PDA Training Course Extractables & Leachables

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Extractable & Leachable Considerations for Small Volume Parenteral Applications

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CONNECTING PEOPLE SCIENCE AND REGULATION®

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

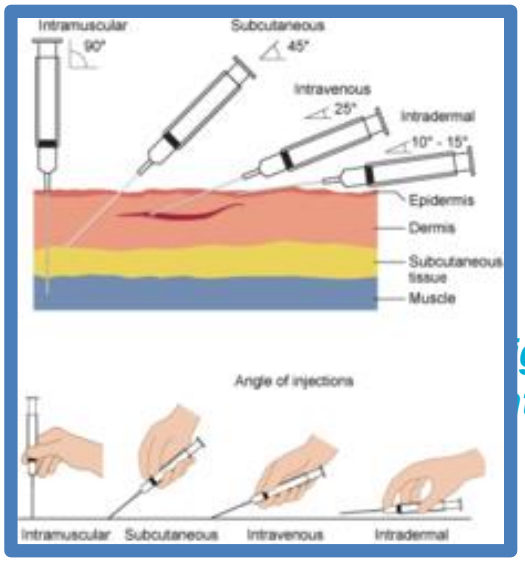
1. Regulatory Expectations for Small Volume Parenterals – Brief Recap

1. Regulatory Expectations - US

LIQUID SVP's

Ranking the Packaging Concerns

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



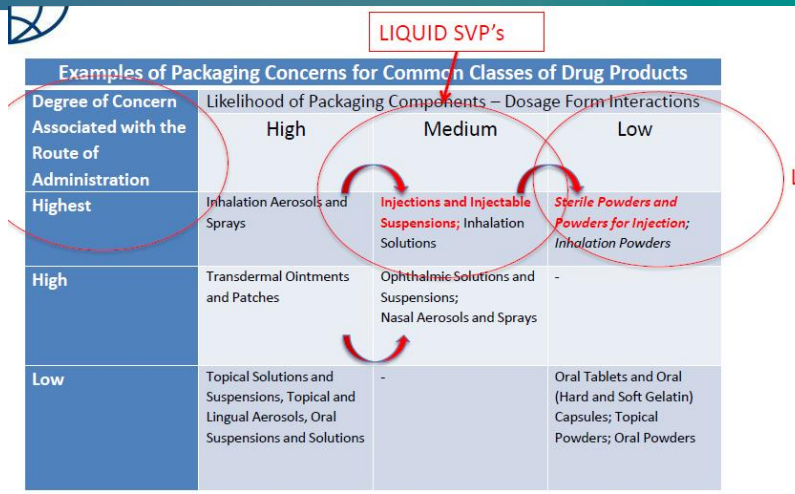
Examples of PACKAGING CONCERNS for Common Classes of Drug Products

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

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

1. Regulatory Expectations - 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. Regulatory Expectations - US

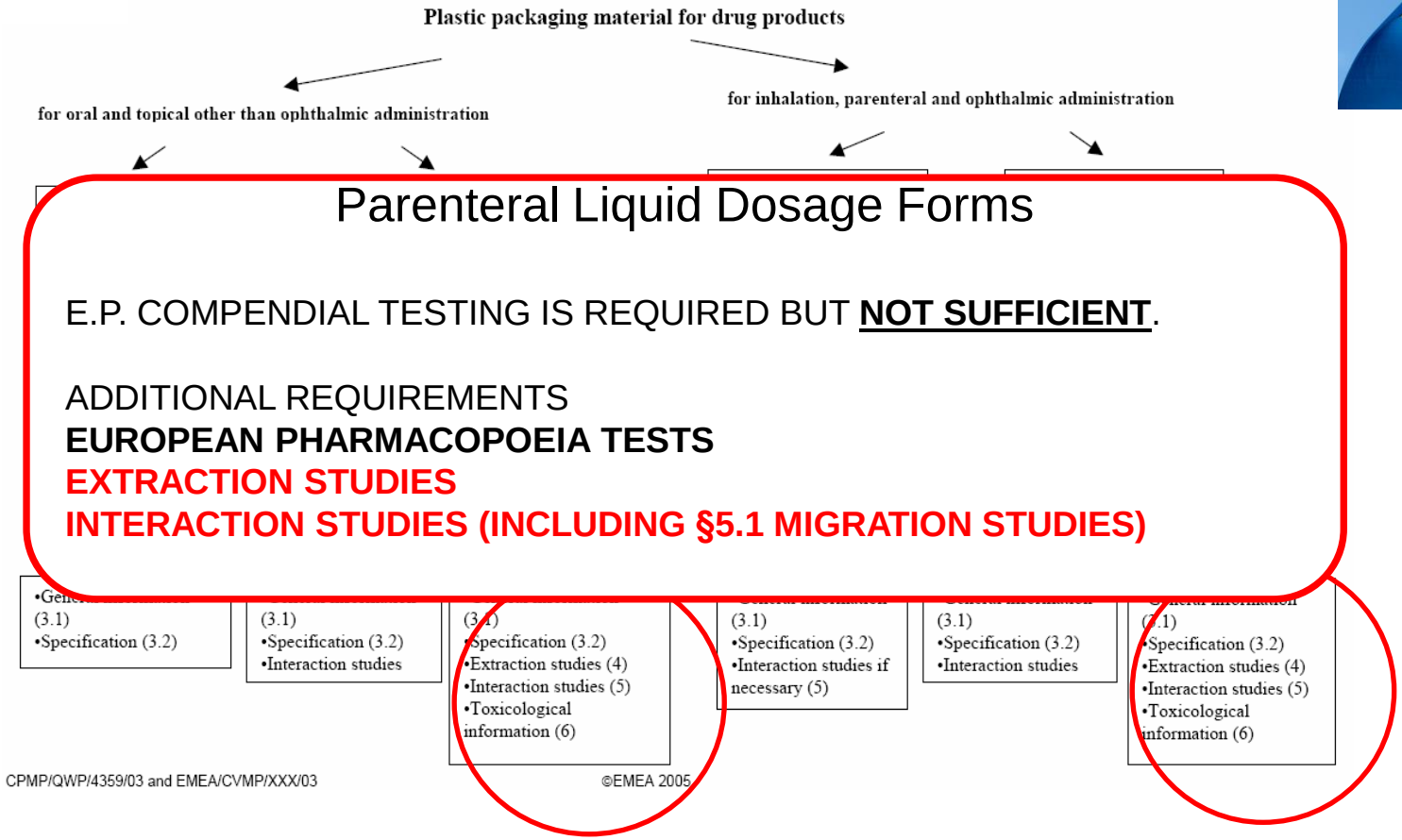
Recent “Informal” Communications from the FDA

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



Parenteral Liquid Dosage Forms

E.P. COMPENDIAL TESTING IS REQUIRED BUT **NOT SUFFICIENT**.

ADDITIONAL REQUIREMENTS
EUROPEAN PHARMACOPOEIA TESTS
EXTRACTION STUDIES
INTERACTION STUDIES (INCLUDING §5.1 MIGRATION STUDIES)

2. Rubbers – An introduction

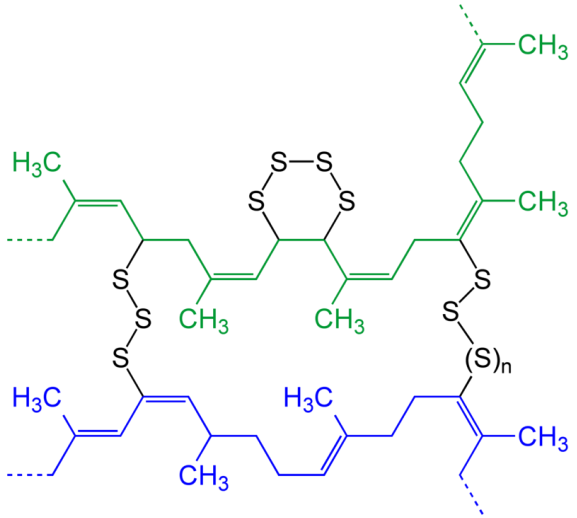
Supported by Datwyler

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

2. Rubbers – an Introduction

Rubber = Compounded material of:

