EXTRACTABLES & LEACHABLES FOR SVP-INJECTABLES

PDA Post-Conference E/L-Workshop
VENICE
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PDA Content

1. Regulatory Considerations for SVPs
    - US
    - EU
2. Typical Materials of Construct (MoC's) for SVP C/C
    - Rubbers 101
    - Glass & Glass related issues for E/L
    - COP/COC
3. Container Closure Systems for SVP's
    - Vials
    - Prefilled Syringes
    - Cartridges
    - Delivery Devices with Short Term Contact
4. Conclusion

1.Regulatory Considerations -SVP

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

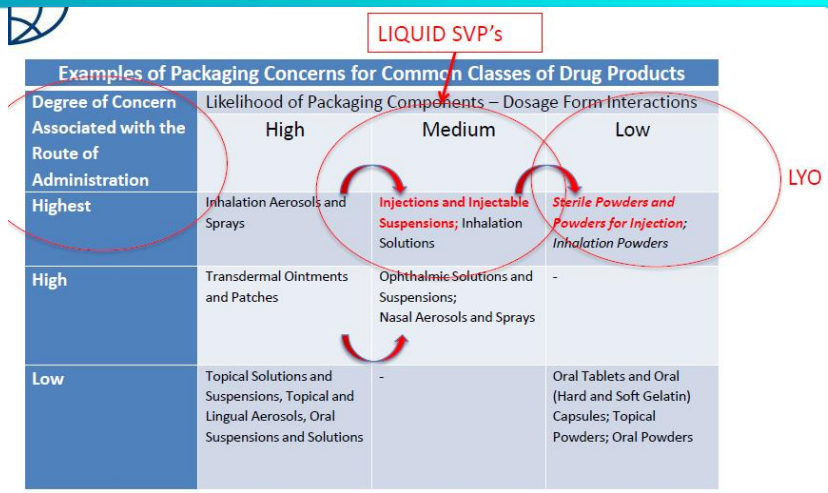
LYO

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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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.

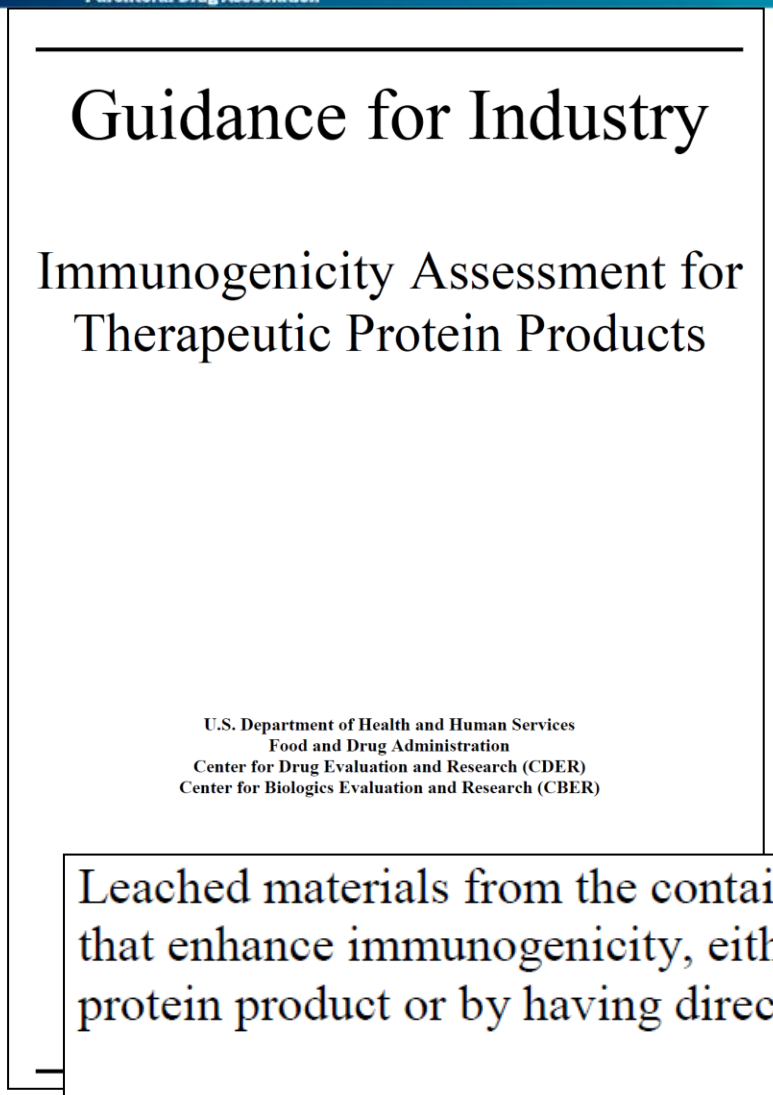
   BE CAREFUL when "rationalizing" a LYO application as being Non Critical!!!

REGULATORY: US

Additional Concern for **BioPharmaceuticals**

Leachables, Leading
to **Immunogenic Responses**
Directly or Indirectly
(via e.g. Protein interactions)

REGULATORY: US



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)

Consequences for EFFICACY – some of the concerns:

Development of "***Neutralizing Antibodies***" *(e.g. through chemically modified therapeutic protein product)* can **block the efficacy** of therapeutic protein products

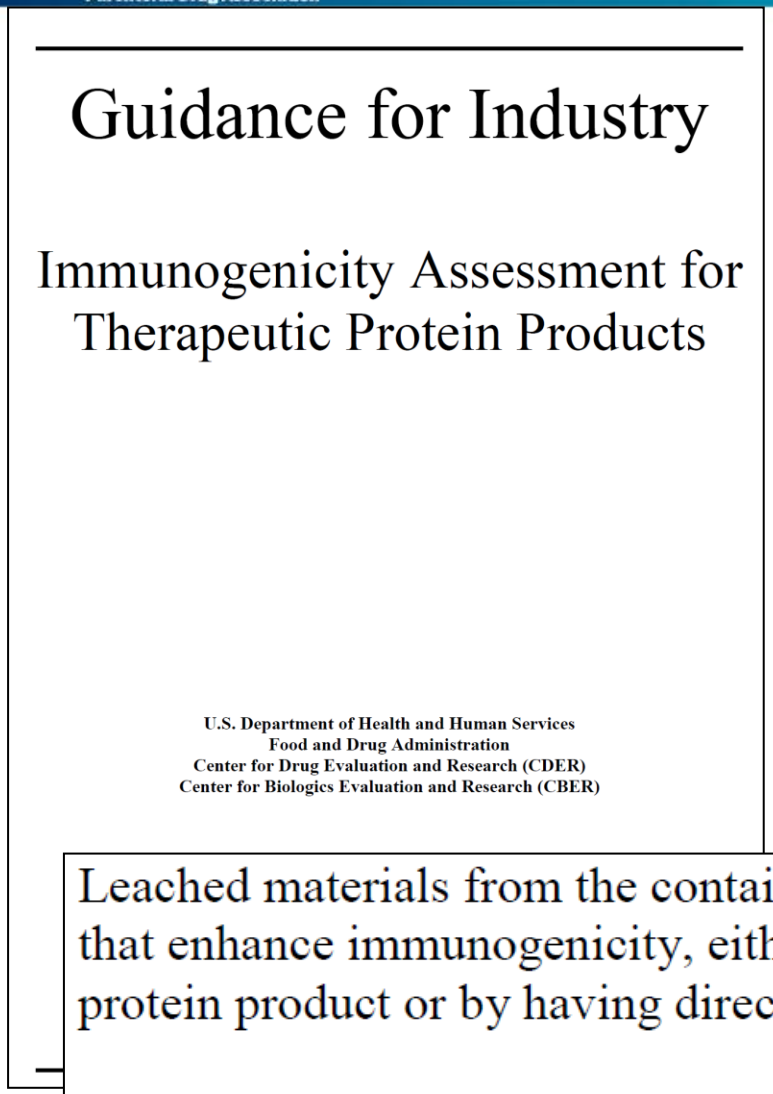
May also change the Pharmacokinetics

- Enhancing Clearance
- Or Prolonging Product Activity

Leached materials from the container closure system may be a source of materials that enhance immunogenicity, either by chemically modifying the therapeutic protein product or by having direct immune adjuvant activity.

FDA Guidance for Industry, 2014

REGULATORY: US


Guidance for Industry

Immunogenicity Assessment for Therapeutic Protein Products

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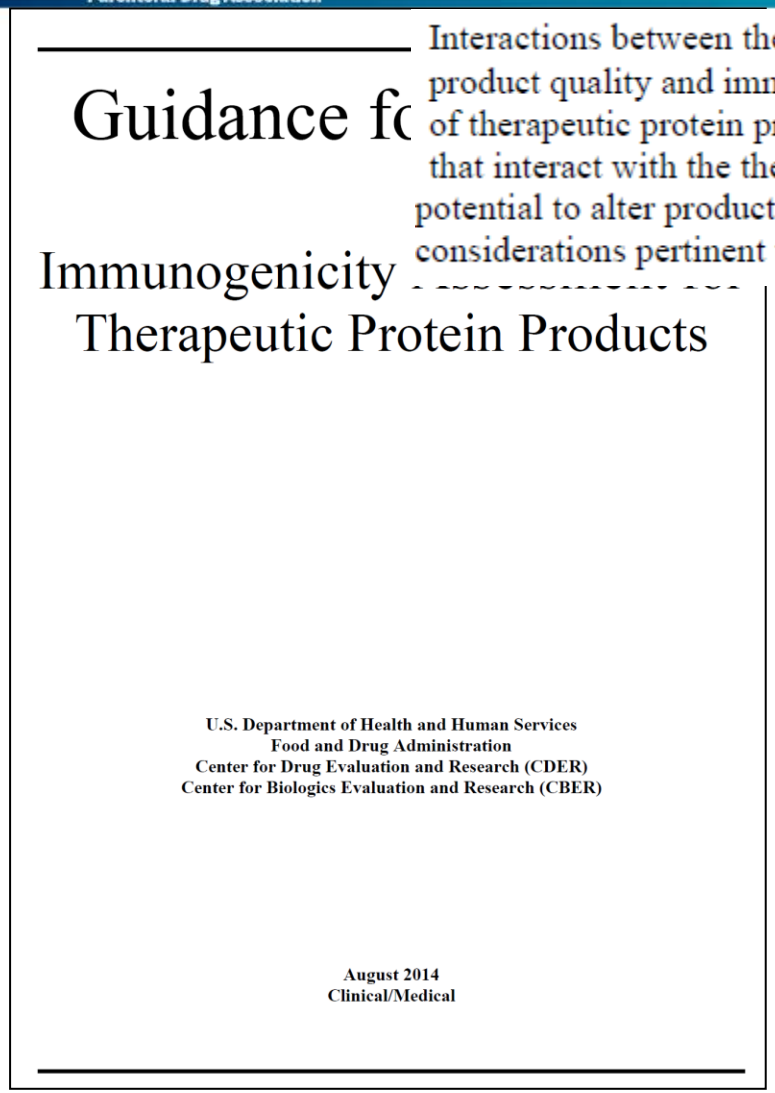
Consequences for SAFETY – some of the concerns: *(e.g. "...through chemically modified therapeutic protein product...")*

- Anaphylaxis (serious, accute allergenic reaction)
- Cytokine Release Syndrome
- "Infusion Reactions"
- Non-Acute Reactions
- Cross-reactivity to Endogeneous Proteins

Leached materials from the container closure system may be a source of materials that enhance immunogenicity, either by chemically modifying the therapeutic protein product or by having direct immune adjuvant activity.

FDA Guidance for Industry, 2014

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..."

