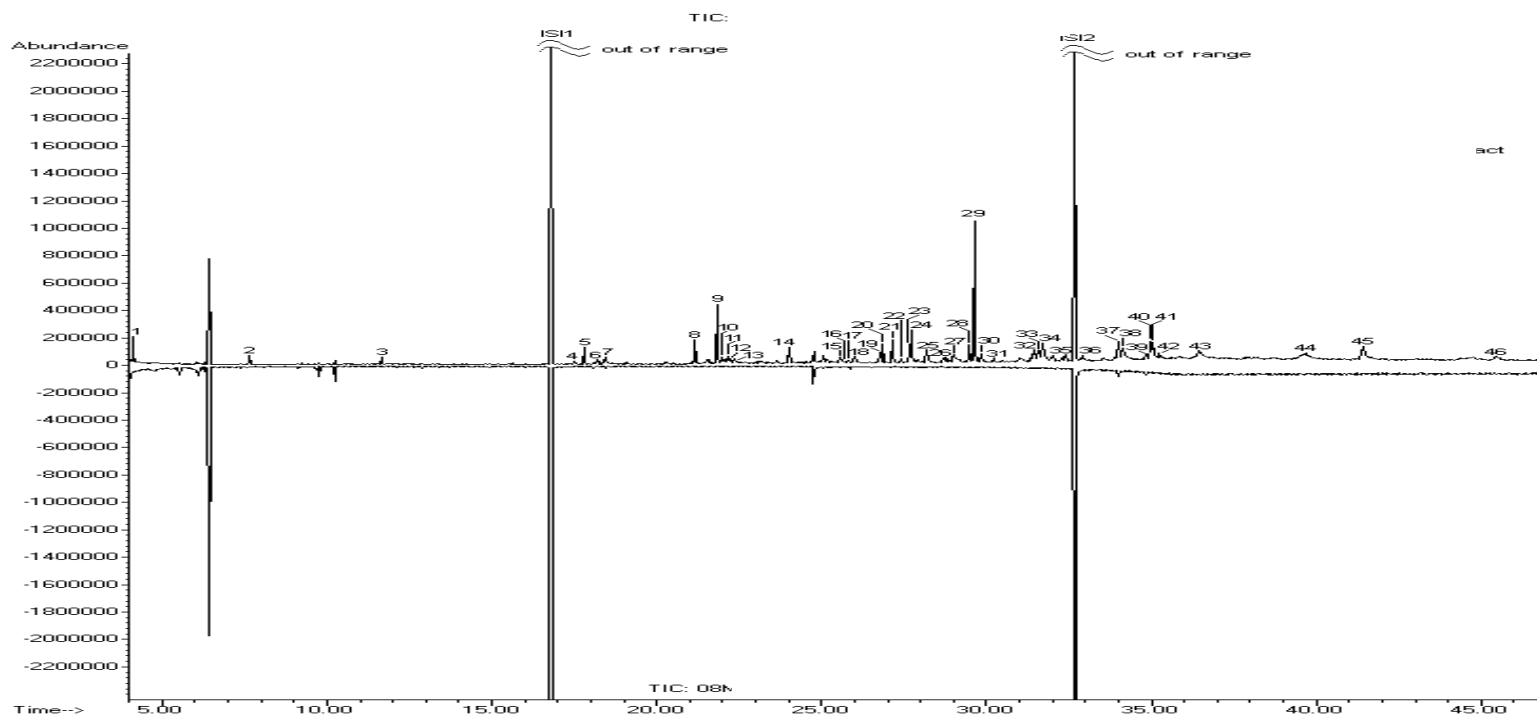


#### ***Typical extractable compounds:***

- Curing agents (e.g. Benzophenone, Irgacure 184,...)
- Solvent residues (e.g. Toluene, acetone)
- Adhesive residues (e.g. Acrylates)
- Paper residues (e.g. (dehydro)abietic acids, abietates)

## 5. Other Materials used in Small Volume Parenteral C/C Mfng

- Example GC/MS Chromatogram of a Label Extract (IPA)