1. Elastomer

2. Filler

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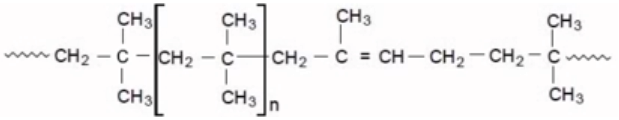
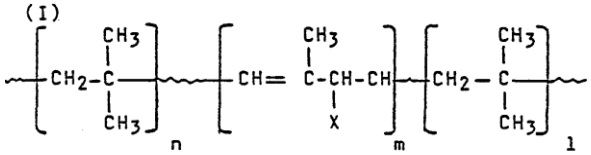
2. Rubbers – an Introduction

Elastomer

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



Butyl



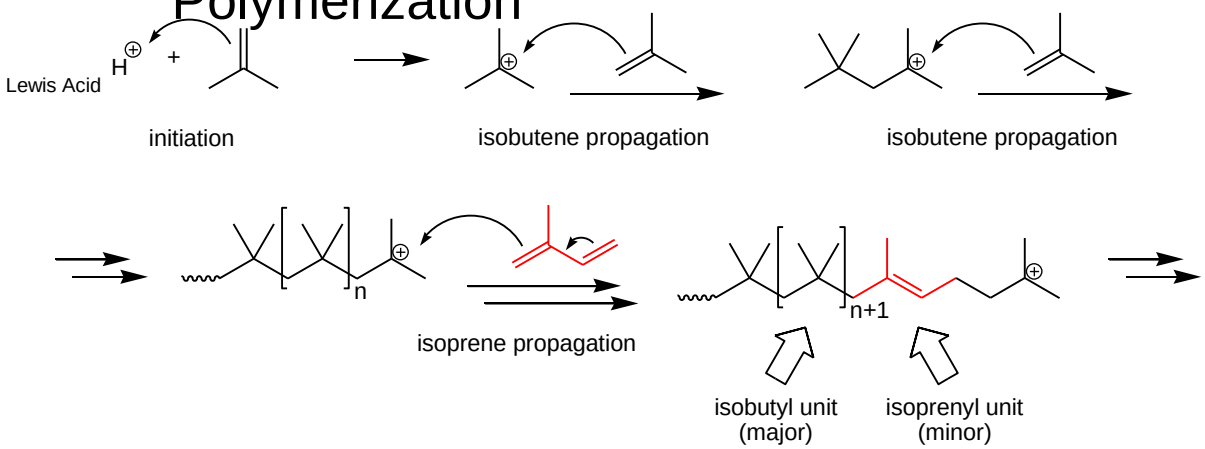
X =Cl or Br

Halobutyl

2. Rubbers – an Introduction

Elastomer

Butyl Elastomer (IIR): Cationic Polymerization



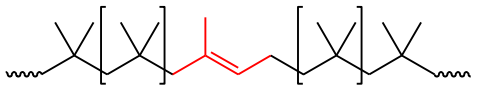
- Note: the Polymerization Starts with a Isobutene Unit (present in high excess!!)
  - *98 – 99 mol% is isobutylene*
  - *1 – 2 mol% is isoprene*

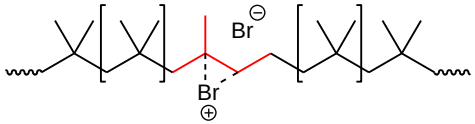
2. Rubbers – an Introduction

Elastomer

Bromobutyl Rubber: Bromination of the Butyl Elastomer (BIIR)

Butyl

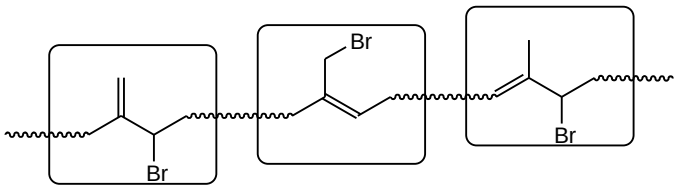




HBr is **split off** during Bromination:

Strong acid

Need to add an **acid scavenger**



Bromobutyl

Type 1 Type 2 Type 3

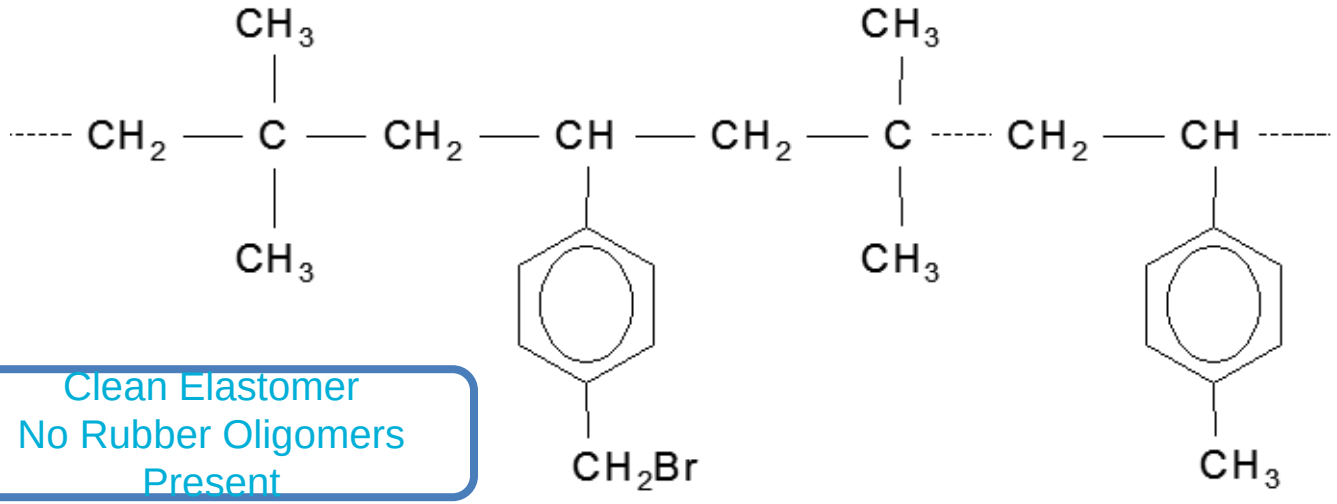
Bromination of the Backbone makes Elastomer more reactive in vulcanization/cross linking

(BIIR has a relatively Low N° 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*)

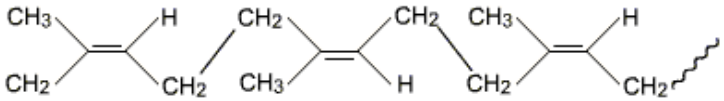


Clean Elastomer
No Rubber Oligomers Present

2. Rubbers – an Introduction

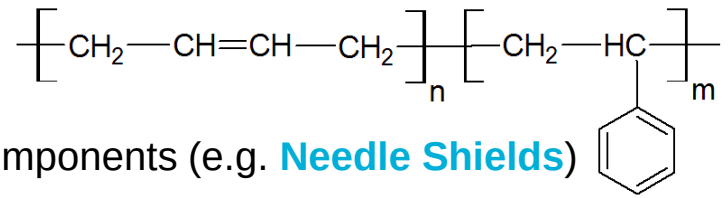
Elastomer

- **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



Natural rubber

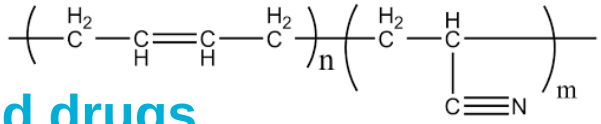
- **SBR** (styrene-butadiene rubber)
  - Random Copolymer
  - Intermediate **permeability**
  - Typically used for pre-assembled **EtO** sterilized components (e.g. **Needle Shields**)



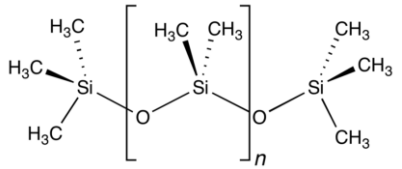
2. Rubbers – an Introduction

Elastomer

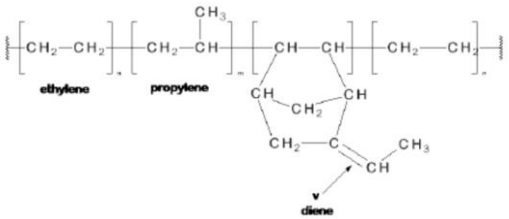
- **Nitrile** rubber
  - Typically used for mineral **oil based drugs**



- **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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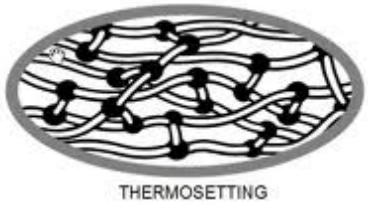
2. Rubbers – an Introduction

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, ...



