PDA VIRTUAL TRAINING COURSE

EXTRACTABLES – LEACHABLES

EXTRACTABLES & LEACHABLE CONSIDERATIONS FOR SMALL VOLUME PARENTERAL APPLICATIONS

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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

LYO

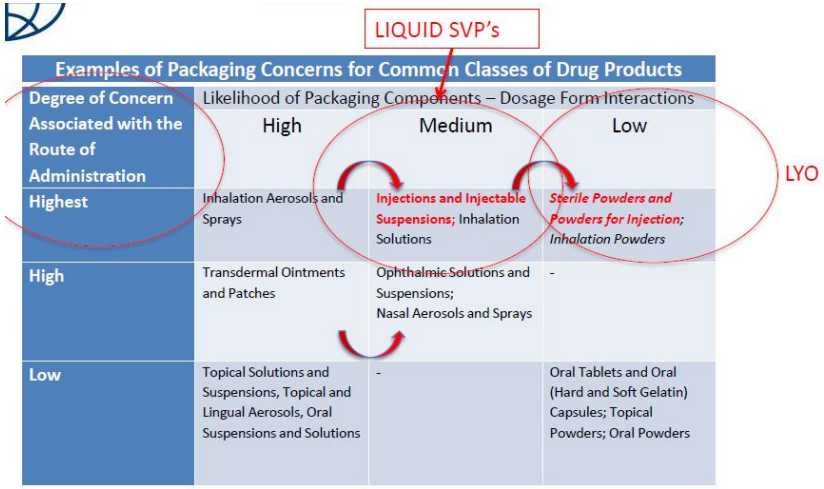
Examples of Packaging Concerns for Common Classes of Drug Products			
Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Components – Dosage Form Interactions		
	High	Medium	Low
Highest	Inhalation Aerosols and Sprays	**Injections and Injectable Suspensions;** Inhalation 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

Revision of "Table 1" in USP <1664>,

Originally Included into the FDA Guidance for Industry (1999):

"Container/Closure systems for Packaging Human Drugs and Biologics"

1. Regulatory Expectations - US



Examples of Packaging Concerns for Common Classes of Drug Products

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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

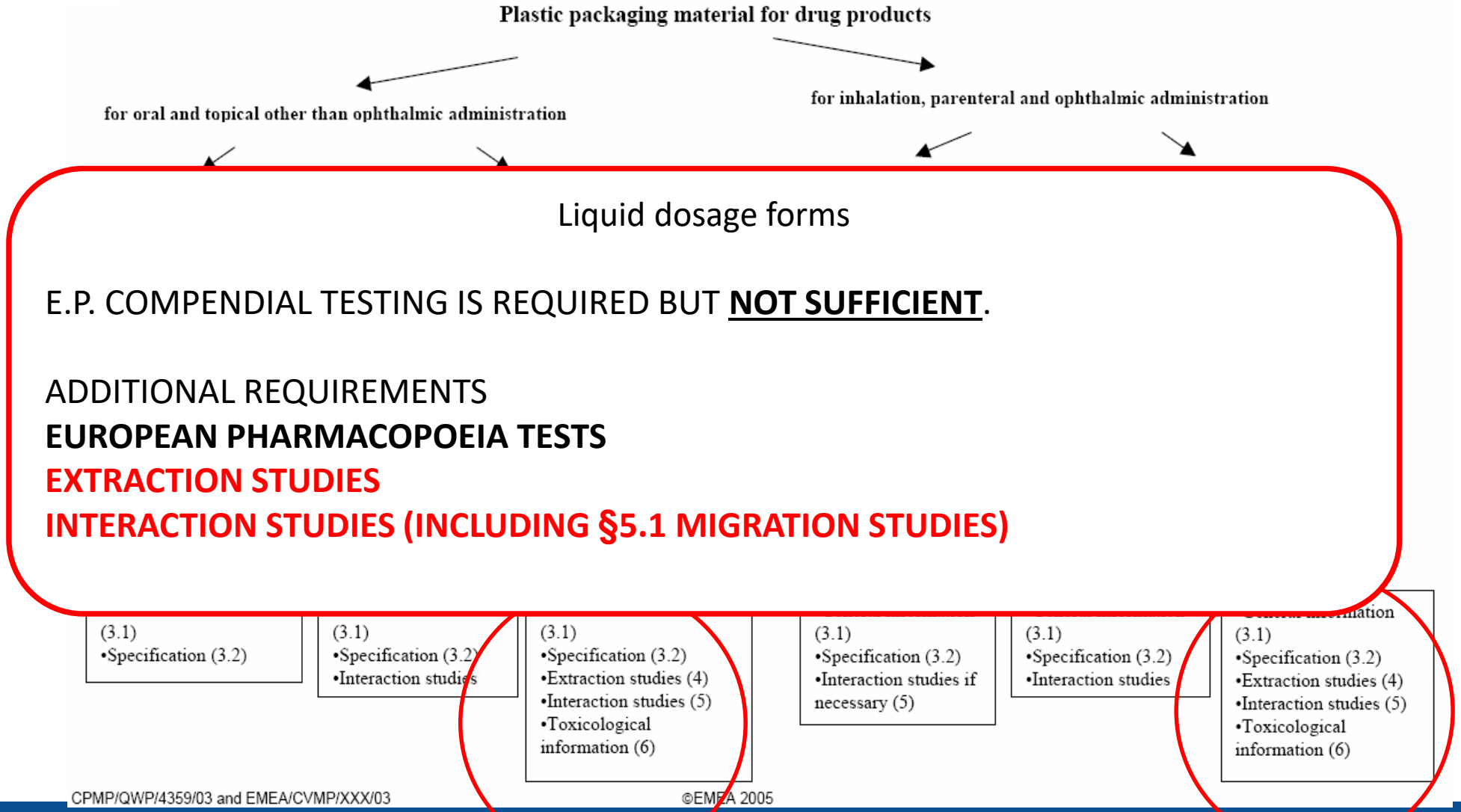
Video of **Dan Mellon** (FDA - CDER)

https://www.youtube.com/watch?v=mol_X2zQeig

1. Identify Compounds above the Qualification Threshold (QT)
2. The use of Inappropriate Threshold Levels
3. Inadequate Sensitivity of the Detection Methods
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**



Elastomeric closures

2. Rubbers – An introduction

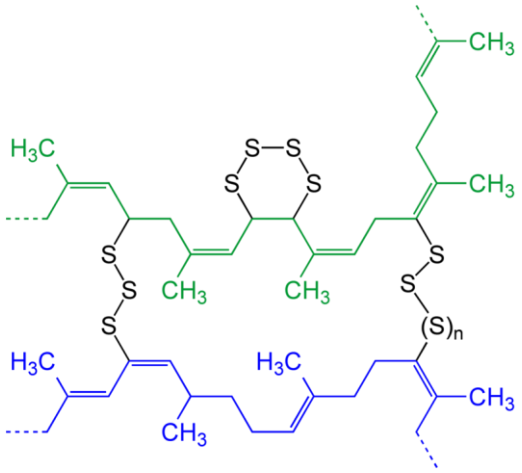
Supported by Datwyler

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

e.g. Elastomer type Additives Filler	e.g. E&L profile Hardness Compression set Tensile strength	e.g. Drug compatibility Container Closure Integrity Gamma/Steam resistance Fragmentation Gliding curve

2. Rubbers – an Introduction

Rubber = Compounded material of:

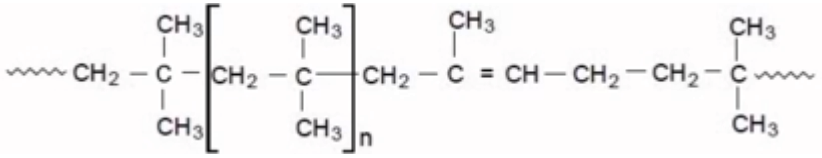
1. **Elastomer**

2. Filler

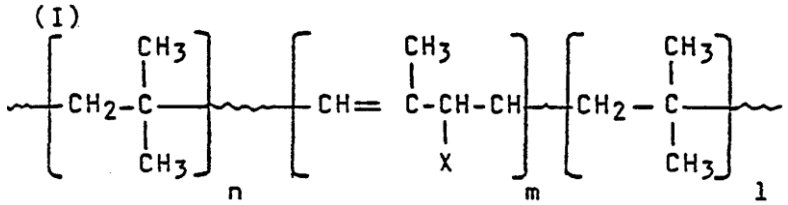
3. Cure system
4. Pigment
5. Other ingredients

2. Rubbers – an Introduction - ELASTOMERS

- **Halobutyl (BromoButyl, ChloroButyl)**
  - *Cleanest curing system*
  - *Lowest permeability*
  - *High resistance to ageing*



