EXTRACTABLES & LEACHABLES FOR SVP-INJECTABLES

PDA TRAINING COURSE
EXTRACTABLES – LEACHABLES
BASEL
27 – 28 FEBRUARY 2020

Dr. Piet Christiaens

PDA Content

1. Typical Materials of Construction (MoC's) for SVP C/C
    - Rubbers 101
    - Glass & Glass related issues for E/L
    - COP/COC
2. Container Closure Systems for SVP's
    - Vials
    - Prefilled syringes
    - Cartridges
3. Rubber oligomers – safety concern

RECAP: REGULATORY: US

LIQUID SVP's

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

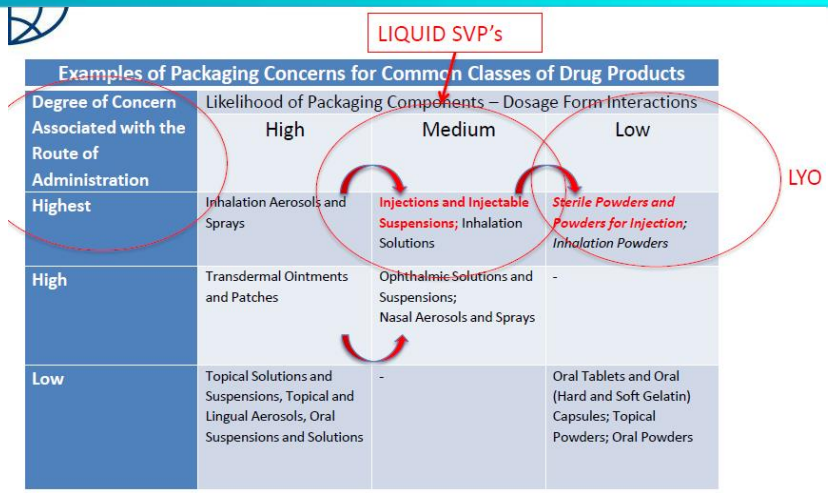
LYO

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"

REGULATORY: US



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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!!!

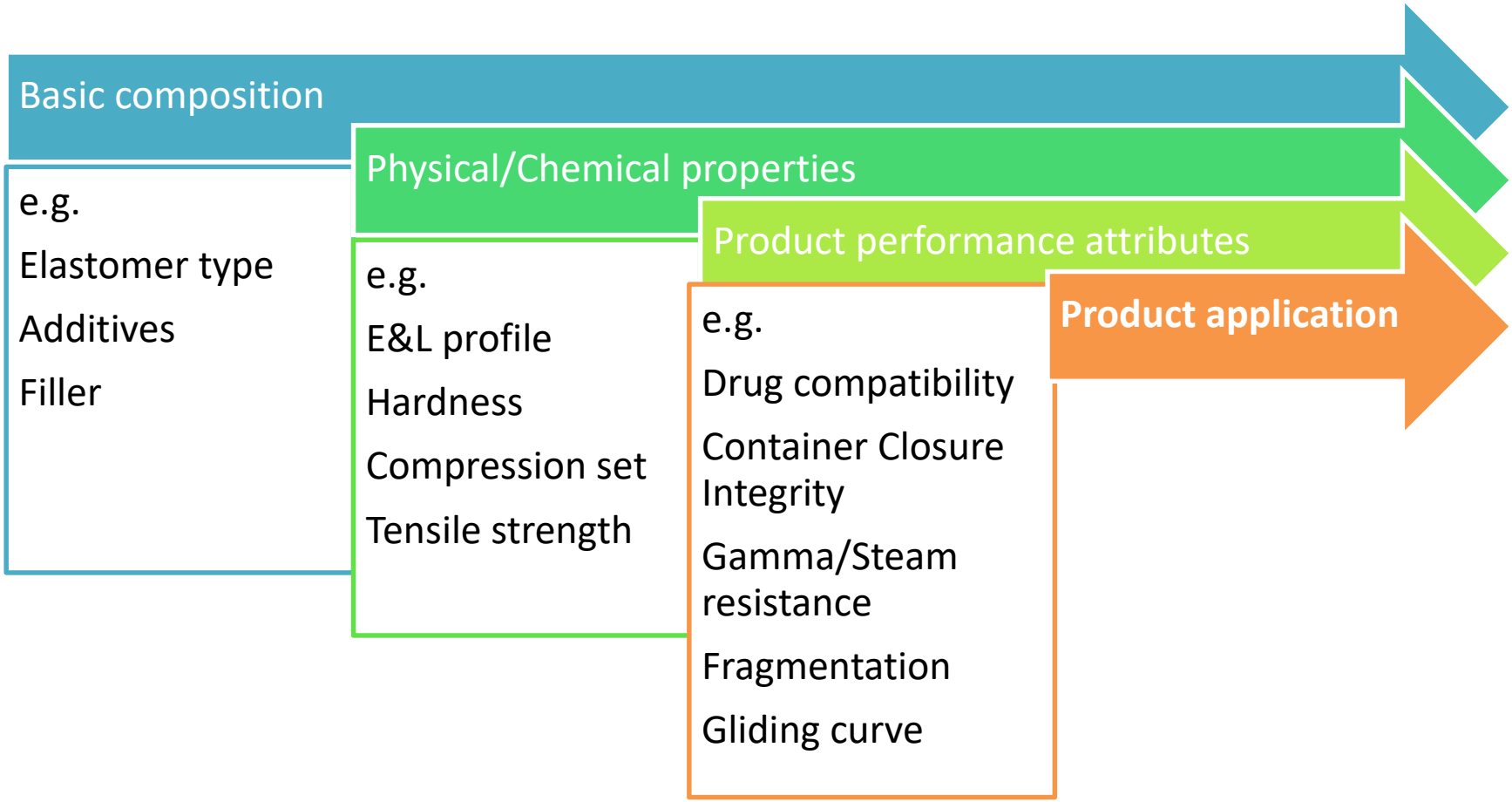
1. Typical Materials of Construction for SVP Container/Closure Systems

Elastomeric closures
Rubber 101

Supported by Datwyler

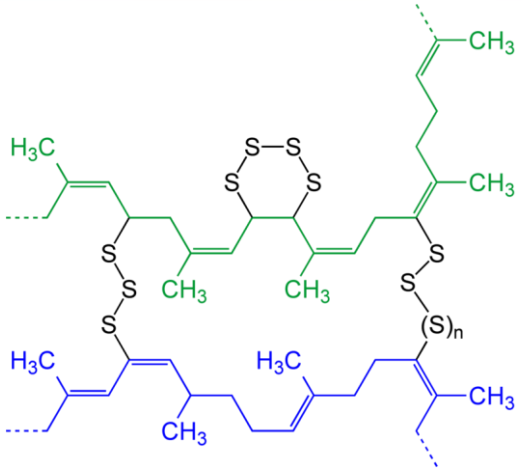
MoC's FOR SVP-INJECTABLES - RUBBERS

MoC's FOR SVP-INJECTABLES - RUBBERS



MoC's FOR SVP-INJECTABLES - RUBBERS

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**

MoC's FOR SVP-INJECTABLES - RUBBERS

Compounded material of:

1. Elastomer

2. Filler

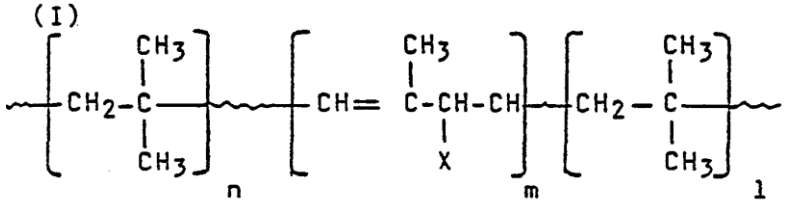
3. Cure system
4. Pigment
5. Other ingredients

MoC's FOR SVP-INJECTABLES - RUBBERS

1. Elastomers

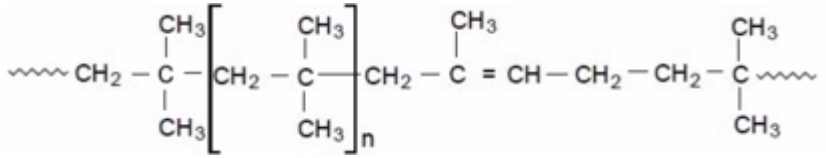
Halobutyl (BromoButyl, ChloroButyl)

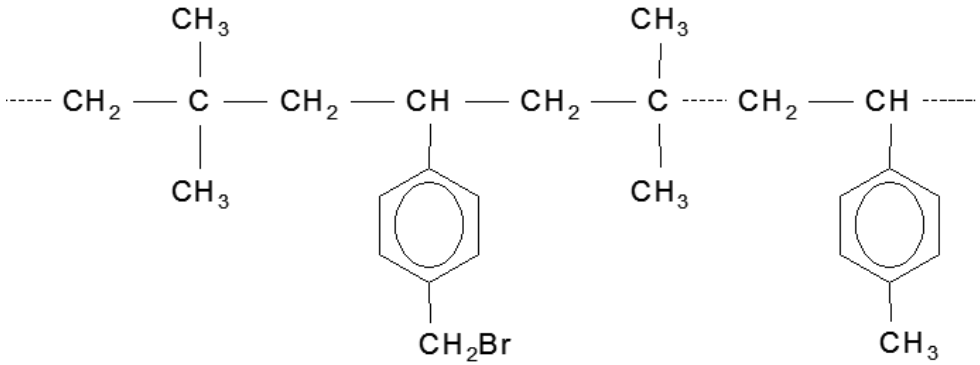
- Cleanest curing system
- Lowest permeability
- High resistance to ageing



X =Cl or Br

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



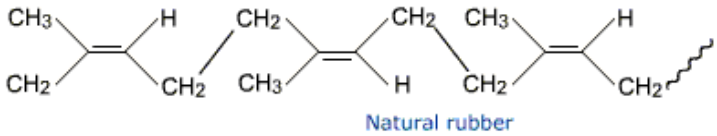


MoC's FOR SVP-INJECTABLES - RUBBERS

1. Elastomers

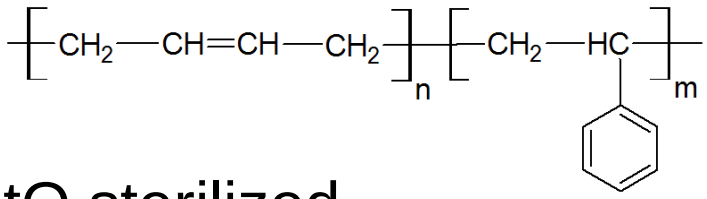
Natural rubber / Polyisoprene

- 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)