Crosslinked polymer chains

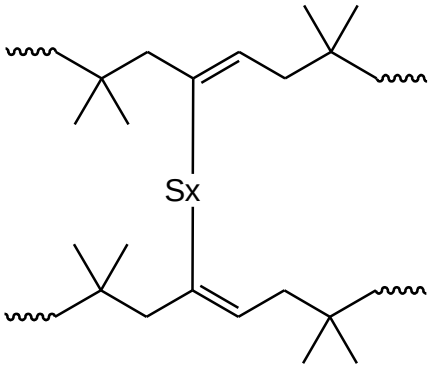
- **Modern cure systems**
  - Aim at giving **little extractables**
- **Historic cure systems**
  - Use **easily extractable organic accelerators**

2. Rubbers – an Introduction

Curing System

Rubber Curing / Vulcanization:

Oldest Curing
Sulfur (S_8) Vulcanization



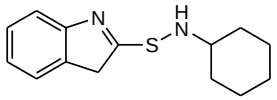
Rubber crosslinking requires S-Donors, activators, accelerators
Activator: ZnO / Stearic acid

2. Rubbers – an Introduction

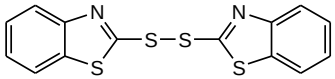
Curing System

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

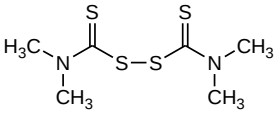
accelerators: known to lead to n-Nitrosamine



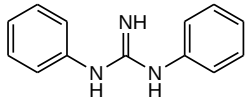
Cyclohexyl benzothiazole sulfenamide



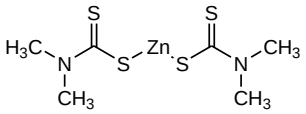
Mercaptobenzothiazole disulfide



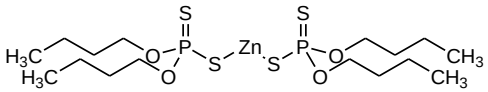
Tetramethylthiuram disulfide(TMTD)



Diphenyl guanidine



Zinc dimethyldithiocarbamate



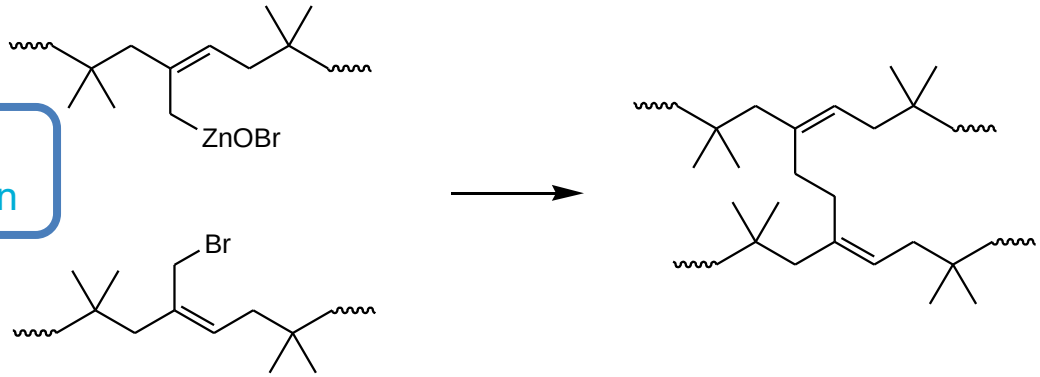
Zinc dibutylphosphorodithiate

2. Rubbers – an Introduction

Curing System

ZnO as Activator Compound in Halobutyl-Rubbers:

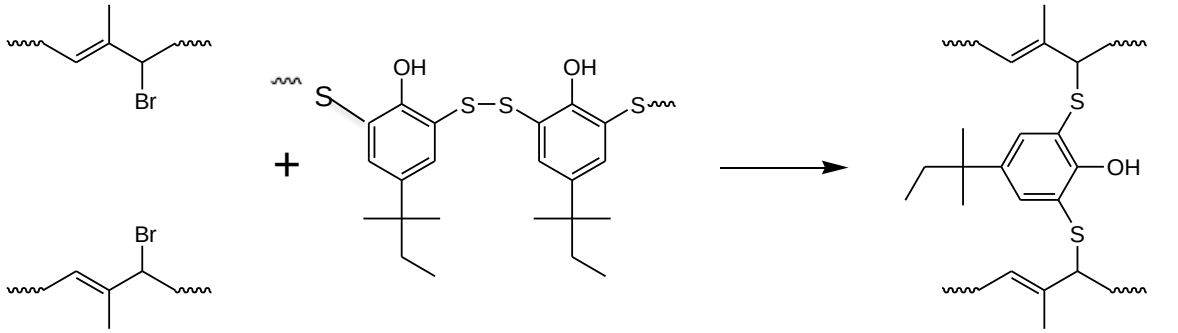
ZnO shows "catalyst" action



2. Rubbers – an Introduction

Curing System

Vultac Vulcanizing Agent for (Halobutyl) Elastomers



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

2. Rubbers – an Introduction

Rubber = Compounded material of:

1. Elastomer

2. Filler

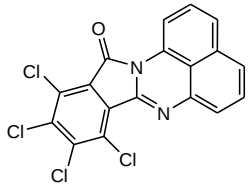
3. Cure system
4. **Pigment**
5. Other ingredients

2. Rubbers – an Introduction

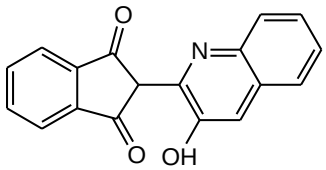
Pigments

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

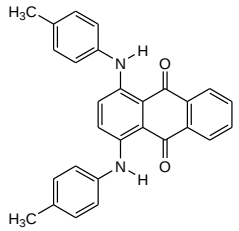
Cosmetic reasons – or-
Differentiate different
Strengths & Presentations



Solvent Red



Solvent yellow 114



Solvent Green 03

2. Rubbers – an Introduction

Rubber = Compounded material of:

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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**