Butyl

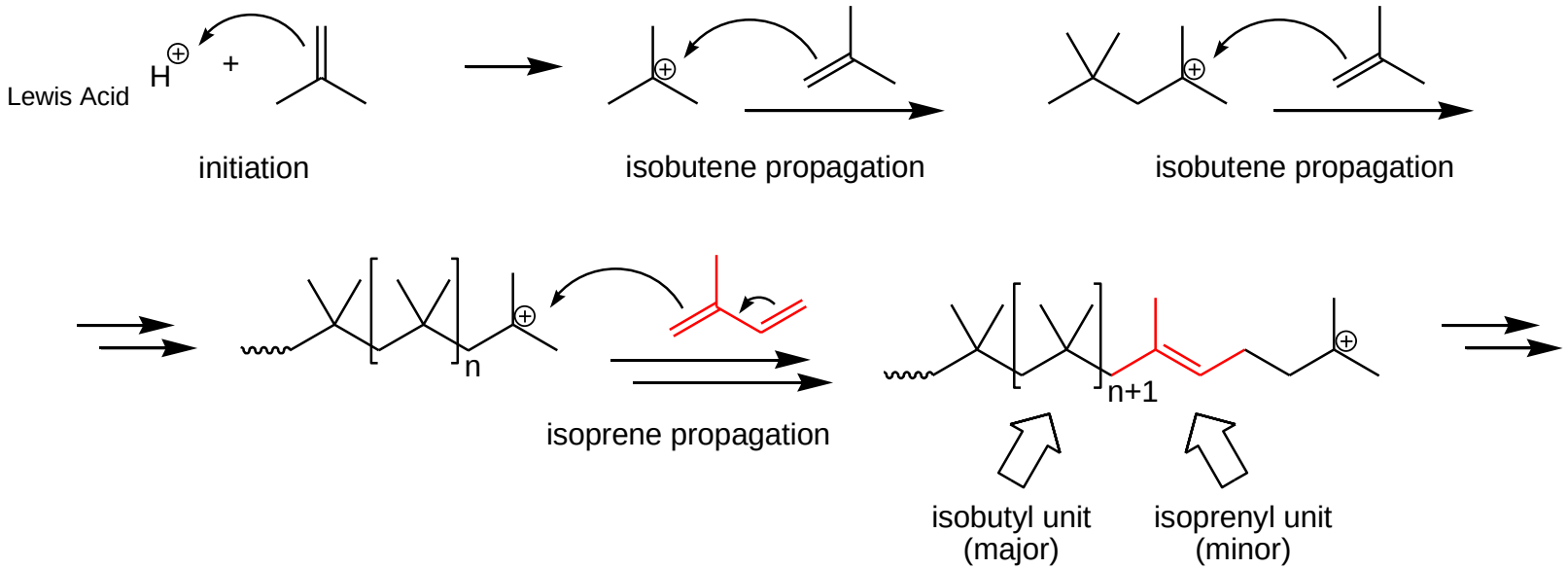


X =Cl or Br

Halobutyl

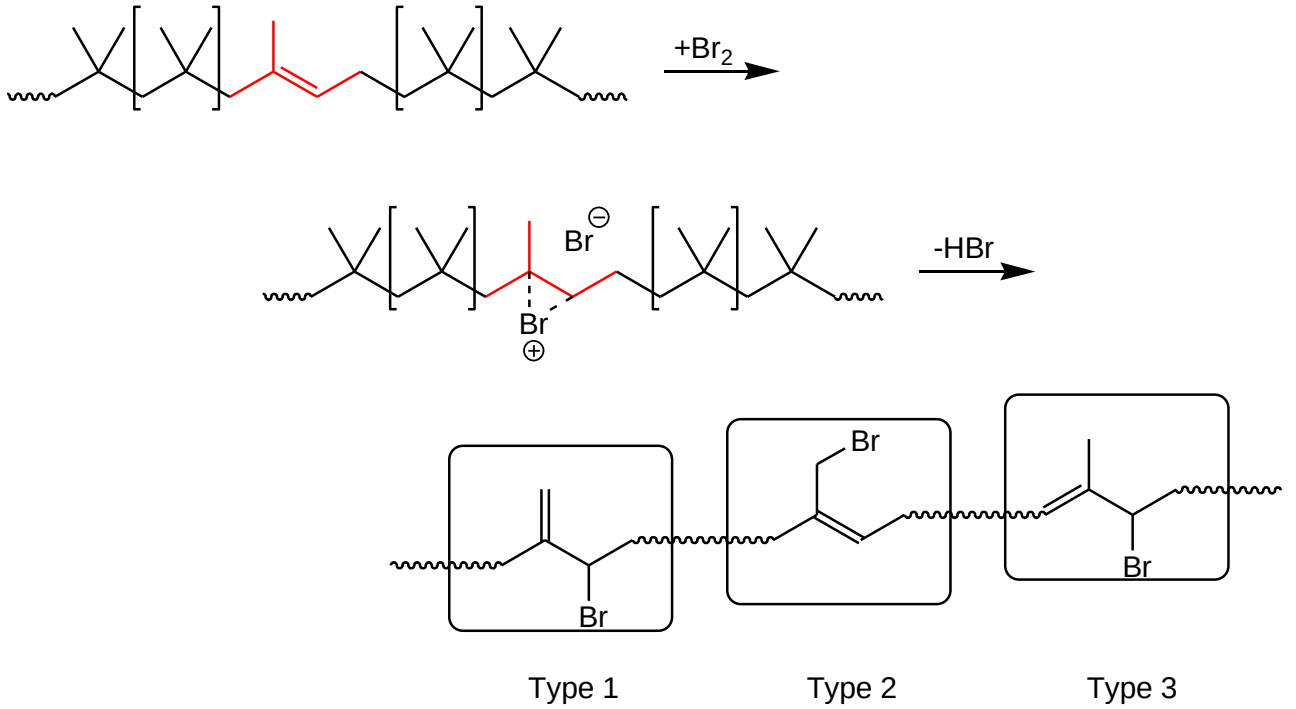
2. Rubbers – an Introduction - ELASTOMERS

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*

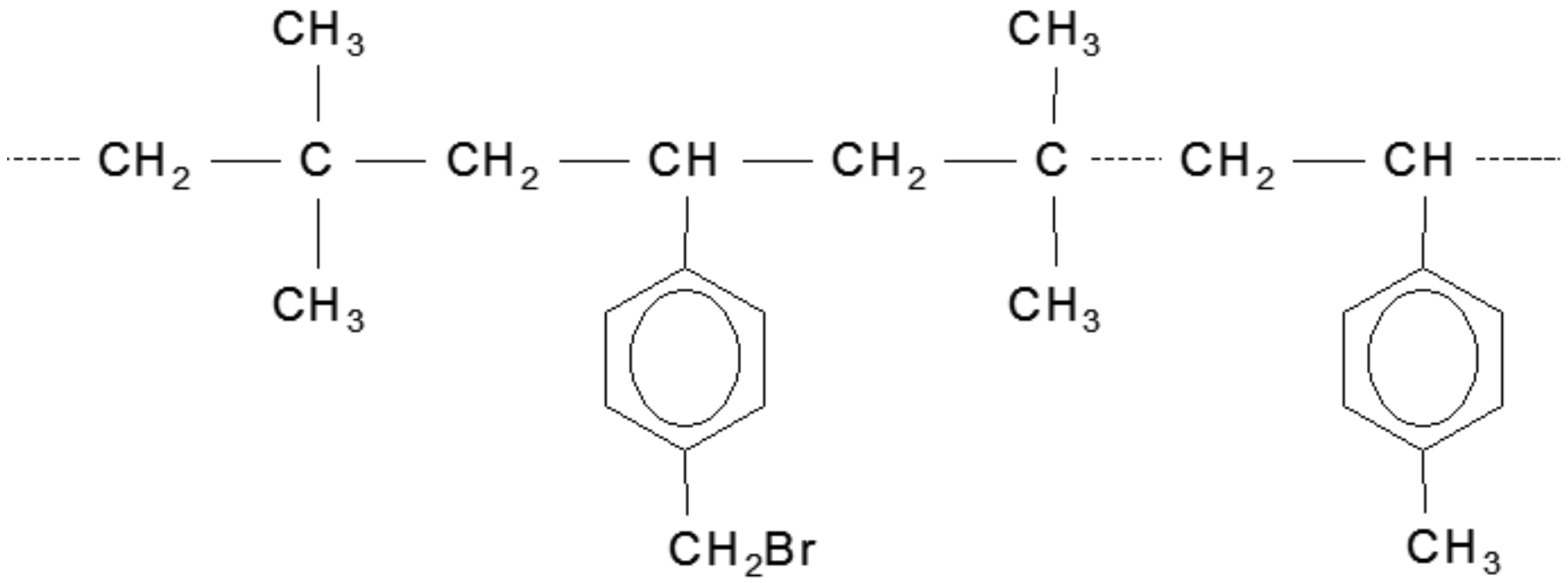
Bromination of a Butyl Elastomer (BIIR)



Bromination of the Backbone makes Elastomer
(with a relatively Low N° of double bonds in backbone)
more reactive in vulcanization/cross linking

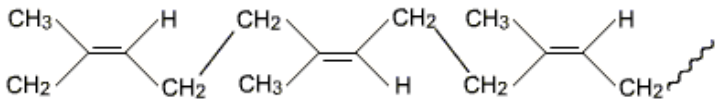
2. Rubbers – an Introduction - ELASTOMERS

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



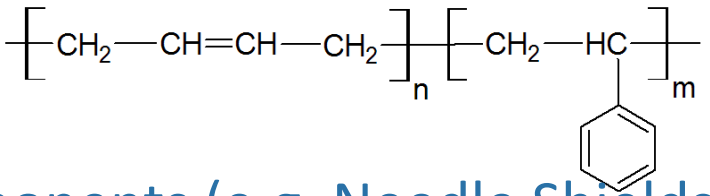
2. Rubbers – an Introduction - ELASTOMERS

- **Natural rubber / Polyisoprene**
  - Natural rubber: latex allergy discussions
  - Historically the oldest elastomer type
  - Need complex curing systems
  - Good elastic properties
  - Polyisoprene (synthetic) replaces Natural rubber



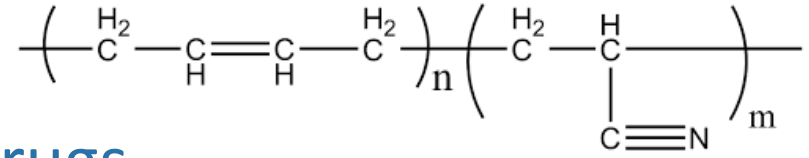
Natural rubber

- **SBR** (styrene-butadiene rubber)
  - Intermediate permeability
  - Typically used for pre-assembled EtO sterilized components (e.g. Needle Shields)

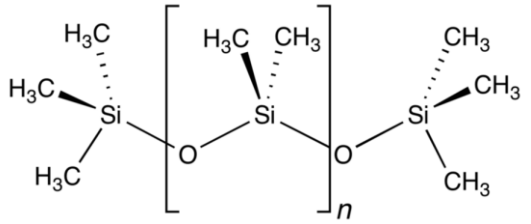


2. Rubbers – an Introduction - ELASTOMERS

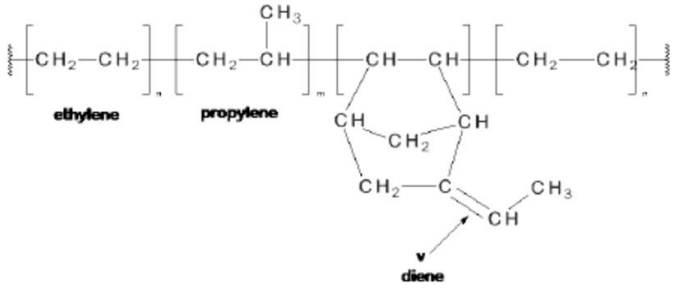
- **Nitrile** rubber
  - Typically used for mineral oil based drugs