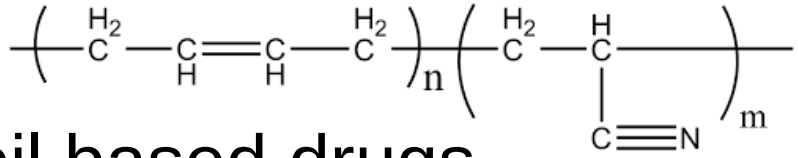


- Intermediate permeability
- Typically used for pre-assembled EtO sterilized components (e.g. Needle Shields)

MoC's FOR SVP-INJECTABLES - RUBBERS

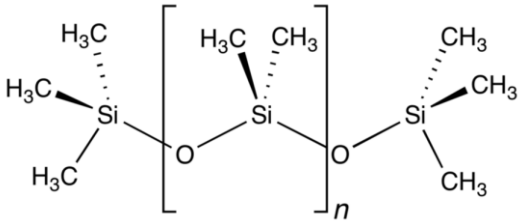
1. Elastomers

Nitrile rubber



Typically used for mineral oil based drugs

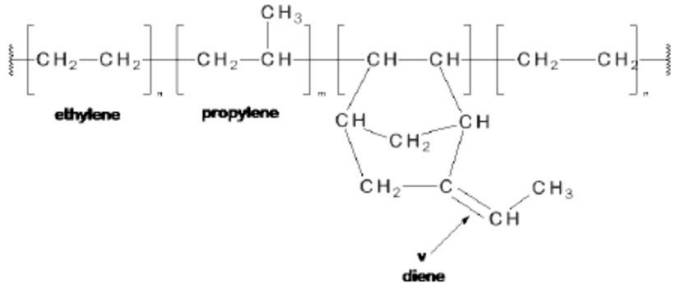
Silicone rubber



High permeability

Typically not used for parenteral applications

EPDM rubber



For niche applications

MoC's FOR SVP-INJECTABLES - RUBBERS

2. 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

MoC's FOR SVP-INJECTABLES - RUBBERS

3. Cure systems

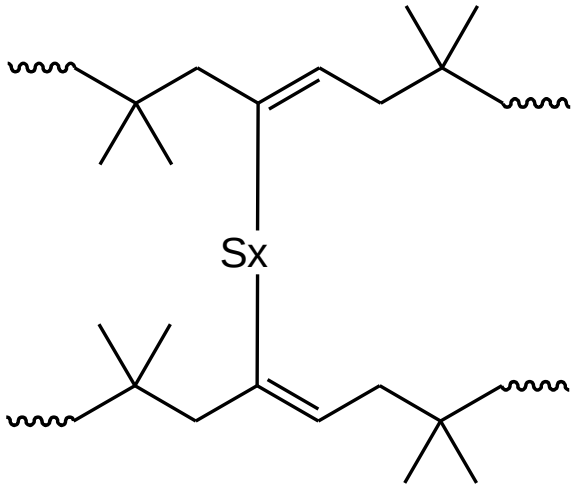
- **Cure system:**
  - Crosslinking agent
  - Activator: gives the onset of vulcanization
  - Accelerator: speeds up the vulcanization
    - Easily extractable organic molecules such as thiurams, sulfonamides, thiazoles, ...

- **Modern cure systems**
  - Aim at giving little extractables

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

MoC's FOR SVP-INJECTABLES - RUBBERS

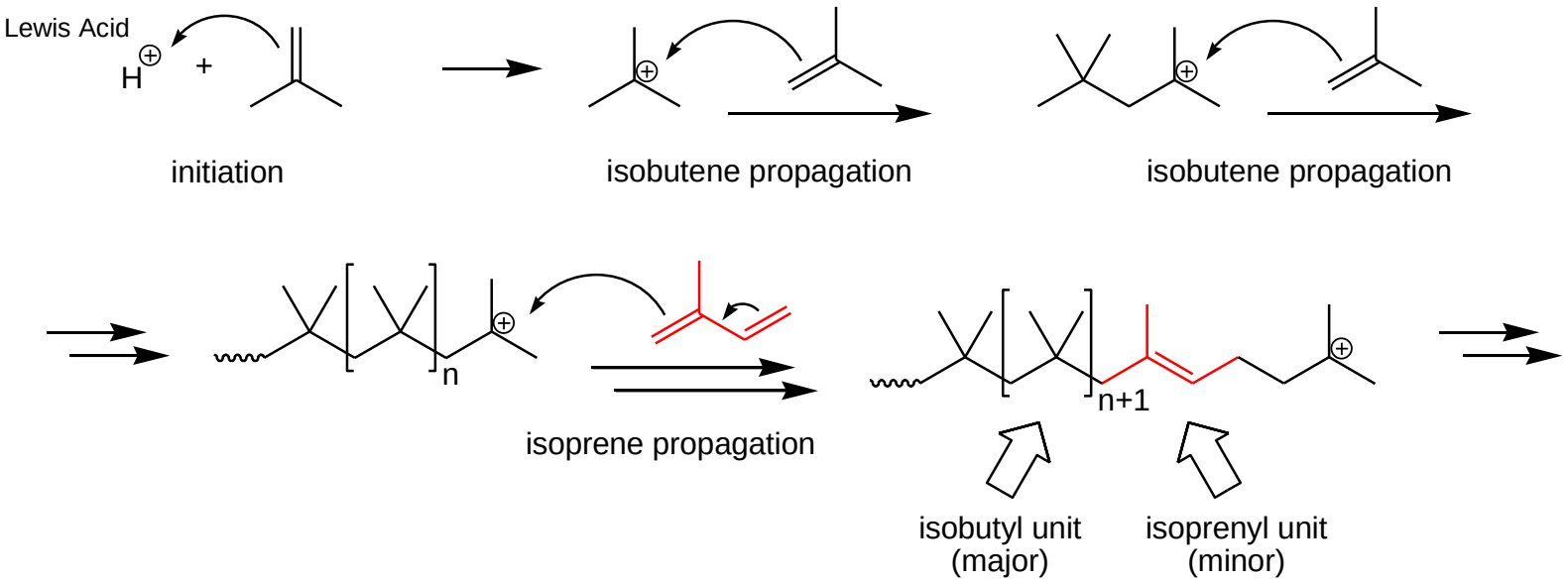
Rubber Curing / Vulcanization:



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

MoC's FOR SVP-INJECTABLES - RUBBERS

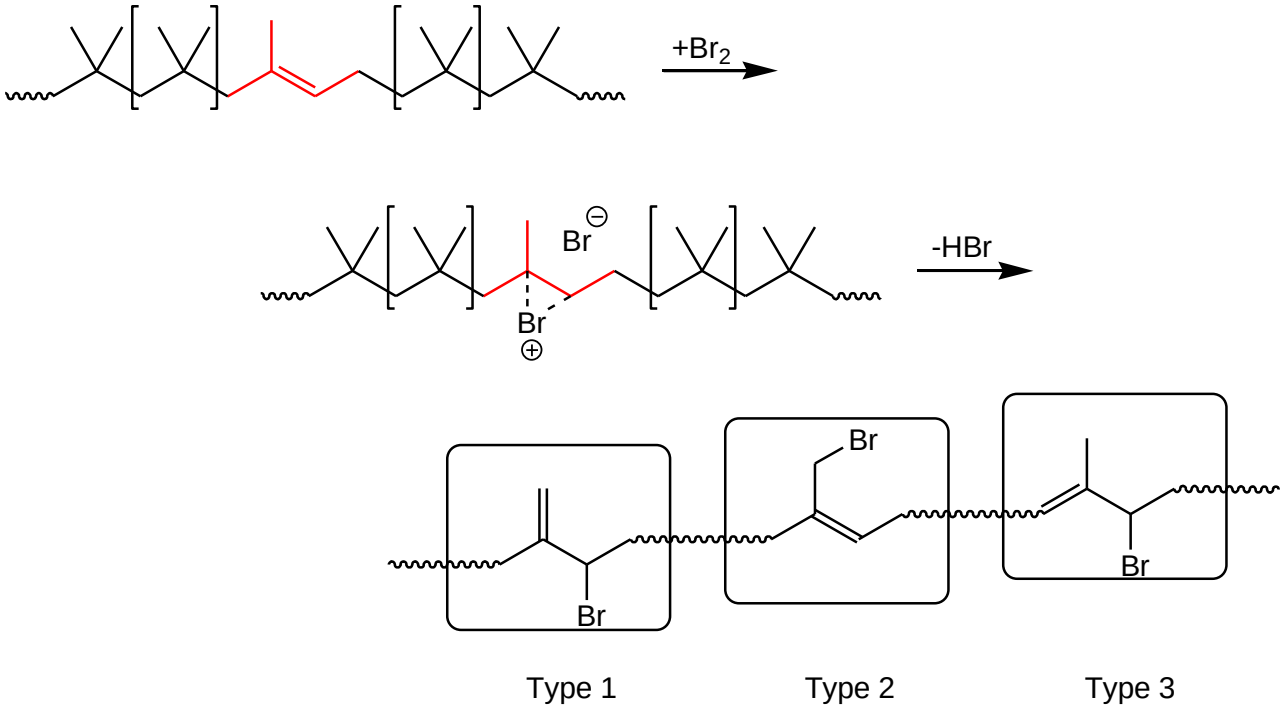
Formation (polymerization) of a Butyl Elastomer (IIR): Cationic Polymerization



- Note: the Polymerization Starts with a Isobutene Unit (present in high excess!!)
  - *98 – 99 mol% is isobutylene*
  - *1 – 2 mol% is isoprene*

MoC's FOR SVP-INJECTABLES - RUBBERS

Bromination of a Butyl Elastomer (BIIR)



Bromination of the Backbone makes Elastomer

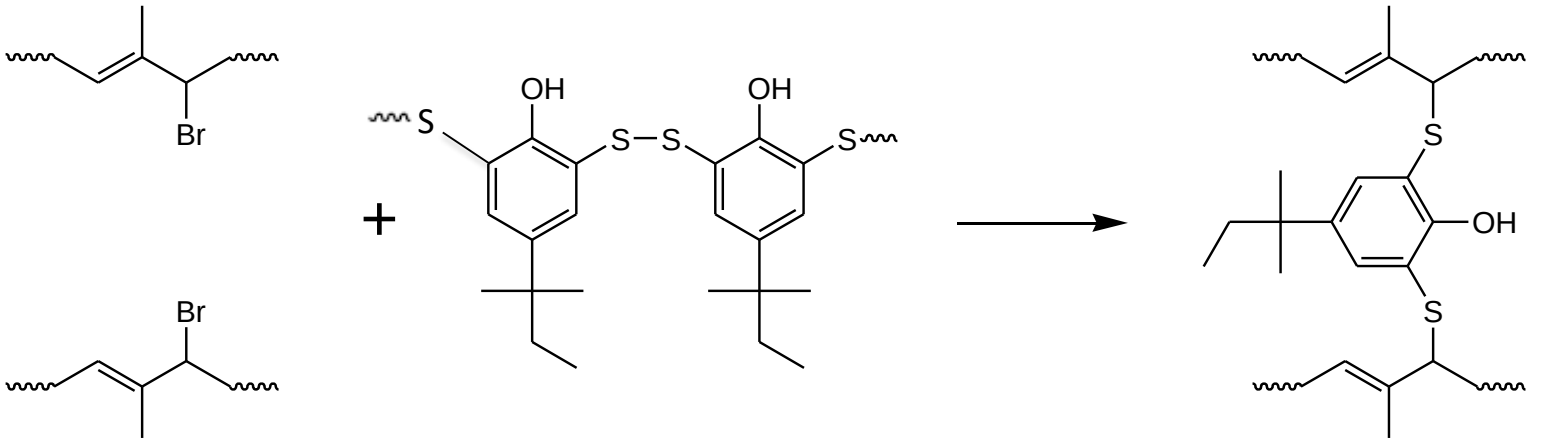
(with a relatively Low N° of double bonds in backbone)

more reactive in vulcanization/cross linking

Ref. 9

MoC's FOR SVP-INJECTABLES - RUBBERS

Vultac Curing of (Halobutyl) Elastomers



Amyl Disulfide Polymer

Phenol Sulfide Crosslink

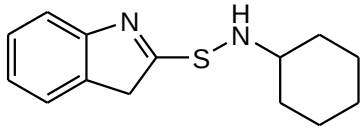
Bromide: good leaving group!