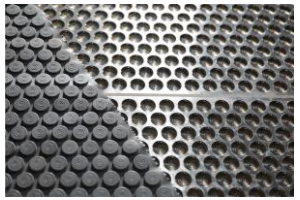
2. Rubbers – an Introduction

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



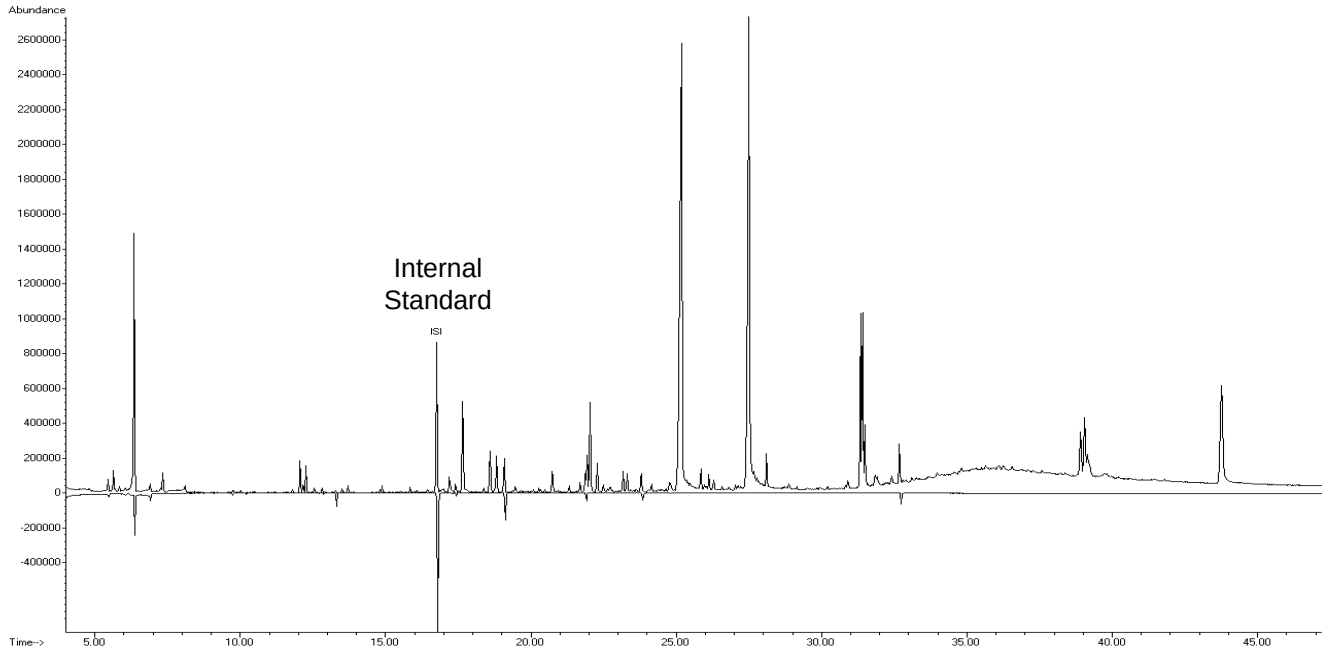
2. Rubbers – an Introduction

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

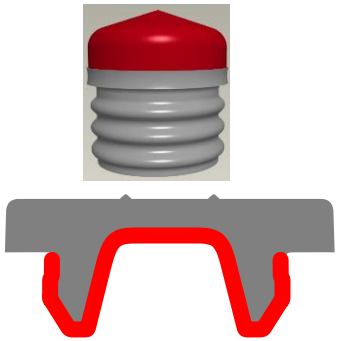
"NEW" RUBBER

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***

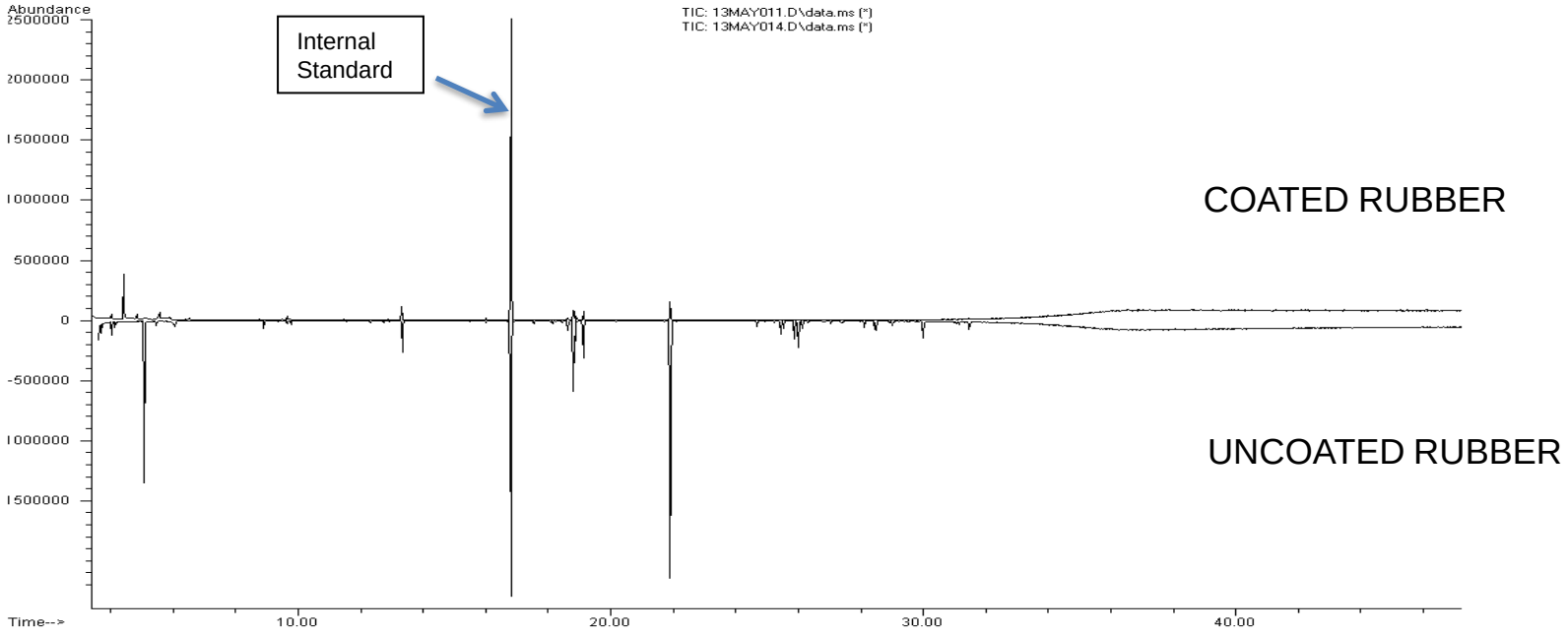
Film coating technology



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

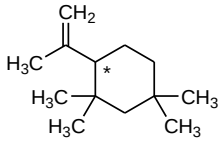
Number of Leachables from rubbers in SVPs is determined by:

- 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)

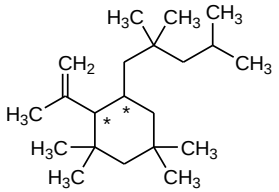
3. Rubber Oligomers: Toxicity & Reactivity

3. Rubber Oligomers: Toxicity & Reactivity

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



C13 oligomer



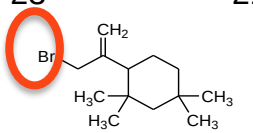
C21 oligomer

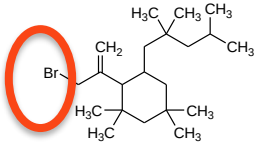
- **Formed** both **during the Polymerization** and the **rubber curing** at high temperatures
- Considered as
  - **Cyclic aliphatic hydrocarbon** compounds
  - **One double bond**
- **No experimental data / Literature** data is known about toxicity of these compounds
- Structure Activity Relationship 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 Hydrobarbon compounds (**Allyl Halide**)
  - **Alkylating Agents**
  - One double bond

- Structure Activity Relationship (SAR) Assessment:

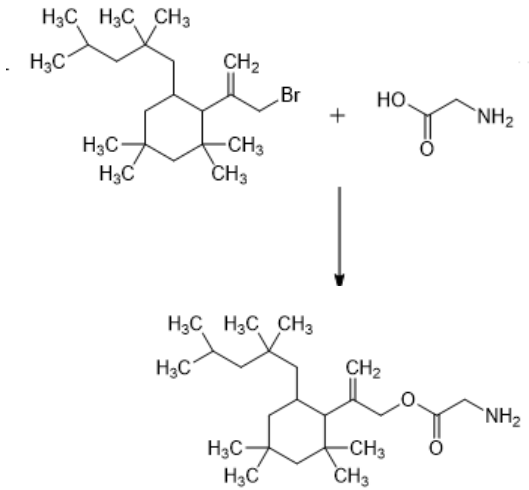
CARCINOGENICITY IN HUMANS IS PLAUSIBLE

- 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: 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