REGULATORY: US

- Glass and air interfaces can denature proteins and cause aggregation in glass syringes and vials.
- Glass vials have been known to delaminate at higher pH and with citrate formulations, potentially creating protein-coated glass particles, which may enhance immunogenicity of the therapeutic protein product (Fradkin et al. 2011). → Delamination
- Silicone oil-coated syringe components provide a chemical and structural environment on which proteins can denature and aggregate. → Silicone Oil
- Appropriate in-use stability studies should be performed to confirm that conditions needed to maintain product quality and prevent degradation are adequately defined. → In Use Stability Studies
- Leached materials from the container closure system may be a source of materials that enhance immunogenicity, either by chemically modifying the therapeutic protein product or by having direct immune adjuvant activity, including the following: → Directly – Indirectly leading to enhanced immunogenicity
    - Organic compounds with immunomodulatory activity may be eluted from container closure materials by polysorbate-containing formulations: a leachable organic compound involved in vulcanization was found in a polysorbate formulated product when the stopper surfaces were not Teflon coated (Boven et al. 2005). → Eprex - Case
    - Metals that oxidize and aggregate therapeutic protein products or activate metalloproteinases have been found in various products contained in prefilled syringes or in vials. For example, tungsten oxide that leached from the syringe barrel was reported to cause protein aggregation (Bee et al. 2009); and leached metals from vial stoppers caused increased proteolysis of a therapeutic protein because of activation of a metalloproteinase that co-purified with the product. → Tungsten Oxide Leading to Protein aggregation

REGULATORY: US

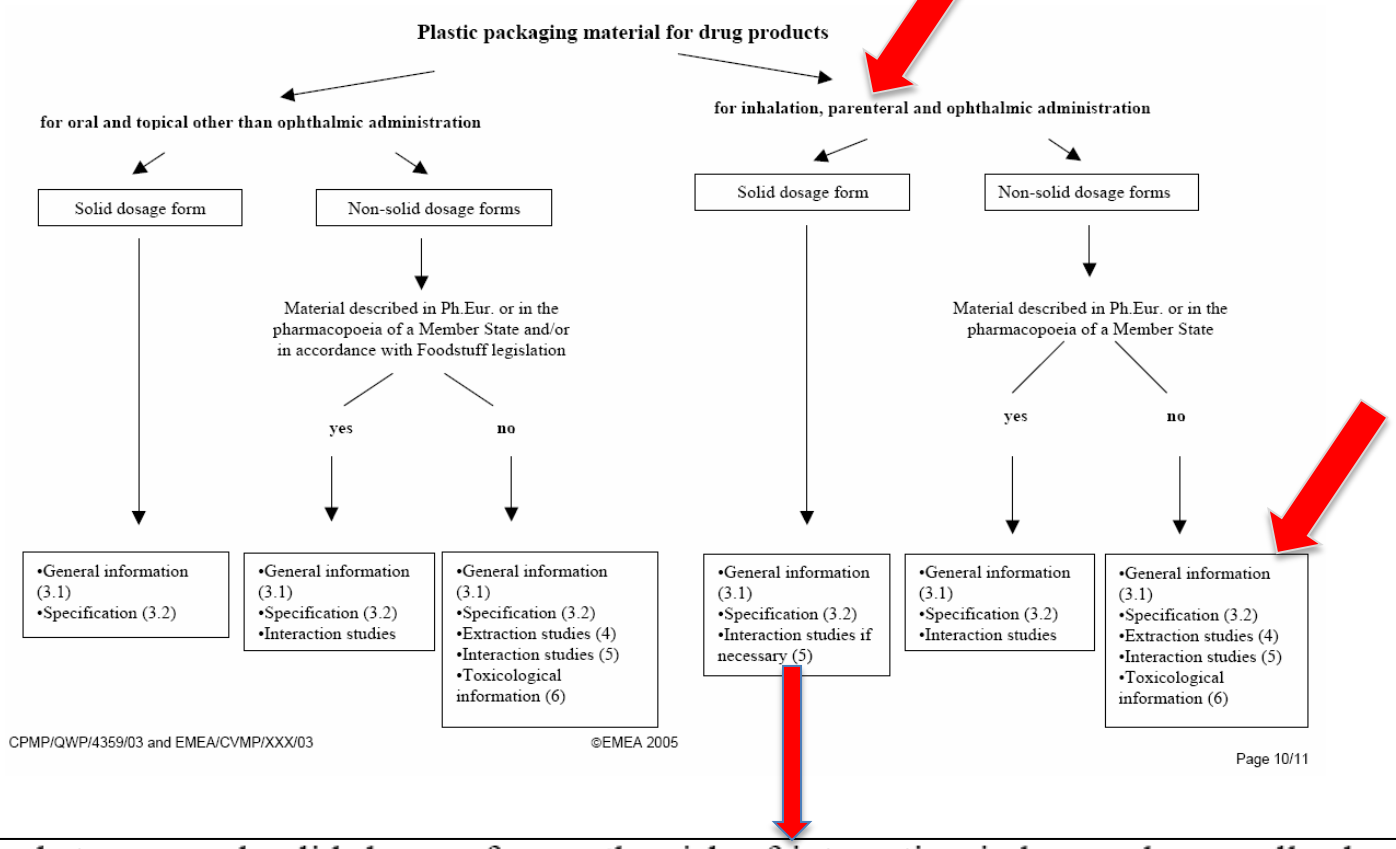
Sponsors should conduct a comprehensive extractables and leachables laboratory assessment using multiple analytical techniques to assess the attributes of the container-closure system that could interact with and degrade protein therapeutic products.

Because the United States Pharmacopeia *elastomeric closures for injections* tests do not adequately characterize the impact of leachables in storage containers on therapeutic protein products under real-time storage conditions, leachables must be evaluated for each therapeutic protein product in the context of its storage container under real-time storage conditions[8].

Testing for leachables should be performed on the product under stress conditions,[9] as well as under real-time storage conditions, because in some cases the amount of leachables increases dramatically over time and at elevated temperatures. Product compatibility testing should be performed to assess the effects of container closure system materials and all leachables on product quality.

REGULATORY: EU

The EM(E)A Guideline on "*Plastic Immediate Packaging Materials*" of 2005



For solid active substances and solid dosage forms: the risk of interaction is low and generally does not require a content/container interaction study. Solid dosage forms intended for inhalation or parenteral use, e.g. lyophilised products, may need interaction studies between the packaging material and the components of the formulation.

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

MoC's FOR SVP-INJECTABLES - RUBBERS

What is rubber?

- An **elastic** material
- A **compounded** material
- Long Term Contact vs. Short Term Contact

- 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

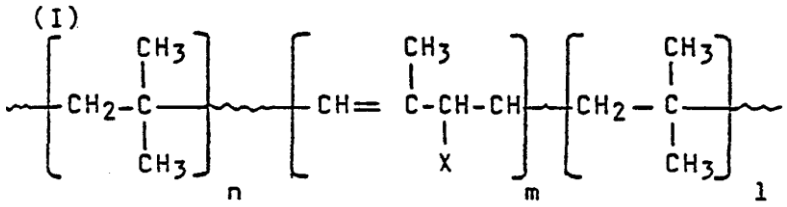
3. Cure system
4. Pigment
5. Other ingredients

MoC's FOR SVP-INJECTABLES - RUBBERS

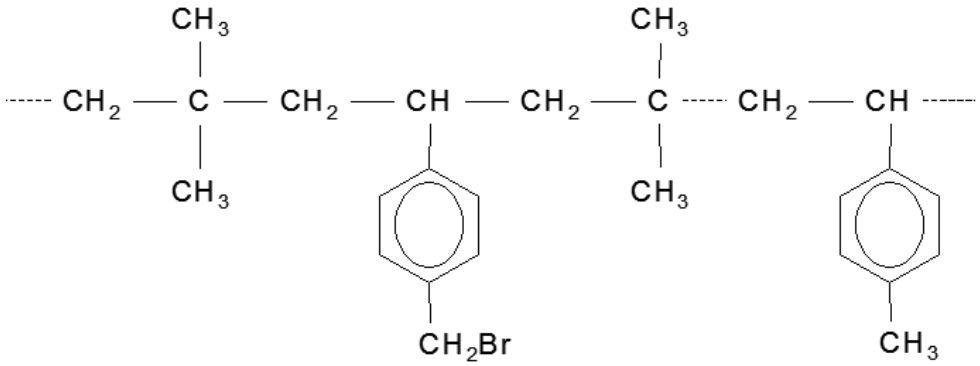
1. Elastomers

Halobutyl (**BromoButyl, ChloroButyl**)

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



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

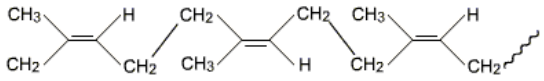


MoC's FOR SVP-INJECTABLES - RUBBERS

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

  → Better **against stickiness** in bulk

  → **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

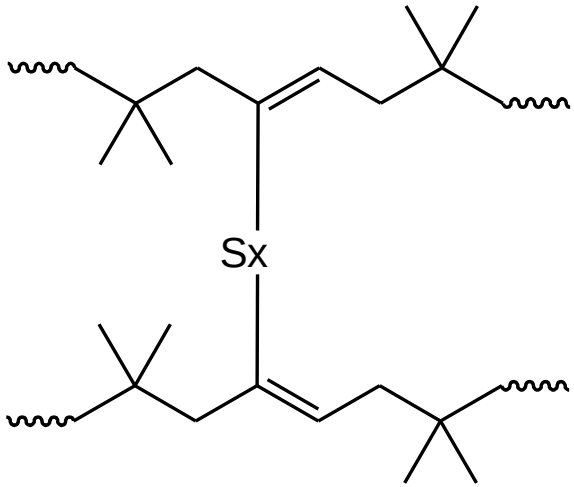
- **Cure system:**
  - –Crosslinking agent
  - –Activator : gives the onset of vulcanization
  - –Accelerator : speeds up the vulcanization
    - Easily extractable organic molecules such as thiurams, sulfonamides, thiazoles, ...

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

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

MoC's FOR SVP-INJECTABLES - RUBBERS

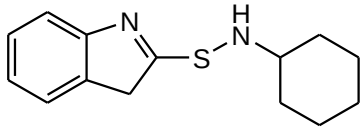
Rubber Curing / Vulcanization:



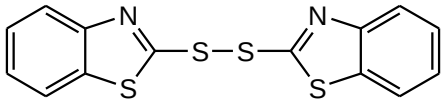
Rubber crosslinking requires S-Donors, activators, accelerators
Activator: ZnO / Stearic acid

MoC's FOR SVP-INJECTABLES - RUBBERS

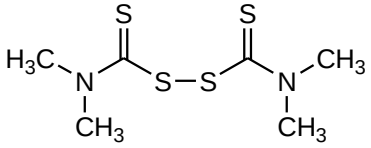
Older Rubber Curing Agents - Accelerators:



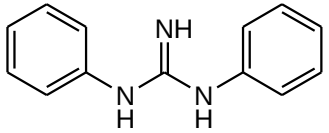
Cyclohexyl benzothiazole sulfenamide



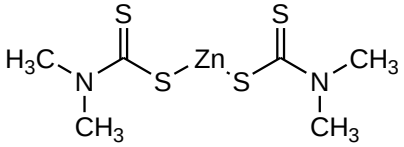
Mercaptobenzothiazole disulfide



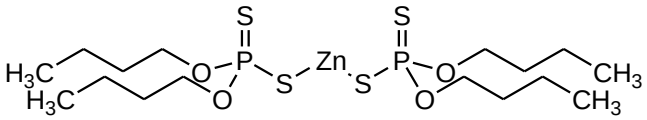
Tetramethylthiuram disulfide(TMTD)