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

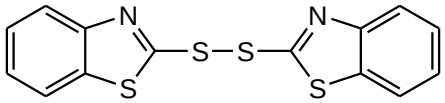
Explains Br^- release from bromobutyl rubbers

MoC's FOR SVP-INJECTABLES - RUBBERS

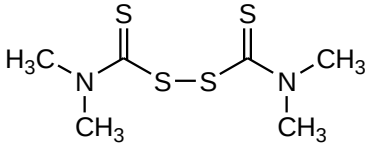
Rubber Curing - Accelerators:



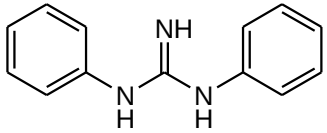
Cyclohexyl benzothiazole sulfenamide



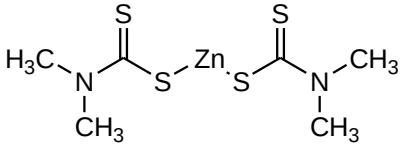
Mercaptobenzothiazole disulfide



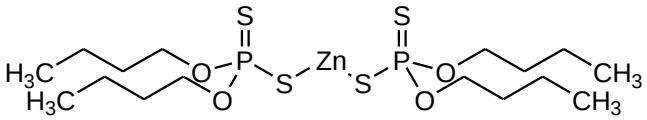
Tetramethylthiuram disulfide(TMTD)



Diphenyl guanidine



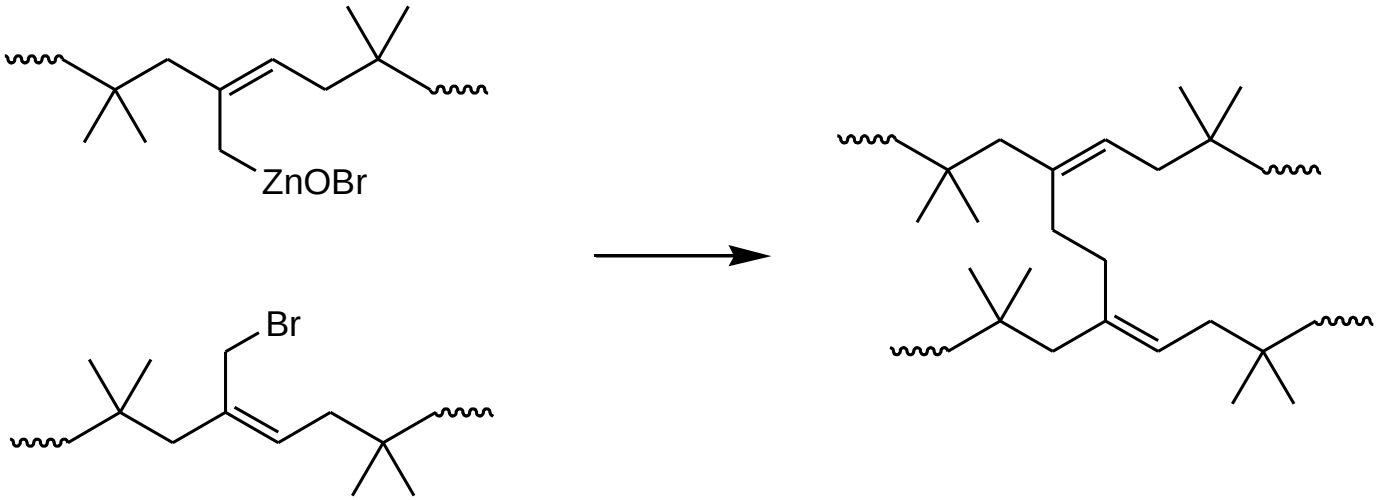
Zinc dimethyldithiocarbamate



Zinc dibutylphosphorodithiate

MoC's FOR SVP-INJECTABLES - RUBBERS

ZnO as Cross-Linking Compound in Halobutyl-Rubbers:



MoC's FOR SVP-INJECTABLES - RUBBERS

4. Pigments

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

MoC's FOR SVP-INJECTABLES - RUBBERS

5. 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**

MoC's FOR SVP-INJECTABLES - RUBBERS

Smart selection of ingredients can tune a rubber compound

E.g. recipe based on hydrophobic ingredients will show better E-profile with aqueous drugs

E.g. blend of halobutyl and SBR can *tune* the permeability

E.g. MgO replaces ZnO to avoid Zn-ion extraction

E.g. low water absorption compounds for lyo applications

MoC's FOR SVP-INJECTABLES - RUBBERS

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

→ *"what you don't put in, can't come out"*

MoC's FOR SVP-INJECTABLES - RUBBERS

THE COMPOSITION OF RUBBERS
CAN BE VERY COMPLEX!!