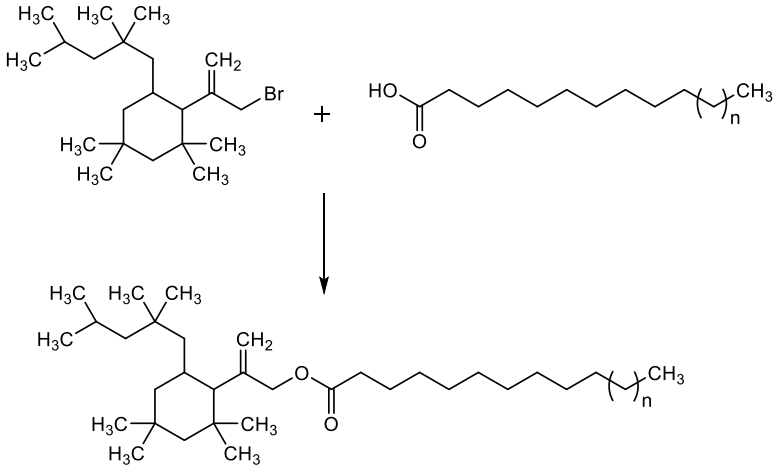


Glycine (excipient, bulking agent)

3. Rubber Oligomers: Toxicity & Reactivity

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

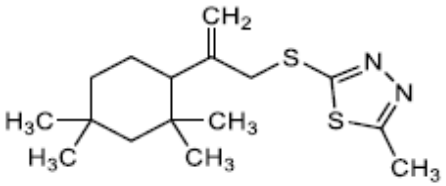
C21H39Br rubber oligomer source
- leachable from a rubber stopper

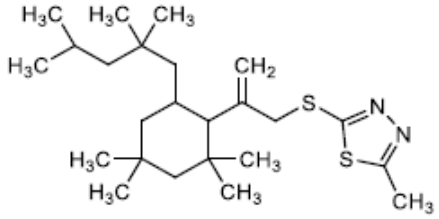


Fatty acids source –
Polysorbate 20

3. Rubber Oligomers: Toxicity & Reactivity

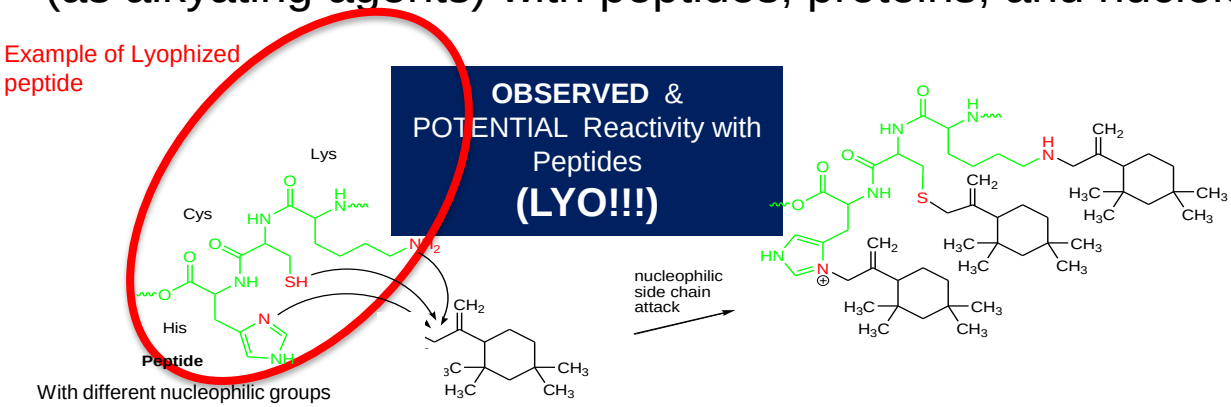
Adduct Formation of an Small Molecule API with the $C_{13}H_{23}Br$ and $C_{21}H_{39}Br$ oligomers





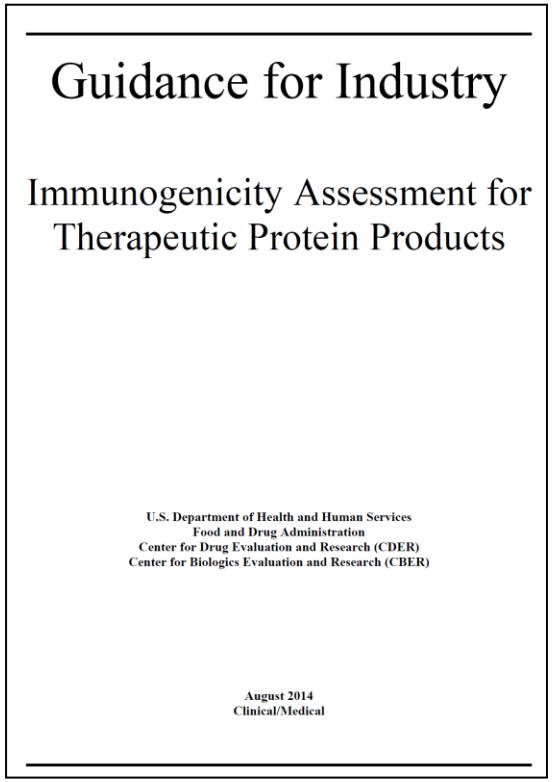
3. Rubber Oligomers: Toxicity & Reactivity

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



Fictious Example of a Peptide with different nucleophilic functional groups

3. Rubber Oligomers: Toxicity & Reactivity



Guidance for Industry

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

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

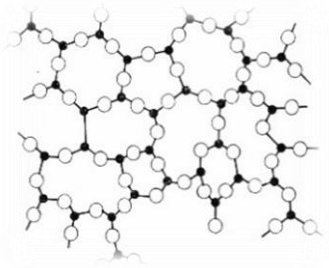
4. Glass & Glass Related Issues
Vials, Prefilled Syringes, Cartridges

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_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

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

4. Glass & Glass Related Issues

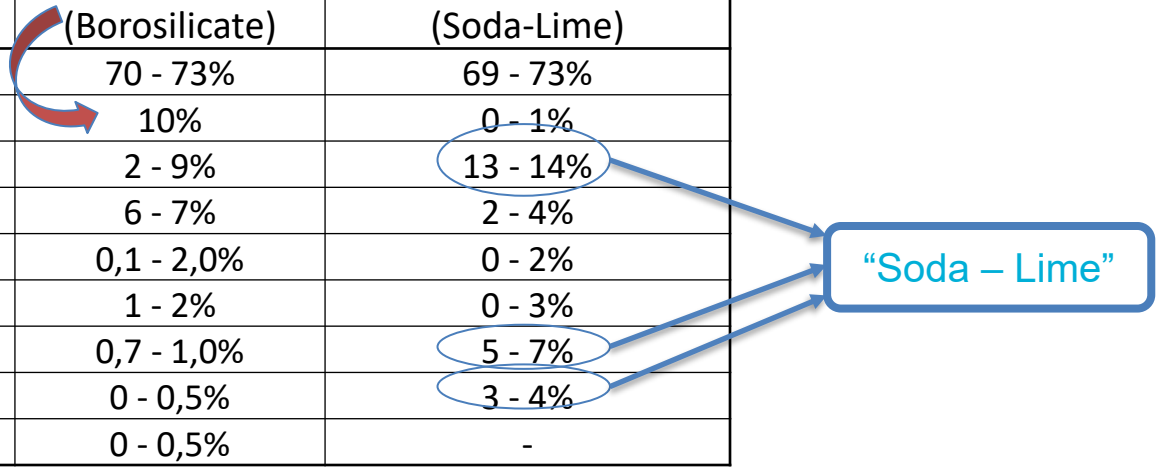
Glass Types

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

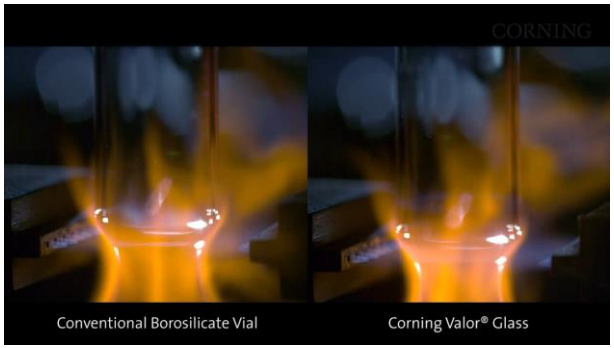
4. Glass & Glass Related Issues

Glass Composition for different Glass Types:

Component	Type I (Borosilicate)	Type II, III, NP (Soda-Lime)
SiO_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 & 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

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

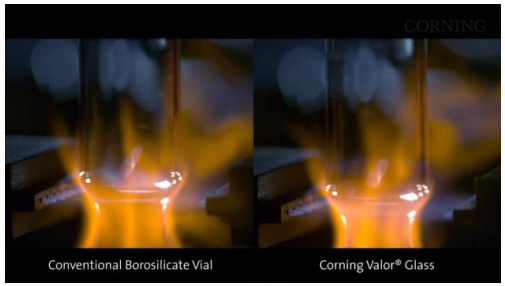
4. Glass & Glass Related Issues

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

4. Glass & Glass Related Issues

How to (try to) prevent Glass Leaching



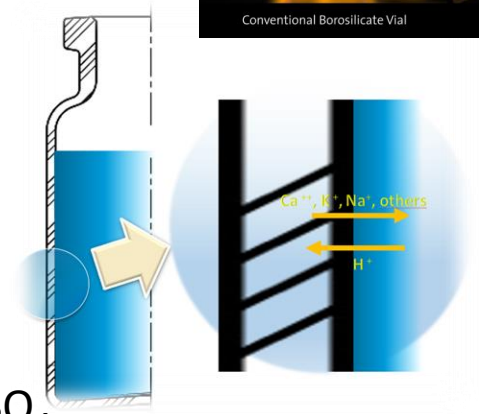
1. Chemical surface treatment

$(NH_4)_2SO_4$ 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 $NaSO_4$



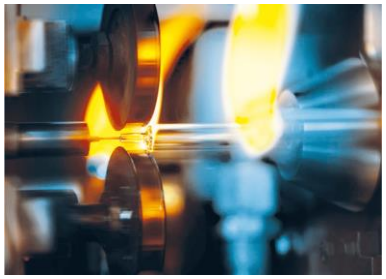
Result: lower pH shift because lower amounts of Na will leach

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

3. Siliconisation will reduce interaction between glass and DP

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

4. Glass & Glass Related Issues

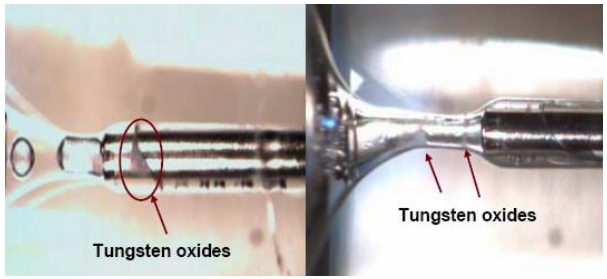


Glass as Barrel Material

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

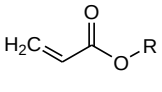
- *Glue is used to **glue in the staked needle** into the PFS-system*
- ***Prolonged contact** with a drug product may release glue components*
- ***Target compounds** may **depend** upon the **glue used (through UV Curing)***

4. Glass & Glass Related Issues

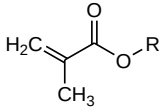
Glass as Barrel Material – Related Compounds

GLUE RESIDUES

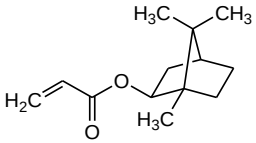
Base Polymer



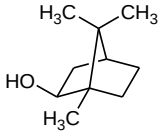
Acrylate



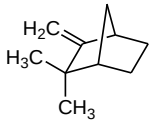
Methacrylate



Isobornyl acrylate

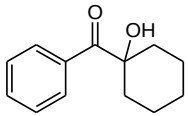


Isoborneol

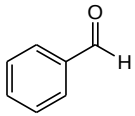


Camphene

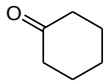
UV curing / activation



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 **denaturate proteins** of 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*

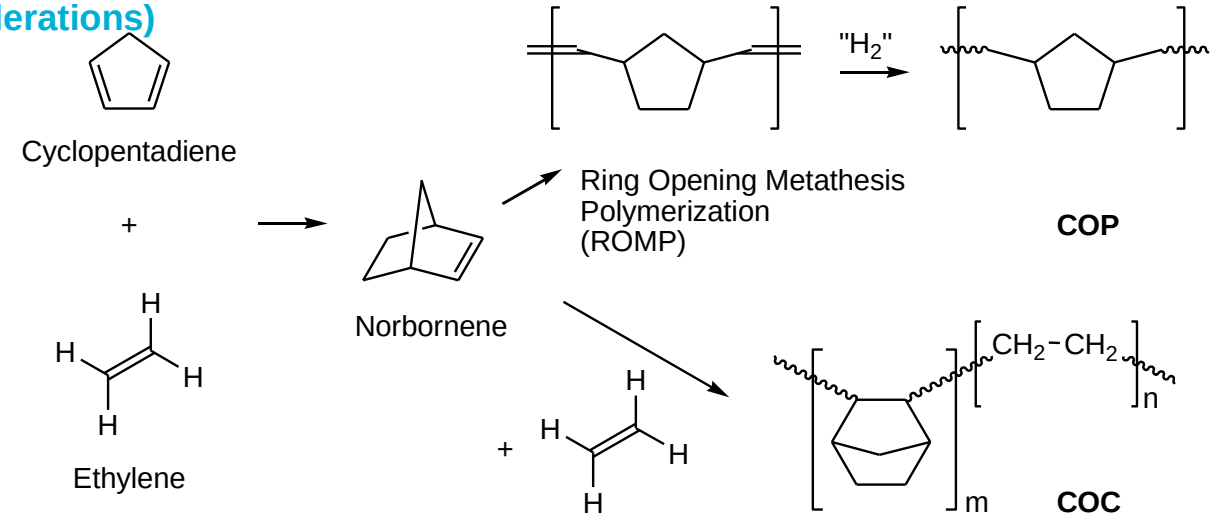
Less of an issue with Baked Silicone

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_2) 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

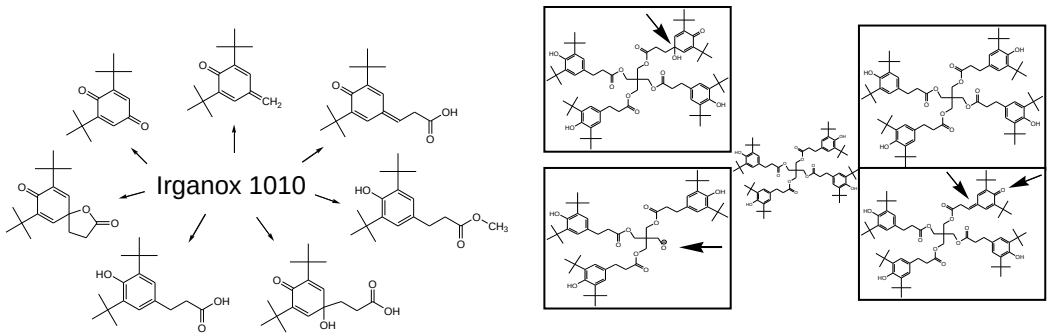
- Additives *(BHT, Irganox 1010, Stearates, Pigments, Clarifiers...)*

- 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,...)