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



- **EPDM** rubber
  - For niche applications



Rubber = Compounded material of:

1. Elastomer

2. **Filler**

3. Cure system
4. Pigment
5. Other ingredients

2. Rubbers – an Introduction - FILLERS

- 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

Rubber = Compounded material of:

1. Elastomer

2. Filler

3. Cure system

4. Pigment

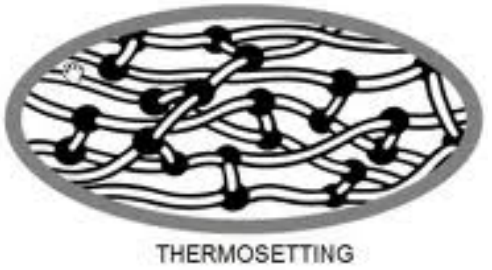
5. Other ingredients

2. Rubbers – an Introduction – CURE SYSTEMS

- **Cure system:**
  - 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

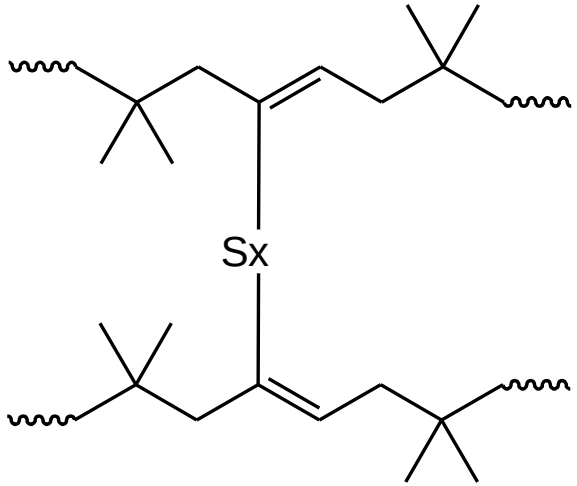
- **Historic cure systems**
  - Use easily extractable organic accelerators



Crosslinked polymer chains

2. Rubbers – an Introduction – CURE SYSTEMS

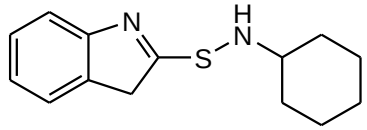
Rubber Curing / Vulcanization:



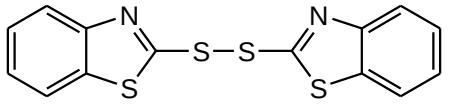
Rubber crosslinking requires S-Donors, activators, accelerators
Activator: ZnO / Stearic acid

2. Rubbers – an Introduction – CURE SYSTEMS

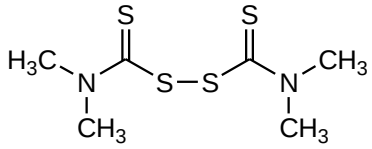
Rubber Curing - Accelerators:



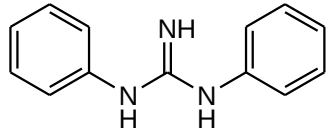
Cyclohexyl benzothiazole sulfenamide



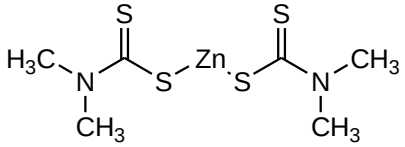
Mercaptobenzothiazole disulfide



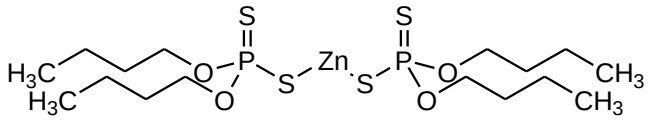
Tetramethylthiuram disulfide(TMTD)



Diphenyl guanidine



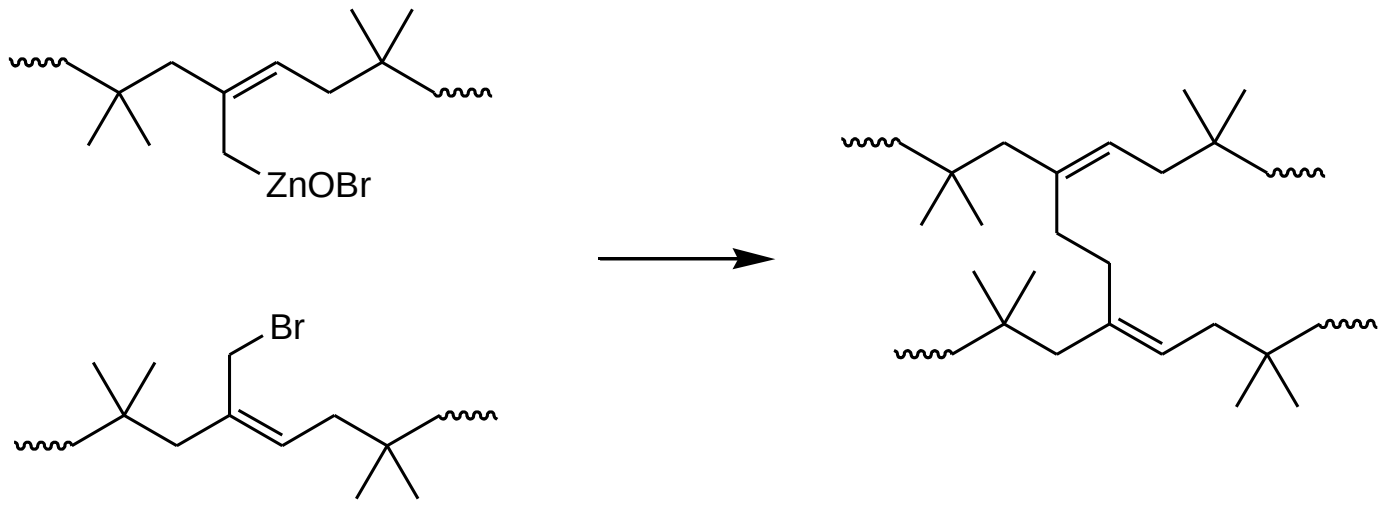
Zinc dimethyldithiocarbamate



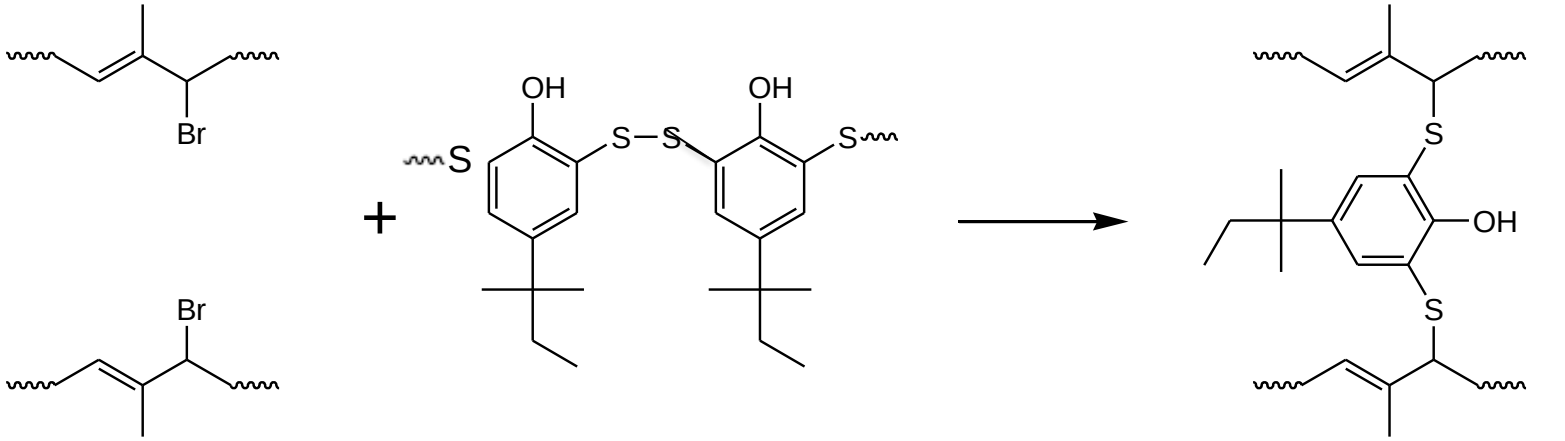
Zinc dibutylphosphorodithiate

2. Rubbers – an Introduction – CURE SYSTEMS

ZnO as Cross-Linking Compound in Halobutyl-Rubbers:



Vultac Curing of (Halobutyl) Elastomers



Amyl Disulfide Polymer

Phenol Sulfide Crosslink

Bromide: good leaving group!