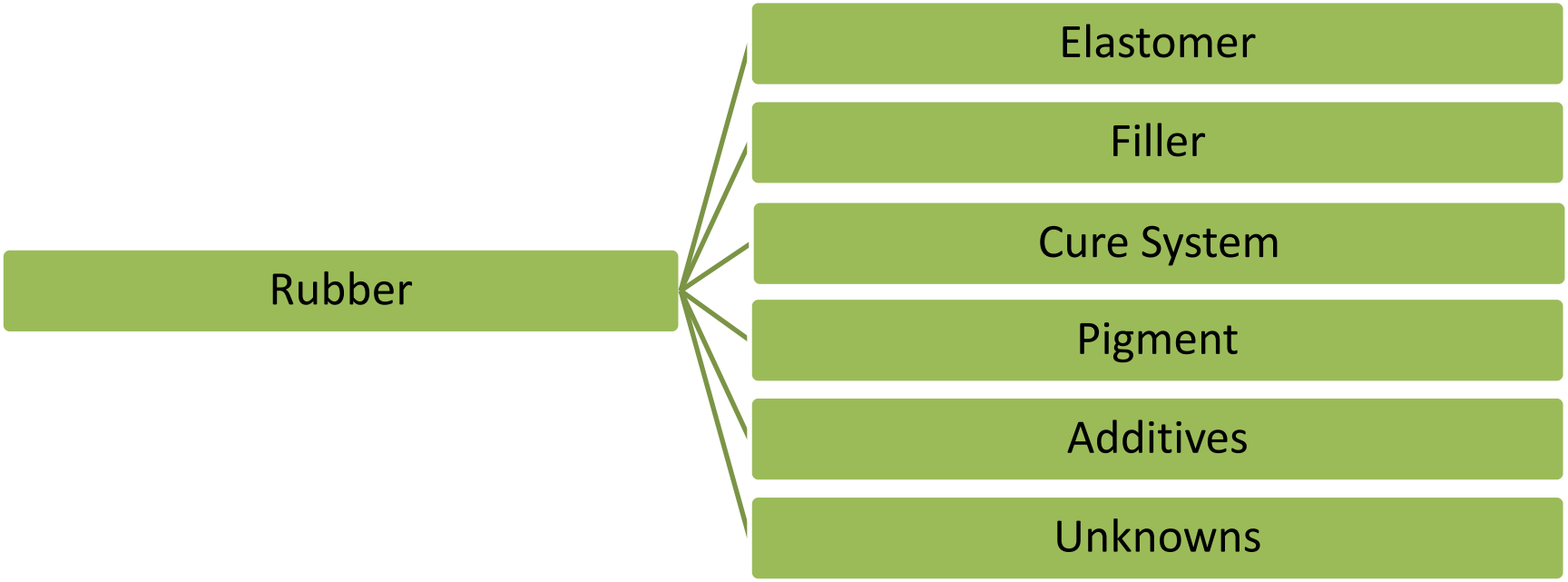
RUBBER EXTRACTABLES: SUM OF

1. **INITIAL INGREDIENTS** OF THE RUBBER FORMULATION

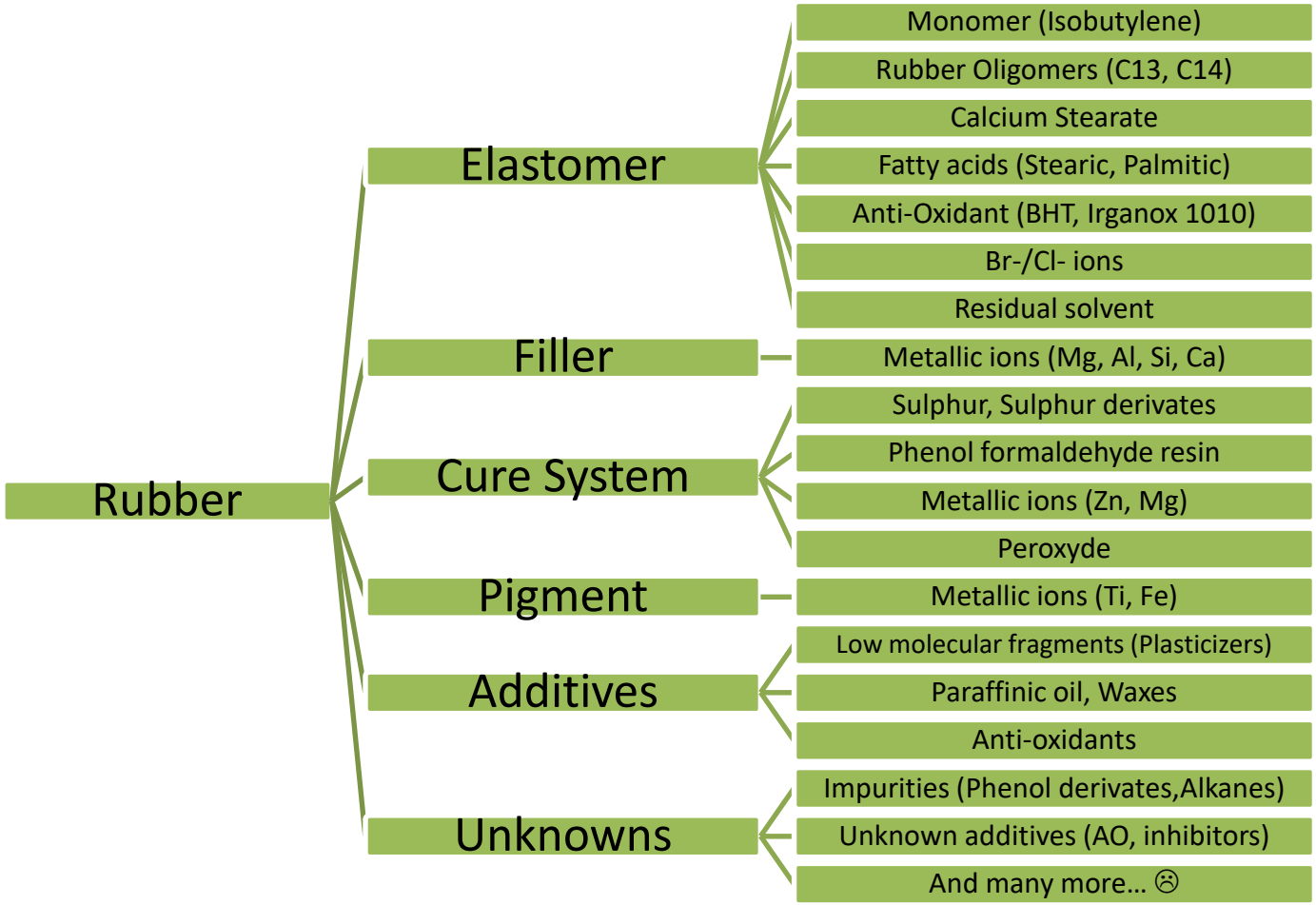
2. **IMPURITIES** OF THESE INGREDIENTS
   *(e.g. Residual Solvents, **Oligomers in Elastomer**, Halides in Halobutyl Rubber…)*

3. **REACTION/DEGRADATION PRODUCTS** DURING RUBBER PRODUCTION

MoC's FOR SVP-INJECTABLES - RUBBERS



MoC's FOR SVP-INJECTABLES - RUBBERS



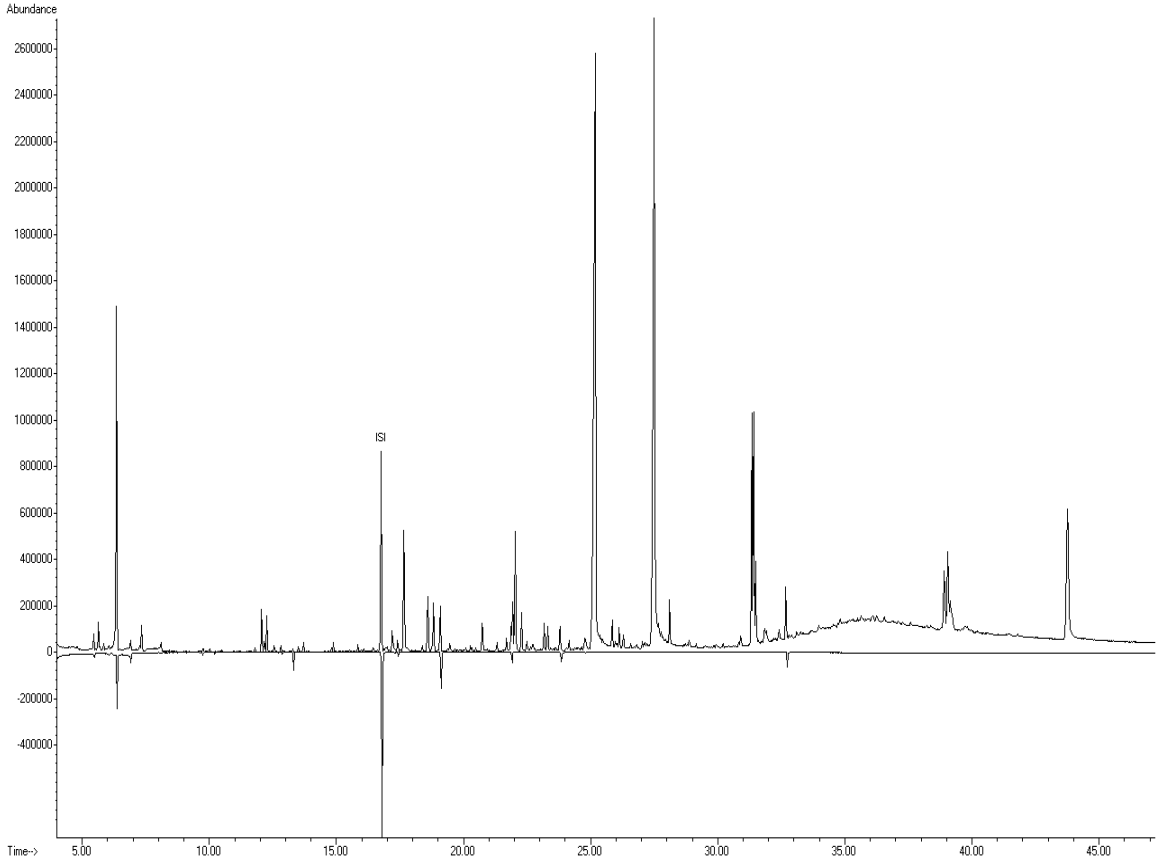
MoC's FOR SVP-INJECTABLES - RUBBERS

Number of Leachables from rubbers in PFS 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)

MoC's FOR SVP-INJECTABLES - RUBBERS

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



"OLD" RUBBER

"NEW" RUBBER

MoC's FOR SVP-INJECTABLES - RUBBERS

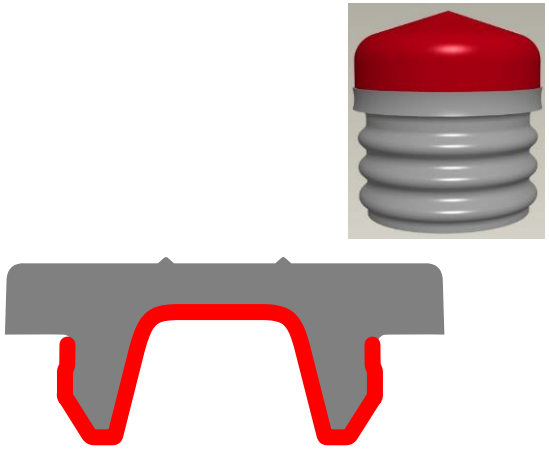
COATED RUBBERS

Coated closures: significant improvement in E&L terms

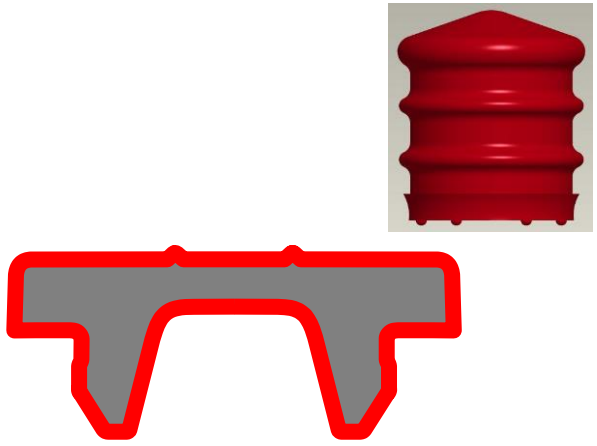
Key attribute: barrier effect from the fluoropolymer!

- *Simplified extractables* profile
- *Improved compatibility* with drugs/excipients

