Connecting People, Science and Regulation

EXTRACTABLES & LEACHABLES FOR INJECTABLES

PDA Post-Conference E/L-Workshop
14 March, 2014

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Toxikon Europe NV

Content

1. Introduction – Regulatory Requirements
2. Types of Elastomeric Closures
3. Rubber Oligomers
4. Designing Extractable Studies for Elastomeric Closures
5. Designing Leachable Studies
6. The PQRI-PODP Threshold Approach
7. Conclusion

1. INTRODUCTION:

DEFINITIONS & REGULATORY REQUIREMENTS

1. Introduction

What is Extractables /Leachables testing?

Determining the Interactions between Pharmaceutical Containers and Drug Products

Can have an impact on:

- Drug Product Efficacy
- Drug Product Safety
- Drug Product Compatibility

For Primary Packaging

For Materials in (Bio)Pharma Production

1. Introduction

REGULATORY ASPECTS – PARENTERALS – NON-LIMITATIVE LIST

<1999: 21CFR 211.94(a) "DRUG PRODUCT CONTAINERS AND CLOSURES"
...not reactive, additive, absorptive to alter
safety, identity, strength, quality or purity of drug...

1999: "CONTAINER/CLOSURE SYSTEMS FOR PACKAGING HUMAN DRUGS AND BIOLOGICS" (FDA-Guidance for Industry)

2003: EU COMMISSION DIRECTIVE 2003/63/EC, (§ 3.2.2.2 g)

- *CCS-information is part of the Market Authorization dossier.*

2005: "GUIDELINE ON PLASTIC IMMEDIATE PACKAGING MATERIALS" (EMEA Guideline)

- *Contains "Decision Tree" for different dosage forms*

2006: ICH Q8 "PHARMACEUTICAL DEVELOPMENT", §2.4 CCS

2006: "PQRI Safety Thresholds and Best Practices for E/L in OINDP's"

- *First technical recommendations for E/L-studies!*
- *Threshold concept!!*

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- *Threshold concept – has been expanded to PODP!*

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Table 1
Examples of Packaging Concerns for Common Classes of Drug Products

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

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LIKELIHOOD OF INTERACTION = HIGH

Packaging Component - Dosage Form

DEGREE OF CONCERN

FOR **ROUTE OF ADMINISTRATION = HIGH**

THEN: 1. CERTIFICATE OF ANALYSIS

- COMPENDIAL testing
- ROUTINE QC testing

2. ADDITIONAL EXTRACTABLES/LEACHABLES DATA

e.g. Inhalation Aerosols (MDI, DPI, Nasal Sprays), Injections, Injectable suspensions (Parenterals : Pre-filled syringes, IV bags…), Ophtalmic solutions/suspensions…