Bond Energy C-H 413 J/mol ⇔ C-Br 209 J/mol

Explains Br^- release from bromobutyl rubbers

Rubber = Compounded material of:

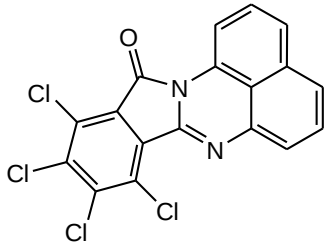
1. Elastomer

2. Filler

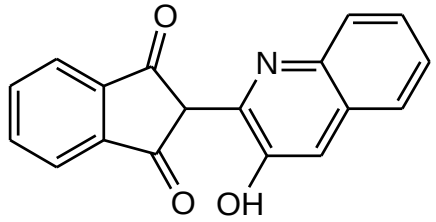
3. Cure system
4. **Pigments**
5. Other ingredients

2. Rubbers – an Introduction – PIGMENTS

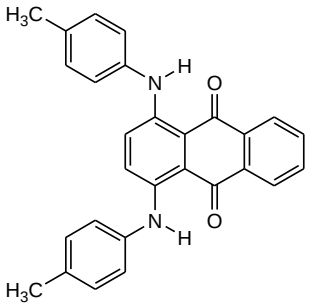
- **Inorganic pigments**
  - Titanium dioxide
  - Traces of carbon black
  - Oxides of iron
- **Organic pigments**
  - Avoided in modern compounds



Solvent Red



Solvent yellow 114



Solvent Green 03

Rubber = Compounded material of:

1. Elastomer

2. Filler

3. Cure system
4. Pigment
5. **Other ingredients**

2. Rubbers – an Introduction – OTHER INGREDIENTS

- **Halobutyl polymer stabilizers**

(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 RUBBER PRODUCTION

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”*

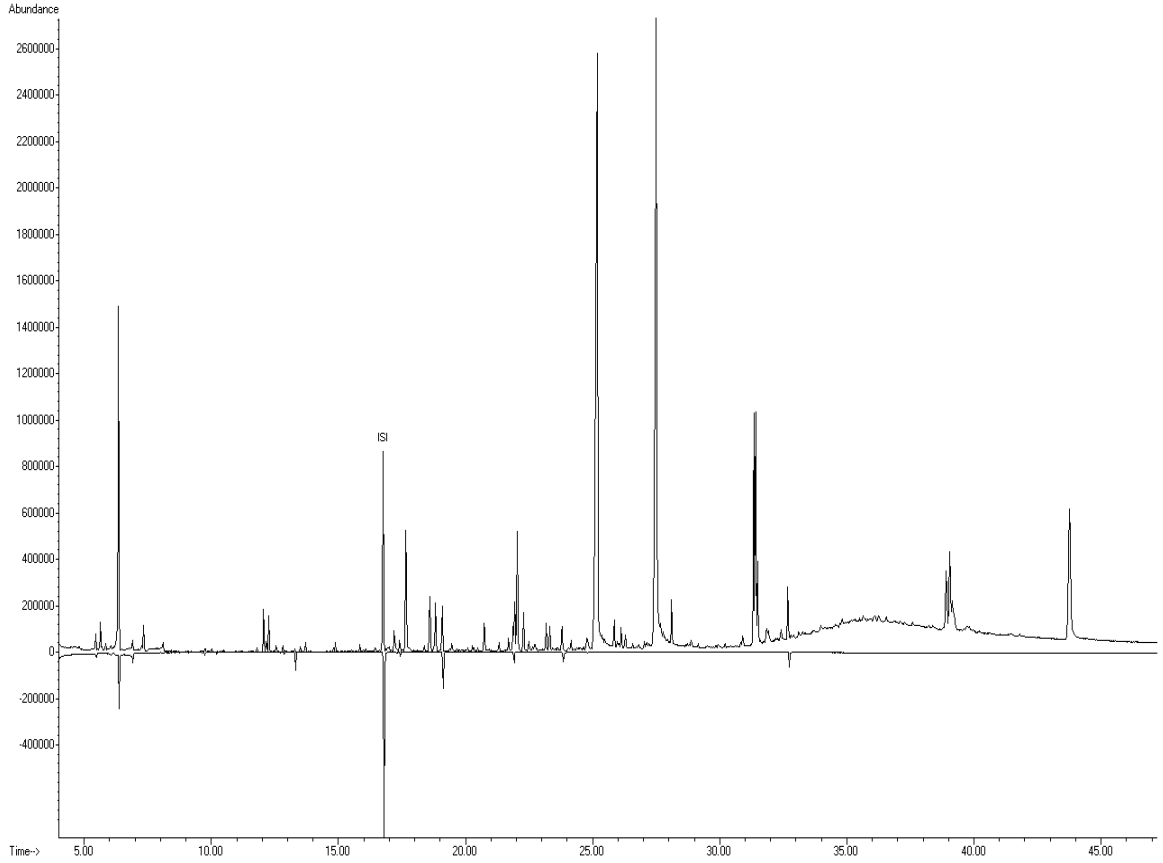
2. Rubbers – an Introduction

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)

2. Rubbers – an Introduction

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



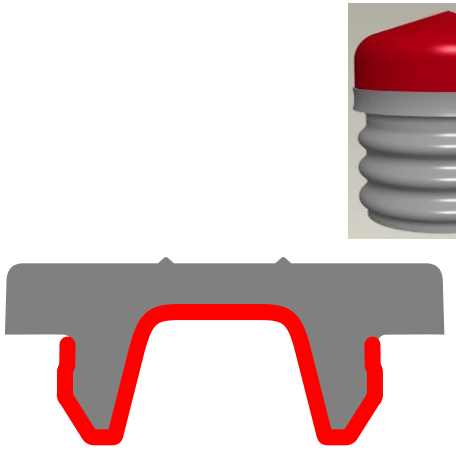
"OLD" RUBBER

"NEW" RUBBER

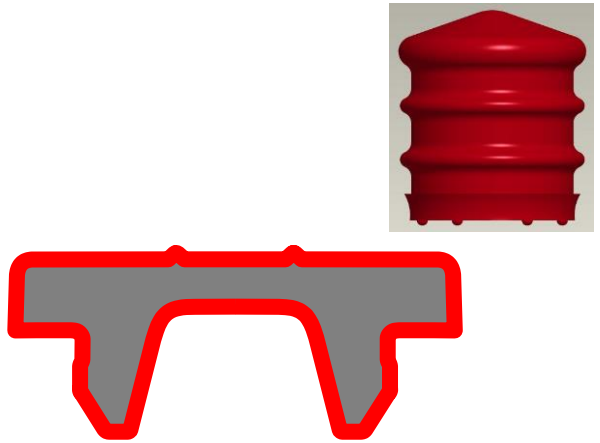
COATED RUBBERS

- Coated closures: significant improvement in E&L terms
- Key attribute: barrier effect from the fluoropolymer!
  - *Simplified extractables* profile
  - *Improved compatibility* with drugs/excipients

Film coating technology

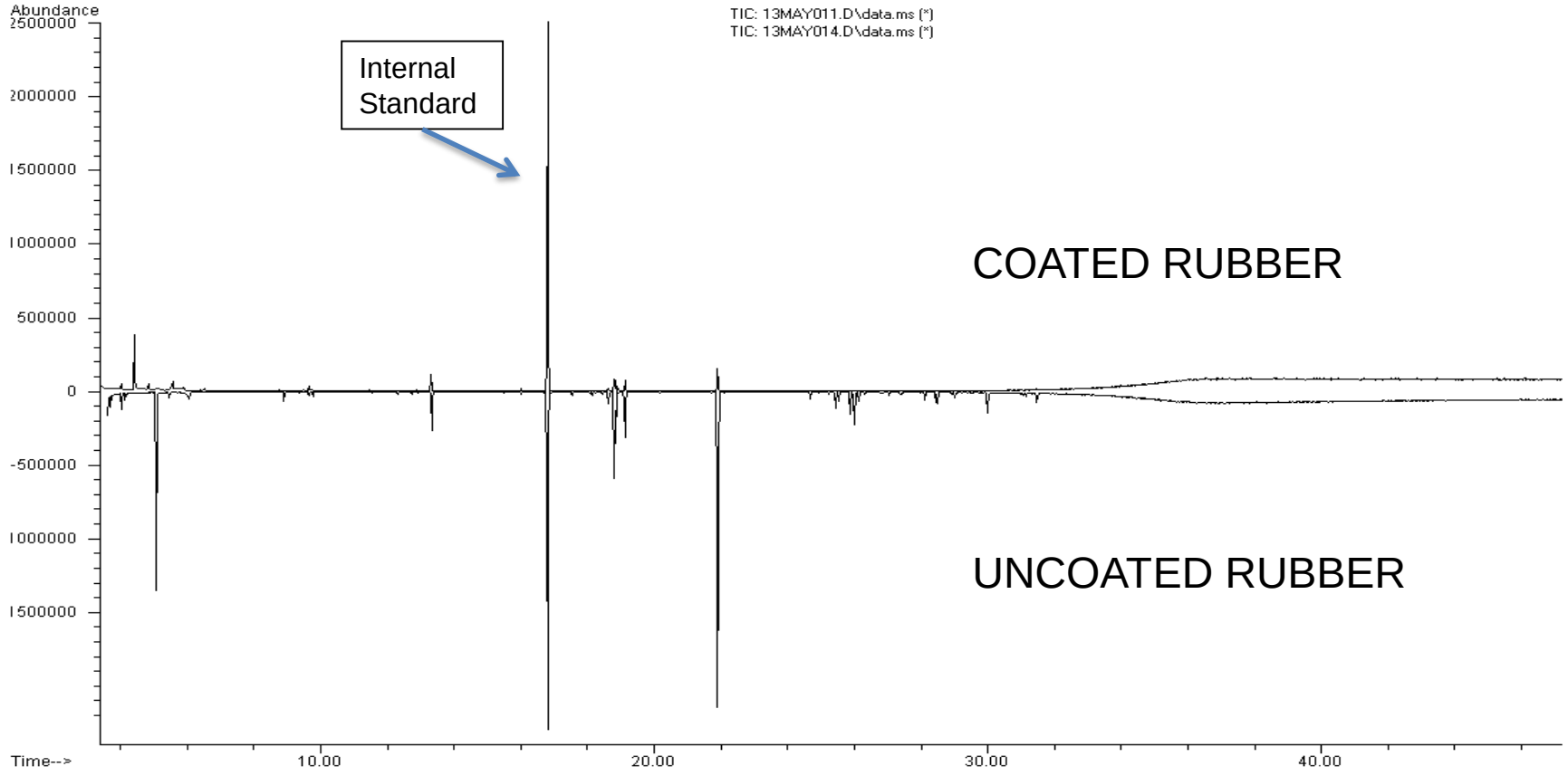


Spray coating technology



2. Rubbers – an Introduction

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

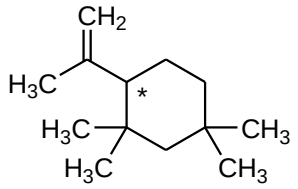


3. Rubber Oligomers: Toxicity & Reactivity

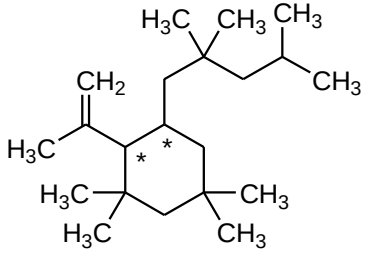
3. Rubbers Oligomers – Toxicity & Reactivity

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

- 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 tox. risk**.