Film coating technology

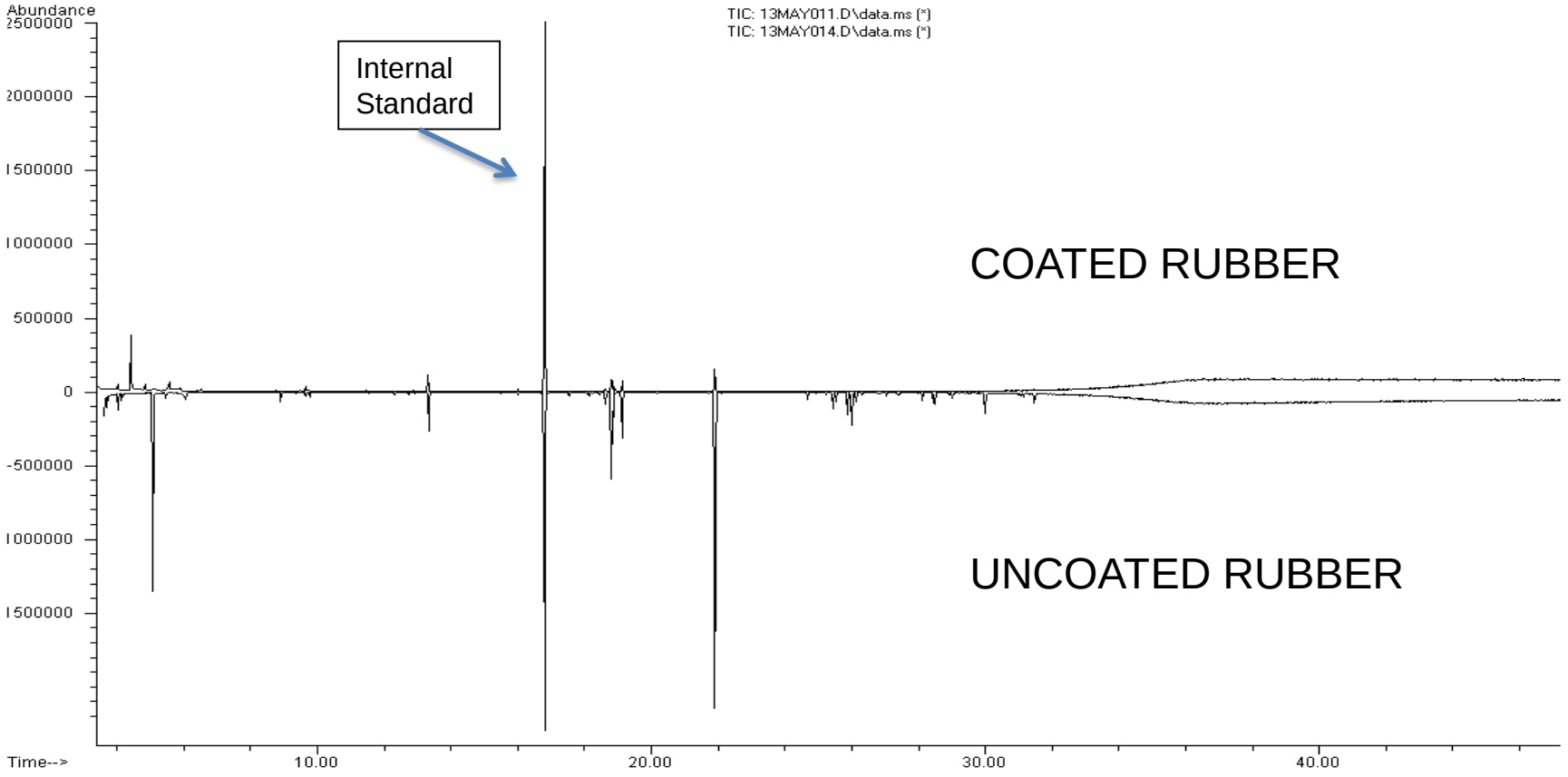


Spray coating technology



MoC's FOR SVP-INJECTABLES - RUBBERS

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



Glass

&

Glass Related Issues

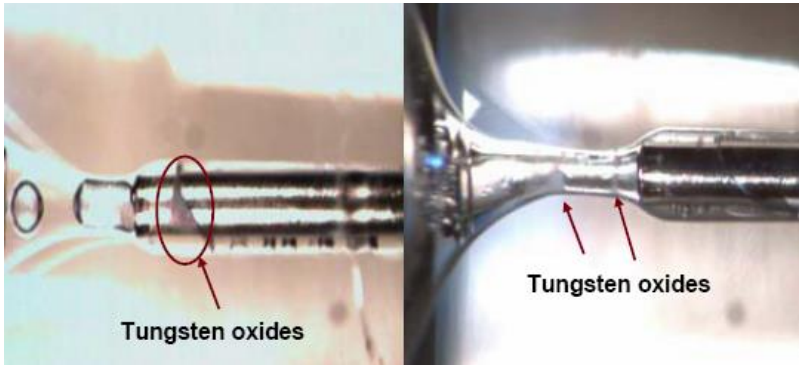
Vials, Prefilled Syringes, Cartridges

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)*

MoC's FOR SVP-INJECTABLES - GLASS

Glass as Barrel Material – Related Compound

1. PRODUCT AND COMPANY IDENTIFICATION

Product name: Loctite 3345
Product type: Ultraviolet adhesive

Company address:
Henkel Corporation
One Henkel Way
Rocky Hill, Connecticut 06067

IDH number: 256930
Item number: 33417
Region: United States

Contact information:
Telephone: 860.571.5100
MEDICAL EMERGENCY Phone: Poison Control Center
1-877-671-4608 (toll free) or 1-303-592-1711
TRANSPORT EMERGENCY Phone: CHEMTREC
1-800-424-9300 (toll free) or 1-703-527-3887
Internet: www.henkelna.com

3. COMPOSITION / INFORMATION ON INGREDIENTS

Hazardous components	CAS NUMBER	%
Polyurethane Methacrylate Resin	Proprietary	30 - 60
Tetrahydrofurfuryl methacrylate	2455-24-5	10 - 30
Hydroxyalkyl methacrylate	27813-02-1	10 - 30
Acrylic acid	79-10-7	5 - 10
High boiling methacrylate	7534-94-3	5 - 10
Propylidynetrimethyl trimethacrylate	3290-92-4	1 - 5
Gamma-glycidoxypropyl trimethoxysilane	2530-83-8	1 - 5

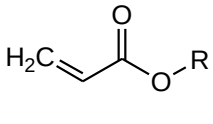
MoC's FOR SVP-INJECTABLES - GLASS

Glass as Barrel Material – Related Compounds

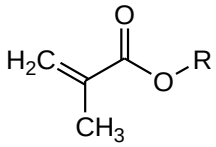
EXTRACTABLES RELATED TO GLASS BARRELS:

GLUE RESIDUES

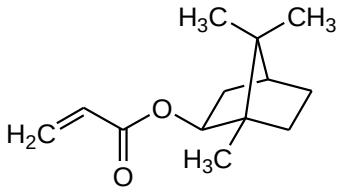
Base Polymer



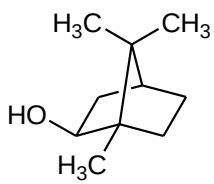
Acrylate



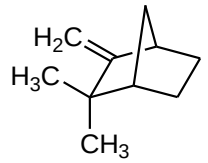
Methacrylate



Isobornyl acrylate

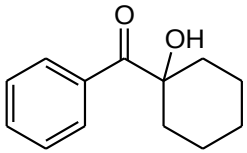


Isoborneol

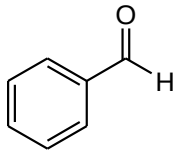


Camphene

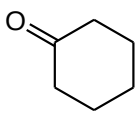
UV curing / activation



Irgacure 184



Benzaldehyde



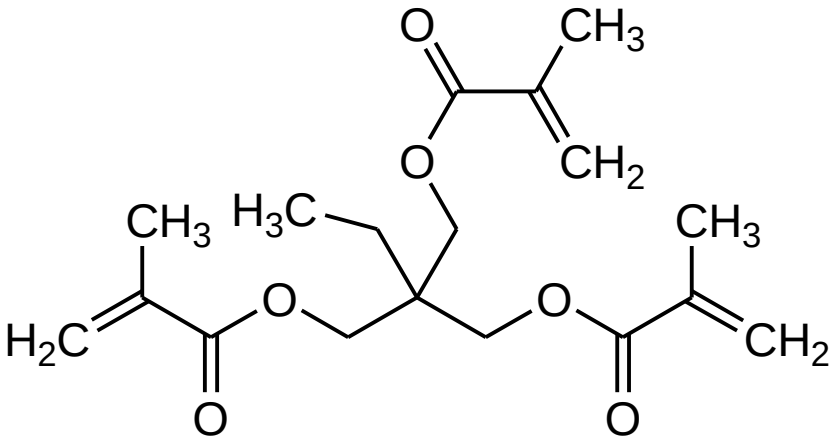
Cyclohexanone

Glass as Barrel Material – Related Compounds

EXTRACTABLES RELATED TO GLASS BARRELS:

GLUE RESIDUES

The key indicator compound TMPTMA



Trimethylolpropane trimethacrylate

MoC's FOR SVP-INJECTABLES - GLASS

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*

Barrel Materials

Polypropylene (PP)

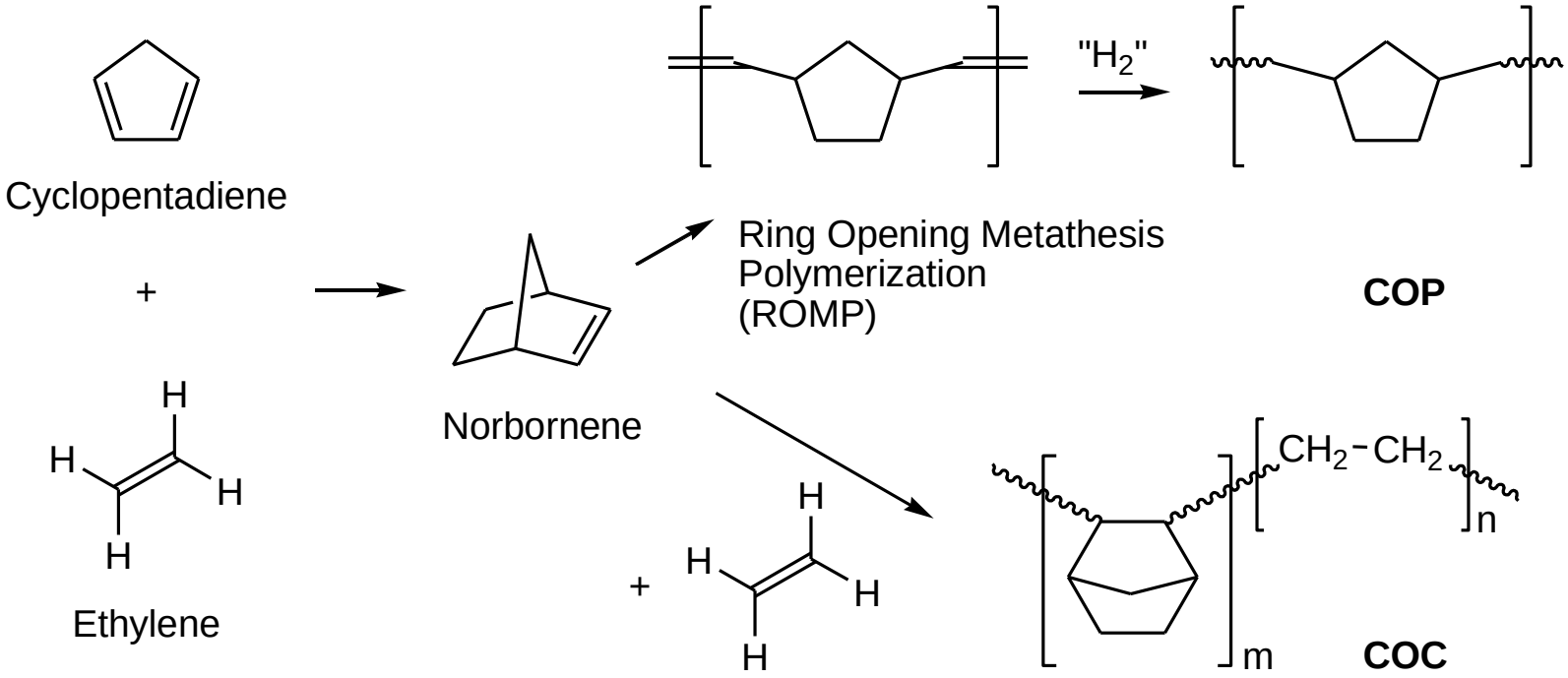
Cyclic Olefin (Co-)Polymer COC/COP

Glass

MoC's FOR SVP-INJECTABLES – COP/COC

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**



MoC's FOR SVP-INJECTABLES – COP/COC

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!