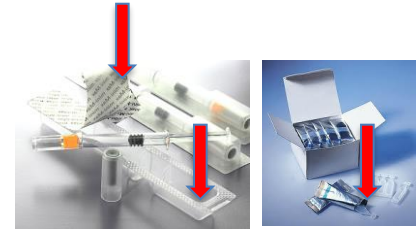


## 5. Other Materials used in Small Volume Parenteral C/C Mfng

### Secondary Packaging

#### ➤ **Overwrap/Overpouch/Blister**

*(to compensate for potential lower barrier properties of the Polymer)*



➤ Multilayer System

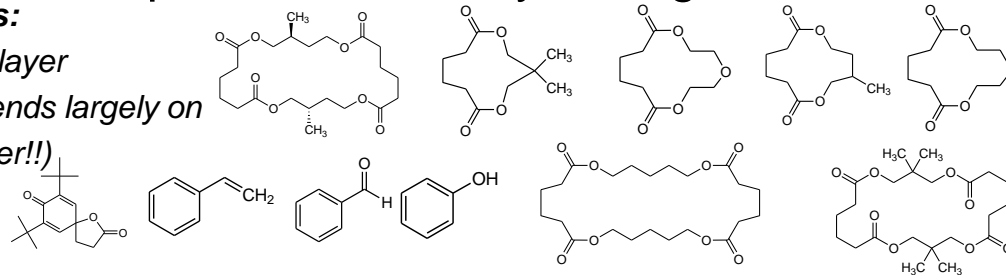
➤ Aluminum as barrier layer

➤ Tie-layers to keep the different layers together

**Typical extractable compounds:**

*Bislactone Compounds from Tie-layer*

*Residues from other layers (depends largely on selected materials of the multilayer!!)*



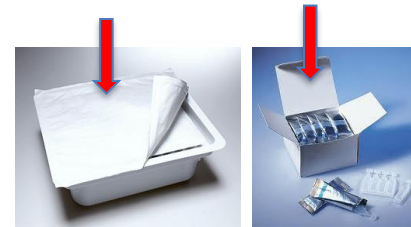
bislactones

...

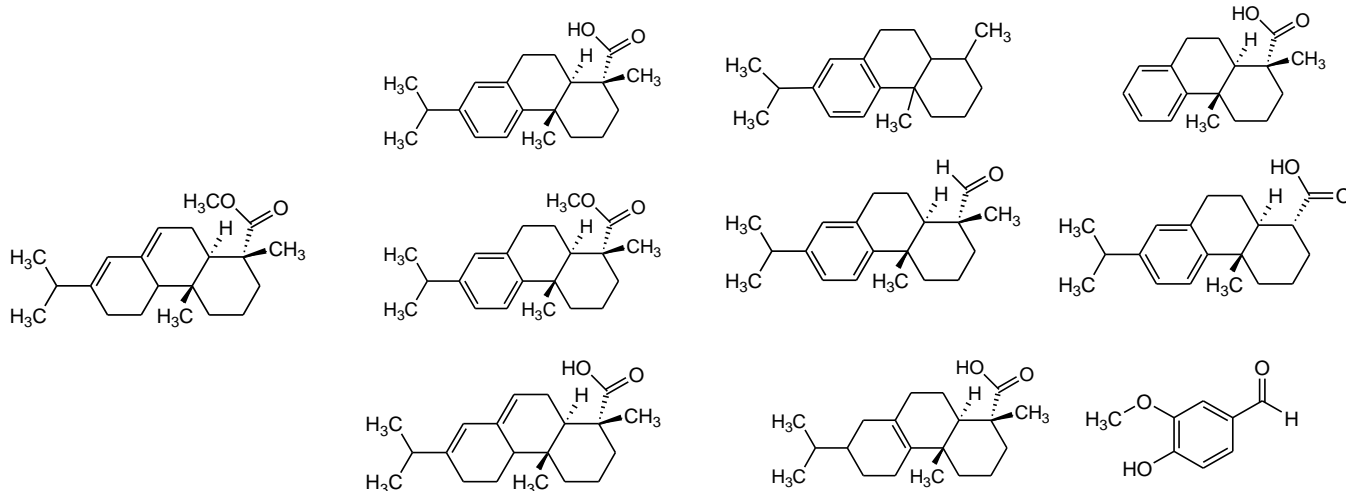
## 5. Other Materials used in Small Volume Parenteral C/C Mfng