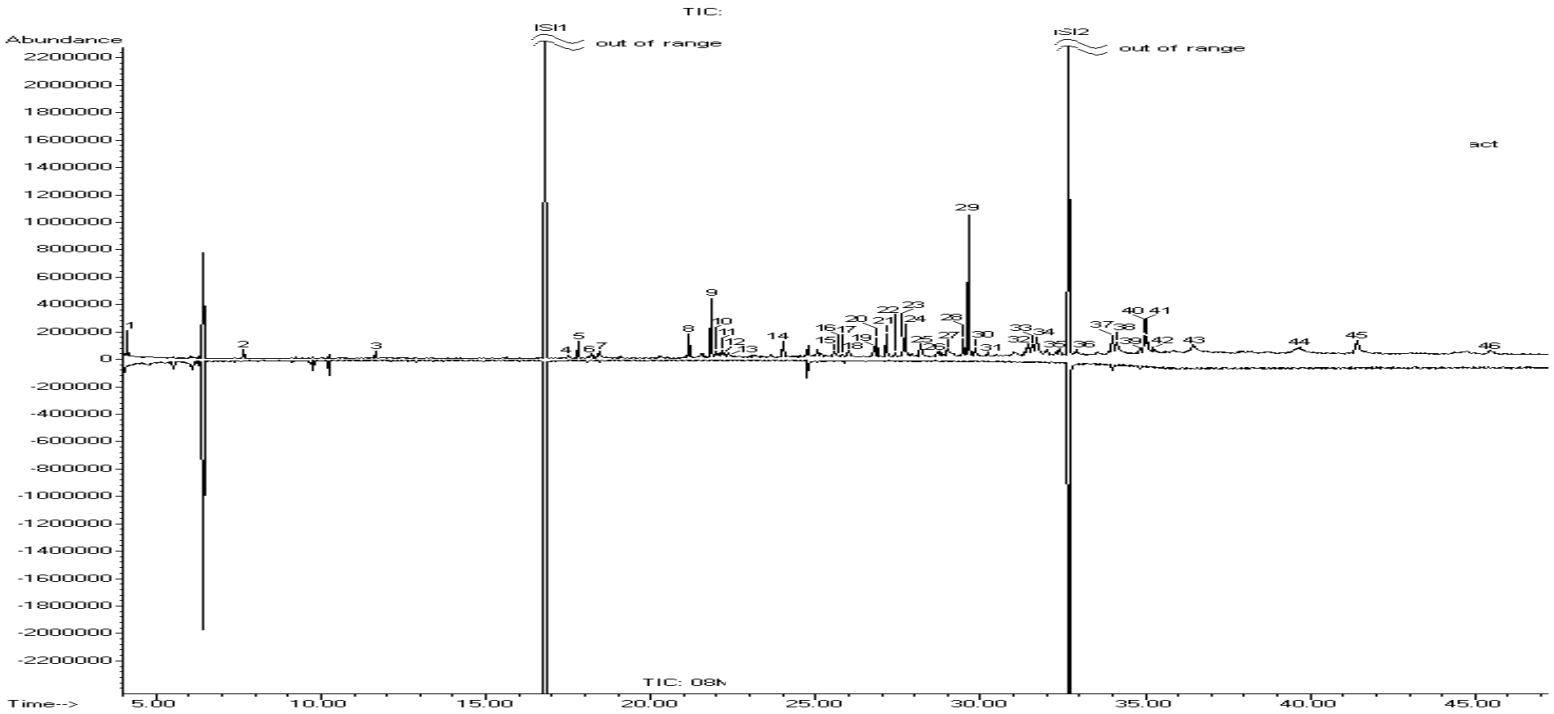
Solvent residues (e.g.Toluene, acetone)

Adhesive residues (e.g. Acrylates)

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

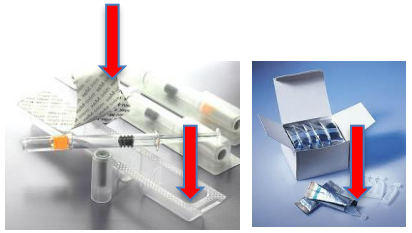
5. Other Materials used in Small Volume Parenteral C/C Mfng

- 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**

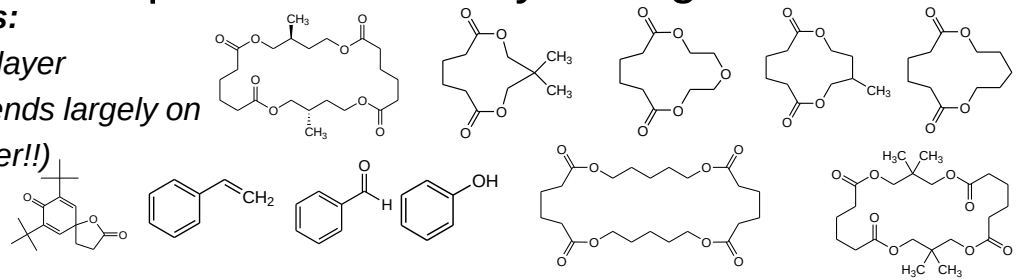
(to compensate for potential lower barrier properties of the Polymer)

- 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!!)

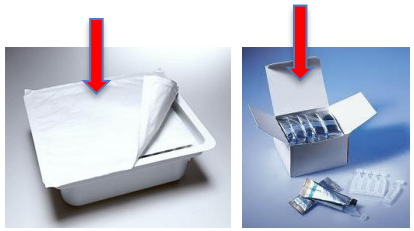


bislactones

...

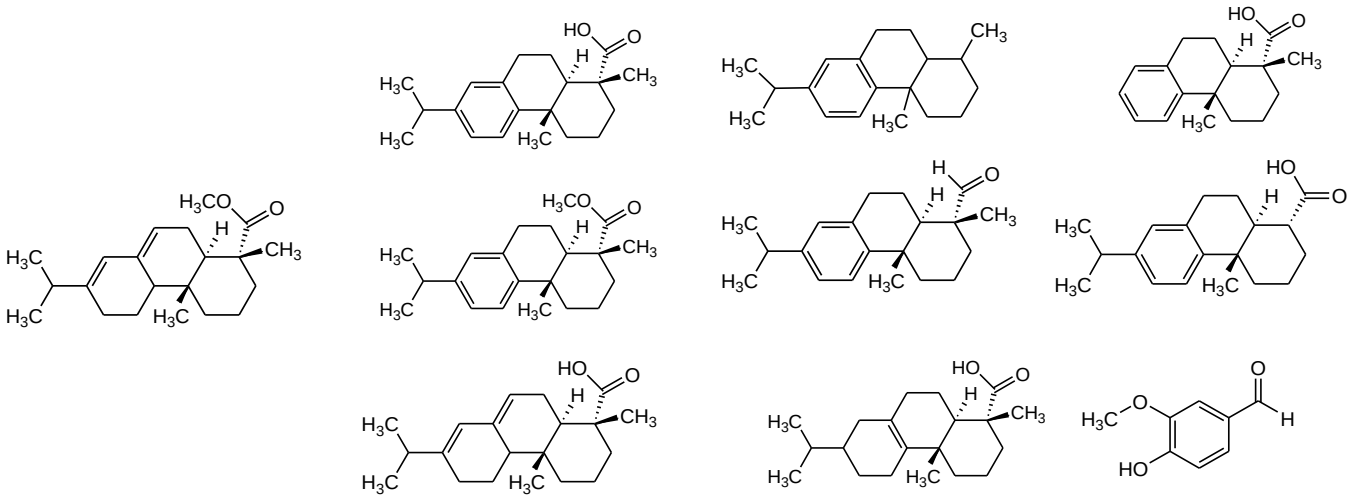
5. Other Materials used in Small Volume Parenteral C/C Mfng

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: Extractrable Considerations

6. Main SVP containers: Extractrable Considerations

1.Vials:

6. Main SVP containers: Extractrable Considerations

Vials

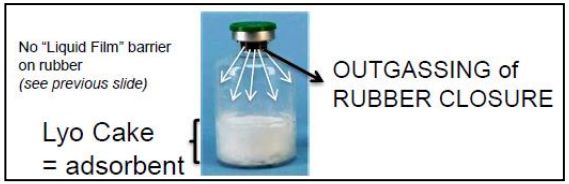
Liquid Drug Products

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”...