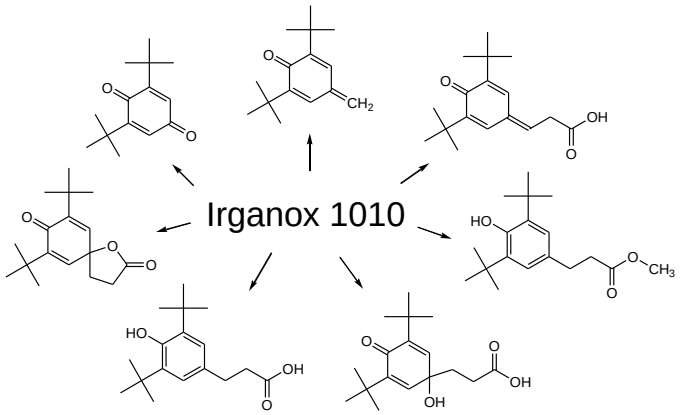
MoC's FOR SVP-INJECTABLES – COP/COC

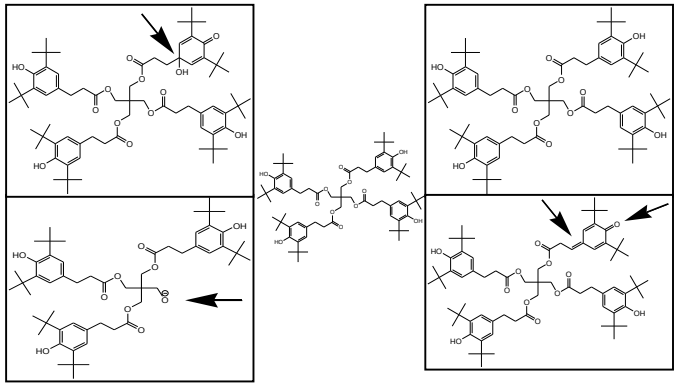
TYPICAL COMPOSITION OF **COMMERCIAL POLYMERS,**

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:





MoC's FOR SVP-INJECTABLES – COP/COC

SECONDARY PACKAGING

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

Typical extractable compounds:

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

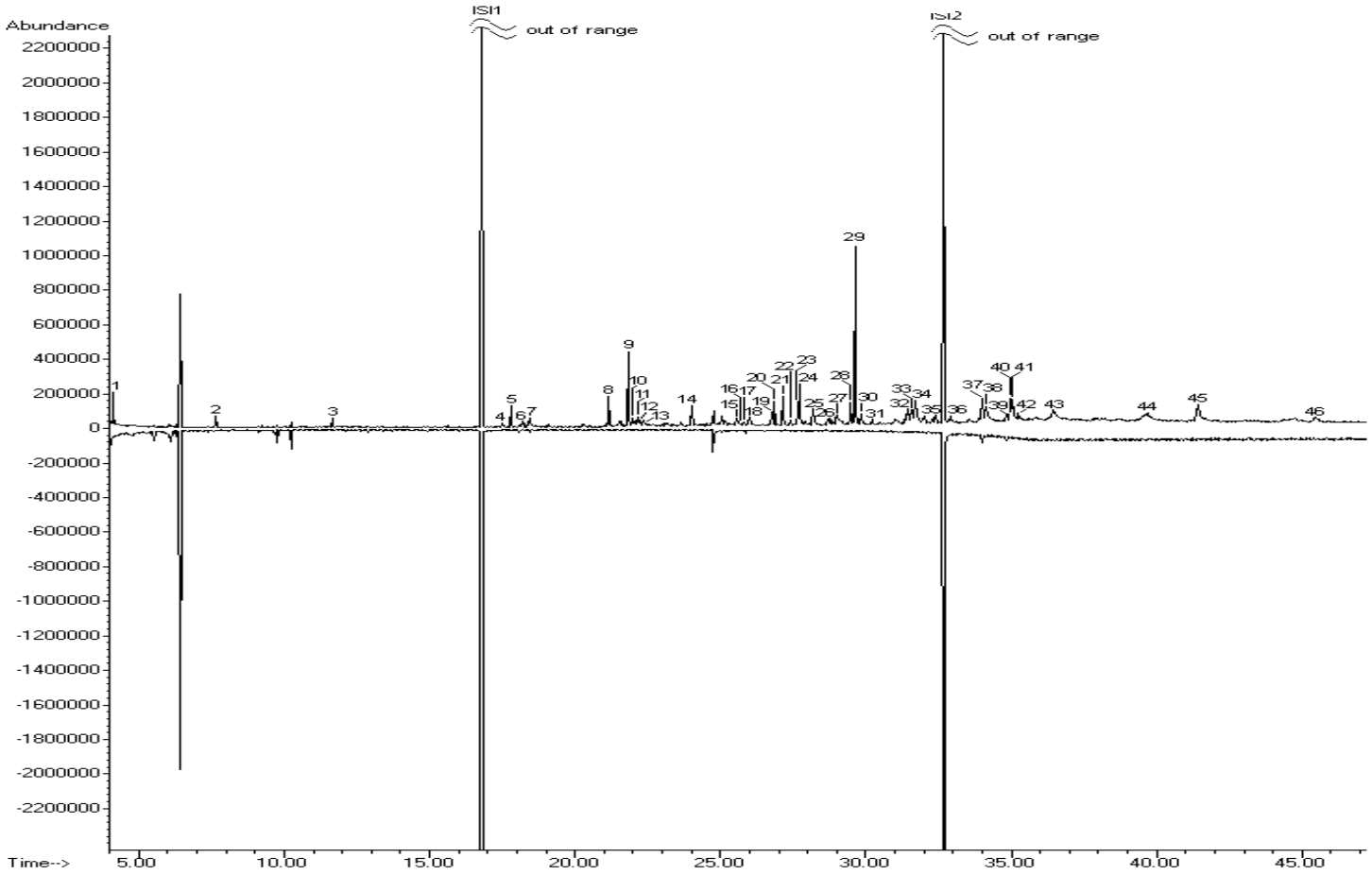
Solvent residues (e.g.Toluene, acetone)

Adhesive residues (e.g. Acrylates)

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

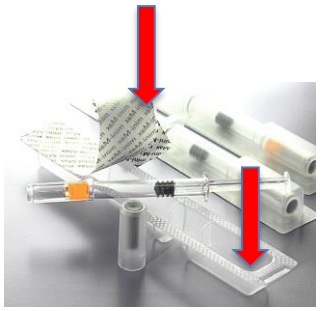
MoC's FOR SVP-INJECTABLES – COP/COC

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



MoC's FOR SVP-INJECTABLES – COP/COC

SECONDARY PACKAGING



- **Overwrap/Overpouch/Blister**

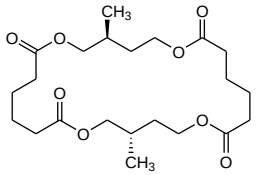
(to compensate for potential lower barrier properties of the Polymer)

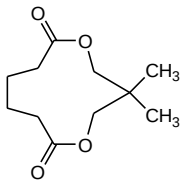
- Multilayer System
- Aluminum as barrier layer
- Tie-layers to keep the different layers together

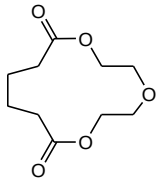
Typical extractable compounds:

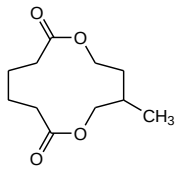
Bislactone Compounds from Tie-layer

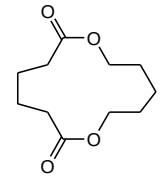
Residues from other layers (depends largely on selected materials of the multilayer!!)

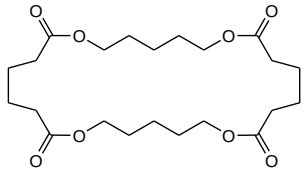


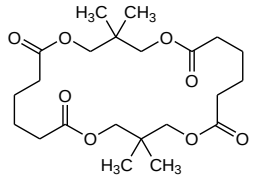


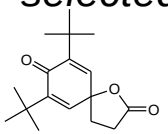


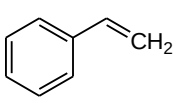


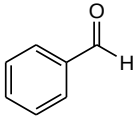


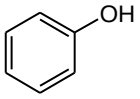








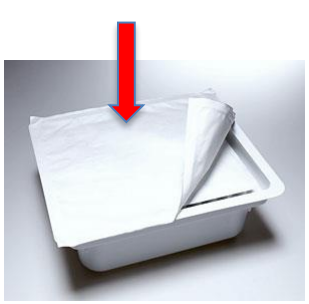




...

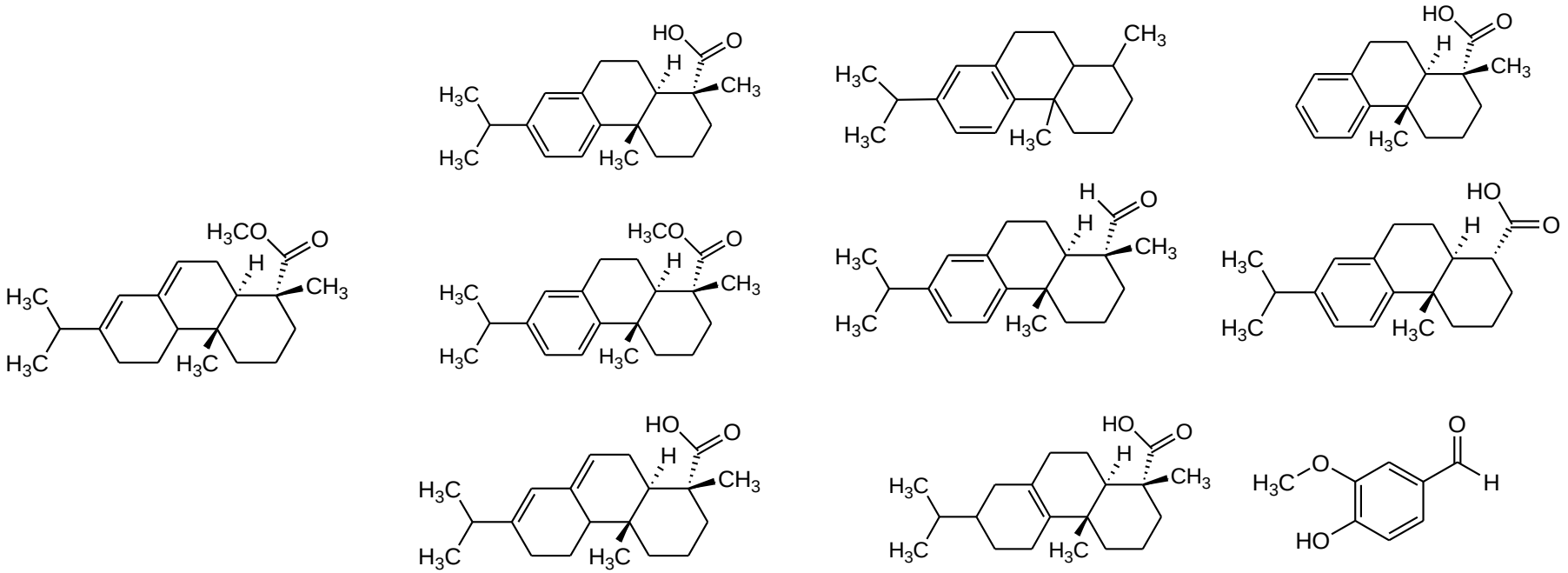
MoC's FOR SVP-INJECTABLES – COP/COC

SECONDARY PACKAGING



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

Example Structures of abietic acids / abietates (& Vanillin)



2. **Container/Closure Systems for SVP's:** Information Relevant to the Design of an E&L Study

2. Container/Closures for SVP's

1.Vials:

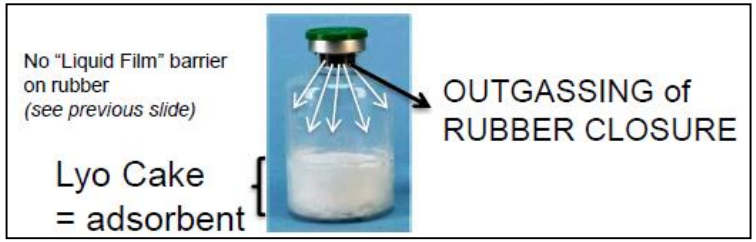
2. Container/Closures for SVP's

VIALS for Liquid Drug Products or 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"...