### Secondary Packaging

- **Tubs** for Nested Syringes (eg Tyvek)
- **Carton / Paper** (may also from label):



*Example Structures of abietic acids / abietates (& Vanillin)*



## 6. Main SVP containers: Extractable Considerations

## 6. Main SVP containers: Extractrable Considerations

### 1. Vials:



## 6. Main SVP containers: Extractable Considerations

Vials

Liquid Drug Products

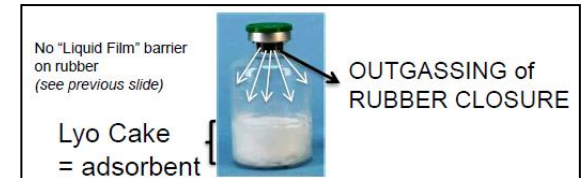
Reconstitution Solution



- If it is a **GLASS VIAL with RUBBER CLOSURE**: Sources of Impurities, coming from packaging:
  - **Glass**: Metals (*may not be necessary to be studied in EXT Study, if glass composition is available, direct assessment in LEA study*)
  - **Rubber Closure**:
    - ✓ Typically, higher migration when solution is in contact (inverted)
    - ✓ Migration will be determined by:
      - Solubility of leachables in **Drug Product** Solution
      - Potential Diffusion of Compounds through rubber, into solution
      - Temperature
    - ✓ VOC, SVOC and NVOC & some metals may cause a **Safety Issue**
    - ✓ VOC, SVOC, NVOC, Silicone Oil and some Metals may also be **Reactive e.g. with reconstituted DP**: also potential Performance & **Quality Issue!**
    - ✓ Also, Ions may need to be “checked off”...

## 6. Main SVP containers: Extractable Considerations

### Lyo-Cake Vials

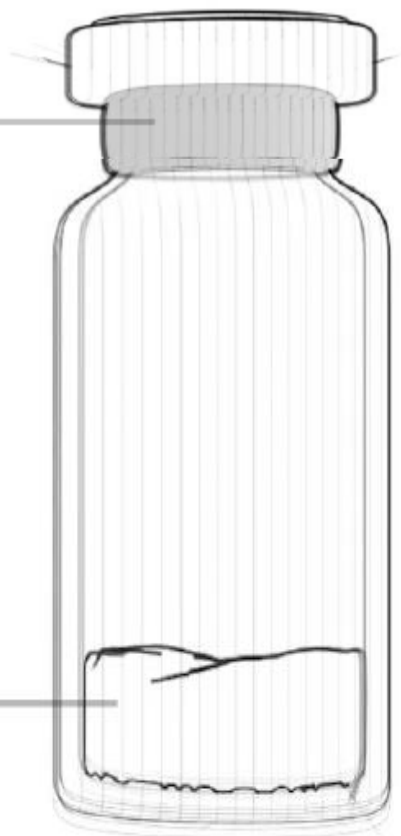


- Sources of impurities, coming from packaging
  - **Glass:** Metals (may not be necessary to be studied in EXT Study, if glass composition is available, direct assessment in LEA study)
  - **Rubber Closure:**
    - ✓ **No Direct Contact** between DP and Closure (upright)
    - ✓ **HOWEVER:** Release of Volatile (VOC) and Semi-Volatile (SVOC) Compounds from the Rubber Closure vial desorption and subsequent adsorption of compounds onto Lyo-Cake!
    - ✓ **Lyo-cake acts as adsorbent for VOC and SVOC compounds! Released Compounds are concentrated over time onto the Lyo Cake**
    - ✓ **Regardless** if vial is in **upright or inverted** position (contact / no contact with DP)
    - ✓ VOC and SVOC may also be **Reactive** with DP: also potential Performance & Quality Issue!
    - ✓ Also NVOC, Metals and Ions need to be “checked off”, because of short term contact with Reconstituted DP.