1. Introduction

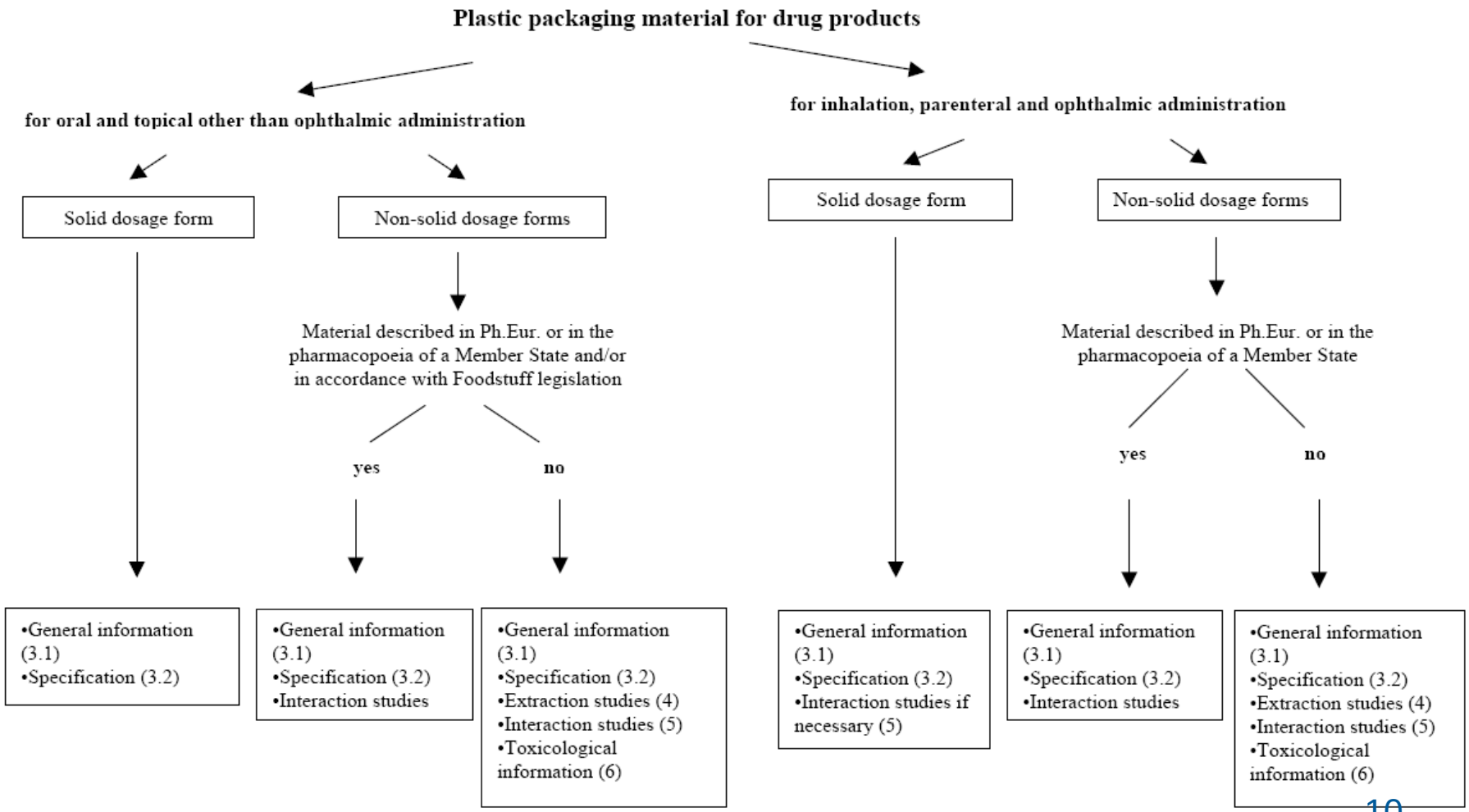
REMARK:

THE REQUIREMENTS FOR DOCUMENTATION, SPECIFIED IN THE *1999 CONTAINER/CLOSURE GUIDANCE* DOCUMENT **DO NOT REFLECT THE ACTUAL POSITION OF THE FDA** WITH REGARD TO THE TESTING AND DOCUMENTATION NEEDED FOR THE CCS

PUT MORE FOCUS ON LEACHABLE TESTING!

2005: "GUIDELINE ON PLASTIC IMMEDIATE PACKAGING MATERIALS" (EMEA Guideline)