Diphenyl guanidine



Zinc dimethyldithiocarbamate



Zinc dibutylphosphorodithiate

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

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

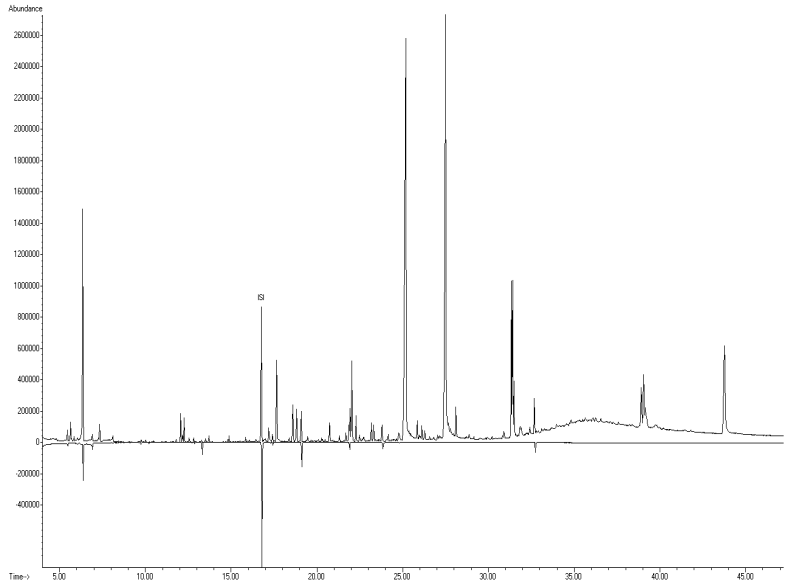
1. **INITIAL INGREDIENTS** OF THE RUBBER FORMULATION

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

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

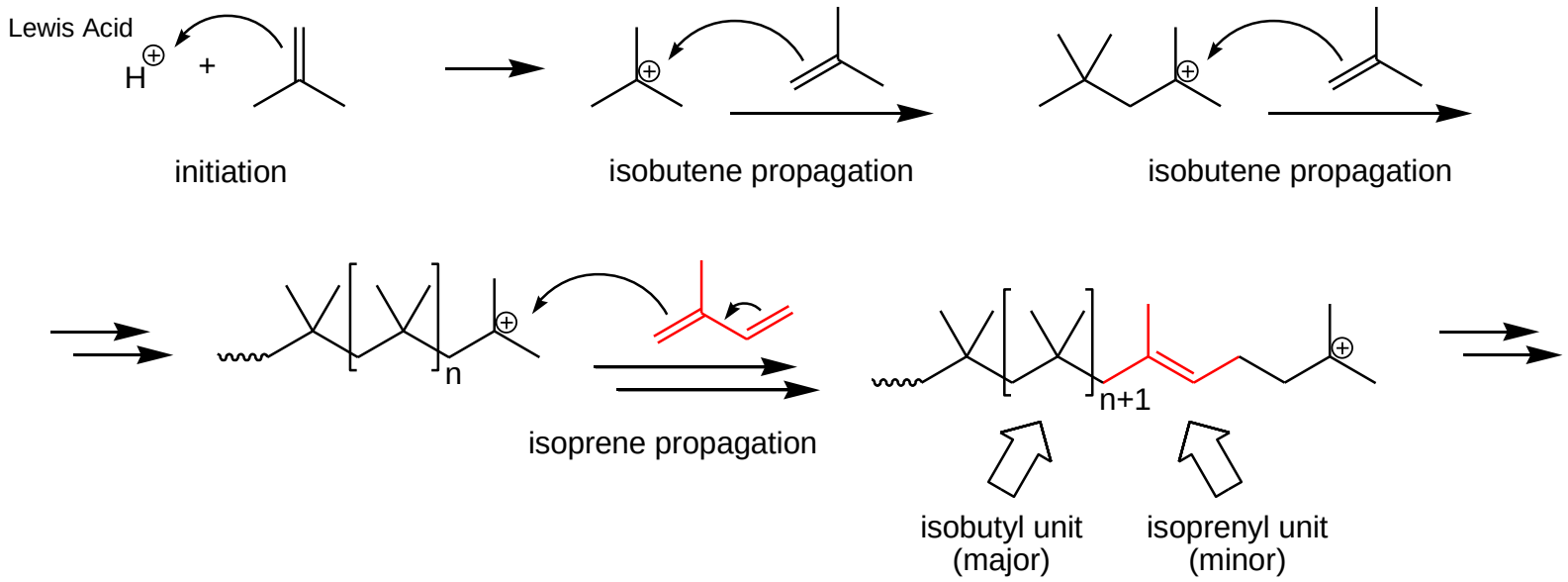


"OLD" RUBBER

"NEW" RUBBER

MoC's FOR SVP-INJECTABLES - RUBBERS

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

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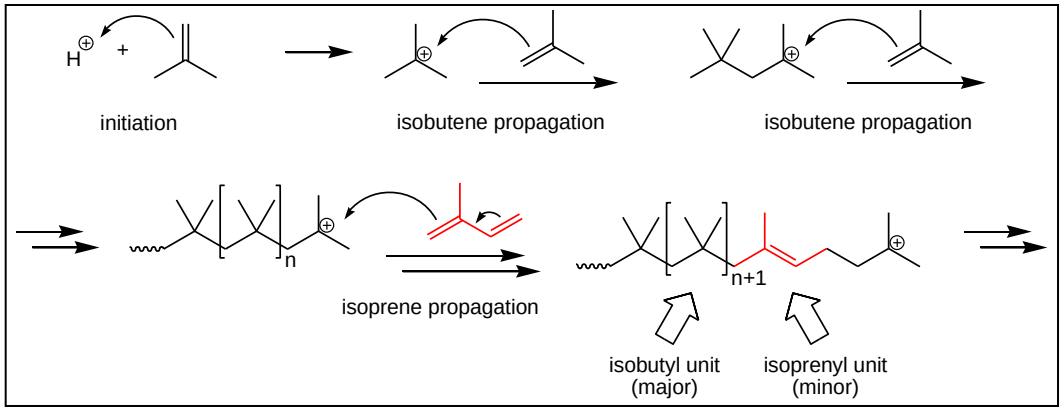


- *98 – 99 mol% is isobutylene*
- *1 – 2 mol% is isoprene*

*Means for **Butyl Elast(IIR)**(that approx. **per 100 C-C bonds** in the back bone, **1 is a double** (C=C) bond (if 2%)*
*Compared with **Polyisoprene**: **Per 100 C-C bonds** in the backbone, approx. **33 will be double** (C=C) bonds*

Less double bonds in IIR means:

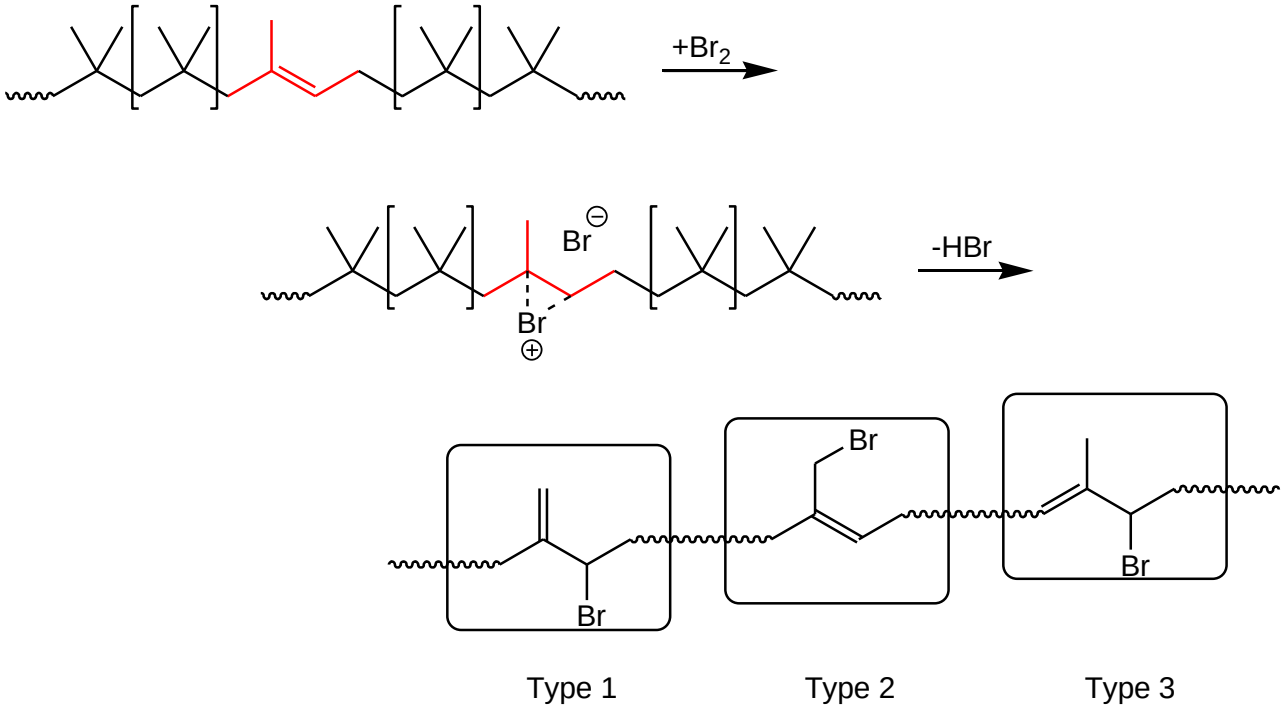
*Butyl Elastomer (IIR) is **less prone to Oxidation***

*Butyl Elastomer (IIR) needs an **more efficient cross linking reaction** compared to Polyisoprene*

Bromination of the backbone helps to address this (Br is a good leaving group)

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

COATED RUBBERS

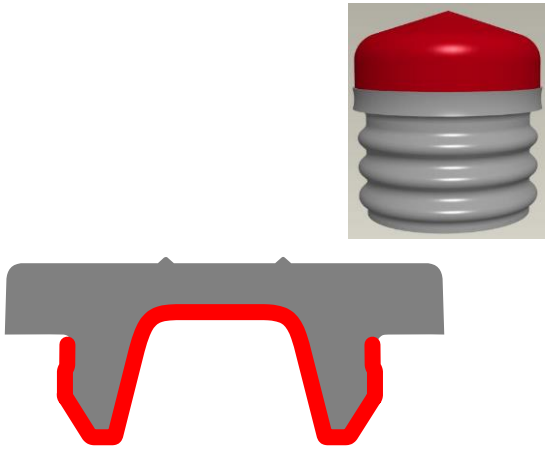
Significant step improvement in E&L terms are the coated closures.

Key attribute : barrier effect from the fluoropolymer !