C13 oligomer

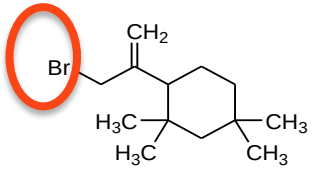


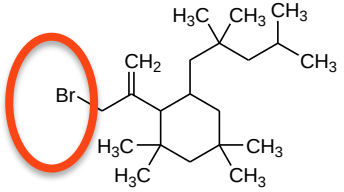
C21 oligomer

3. Rubbers 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 Hydrobarbon compounds (Allyl Halide)
  - **Alkylating Agents**
  - One double bond

- Structure Activity Relationship (SAR) Assessment:

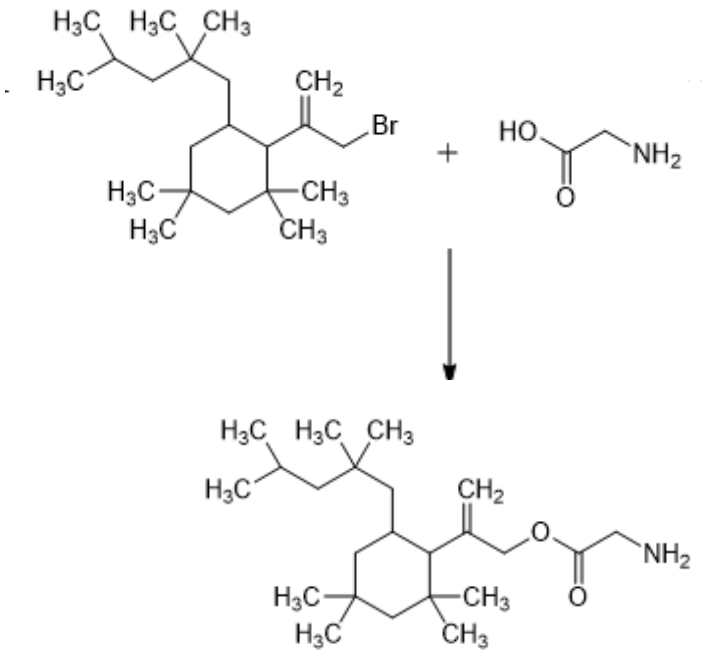
CARCINOGENICITY IN HUMANS IS PLAUSIBLE

- 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. Rubbers Oligomers – Toxicity & Reactivity

Lyophilized Drug Product B in a glass vial with a rubber stopper (without coating):
Excipients a.o.: Glycine

C21H39Br rubber oligomer source - leachable from a rubber stopper

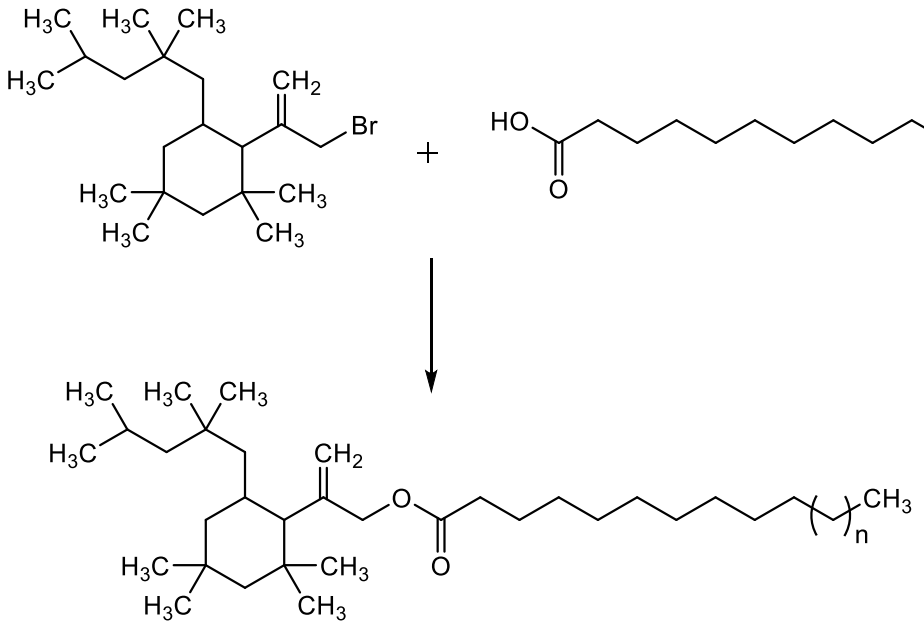


Glycine (excipient, bulking agent)

3. Rubbers Oligomers – Toxicity & Reactivity

Lyophilized Drug Product A in a glass vial with a rubber stopper (without coating):
Excipients a.o.: Polysorbate 20

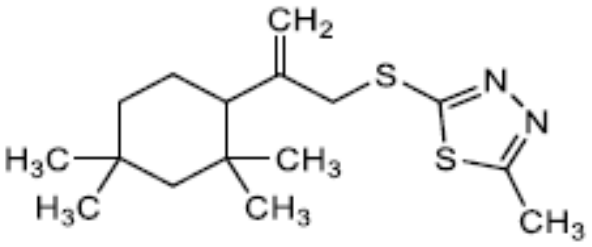
C21H39Br rubber oligomer source - leachable from a rubber stopper

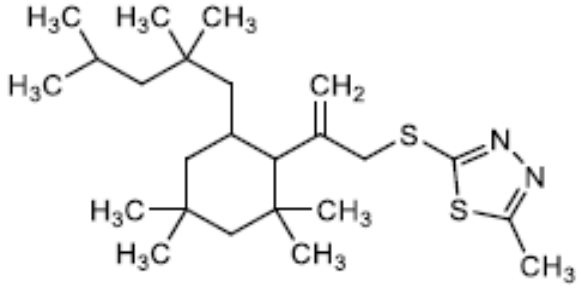


Fatty acids source – Polysorbate 20

3. Rubbers Oligomers – Toxicity & Reactivity

Adduct Formation of an API (Antibiotic) with the $C_{13}H_{23}Br$ and $C_{21}H_{39}Br$ oligomers





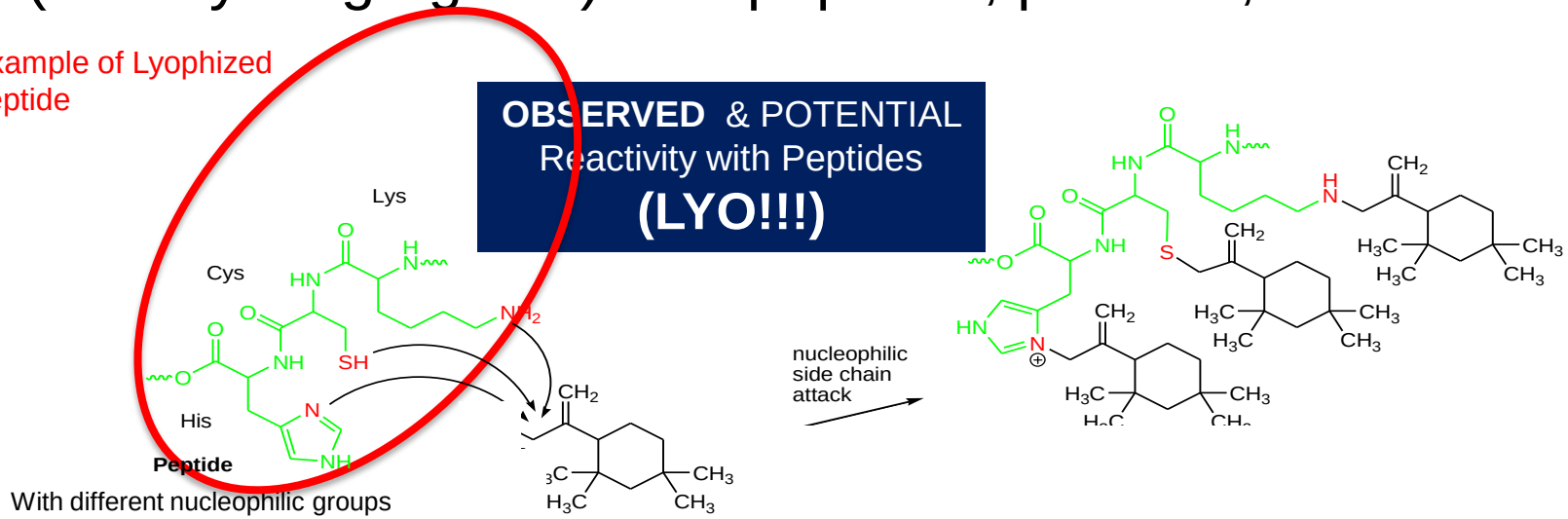
3. Rubbers Oligomers – Toxicity & Reactivity