- *"**Decision Tree**" what information to provide for different dosage forms*

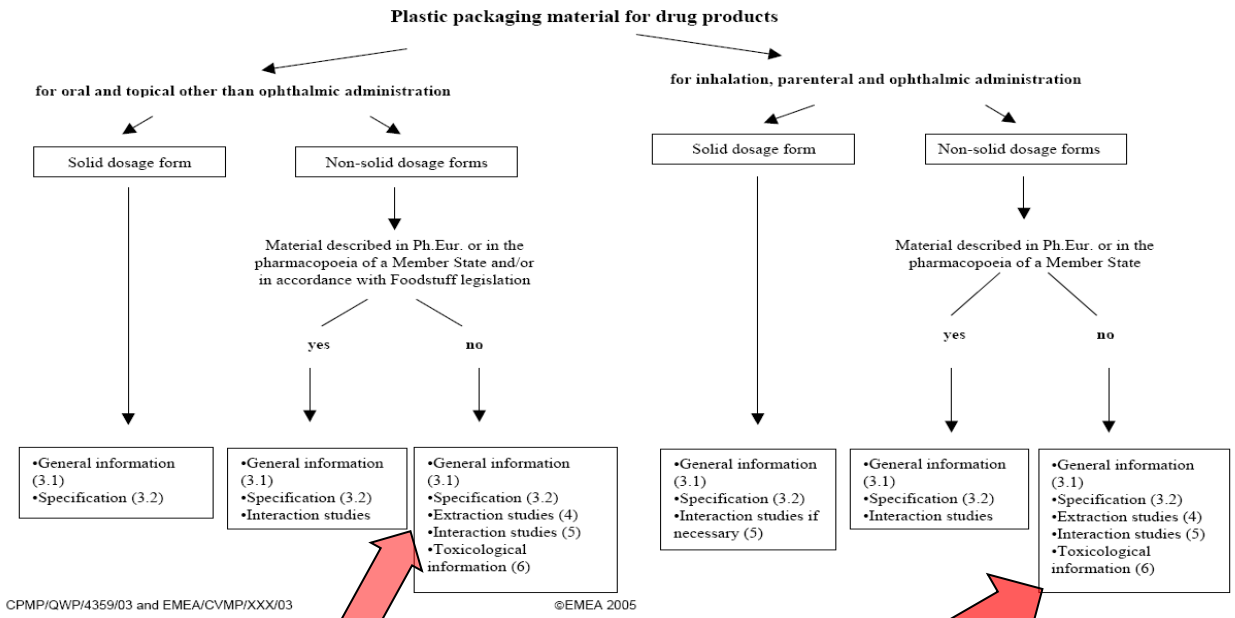


CPMP/QWP/4359/03 and EMEA/CVMP/XXX/03

©EMEA 2005

"OTHER" DOSAGE FORMS:

LIKELIHOOD OF **INTERACTION** IS **HIGH**



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

ADDITIONAL REQUIREMENTS

1. **EUROPEAN PHARMACOPOEIA TESTS**
2. **EXTRACTION STUDIES**
3. **INTERACTION STUDIES (INCLUDING §5.1 MIGRATION STUDIES)**

1. Introduction

Some Side Notes to the EMA Immediate Packaging Guideline (2005)

- Not for Elastomers (?) = > In reality: **ALSO** fo rubbers

- If a Material is described in the E.P. And if it complies with the specifications therein, no Extractable testing may be needed.
  NOT THE ACTUAL POSITION OF EUROPEAN REGULATORS

- If Extractable Testing shows only compounds with low risk (at low concentrations) no leachable study is necessary.
  NOT THE ACTUAL POSITION OF EUROPEAN REGULATORS

2. TYPES OF ELASTOMERIC CLOSURES

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1. Vial With Rubber Stopper:

- Glass Vial
- Rubber Stopper
- Dual Chamber Vial/Syringe

2. TYPES OF ELASTOMERIC CLOSURES

2. Pre-Filled Syringes (from Elastomeric Closure point of view):

Pre-Filled Syringe

Needle Shields

Tip Caps

Rubber Plungers/Pistons

2. TYPES OF ELASTOMERIC CLOSURES

3. Cartridges:

Sealing disks

Rubber Plunger

4. Ports:

IV-Bag System

2. TYPES OF ELASTOMERIC CLOSURES

Each Container/Closure & Admininistration system has **different impact** on **safety** and **quality** of DP

Is **reflected in potential different approaches** for each system in both
Extractable & Leachable Studies!

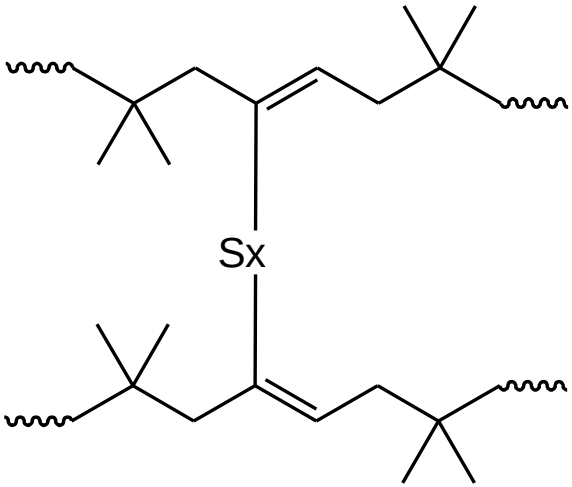
Rubber Sealings

Types of rubbers:

Natural rubber (Latex) ***(needle shields)***
Synthetic (polyisoprene) rubbers ***(Needle shields, tip caps)***
Butyl rubber ***(PFS-plungers)***
Chlorobutyl rubber ***(PFS-plungers)***
Bromobutyl rubber ***(PFS-plungers)***
Styrene Butadiene rubbers (SBR)
Ethylene Propylene diene rubber (EPDM)
Silicone rubber
Nitrile Rubber
Thermo Plastic Elastomer (TPE) ***(Needle shields, Tip Caps)***

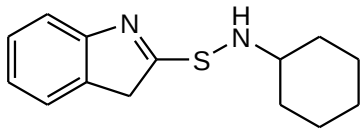
2. TYPES OF ELASTOMERIC CLOSURES

Rubber Curing / Vulcanization:

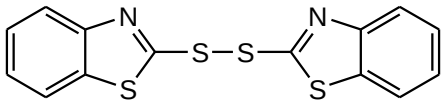


Rubber crosslinking requires S-Donors, activators, accelerators
Activator: ZnO / Stearic acid

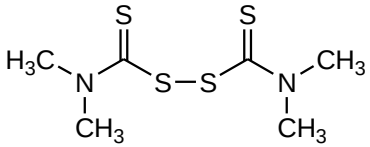
Rubber Curing - Accelerators:



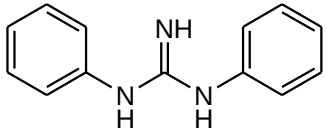
Cyclohexyl benzothiazole sulfenamide



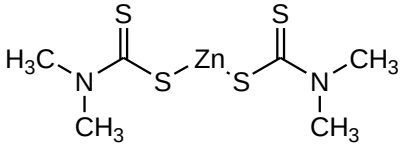
Mercaptobenzothiazole disulfide



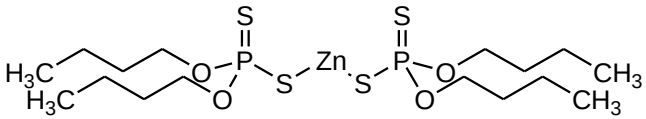
Tetramethylthiuram disulfide(TMTD)



Diphenyl guanidine

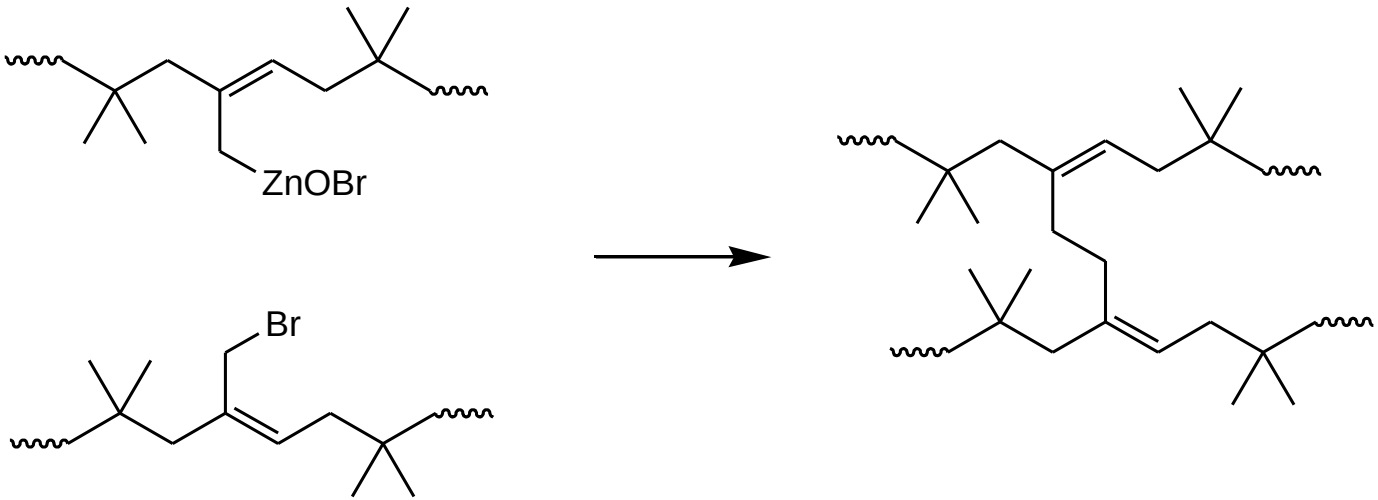


Zinc dimethyldithiocarbamate



Zinc dibutylphosphorodithiate

ZnO as Cross-Linking Compound in Halobutyl-Rubbers:



RUBBER: BASIC INGREDIENTS

ELASTOMER (Halobutyl: Bromobutyl/Chlorobutyl): Base Material

- Lowest Permeability
- Cleanest Cross-Linking
- Highest Resistance

FILLER: Strength, Physical properties *(Clay, Talc, Carbonates)*

ANTIOXIDANT: Elastomer protection *(e.g. BHT, Irganox 1010)*

CURING AGENT: Cross Linking *(e.g. S, S-donor, Phenol-formaldehyde…)*

ACTIVATOR: gives onset of vulcanisation *(e.g. ZnO + Stearic Acid)*

ACCELERATOR: speeds up vulcanisation *(e.g. carbamates, sulfenamides…)*

OTHER INGREDIENTS: Pigments, Stabilizers, Plasticizers, Release Agents…

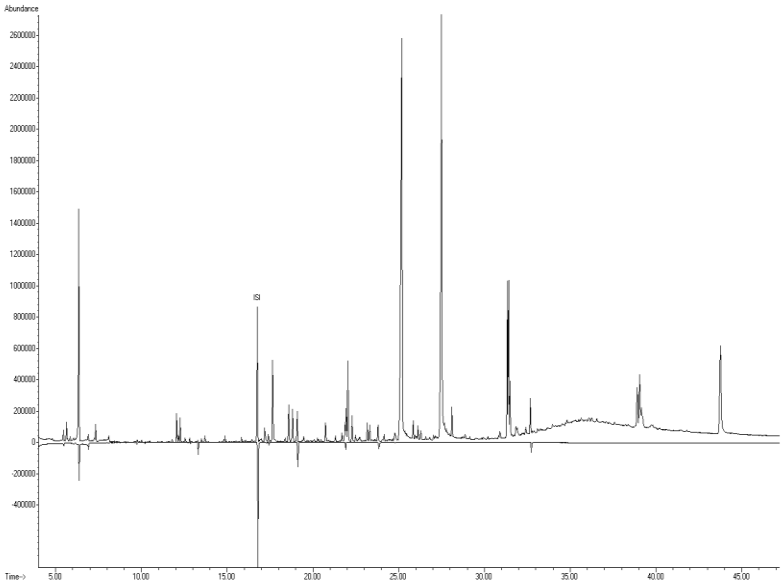
2. TYPES OF ELASTOMERIC CLOSURES

Number of Leachables from rubbers in PFS is determined by:

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

2. TYPES OF ELASTOMERIC CLOSURES

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

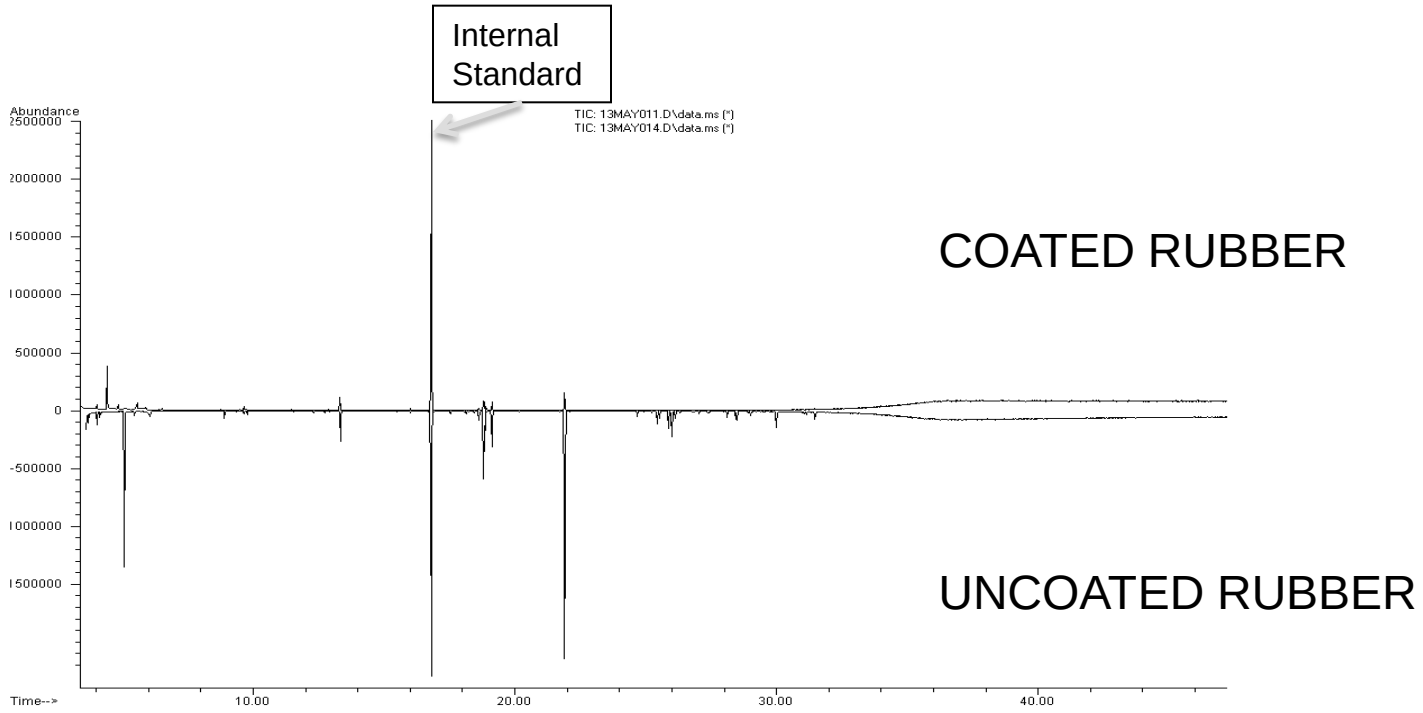


“OLD” RUBBER

“NEW” RUBBER

2. TYPES OF ELASTOMERIC CLOSURES

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



Coated Stoppers

- One of the compounds in the complex rubber blend may interact with one of the matrix components

Datwyler Pharma: Omniflex

Totally Coated

West Pharmaceutical: Flurotec

Partially Coated

THE COMPOSITION OF RUBBERS IS 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

RUBBER OLIGOMERS

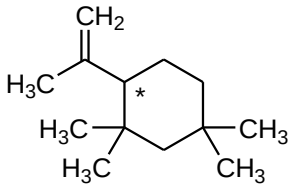
3. RUBBER OLIGOMERS

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

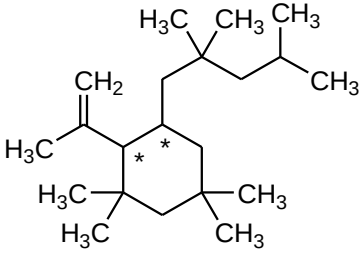
- Considered as
  - Cyclic aliphatic hydrobarbon compounds
  - One double bond

- 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

3. RUBBER OLIGOMERS

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

- Considered as
  - **HALOGENATED** Cyclic Aliphatic Hydrobarbon compounds (Allyl Halide)
  - **Alkylating Agents**
  - One double bond

- Structure Activity Relationship (SAR) Assessment:

CARCINOGENICITY IN HUMANS IS PLAUSIBLE

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

3. RUBBER OLIGOMERS

For potential Mutagenic/Carcinogenic compounds:

SCT: 0.15 µg/day (PQRI OINDP)

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

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

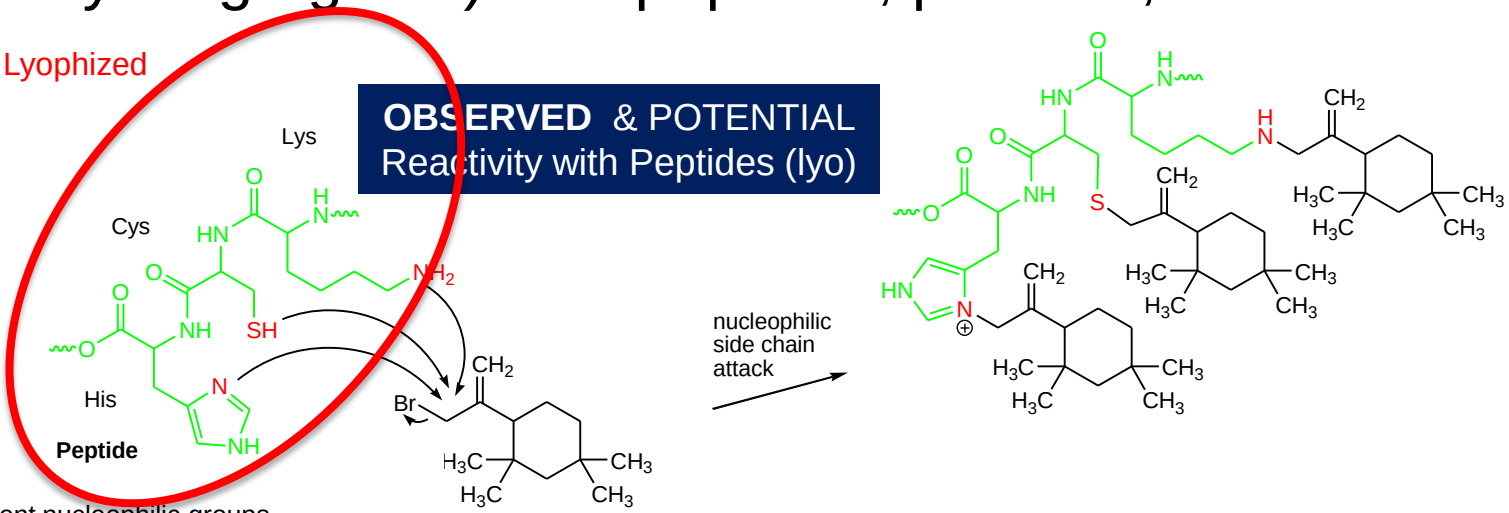
- Low associated AET levels
- High level of method optimization to obtain these levels (certainly with LVP)
- e.g. SIM mode for GC/MS
- Can only be performed with appropriate analytical standards with known purity
  - *Method Selectivity*
  - *Accuracy*
  - *Sensitivity*
  - *Precision*
  - *...*