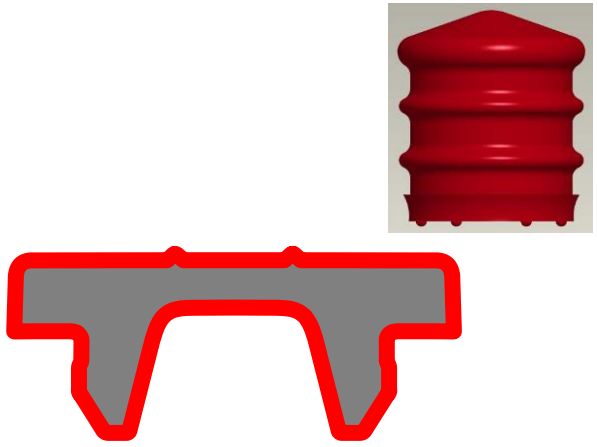
Simplified extractables profile

Improved compatibility with drugs/excipients

Film coating technology

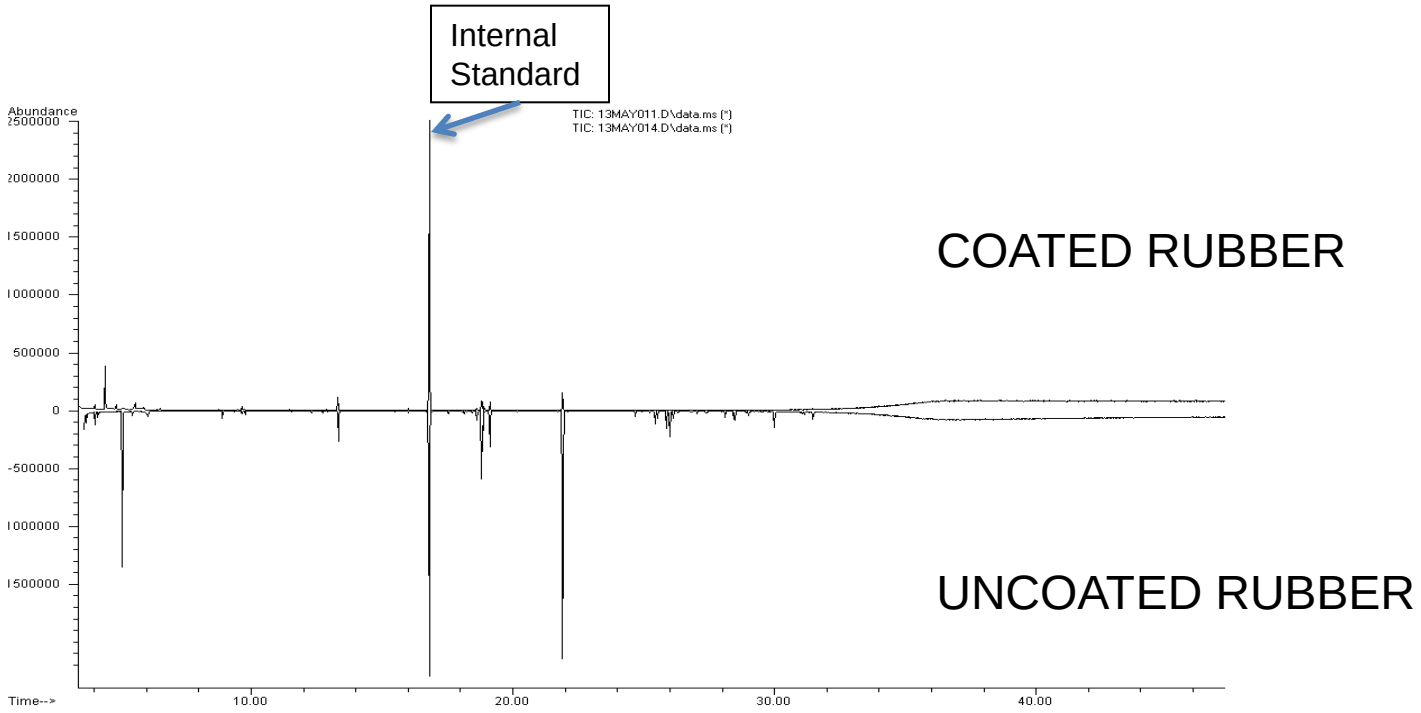


Spray coating technology



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*)



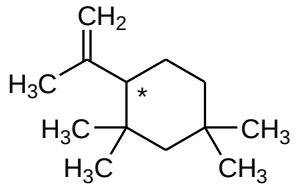
MoC's FOR SVP-INJECTABLES - RUBBERS

RUBBER OLIGOMERS:
MAY NEED MORE ATTENTION

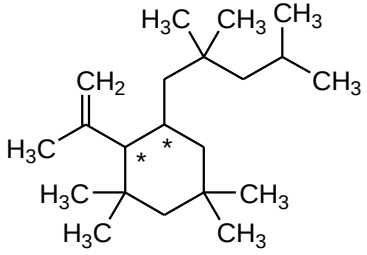
MoC's FOR SVP-INJECTABLES - RUBBERS

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

- Considered as
  - Cyclic aliphatic hydrobarbon 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.

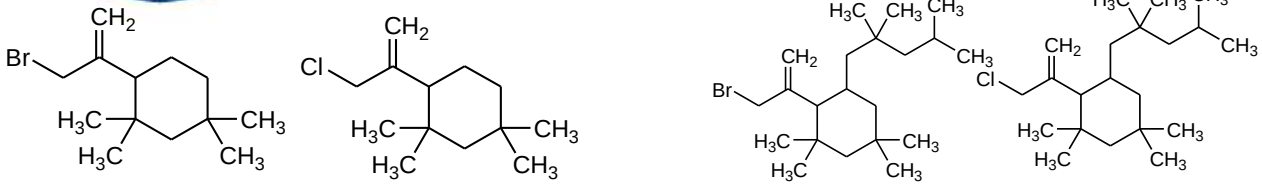


C13 oligomer



C21 oligomer

MoC's FOR SVP-INJECTABLES - RUBBERS



$C_{13}H_{23}Br$/ $C_{13}H_{23}Cl$ 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

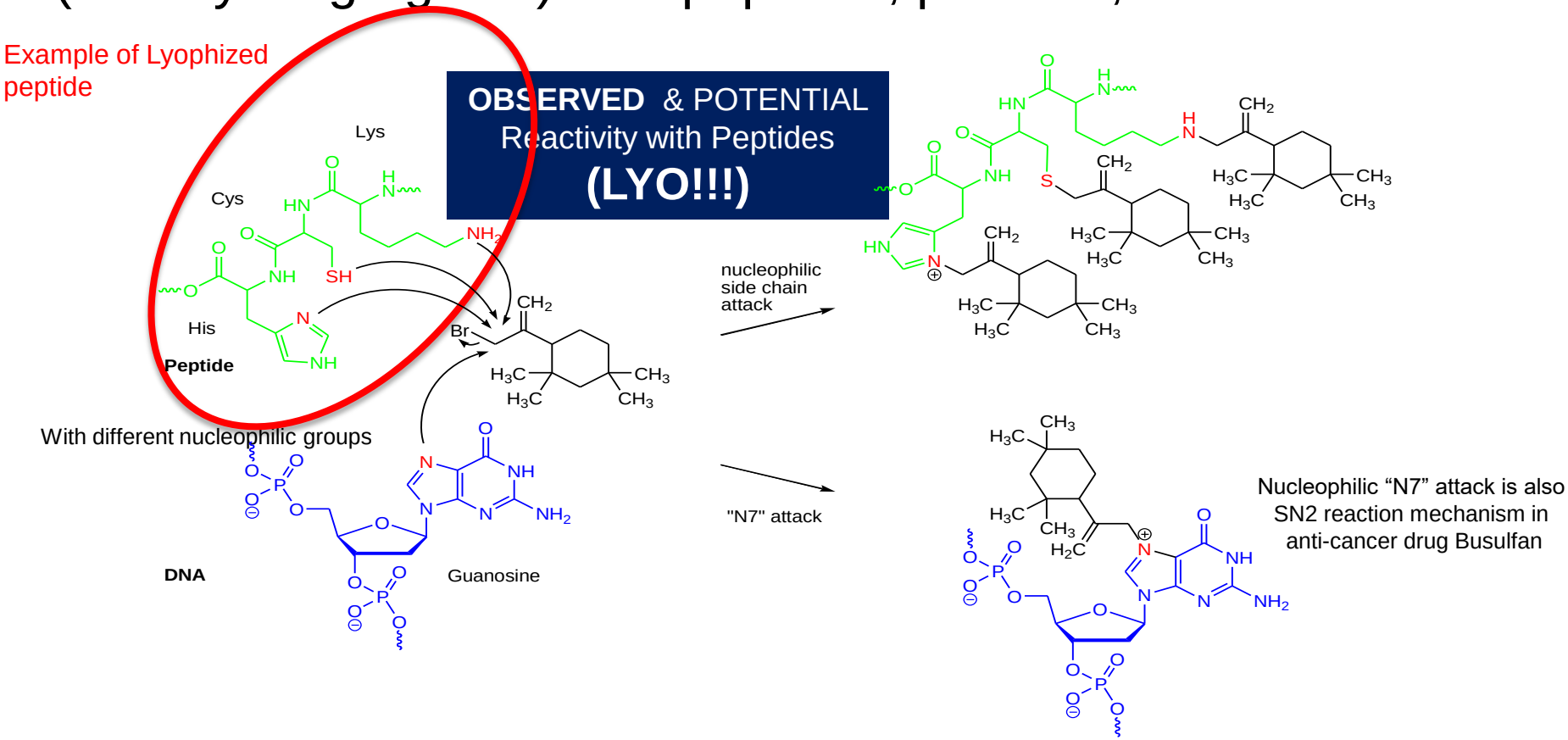
- Structure Activity Relationship (SAR) Assessment:

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

MoC's FOR SVP-INJECTABLES - RUBBERS

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



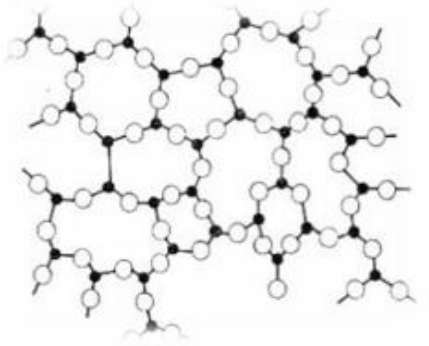
Glass

&

Glass Related Issues

Vials, Prefilled Syringes, Cartridges

Glass as Vial/Barrel Material



- SiO_2 is the backbone structure
- CaO increases the hardness and chemical resistance
- Al_2O_3 increases the chemical resistance
- Na_2O, B_2O_3 lowers the melting point
- COLOURED Glass:
  - *Fe_2O_3, TiO_2: amber glass*
  - *CuO: Blue Glass*
  - *Mn^{3+}: Violet*

MoC's FOR SVP-INJECTABLES - GLASS

Glass as Vial/Barrel Material

MAJOR EXTRACTABLES FROM GLASS:

- *Alkali release (e.g. Na_2O) impacted by contact time, temperature, sterilization*
- *Silica release (Si_2O) impacted by contact time, pH (alkaline!) temperature, sterilization*

MINOR EXTRACTABLES FROM GLASS:

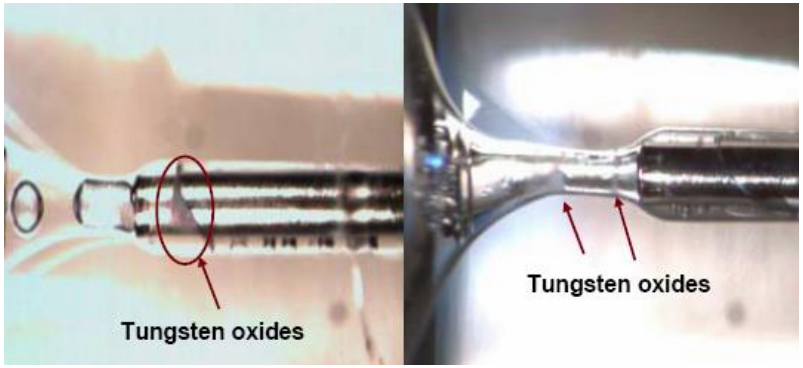
- *K (K_2O), B (B_2O_3), Ca (CaO), Al (Al_2O_3) more in Alkaline environment!*

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)

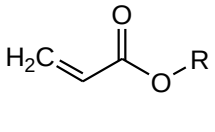
MoC's FOR SVP-INJECTABLES - GLASS

Glass as Barrel Material – Related Compounds

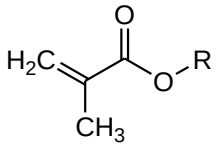
EXTRACTABLES RELATED TO GLASS BARRELS:

GLUE RESIDUES

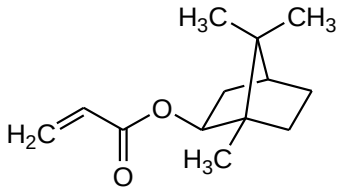
Base Polymer



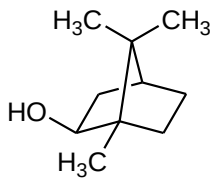
Acrylate



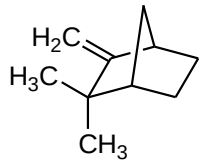
Methacrylate



Isobornyl acrylate

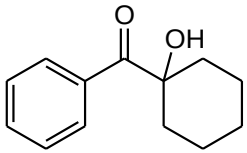


Isoborneol

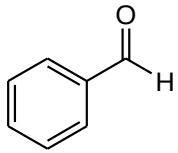


Camphene

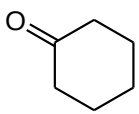
UV curing / activation



Irgacure 184



Benzaldehyde



Cyclohexanone

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

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!

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."