Observed Reactivity of $C_{13}H_{23}Br$ and $C_{21}H_{39}Br$

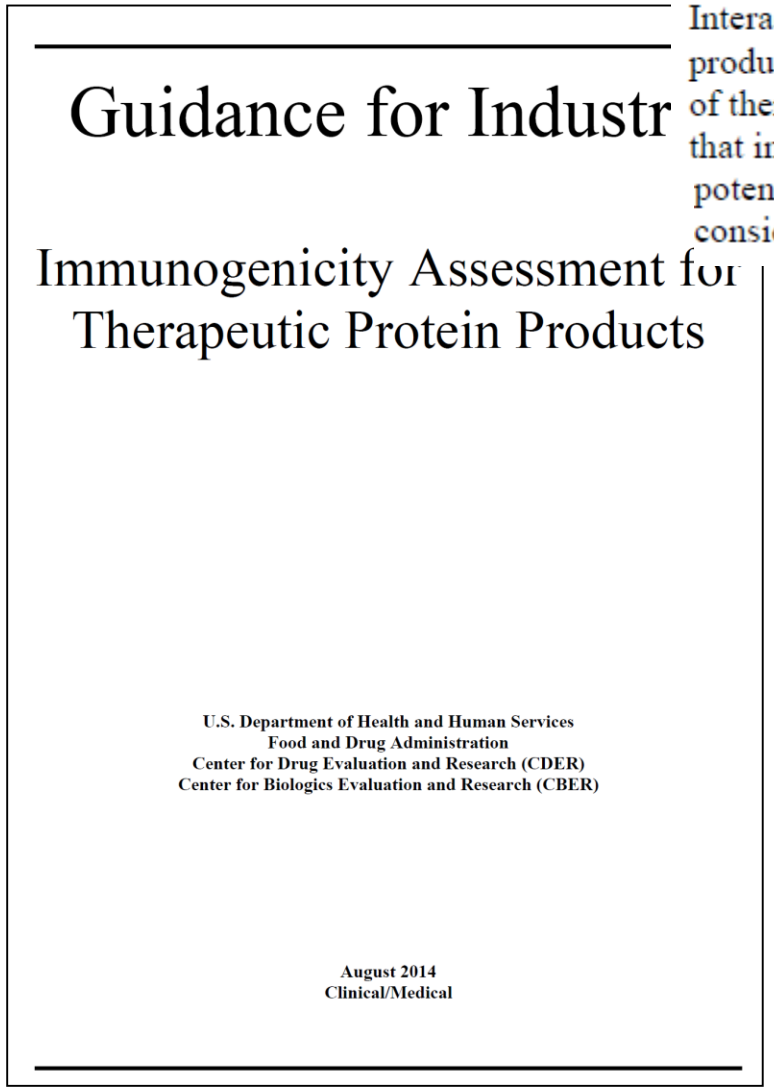
(as alkyating agents) with peptides, proteins, and nucleic acids

Example of Lyophized peptide

OBSERVED & POTENTIAL
Reactivity with Peptides
(LYO!!!)



3. Rubbers Oligomers – Toxicity & Reactivity



Guidance for Industr

Immunogenicity Assessment for Therapeutic Protein Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2014
Clinical/Medical

FDA Guidance for Industry, 2014

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..."

4. Glass & Glass Related Issues

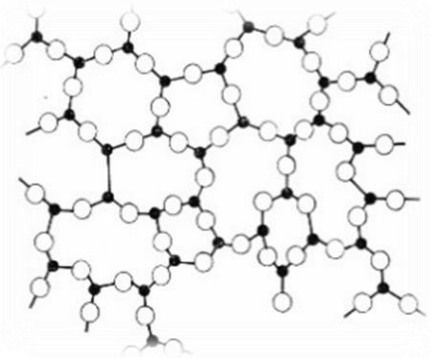
Vials, Prefilled Syringes, Cartridges

4. Glass and Related Glass Container 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.

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4. Glass and Related Glass Container issues

Composition of Glass – Function of Ingredients

- SiO_2 : Backbone structure
- CaO : Increasing hardness & Chemical resistance
- Al_2O_3 : Increasing Chemical Resistance
- Na_2O & B_2O_3 : Lowering the melting point
- Fe_2O_3, TiO_2 : Amber Glass
- CuO : Blue Glass
- Mn^{3+} : Violet Glass

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4. Glass and Related Glass Container 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 and Related Glass Container issues

Glass Composition for different Glass Types:

Component	Type I (Borosilicate)	Type II, III, NP (Soda-Lime)
SiO_2	70 - 73%	69 - 73%
B_2O_3	10%	0 - 1%
Na_2O	2 - 9%	13 - 14%
Al_2O_3	6 - 7%	2 - 4%
BaO	0,1 - 2,0%	0 - 2%
K_2O	1 - 2%	0 - 3%
CaO	0,7 - 1,0%	5 - 7%
MgO	0 - 0,5%	3 - 4%
ZnO	0 - 0,5%	-

4. Glass and Related Glass Container 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**

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- **Small volume** containers are **more impacted** than larger containers

4. Glass and Related Glass Container 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 and Related Glass Container 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 tranparency. Arsenic is toxic!
- **Release of metals**, causing precipitation with some salts, present in the DP
  Ba => $BaSO_4$, Al => $Al(OH)_3$

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4. Glass and Related Glass Container issues

How to (try to) prevent Glass Leaching

1. Chemical surface treatment

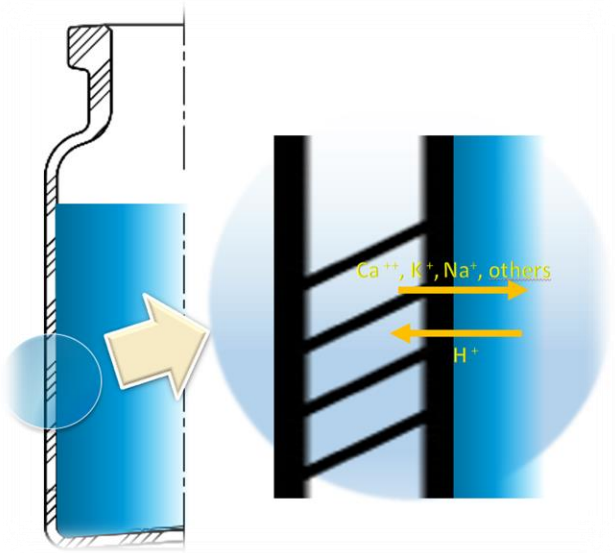
$(NH_4)_2SO_4$ is injected before annealing

$(NH_4)_2SO_4$ ➔ $(NH_4)\ HSO_4 + NH_3$

$2Na^+ + (NH_4)HSO_4$ ➔ $Na_2SO_4 + NH_3 + 2H^+$

Afterwards, rinsing with Water to remove soluble $NaSO_4$

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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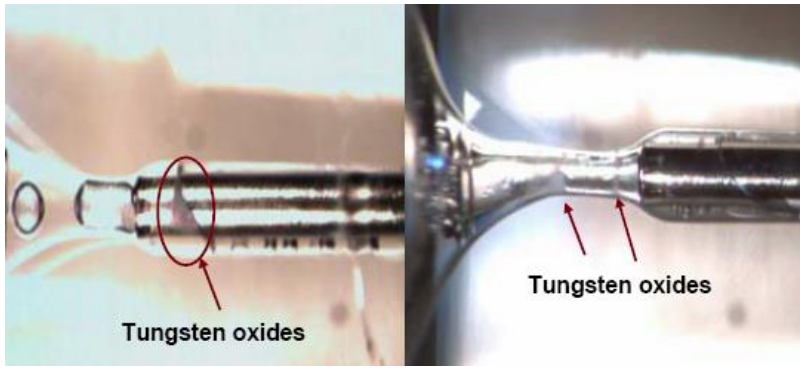
Glass as Barrel Material

TUNGSTEN RESIDUES

- *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)*



Glass as Barrel Material

GLUE RESIDUES

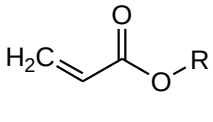
- *Glue is used to glue in the staked needle into the PFS-system*
- *Prolonged contact with a drug product may release glue components*
- *Target compounds may depend upon the glue used*
  (e.g. Loctite 3345, Loctite 3081, or other grades)

Glass as Barrel Material – Related Compounds

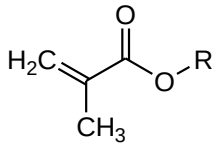
EXTRACTABLES RELATED TO GLASS BARRELS:

GLUE RESIDUES

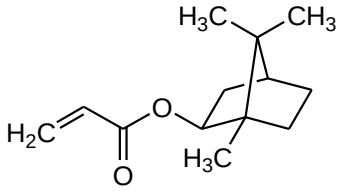
Base Polymer



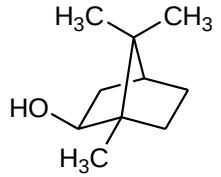
Acrylate



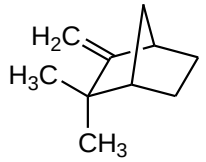
Methacrylate



Isobornyl acrylate

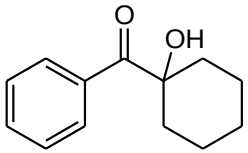


Isoborneol

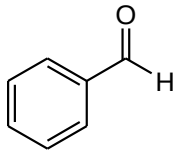


Camphene

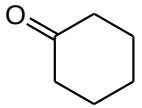
UV curing / activation



Irgacure 184



Benzaldehyde



Cyclohexanone

Glass as Barrel Material – Related Compounds

SILICONE OIL RESIDUES

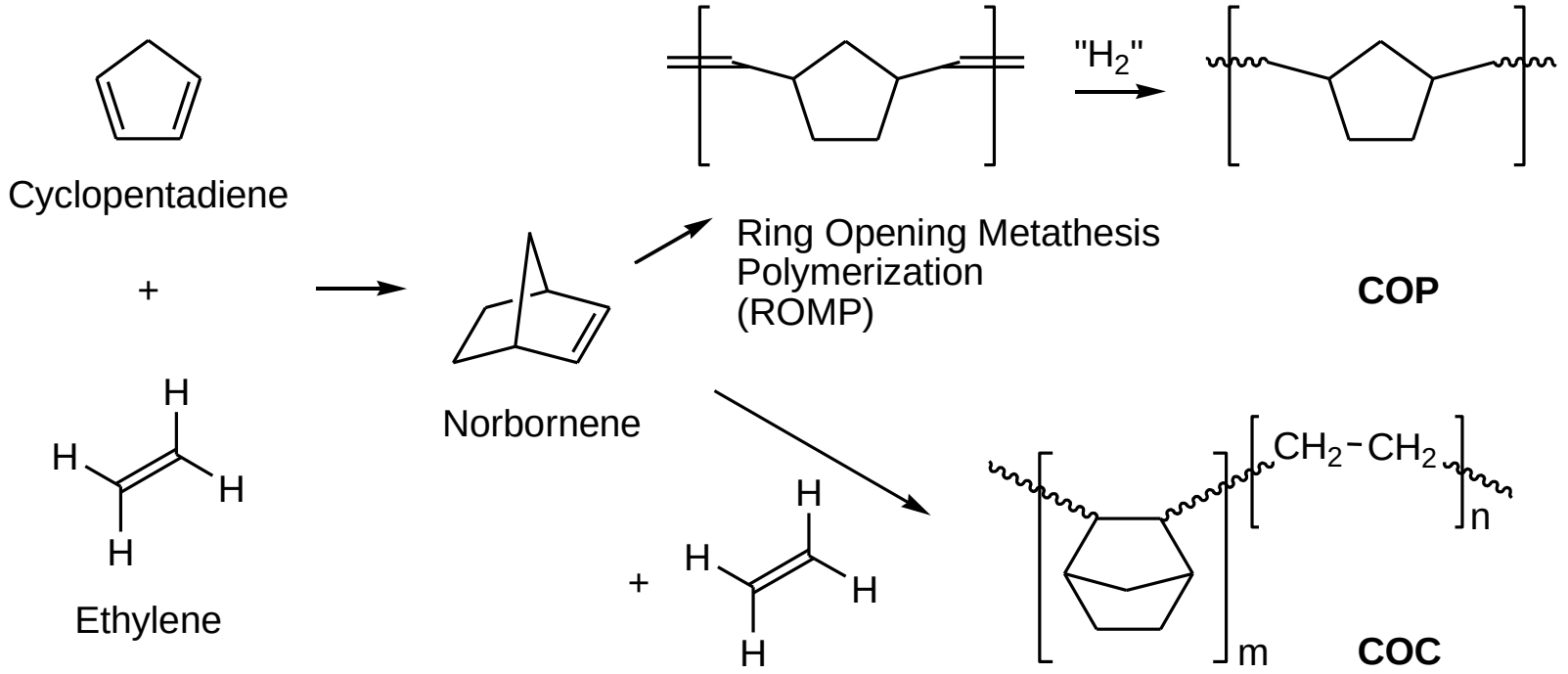
- *Glass surfaces are siliconized a.o. to reduce potential interactions with aqueous contact solutions*
- *Hydrophobic surface / reduced wettability*
- *Reduced alkali release*
- *Silicone oil remainders become leachables*

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

5. Other Materials used in SVP C/C Manuacturing

COP: Cyclic Olefin Polymers
COC: Cyclic Olefin Copolymers

- Relatively Clean Materials
- High Tg, rigid materials
- However, low gas barrier (O_2) properties
- Risk for diffusion: potential (regulatory) risk for **label migration**



5. Other Materials used in SVP C/C Manuacturing

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!

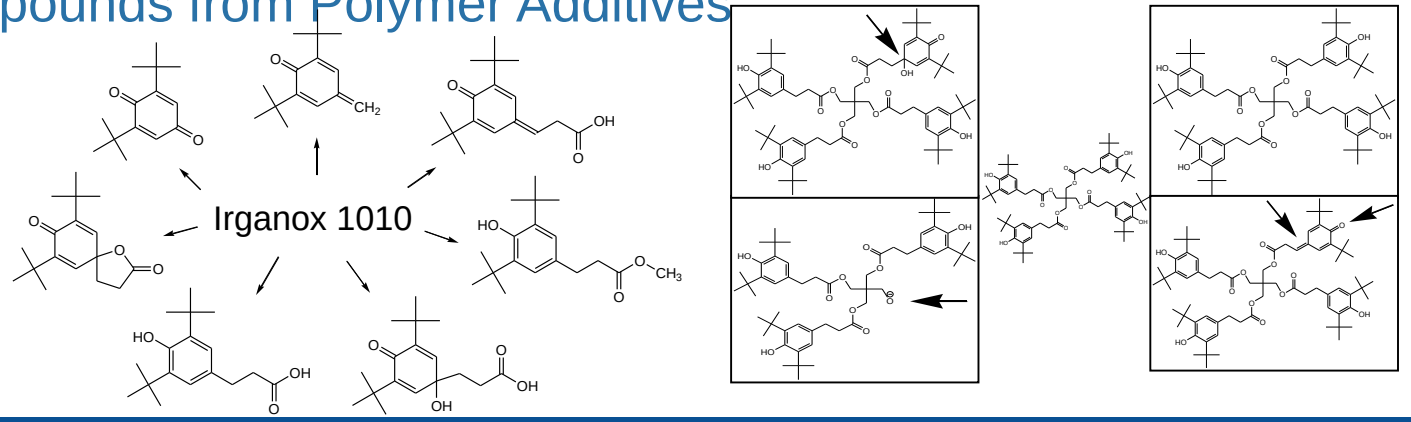
5. Other Materials used in SVP C/C Manuacturing

TYPICAL COMPOSITION OF **COMMERCIAL POLYMERS,**

e.g. For Barrel Manufacture

- Additives *(BHT, Irganox 1010, Stearates, Pigments, Clarifyers...)*
- 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

Example:



5. Other Materials used in SVP C/C Manuacturing

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 SVP C/C Manuacturing

SECONDARY PACKAGING

- **Label**
  - Adhesive
  - Paper
  - Ink
  - Varnish

Typical extractable compounds:

Curing agents (e.g. Benzophenone, Irgacure 184,...)

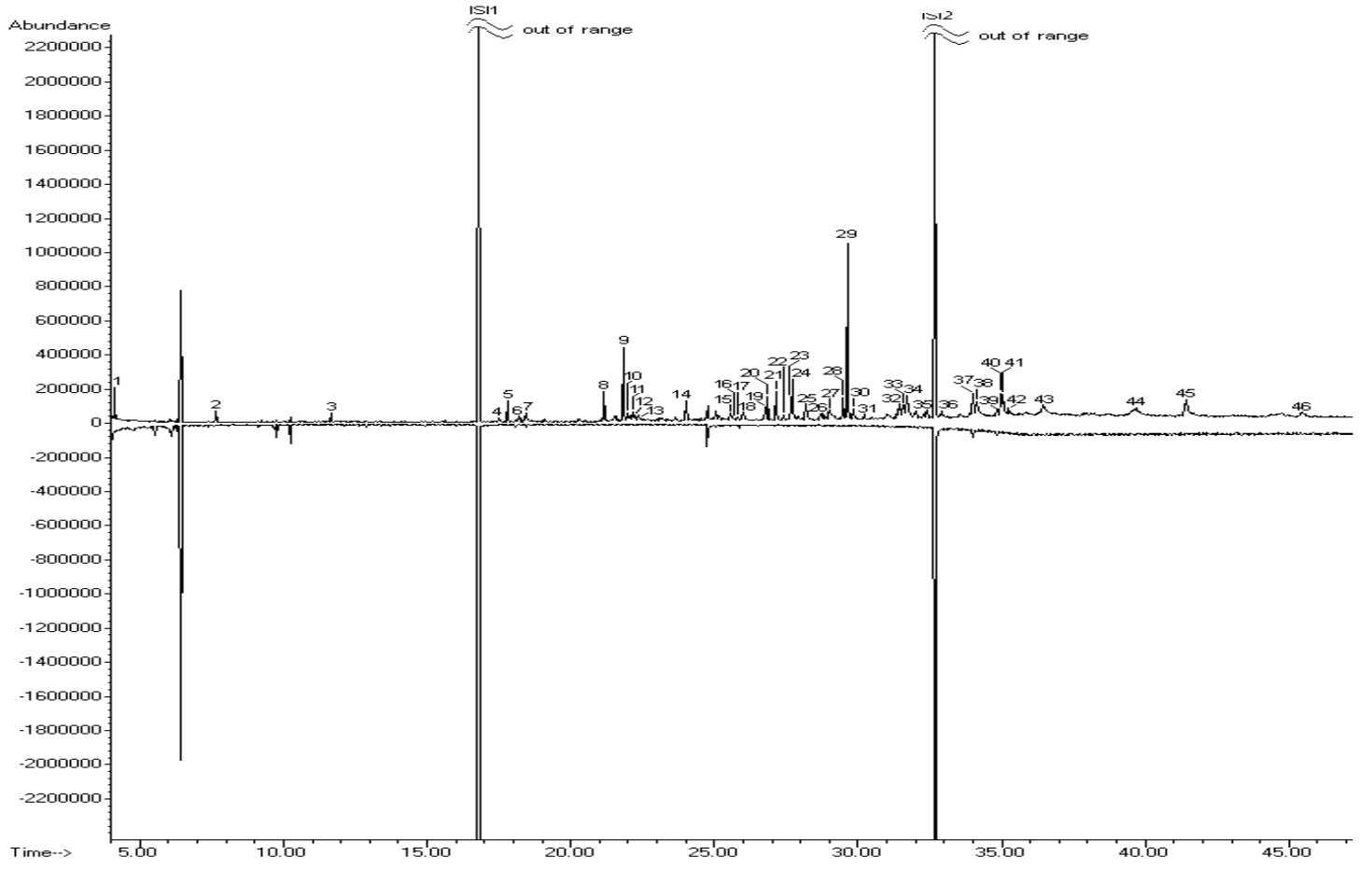
Solvent residues (e.g.Toluene, acetone)

Adhesive residues (e.g. Acrylates)

Paper residues (e.g. (dehydro)abietic acids, abietates)

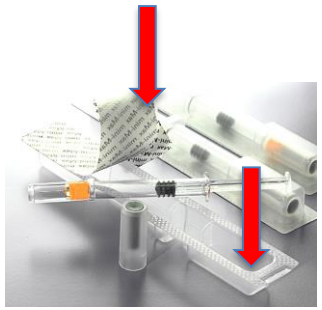
5. Other Materials used in SVP C/C Manuacturing

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



5. Other Materials used in SVP C/C Manuacturing

- **SECONDARY PACKAGING**



➢ **Overwrap/Overpouch/Blister**

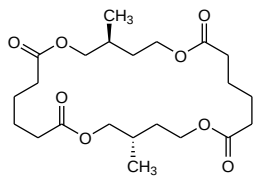
(to compensate for potential lower barrier properties of the Polymer)