# The Interaction Mechanism: During Long Term STORAGE of the LYO-Cake

RUBBER

**OUTGASSING OF  
RUBBER STOPPER**



LYO CAKE

***Outgassing of rubbers is mainly an issue for:***

- *Volatile Organic Compounds*
- *Semi-Volatile Organic Compounds*

***LYO CAKE: EXTREMELY GOOD ADSORBENT***

- *High Surface Area*
- *Extremely Dry*

# Rubber Stopper

## OUTGASSING OF RUBBER STOPPER

The “Extent” of outgassing will also depend upon the Rubber Quality / Grade

Outgassing of rubbers is mainly an issue for:

- Volatile Organic Compounds
- Semi-Volatile Organic Compounds

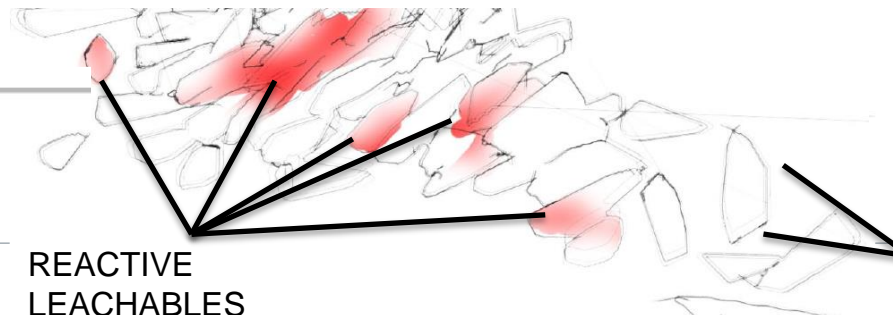
**LYO CAKE: EXTREMELY GOOD ADSORBENT**

- High Surface Area
- Extremely Dry

**ACCUMULATION OF VOC/SVOC LEACHABLES**

- Over Shelf Life of the DP
- Potential Interactions (Reactive Leachables)

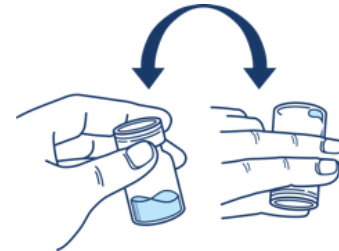
LYO CAKE





# The Interaction Mechanism: During RECONSTITUTION of the Lyophilized DP

## RECONSTITUTION



**SOLUBILIZATION**  
of adsorbed leachables in reconstitution  
solution

Mainly **Volatile & Semi-Volatile Organic**  
compounds (**OUTGASSING**)

Reconstituted (Liquid) DP  
**Liquid Interaction** with  
Primary Packaging Components

Although **SHORT TERM** Contact, also  
**Non-Volatile Compounds, Metals and Ions**  
may be released

More information on E/L for Lyo-products can be found on the  
**Sotera Health Academy**

## 2022 Nelson Labs Virtual Symposium

**Table of contents**

- Nelson Labs 2022
- Small Volume
- Parenteral Packaging
- Symposium
- Nelson Labs 2022 Sm**

### 2022 Nelson Labs Virtual Symposium



**Nelson Labs 2022  
Small Volume  
Parenteral  
Packaging  
Symposium**

0% COMPLETE

Setting up Extractables & Leachable Studies for Small Vol...



**Nelson Labs.**  
A Sotera Health company

**The Necessity of Extractable and Leachable Qualifications for Lyophilized Drug Products: Some Fallacies Addressed**

Sona Kovackova, PhD  
E&L Expert SVP, Nelson Labs Europe

EXIT COURSE

Contact the [Academy](#) for more information

## 6. Main SVP containers: Extractable Considerations

### 2. Pre-Filled Syringe:



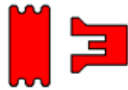
## 6. Main SVP containers: Extractable Considerations



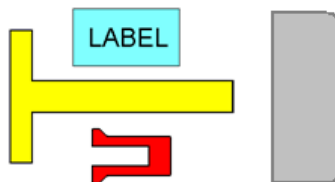
BARREL –  
Glass, COC/COP, PP, Silicone Oil, ...