SECONDARY PACKAGING

- **Label**
  - Adhesive
  - paper
  - Ink
  - Varnish

Typical extractable compounds:

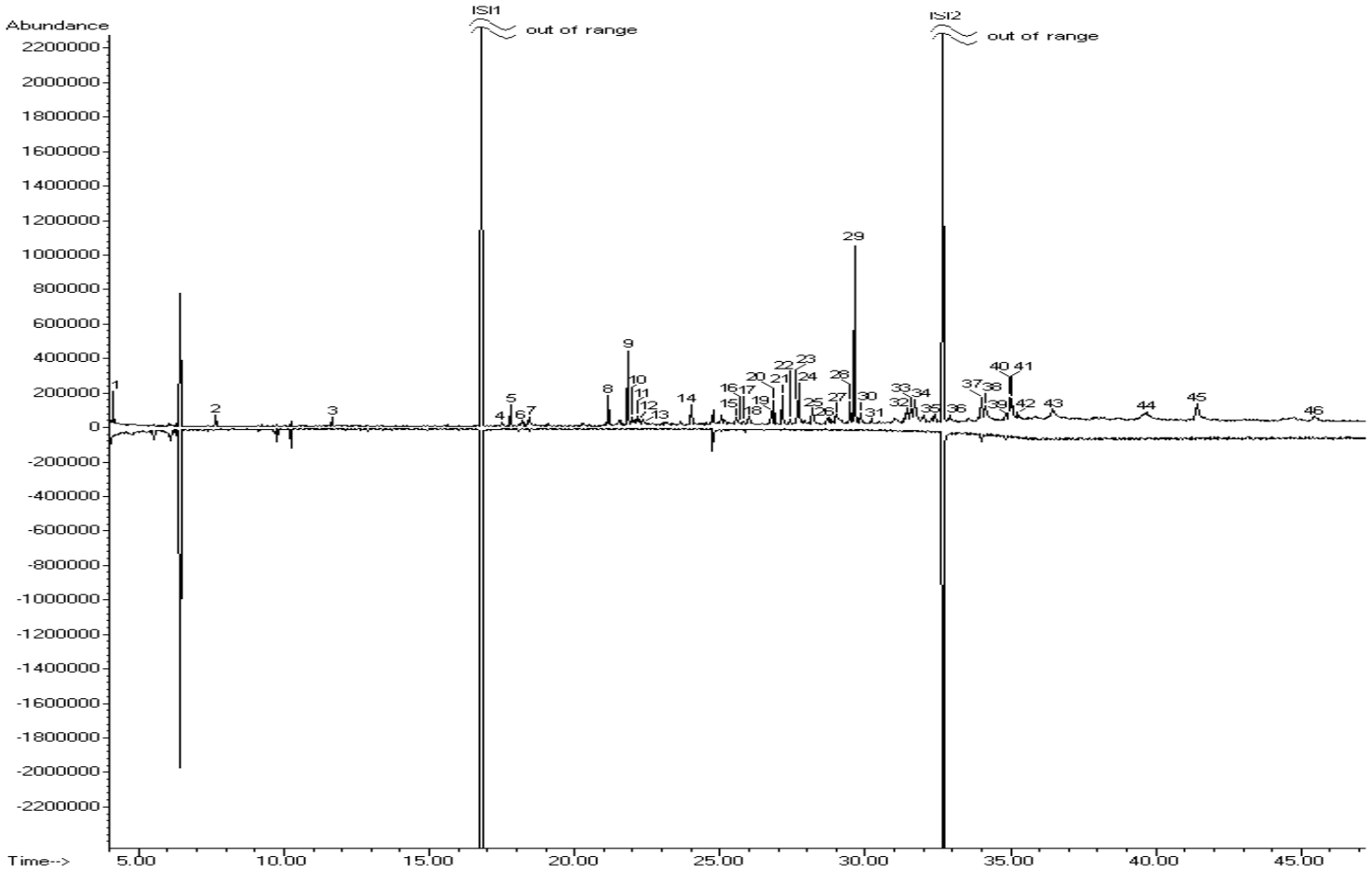
Curing agents (e.g. Benzophenone, Irgacure 184,...)

Solvent residues (e.g.Toluene, acetone)

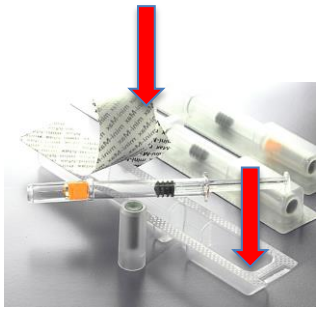
Adhesive residues (e.g. Acrylates)

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

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



SECONDARY PACKAGING



➢ Overwrap/Overpouch/Blister

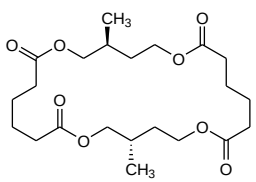
(to compensate for potential lower barrier properties of the Polymer)

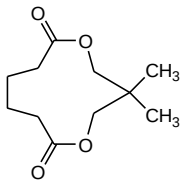
- ➢ Multilayer System
- ➢ Aluminum as barrier layer
- ➢ Tie-layers to keep the different layers together

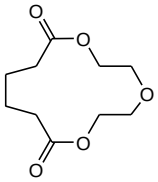
Typical extractable compounds:

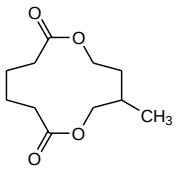
Bislactone Compounds from Tie-layer

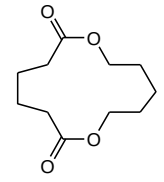
Residues from other layers (depends largely on selected materials of the multilayer!!)

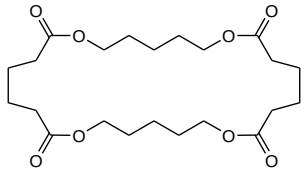


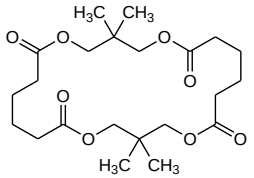


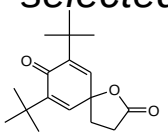


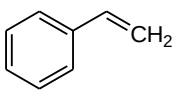


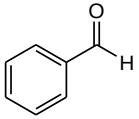


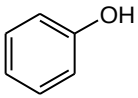












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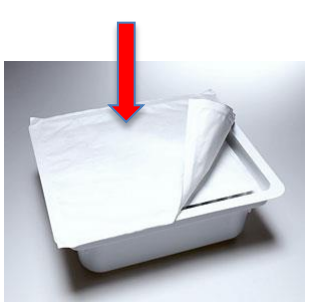
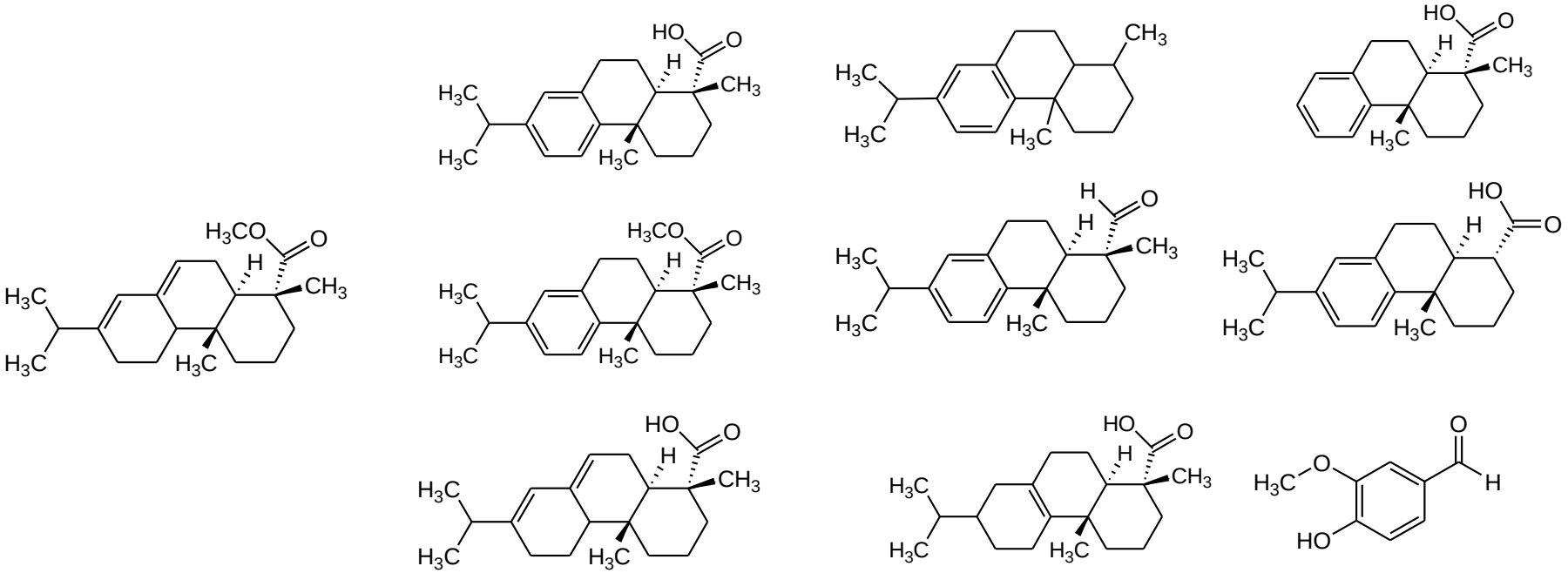
SECONDARYY PACKAGING



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

Example Structures of abietic acids / abietates (& Vanillin)



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

3. Container/Closures for SVP's

1.Vials:

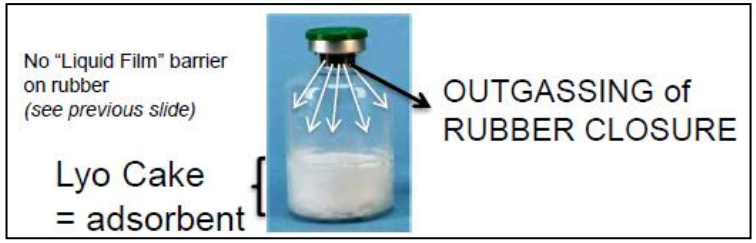
3. Container/Closures for SVP's

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"...

3. 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 (see case study): also potential Performance & Quality Issue!
    - ✓ Also NVOC, Metals and Ions need to be "checked off", because of short term contact with Reconstituted DP.

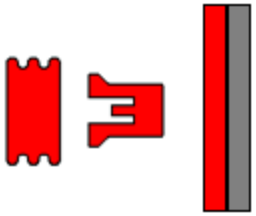
3. Container/Closures for SVP's

2. Pre-Filled Syringe:

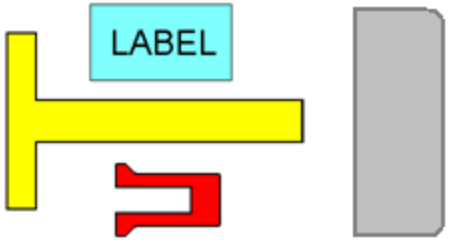
3. Container/Closures for SVP's

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, ...

3. 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

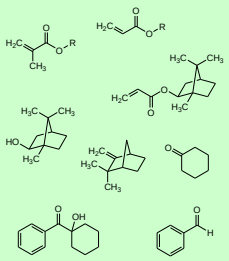
- **Rubber Plunger** ***(very similar to rubber stopper for vial):***
  - ✓ Typically, higher migration when solution is <u>in contact</u>
  - ✓ Migration will be determined by:
    - Solubility of leachables in **Drug Product** Solution
    - Potential **Diffusion of Compounds through rubber**, into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

3. 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 (see case study): also potential Performance & Quality Issue!
  - Typically **No NVOC, Metals and Ions** investigation is necessary for a Needle Shield.