2. Container/Closures for SVP's

LYO-CAKE VIAL



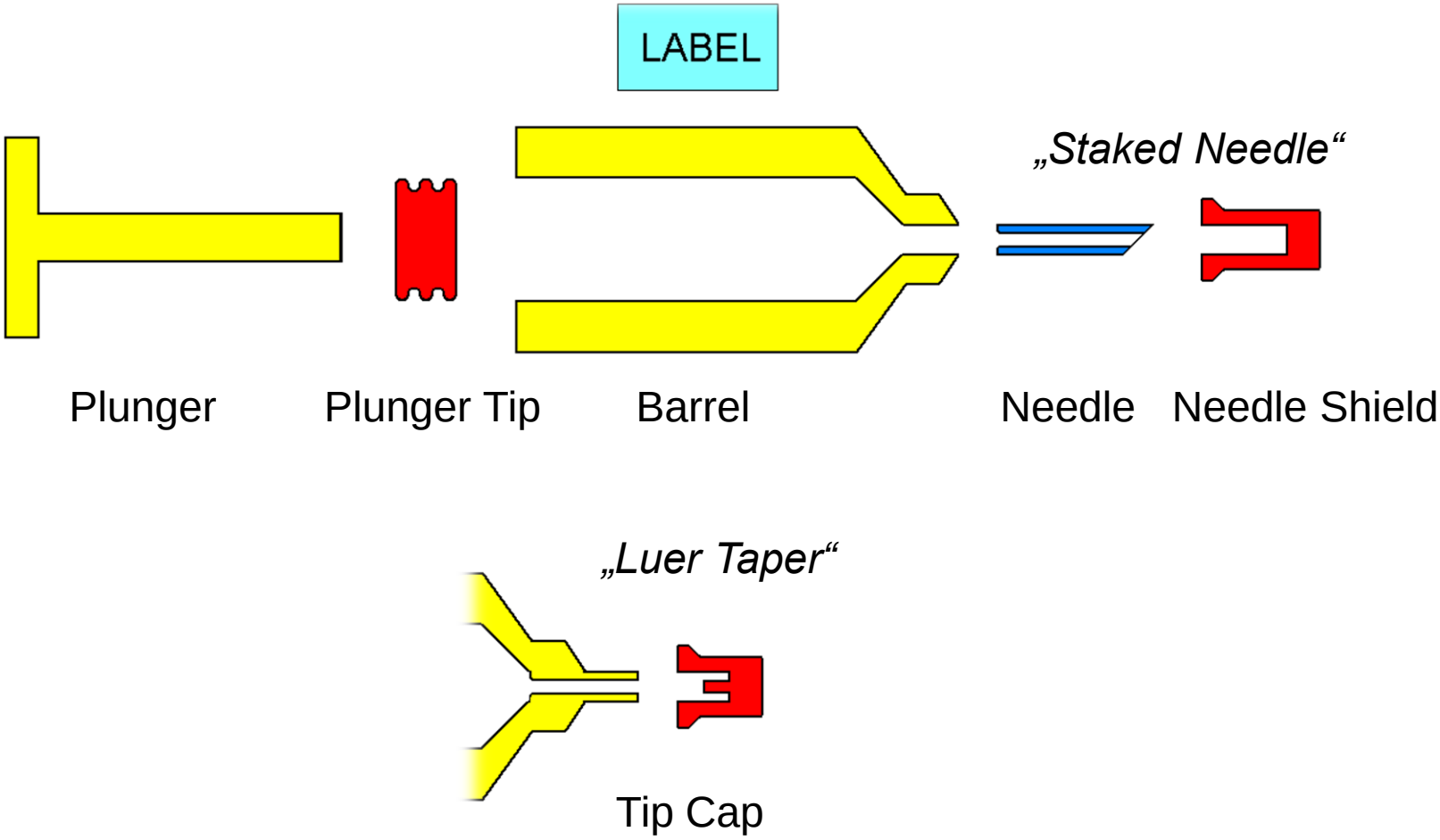
- Sources of impurities, coming from packaging
  - **Glass**: Metals (may not be necessary to be studied in EXT Study, if glass composition is available, direct assessment in LEA study)
  - **Rubber Closure:**
    - ✓ **No Direct Contact** between DP and Closure (upright)
    - ✓ **HOWEVER:** Release 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.

2. Container/Closures for SVP's

2. Pre-Filled Syringe:

2. Container/Closures for SVP's

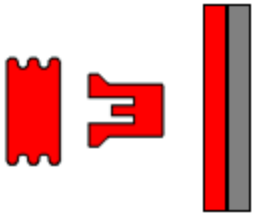
PRE-FILLED SYRINGE: COMPOSING PARTS



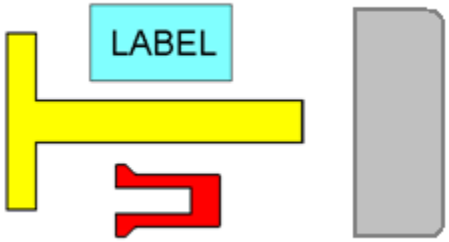
2. Container/Closures for SVP's

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, ...

2. Container/Closures for SVP's

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

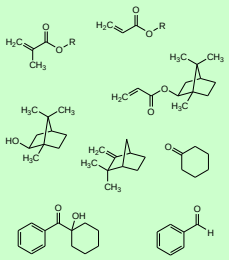
- **Rubber Plunger *(very similar to rubber stopper for vial):***
  - ✓ Typically, higher migration when solution is <u>in contact</u>
  - ✓ Migration will be determined by:
    - Solubility of leachables in **Drug Product** Solution
    - Potential **Diffusion of Compounds through rubber**, into solution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

2. Container/Closures for SVP's

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.

2. Container/Closures for SVP's

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***

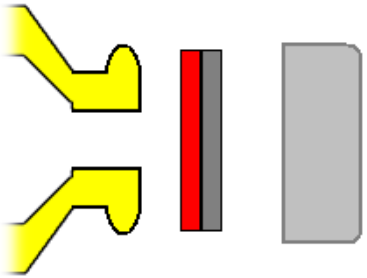
Piston / Needle Shield / Tip Cap

2. Container/Closures for SVP's

3. Cartridges

2. Container/Closures for SVP's

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

2. Container/Closures for SVP's

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"...

3. RUBBER OLIGOMERS

RUBBER OLIGOMERS:
MAY NEED MORE ATTENTION

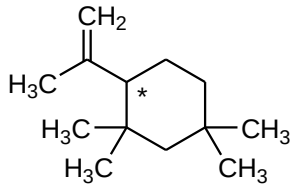
3. RUBBER OLIGOMERS

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

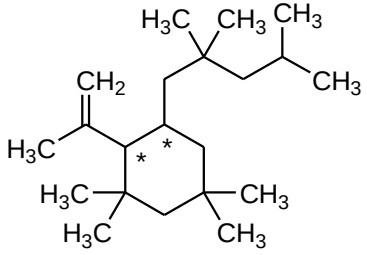
- Considered as
  - Cyclic aliphatic hydrocarbon compounds
  - One double bond

- No experimental data / Literature data is known about toxicity of these compounds

- Structure Activity Relationship Assessment (SAR): compound of low tox. risk.



C13 oligomer

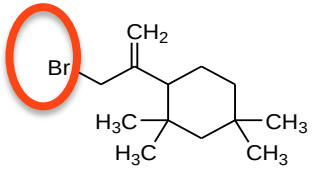


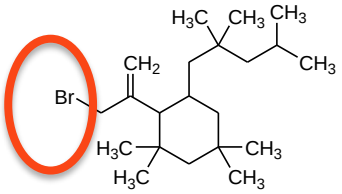
C21 oligomer

3. RUBBER OLIGOMERS

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. RUBBER OLIGOMERS

For potential Mutagenic/Carcinogenic compounds:

SCT: 0.15 µg/day (PQRI OINDP)

SCT: 1.5 µg/day (PQRI-PODP; ICH guideline on Genotoxic Impurities)

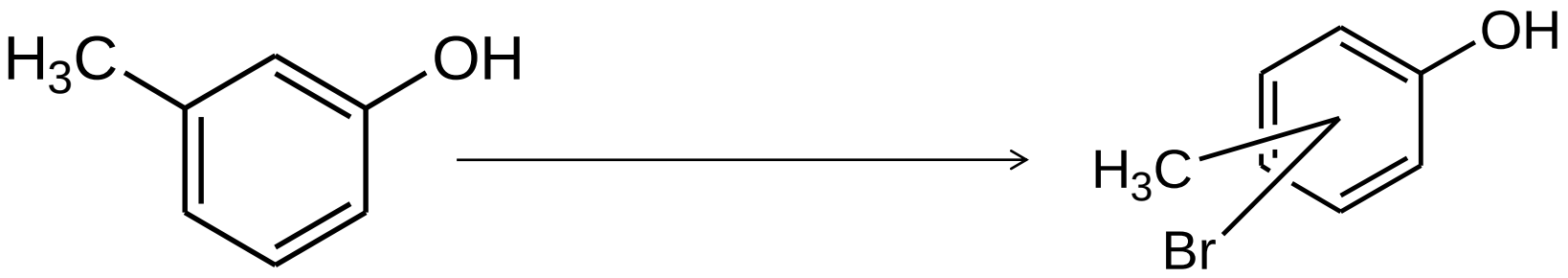
The low SCT/TTC levels for the Halogenated Oligomers mean:

- Low associated AET levels
- High level of method optimization to obtain these levels (certainly with LVP)
- e.g. SIM mode for GC/MS
- Can only be performed with appropriate analytical standards with known purity
  - *Method Selectivity*
  - *Accuracy*
  - *Sensitivity*
  - *Precision*
  - *…*