3. RUBBER OLIGOMERS

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

Example of Lyophized peptide

OBSERVED & POTENTIAL
Reactivity with Peptides (lyo)



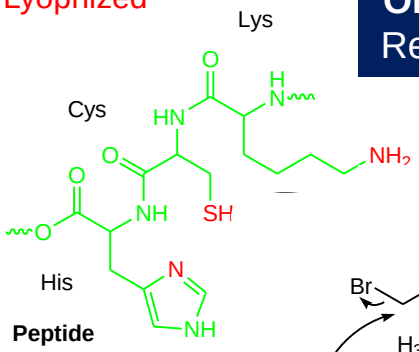
With different nucleophilic groups

Ref. 7

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

Example of Lyophized peptide

OBSERVED & POTENTIAL Reactivity with Peptides (lyo)



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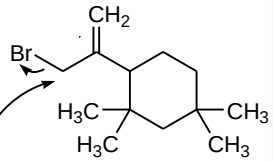
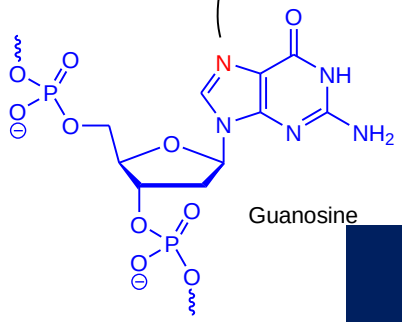
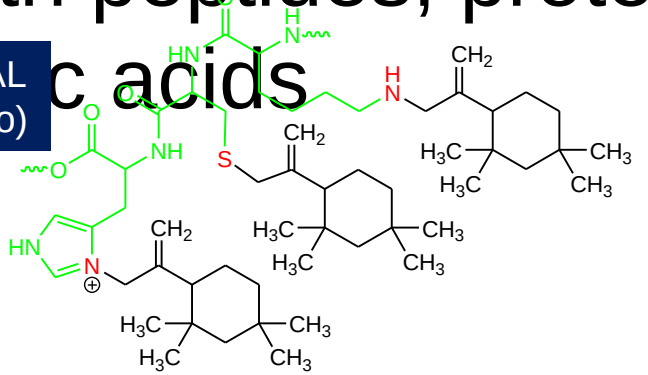




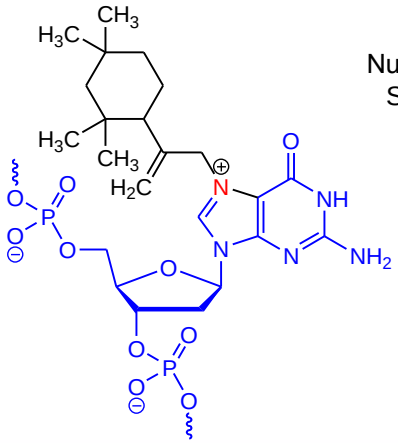
DNA

nucleophilic side chain attack



"N7" attack

Most nucleophilic site



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

POTENTIAL Reactivity with DNA

Ref. 7

ANALYTICS OF RUBBER OLIGOMERS

3. RUBBER OLIGOMERS

Extractable studies of Pharmaceutical Rubbers use a combination of Polar and Non-Polar solvents (PQRI)

- DCM, IPA, Hexane, EtOH, WFI/EtOH mix, WFI
- Typical conditions are e.g. Refluxing for 8h at relevant material to solvent ratios
- The more Polar an extraction solvent gets, the lower the extraction yields for non-polar compounds.
  - Lower interaction with rubber material (no “swelling”)
  - Lower solubility of Organic target compounds like $C_{13}H_{24}$ and $C_{21}H_{40}$...
- However, you need to select the extraction conditions that will allow you to perform a proper safety assessment in preparation of you leachable efforts!!
  - Do not take extraction conditons that are too mild...