3. 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

3. Container/Closures for SVP's

3. Cartridges

3. 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. Container/Closures for SVP's

Cartridges

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

3. Container/Closures for SVP's

4. Administration of Reconstituted Drug Product:

Disposable Syringe

IV-Bag System
(+Administration Set)

Pump System

SEE CASE STUDY LATER

3. Container/Closures for SVP's

Disposable Syringe for reconstitution
(in case of vial container for reconstitution solution)

- **Short Term Contact** between Reconstitution Solution and Disposable Syringe
- Disposable Syringe is considered as **Medical Device**, should comply with ISO10993 for external communication devices
- Check off the **impact of the reconsitution procedure** (using the disposable syringe) **on the impurities profile** of the drug product (*see case study 2 for similar device (administration set)).*
- ***"In Use" Stability Studies may be required***

3. Container/Closures for SVP's

Container for Administration of Reconstituted Drug Product

- If the Container for Aministration (e.g. Disposable Syringe, IV bag, Pump) falls under one of the definitions of a **COMBINATION PRODUCT** :

  - (Medical Device Regulation: Biocompatibility for external communicating Devices (ISO *10993))*
  - **Suggestion: Perform a Simulation Study** (instead of an EXT Study)
    - Using **Simulants** (e.g. XX% EtOH /WFI mixture) instead of DP as an alternative (allows analytical screening).
    - This way, the **whole device** can be tested as one (not separate parts of device) = reducing efforts
    - **Define a worst case condition**, compared to the actual contact during administration
      - ✓ Length of contact, Temperature
      - ✓ Static versus dynamic
      - ✓ Simulant Composition (organic composition, pH,...)

3. Container/Closures for SVP's

For Containers/Closures having LONG TERM EXPOSURE to either the Lyo Cake or the Reconstitution Solution

- *Vial with Rubber Closure (Lyo Cake)*
- *Vial with Rubber Closure (Reconsitution Solution)*
- *Pre-Filled Syringe (Reconstitution Solution)*

FULL LEACHABLE STUDY

- ***Long Term*** Ageing Conditions
- ***Accelerated*** Ageing Conditions can be considered, in support of LT Ageing
- ***Monitoring Concentrations*** of target compounds from EXT study, after an initial toxicological/risk assessment (if using a threshold approach, see part 6)
- At different ***time points***
- ***Quantitative*** Methods (Validation) to quantify the compounds in DP
- ***Screening*** Methods (semi-quantitative), to pick up unexpected leachables

Leachables Study Design

For Containers/Closures having SHORT TERM EXPOSURE to either the Reconstitution or Reconstituted Solution

- Disposable Syringe for Reconstitution Solution
- IV-Bag for Administration
- Pump for Administration
- Disposable Syringe for Administration

LIMITED LEACHABLE STUDY

In addition to the "Short Term Stability" Study for the DP

At least, check of the following:

- Impact of reconstitution / administration procedure on the impurities profile of DP.
- *When the results of an extraction study, performed on these items, shows the potential release of Toxic Compounds: Monitoring Concentrations* of target compounds, after initial risk assessment.
- Procedure needs to be verified at least one, preferably 2x (beginning and end of storage => ageing of device)
- In a lot of cases, *Screening* Methods (semi-quantitative), will be sufficient to assess leachables from disposable/administration systems (however, not always!)

Case Study

CASE STUDY:

Leachable Study on Reconsituted Lyo DP after Administration Procedure

Drug Product: Lyo, Stored in Vial with Rubber Stopper
Reconstitution: Performed in Hospital/Lab with 0.9% NaCl (no comb. product)
Administration: I.V. Bag + Administration Set

Purpose of Study:

- Impact of Rubber Closure on **Leachable Profile of Lyo Powder** (long term)
- Impact of Length of **Storage of reconstituted DP in I.V.-Bag** (short term)
  - **1 Day** storage in Bag at **5°C** *versus* **1 Day** Storage in Bag at **25°C**
  - **1 Day** storage in Bag at **25°C** *versus* **2 Day** Storage in Bag at **25°C**
  - **2 Day** storage in Bag at **25°C** *versus* **3 Day** Storage in Bag at **25°C**
  - **3 Day** storage in Bag at **25°C** *versus* **8 Day** Storage in Bag at **5°C** + 2 days at **25°C**

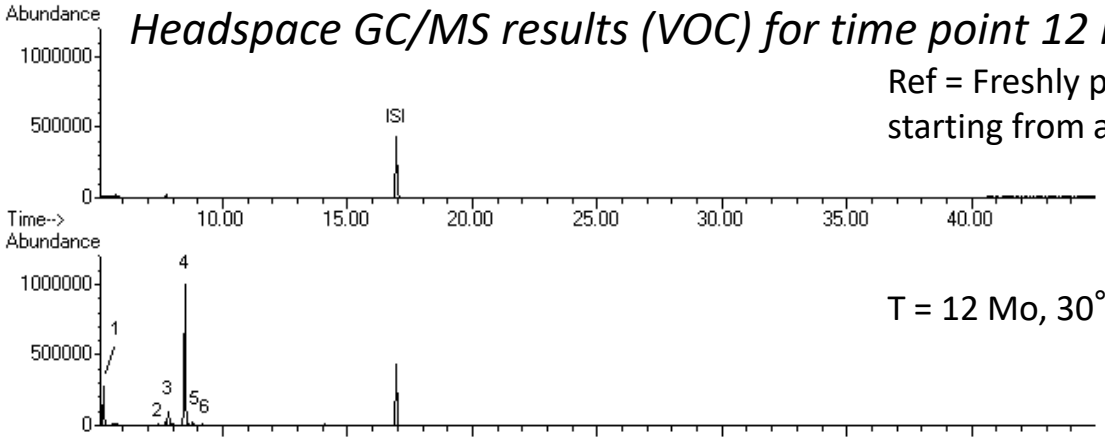
➢Allows to define the Worst Case condition

- Impact of the I.V. Set on Leachable Profile during Administration (short term)

Case Study

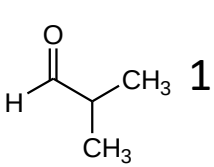
1. Drug Product: Lyo DP, Stored in Vial with Rubber Stopper

Headspace GC/MS results (VOC) for time point 12 Mo

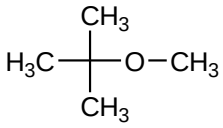


Ref = Freshly prepd lyo soln, starting from all ingredients

T = 12 Mo, 30° C, 75%RH



1



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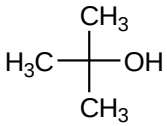

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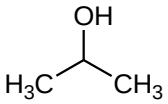

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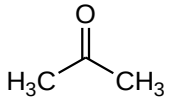

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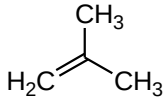
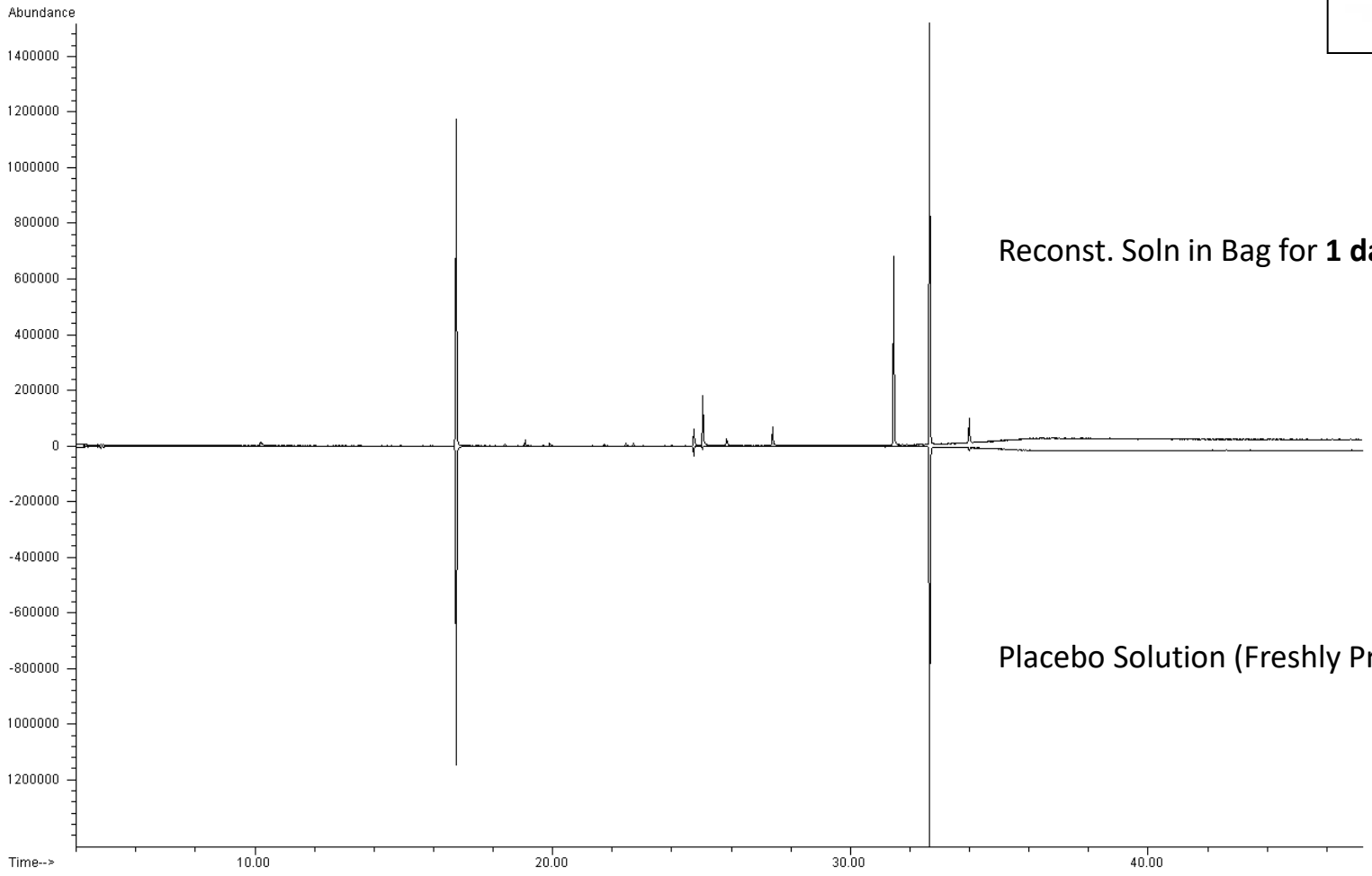