NEEDLE –  
Metals, Tungsten (W), Needle Glue, ...



RUBBER SEALINGS (Plunger, Tip Cap,..)



SECONDARY (Needle Shield, Label, Stem, ...) –  
Rubber, Label Adhesive, Overwrap for Polymer based Containers...

## 6. Main SVP containers: Extractable Considerations

### Pre-Filled Syringes



- **BARREL:** *Metals* (may not be necessary to be studied in EXT Study, if glass composition is available, direct assessment in LEA study)  
*Silicone Oil* residues may cause protein aggregation
- **Rubber Plunger** (*very similar to rubber stopper for vial*):
  - ✓ Typically, higher migration when solution is in contact
  - ✓ Migration will be determined by:
    - Solubility of leachables in **Drug Product** Solution
    - Potential **Diffusion of Compounds through rubber**, into solution
    - **Temperature**
  - ✓ VOC, SVOC and NVOC may cause a safety issue
  - ✓ VOC, SVOC, NVOC, Silicone Oil and some Metals may also be **Reactive** with reconstituted DP: also potential Performance & Quality Issue!
  - ✓ Also, Ions may need to be “checked off”...
  - ✓ Coated versus Non-Coated plungers

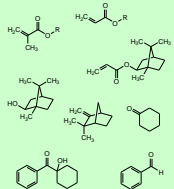
## 6. Main SVP containers: Extractable Considerations

### Pre-Filled Syringes



- **GLUE for staked needle:** Glue residues may for protein denaturation
- **TUNGSTEN Residues:** May cause protein aggregation
- **NEEDLE SHIELD:**
  - **No Direct Contact** between DP and Needle Shield
  - **HOWEVER:** Release of **Volatile (VOC)** and **Semi-Volatile (SVOC)** Compounds from the Needle shield into the content of the PFS is possible!
  - VOC and SVOC may also be **Reactive with DP:** also potential Performance & Quality Issue!
  - Typically **No NVOC, Metals and Ions** investigation is necessary for a Needle Shield.

## 6. Glass versus Polymer SVP-Containers

Concern for - Glass PFS - Polymer PFS	Concern for - Glass PFS	Concern for - Glass PFS	Concern for - Glass PFS	Concern for - Polymer PFS	Concern for - Polymer PFS
<b>(COATED) RUBBER</b>	<b>NEEDLE GLUE</b>	<b>TUNGSTEN (W)</b>	<b>GLASS BARREL</b>	<b>COC/COP/PP BARREL</b>	<b>LABEL (ADHESIVE)</b>
<p>MONOMER REMAINDERS &amp; POLYMER FRAGMENTS</p> <p>FILLERS: <i>Clay, Talc, Carbonates...</i></p> <p>ANTIOXIDANTS: <i>BHT, Irganox 1010, Irgafos 128, ...</i></p> <p>CURING AGENTS: <i>S,S-Donors, Phenol-Formaldehyde...</i></p> <p>ACTIVATORS: <i>ZnO / Stearic Acid</i></p> <p>ACCELERATORS: <i>Carbamates, Sulfenamides...</i></p> <p>OTHERS: <i>Pigments, Stabilizers, Release agents...</i></p> <p>Piston / Needle Shield / Tip Cap</p>	<p>- POLYMER FRAGMENTS</p> <p>- UV CURING-ACTIVATORS</p> 	<p>A Tungsten pin is used in the production of glass pre-filled syringes to keep the syringe hub open (cavity where the staked needle is glued in)</p>	<p>Major: Silica (SiO<sub>2</sub>)</p> <p>Alkali (e.g. Na<sub>2</sub>O)</p> <p>Minor:</p> <p>K (K<sub>2</sub>O),</p> <p>B (B<sub>2</sub>O<sub>3</sub>),</p> <p>Ca (CaO),</p> <p>Al (Al<sub>2</sub>O<sub>3</sub>)</p> <p>Colored glass: Fe<sub>2</sub>O<sub>3</sub>, TiO<sub>2</sub>, CuO, Mn<sup>3+</sup></p> <p>Sulfate (from dealkalization)</p> <p>Silicone oil (provides lubricity)</p>	<p>POLYMER FRAGMENTS SOLVENTS</p> <p>ANTIOXIDANTS: <i>BHT, Irganox 1010, ...</i></p> <p>ACID SCAVENGERS: <i>Stearate,...</i></p> <p>LUBRICANTS: <i>FA Esters, ...</i></p> <p>WAXES</p> <p>SLIP ADDITIVES: <i>Erucamide, Oleamide, ...</i></p> <p>PLASTICIZERS</p> <p>RELEASE AGENTS</p> <p>PIGMENTS</p> <p>Optional: Silicone Oil</p>	<p>Permeable Plastic Materials (e.g. PP, ...)</p> <p>INK and ADHESIVE constituents in a complex composition, but at low concentrations</p> <p>POLYMER FRAGMENTS, SOLVENTS, PHOTO-INITIATORS, STABILIZERS, TACKIFIERS, ...</p> <p>e.g. <i>Acrylates, PVA, NR, Benzophenone, Irgacure 184, Irgacure 651, Irganox 1010, Dehydroabiatic Acid, DCHP, TBPP, Siloxanes, ...</i></p> <p><b>Potential Concern: SECONDARY PACKAGING</b></p>