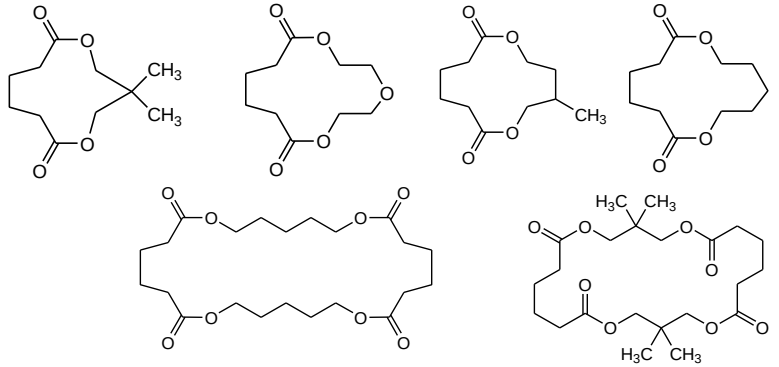
- ➢ Multilayer System
- ➢ Aluminum as barrier layer
- ➢ Tie-layers to keep the different layers together

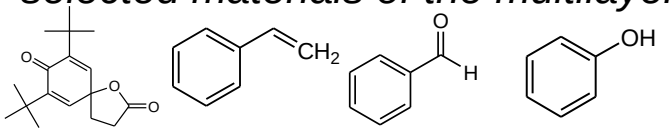
Typical extractable compounds:

Bislactone Compounds from Tie-layer

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



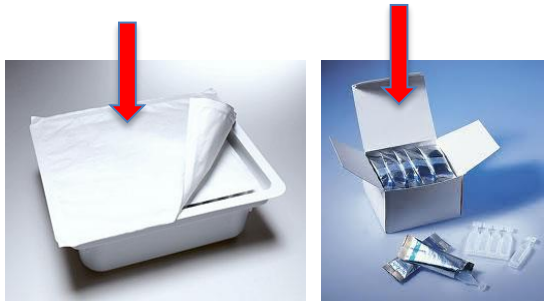




...

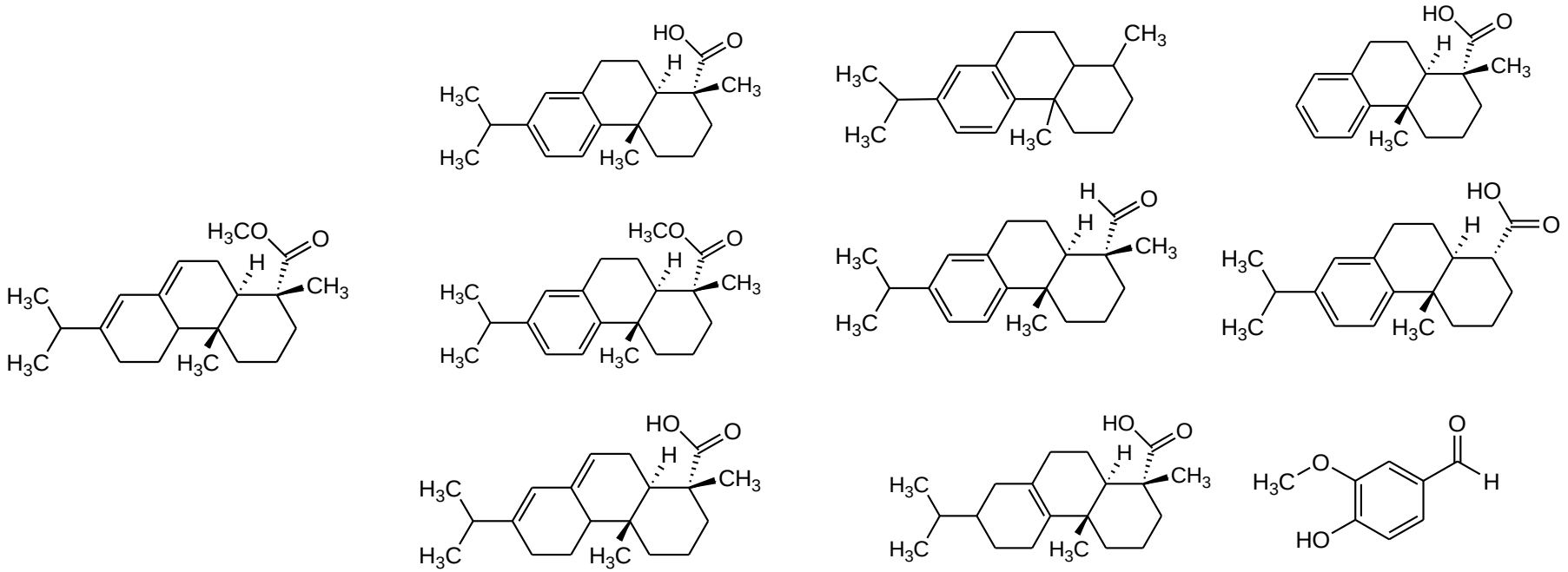
5. Other Materials used in SVP C/C Manuacturing

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: Extractrable Considerations

5. Main SVP Containers: Extractable Considerations

1.Vials:

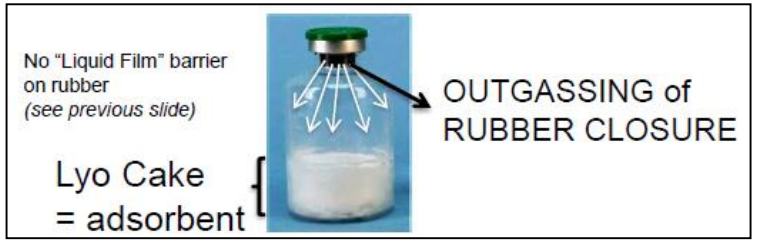
5. Main SVP Containers: Extractable Considerations

VIALS for <u>Liquid Drug Products or Reconstitution Solution</u>

- 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"...

5. Main SVP Containers: Extractable Considerations

LYO-CAKE VIAL



- 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 adsorbtion 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.

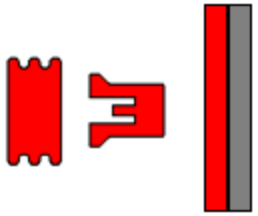
5. Main SVP Containers: Extractable Considerations

2. Pre-Filled Syringe:

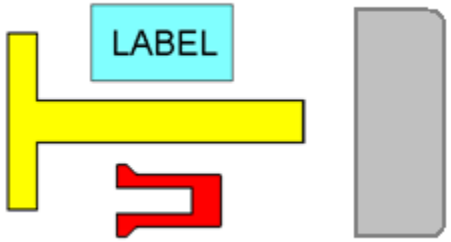
5. Main SVP Containers: Extractable Considerations

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

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



RUBBER SEALINGS (Plunger Tip, Tip Cap, Disks) -
Rubber, Silicone, ...



SECONDARY (Needle Shield, Label, Stem, ...) –
Rubber, Label Adhesive, ...

5. 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

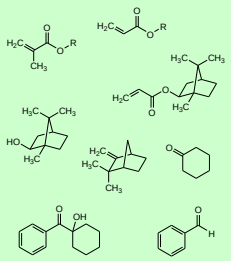
- **Rubber Plunger** ***(very similar to rubber stopper for vial):***
  - ✓ Typically, higher migration when solution is <u>in contact</u>
  - ✓ Migration will be determined by:
    - Solubility of leachables in **Drug Product** Solution
    - Potential **Diffusion of Compounds through rubber**, into 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

5. 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.

5. Main SVP Containers: Extractable Considerations

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**
(COATED) RUBBER	**NEEDLE GLUE**	**TUNGSTEN (W)**	**GLASS BARREL**	**COC/COP/PP BARREL**	**LABEL (ADHESIVE)**
MONOMER REMAINDERS & POLYMER FRAGMENTS FILLERS: *Clay, Talc, Carbonates…* ANTIOXIDANTS: *BHT, Irganox 1010, Irgafos 128, ...* CURING AGENTS: *S,S-Donors, Phenol-Formaldehyde…* ACTIVATORS: *ZnO / Stearic Acid* ACCELERATORS: *Carbamates, Sulfenamides…* OTHERS: *Pigments, Stabilizers, Release agents…*	- POLYMER FRAGMENTS - UV CURING-ACTIVATORS 	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)	Major: Silica (SiO_2) Alkali (e.g. Na_2O) Minor: K (K_2O), B (B_2O_3), Ca (CaO), Al (Al_2O_3) Colored glass: Fe_2O_3,TiO_2,CuO, Mn^{3+} Sulfate (from dealkalization) Silicone oil (provides lubricity)	POLYMER FRAGMENTS SOLVENTS ANTIOXIDANTS: *BHT, Irganox 1010, ...* ACID SCAVENGERS: *Stearate,...* LUBRICANTS: *FA Esters, ...* WAXES SLIP ADDITIVES: *Erucamide, Oleamide, ...* PLASTICIZERS RELEASE AGENTS PIGMENTS Optional: Silicone Oil	Permeable Plastic Materials (e.g. PP, …) INK and ADHESIVE constituents in a complex composition, but at low concentrations POLYMER FRAGMENTS, SOLVENTS, PHOTO-INITIATORS, STABILIZERS, TACKIFIERS, ... *e.g. Acrylates, PVA, NR, Benzophenone, Irgacure 184, Irgacure 651, Irganox 1010, Dehydroabietic Acid, DCHP, TBPP, Siloxanes, ...* ***Potential Concern: SECONDARY PACKAGING***

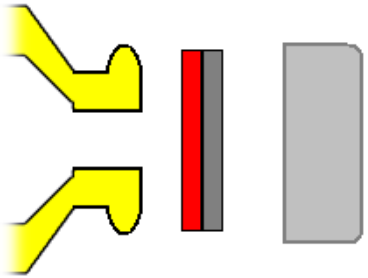
Piston / Needle Shield / Tip Cap

5. Main SVP Containers: Extractable Considerations

3. Cartridges

5. Main SVP Containers: Extractable Considerations

Cartridges



Sealing Disk

- **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

5. 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”...

TIME FOR QUESTIONS

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