6

No S-VOC (GC/MS) and N-VOC (LC/MS) were detected

Case Study

2. Administration: I.V. Bag

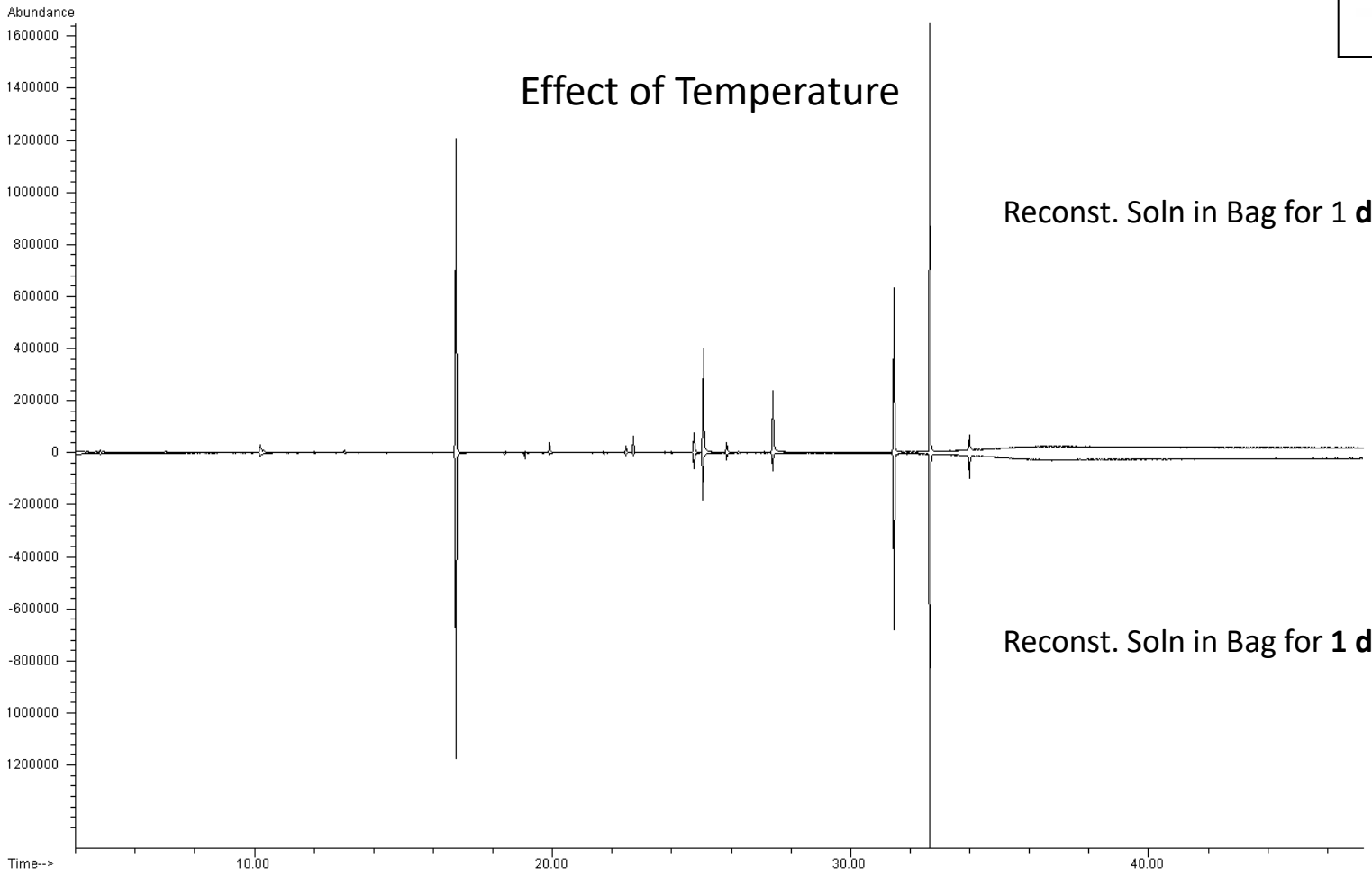


Reconst. Soln in Bag for **1 day** at **5° C**

Placebo Solution (Freshly Prepared)