3. RUBBER OLIGOMERS

Halogenated Rubber Oligomers – Reactive Leachables

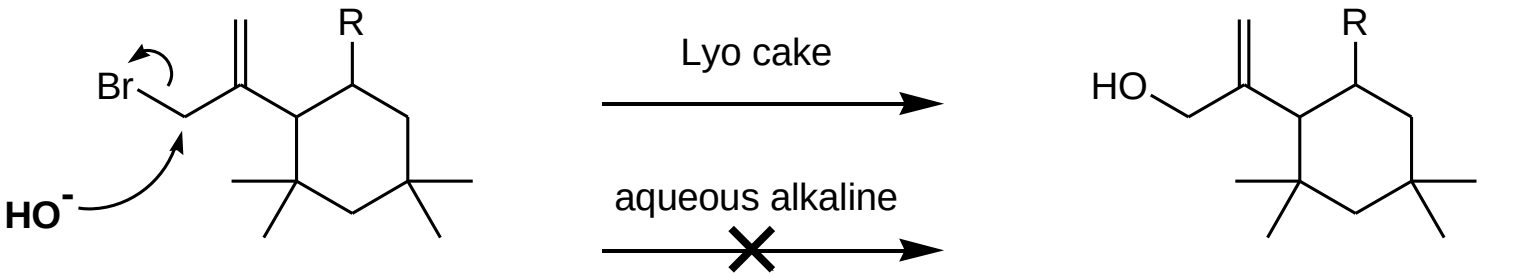
Cresol containing drug products, Bromocresol may be formed in the presence of Bromobutyl Stoppers (Mechanism is unknown)



3. RUBBER OLIGOMERS

Halogenated Rubber Oligomers – Reactive Leachables

Formation of $C_{13}H_{23}OH$ out of $C_{13}H_{23}Br$ in Lyo Products



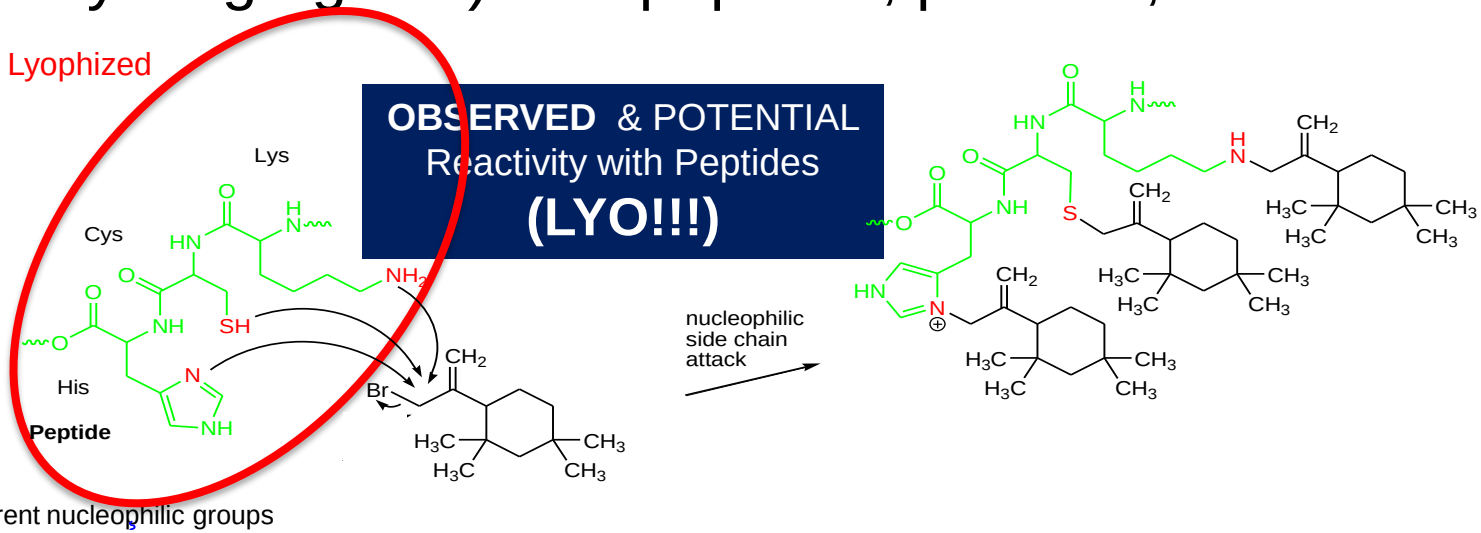
halogenated rubber oligomer

hydroxylated rubber oligomer

3. RUBBER OLIGOMERS

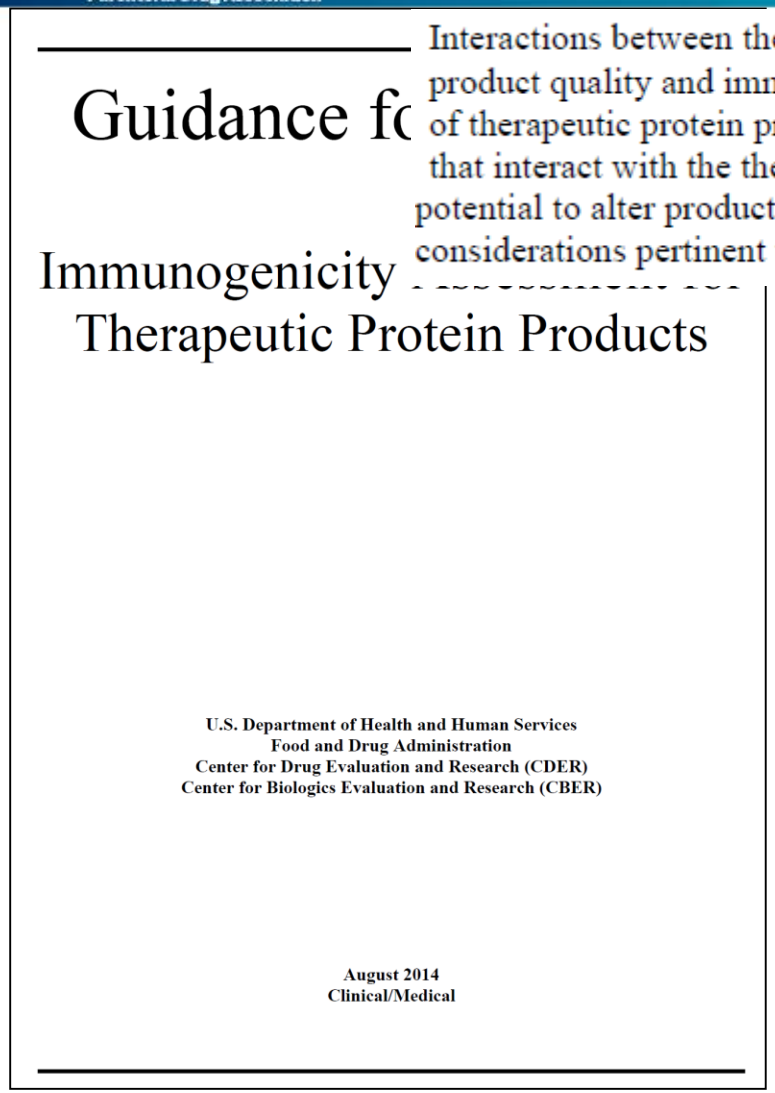
Observed Reactivity of $C_{13}H_{23}Br$ and $C_{21}H_{39}Br$ (as alkyating agents) with peptides, proteins, and nucleic acids

Example of Lyophized peptide



With different nucleophilic groups

REGULATORY: US



Guidance fc

Immunogenicity
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

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:

FDA Guidance for Industry, 2014

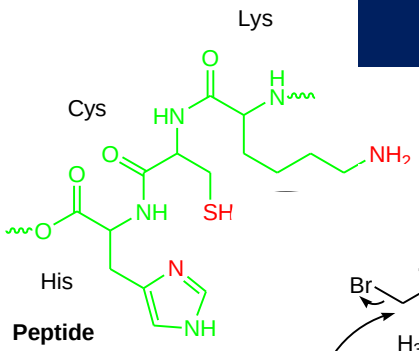
"... Interactions are more likely with prefilled syringes of therapeutic protein products..."

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

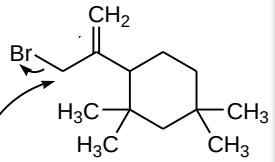
3. RUBBER OLIGOMERS

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

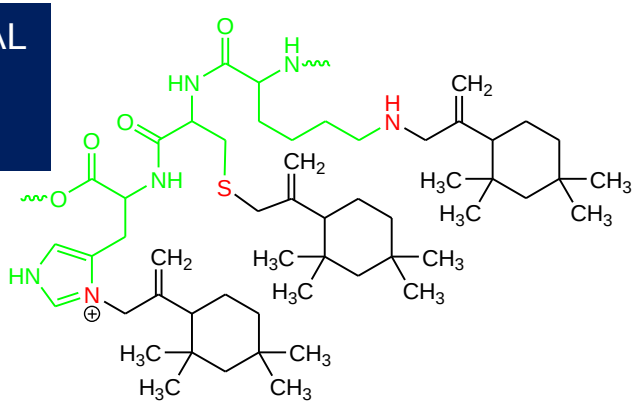
OBSERVED & POTENTIAL Reactivity with Peptides **(LYO!!!)**



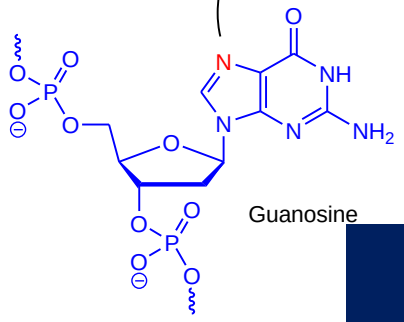
With different nucleophilic groups



nucleophilic side chain attack

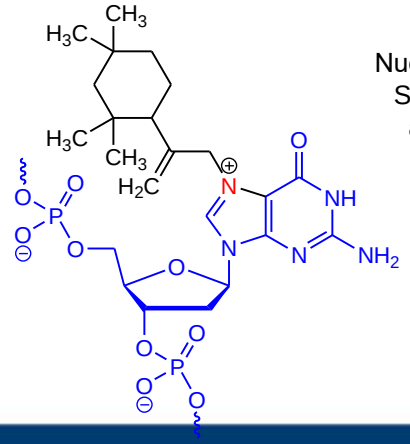


DNA



"N7" attack

Most nucleophilic site



Nucleophilic “N7” attack is also SN2 reaction mechanism in anti-cancer drug Busulfan

POTENTIAL Reactivity with DNA

Ref. 7

ANY QUESTIONS?