## 6. Main SVP containers: Extractable Considerations

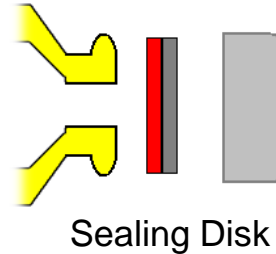
### 3. Cartridges





## 6. Main SVP containers: Extractable Considerations

### Cartridges



- **Sealing Disk:**
  - ✓ Typically, a sealing disk is a **two-layered** system
  - ✓ The **inner layer** has **product contact** (primary contact), should be the focus of the investigation
  - ✓ **“One Sided” extraction** mimics the product contact, avoids contribution of the outer layer
  - ✓ **Complete Extraction** of the 2 layered sealing disk can be considered as **“Worst Case”**
  - ✓ Both approaches can be taken and have found regulatory acceptance

## 6. Main SVP containers: Extractable Considerations

### Cartridges



- **BARREL: *Metals*** (may not be necessary to be studied in EXT Study, if glass composition is available, direct assessment in LEA study)
  - Silicone Oil*** residues may cause protein aggregation
- **Cartridge Plunger (same as for PFS!):**
  - ✓ Typically, higher migration when solution is in contact (inverted)
  - ✓ Migration will be determined by:
    - Solubility of leachables in Reconstitution Solution (typically inorganic aqueous solution (*typically low solubility for most non-polar organic compounds*))
    - Potential Diffusion of Compounds through rubber, into solution
    - Temperature
  - ✓ VOC, SVOC and NVOC may cause a safety issue
  - ✓ VOC, SVOC, NVOC, Silicone Oil and some Metals may also be **Reactive** with reconstituted DP: also potential Performance & Quality Issue!
  - ✓ Also, Ions may need to be “checked off”...

## Setting up an Extractable & Leachable Program: for Small Volume Parenterals

### Focus on the Application

- **Aqueous** versus **Non-Aqueous** Drug Products
- **Liquid** versus **Solid** (Lyo) drug product
- **Dosing Regimen** (*frequency, volume*) determines **AET level**
  - *Vaccine (e.g. once in a lifetime)*
  - *Life time treatment (e.g. Insulin cartridges)*
- Both at the level of an **Extraction Study & a Leachable Study**
- **Single Use Vial** versus **Multi Use Cartridge**
- **Biologics** versus **Small Molecule** Drug Products

### See presentations

How to Set-up Extractable Studies

How to Set-up Leachable Studies

Introduction to Toxicology (101)

# Questions?



Dr. Piet Christiaens, Scientific Director - Nelson Labs Europe  
e-mail: [pchristiaens@nelsonlabs.com](mailto:pchristiaens@nelsonlabs.com)  
Tel: +32 16 40 04 84