Case Study

2. Administration: I.V. Bag



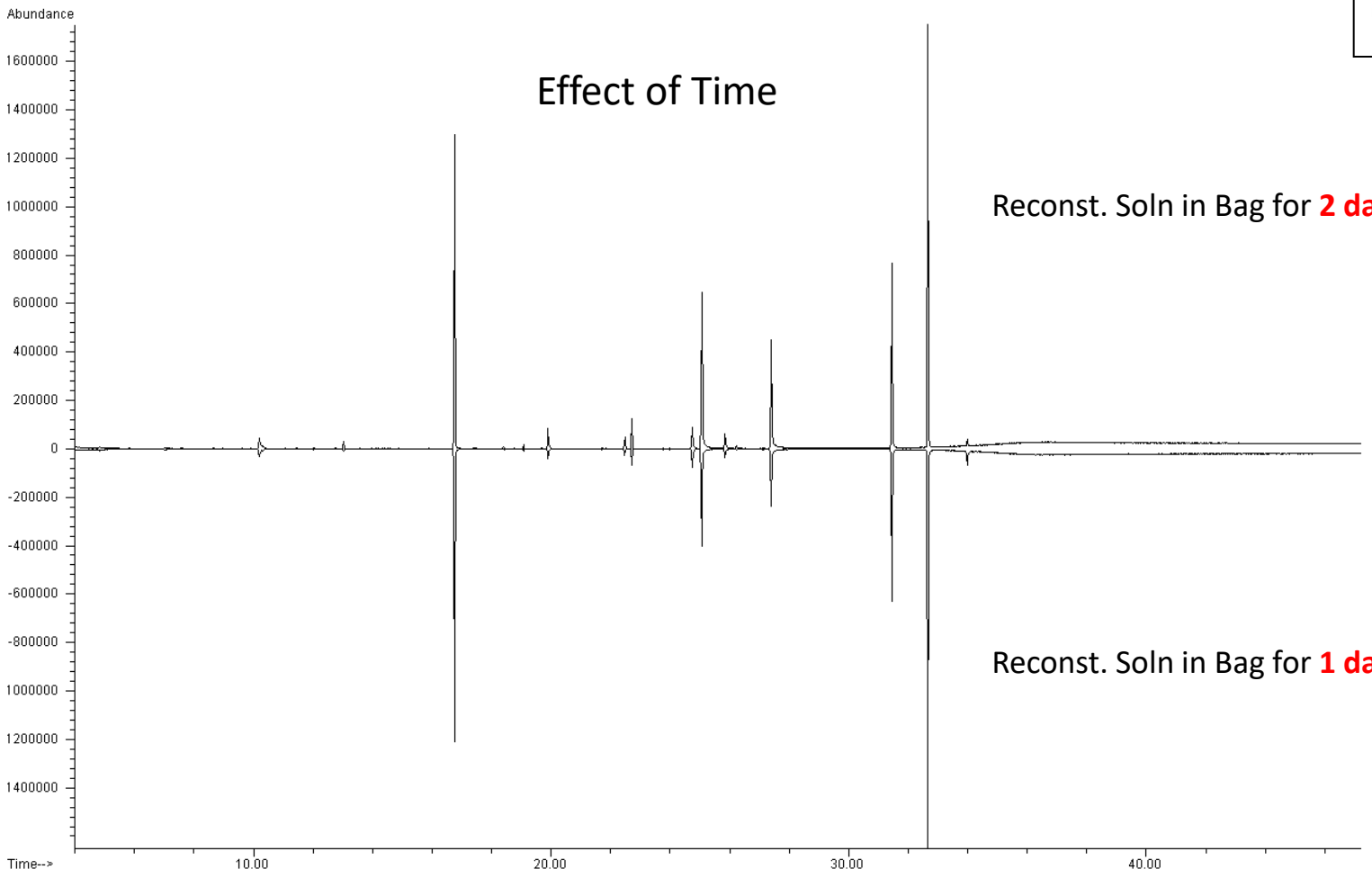
Effect of Temperature

Reconst. Soln in Bag for 1 **day** at **25° C**

Reconst. Soln in Bag for **1 day** at **5° C**

Case Study

2. Administration: I.V. Bag



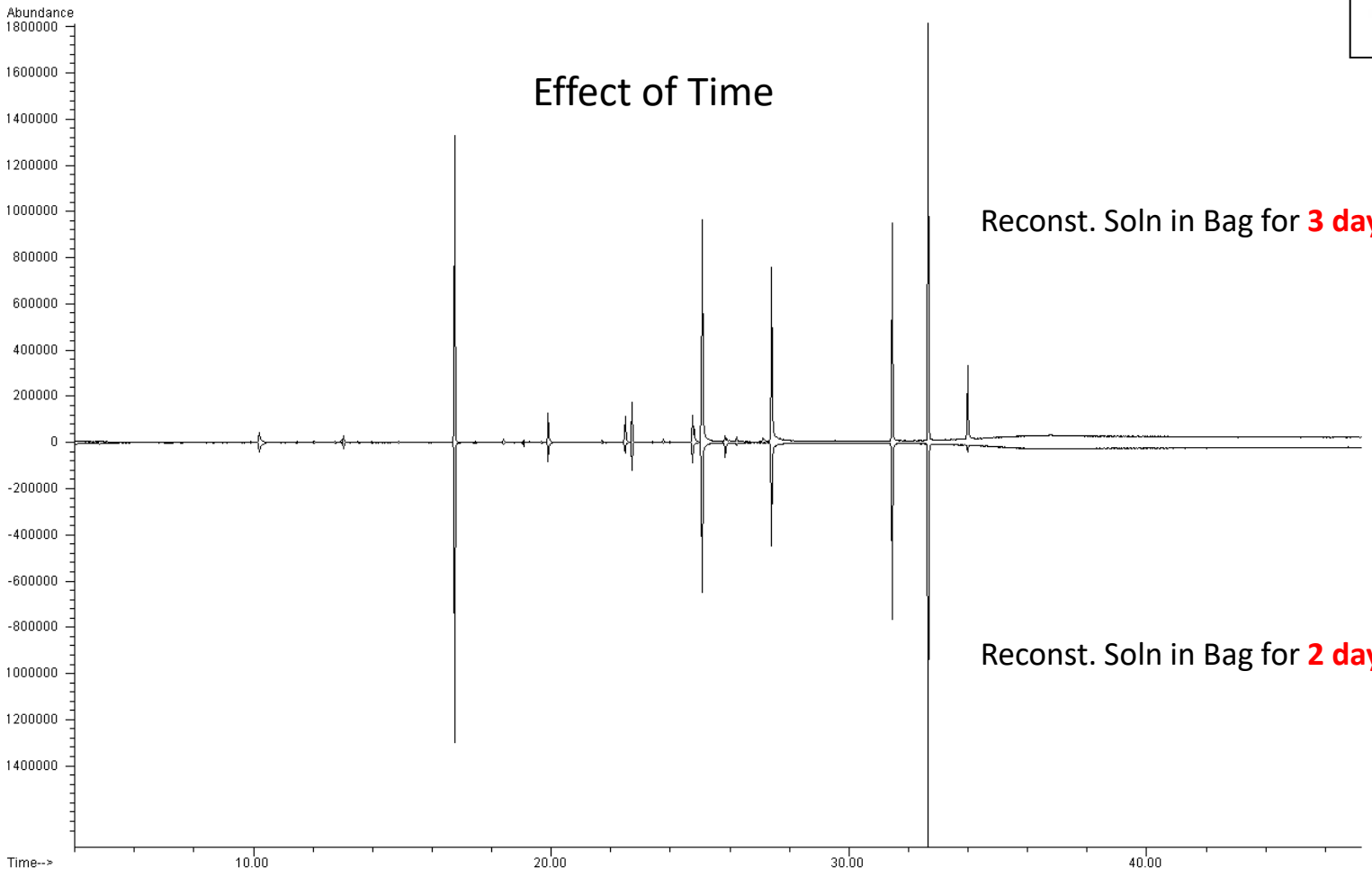
Effect of Time

Reconst. Soln in Bag for **2 days** at **25° C**

Reconst. Soln in Bag for **1 day** at **25° C**

Case Study

2. **Administration**: I.V. Bag



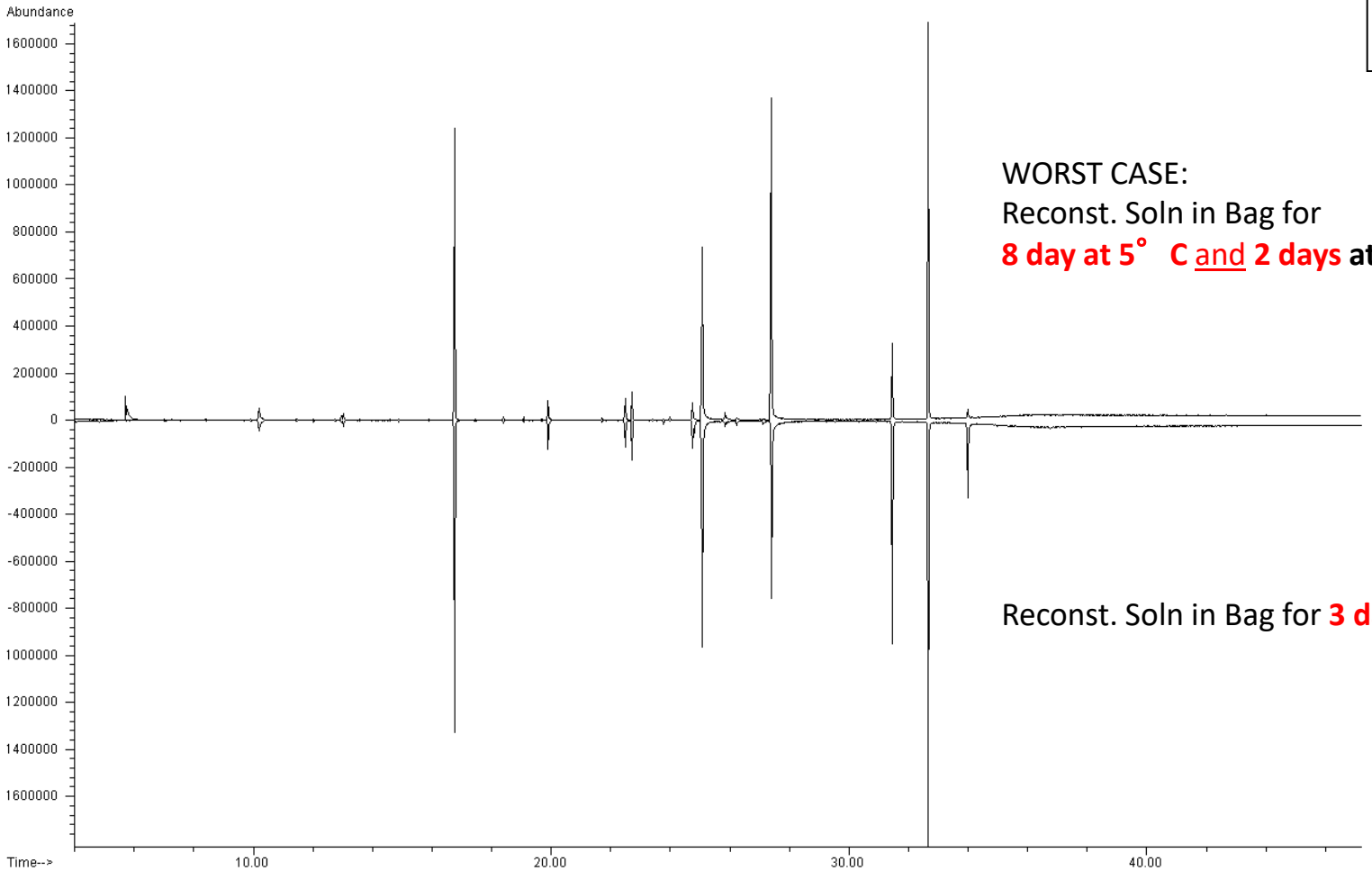
Effect of Time

Reconst. Soln in Bag for **3 days** at **25° C**

Reconst. Soln in Bag for **2 days** at **25° C**

Case Study

2. **Administration**: I.V. Bag

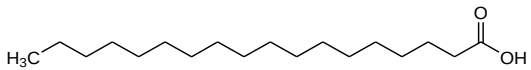


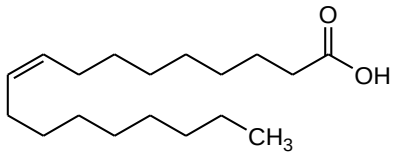
WORST CASE:
Reconst. Soln in Bag for
8 day at 5° C and **2 days at 25° C**

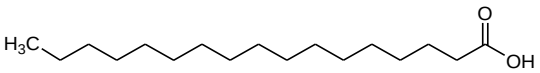
Reconst. Soln in Bag for **3 days** at **25° C**

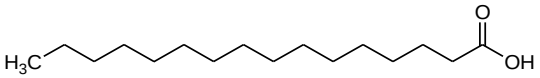
For most compounds, highest concentrations found in 3days at 25° C!!

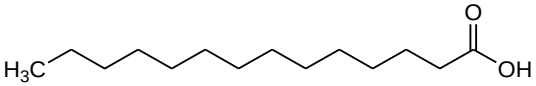
Case Study

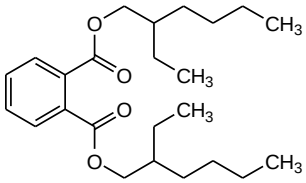

H3C
O
OH

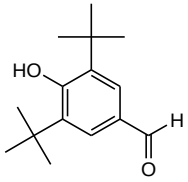

O
OH
CH3

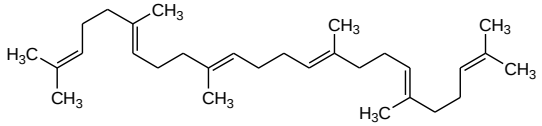

H3C
O
OH

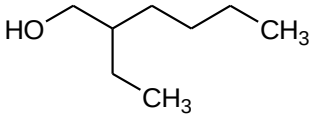

H3C
O
OH


H3C
O
OH


O
O
CH3
CH3
O
O
CH3
CH3


HO
H
O

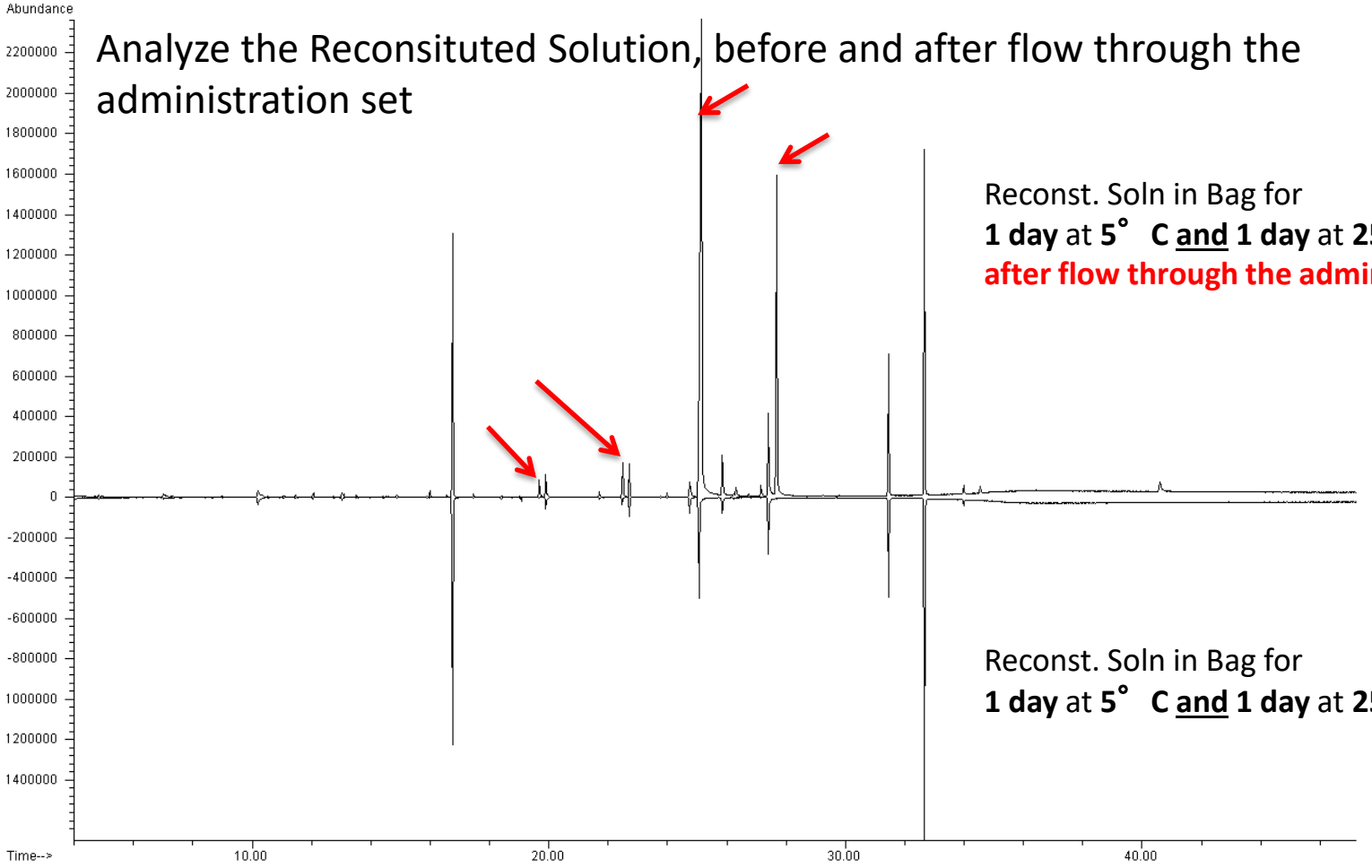

H3C
CH3
CH3
CH3
CH3
CH3
CH3
CH3
H3C


HO
CH3
CH3

Case Study

3. **Administration**: Contribution of Administration Set

Analyze the Reconsituted Solution, before and after flow through the administration set

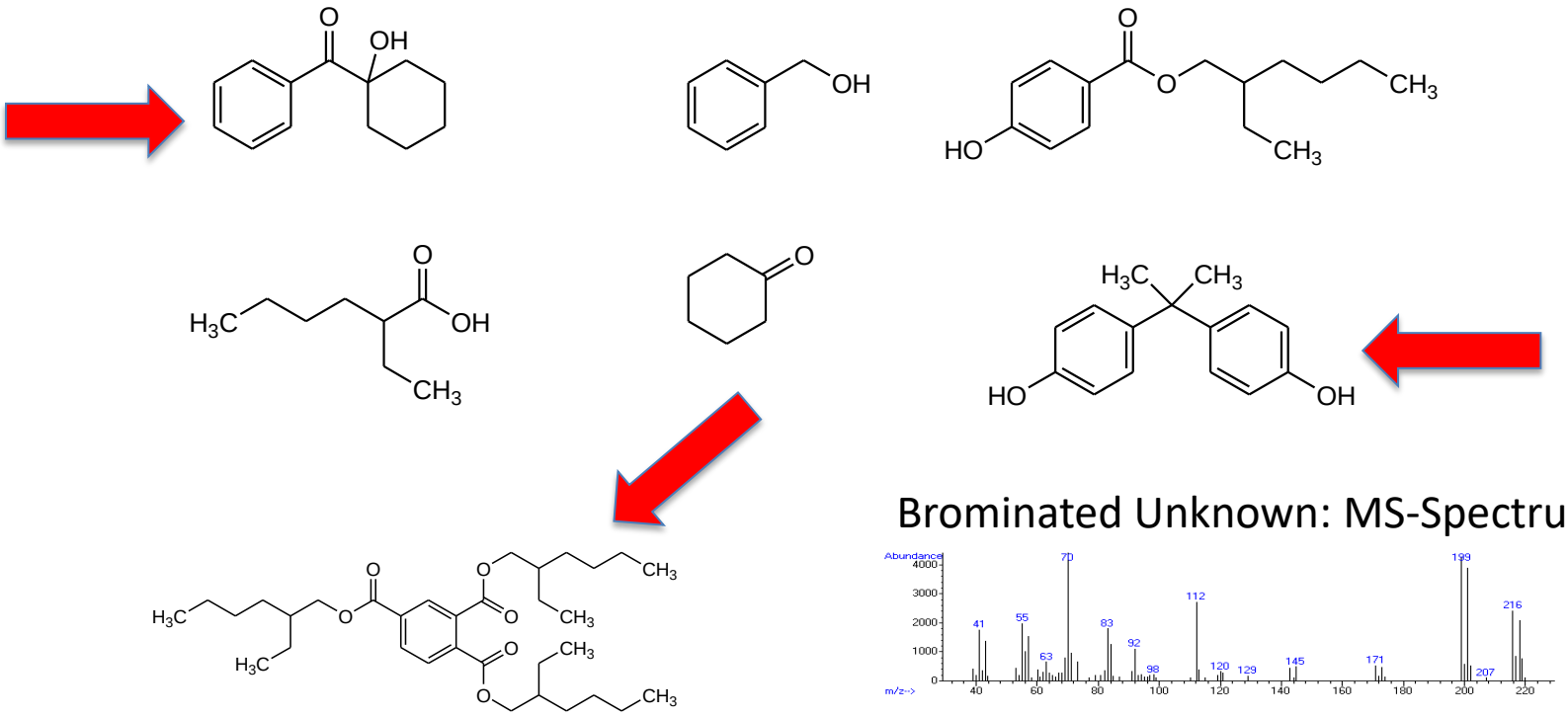


Reconst. Soln in Bag for
1 day at **5° C** **and** **1 day** at **25° C**
after flow through the administration set

Reconst. Soln in Bag for
1 day at **5° C** **and** **1 day** at **25° C**

Case Study

3. Administration: Contribution of Administration Set



Brominated Unknown: MS-Spectrum

ANY QUESTIONS?