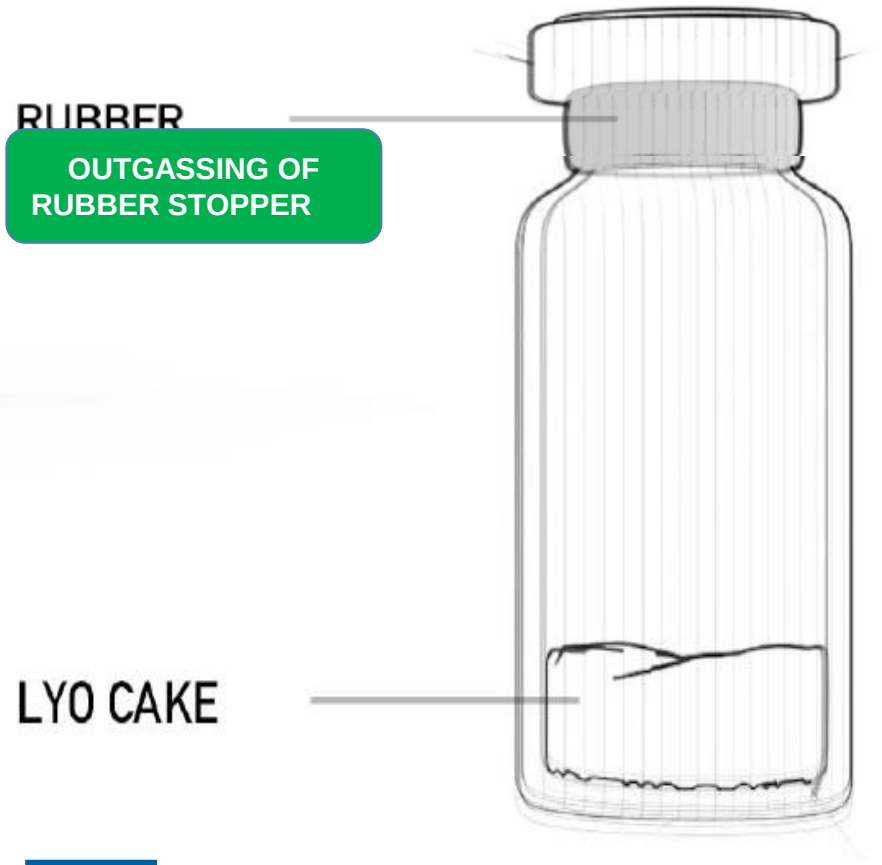
6. Main SVP containers: Extractrable Considerations

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 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.

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



Outgassing of rubbers is mainly an issue for:

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

LYO CAKE: EXTREMELY GOOD ADSORBENT

- *High Suface 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:

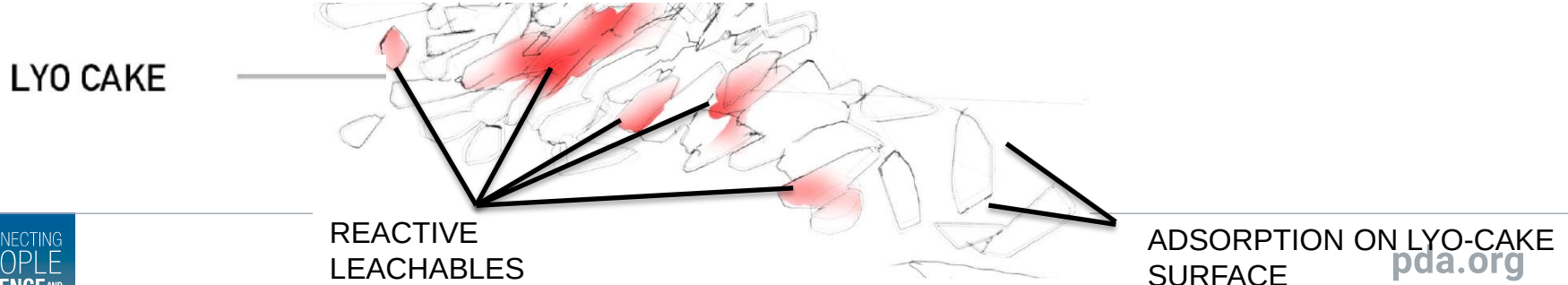
- *Volatile Organic Compounds*
- *Semi-Volatile Organic Compounds*

LYO CAKE: EXTREMELY GOOD ADSORBENT

- *High Suface Area*
- *Extremely Dry*

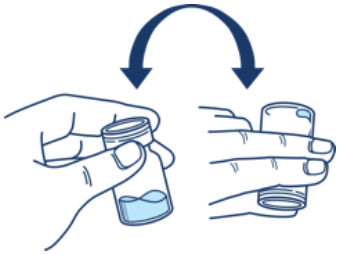
ACCUMULATION OF VOC/SVOC LEACHABLES

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



The Interaction Mechanism: During RECONSTITUTION of the Lyophilized DP

RECONSTITUTION



SOLUBILIZATION
of adsorbed leachables in reconstitution solution

Reconstituted (Liquid) DP
Liquid Interaction with
Primary Packaging Components

Mainly Volatile & Semi-Volatile Organic compounds (OUTGASSING)

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**

(1) LinkedIn | Saba

soterahealthacademy-ext.sabacloud.com/Saba/Web_spf/NA10P1PRD067/app/content-player?contextid=ctctx0000000000008884&assignmentid=cnin...

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2022 Nelson Labs Virtual Symposium

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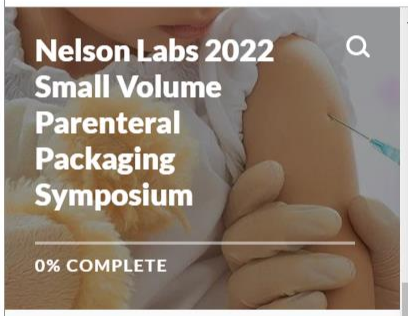
2022 Nelson Labs Virtual Symposium



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

Contact the Academy for more information

9°C Zonnig ENG 07:51

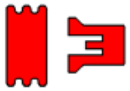
6. Main SVP containers: Extractrable Considerations

2. Pre-Filled Syringe:

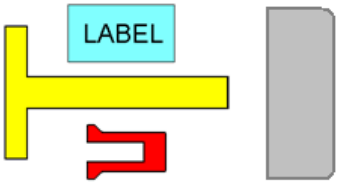
6. Main SVP containers: Extractrable Considerations

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: Extractrable Considerations

Pre-Filled Syringes

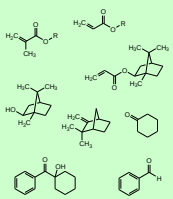
- **BARREL**: ***Metals*** (may not be necessary to be studied in EXT Study, if glass composition is available, direct assessment in LEA study)
  Silicone Oil residues may cause protein aggregation
- **Rubber Plunger *(very similar to rubber stopper for vial):***
  - ✓ Typically, higher migration when 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

6. Main SVP containers: Extractrable 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

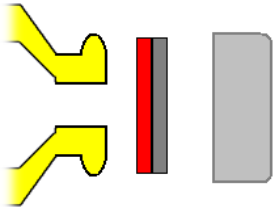
Concern for - Glass PFS **- Polymer PFS**	Concern for – **Glass PFS**	Concern for **– Glass PFS**	Concern for **– Glass PFS**	Concern for **- Polymer PFS**	Concern for **- Polymer PFS**
(COATED) RUBBER	**NEEDLE GLUE**	**TUNGSTEN (W)**	**GLASS BARREL**	**COC/COP/PP BARREL**	**LABEL (ADHESIVE)**
MONOMER 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…* Piston / Needle Shield / Tip Cap	- 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***

6. Main SVP containers: Extractrable Considerations

3. Cartridges

6. Main SVP containers: Extractrable 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

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

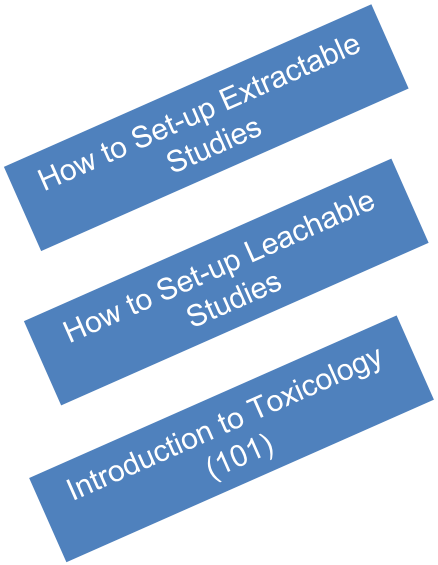
- **Cartridge Plunger (same as for PFS!):**
  - ✓ Typically, higher migration when solution is in contact (inverted)
  - ✓ Migration will be determined by:
    - Solubility of leachables in Reconstitution Solution (typically inorganic aqueous solution (*typically low solubility for most non-polar organic 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



Questions?

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