3. RUBBER OLIGOMERS

Typical (Estimated) Concentrations of $C_{13}H_{24}$ and $C_{21}H_{40}$ in Halobutyl Rubbers:

- 10 - 50 mg/Kg of $C_{13}H_{24}$
- 150 – 500 mg/Kg of $C_{21}H_{40}$

➢ Or, for 1 rubber closure of 1 g, the amount of $C_{21}H_{40}$ can go to 500 µg/Closure

➢ 1% $C_{21}H_{40}$ migrating out of the rubber, represents 5µg in Drug Product

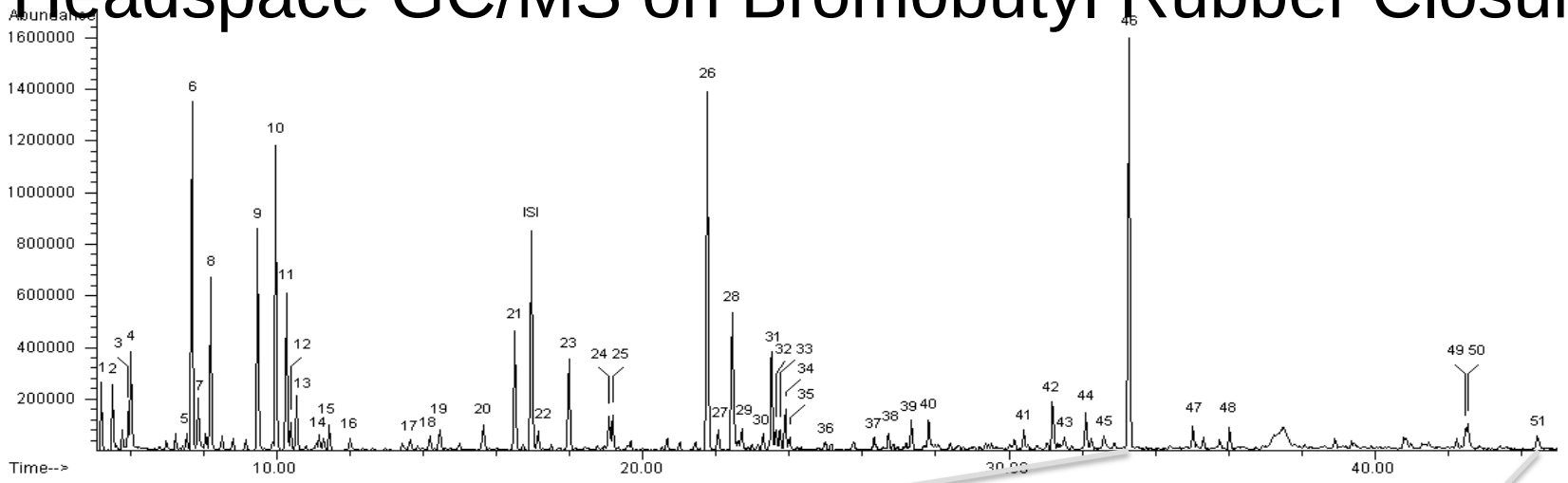
3. RUBBER OLIGOMERS

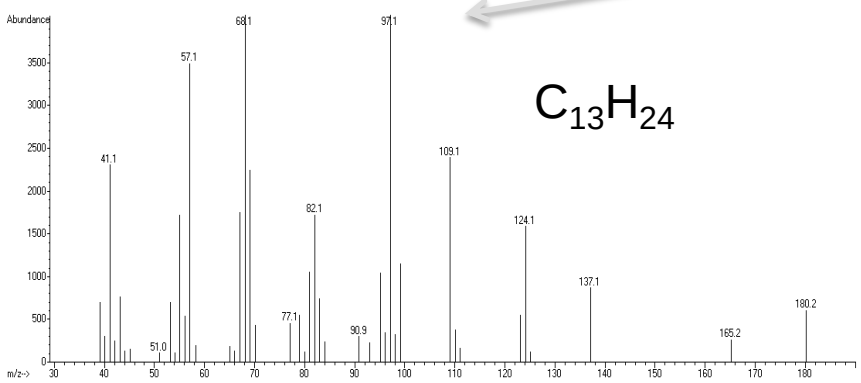
Cases where Rubber Oligomers have been detected as LEACHABLES:

- Vials /PFS whith a drug product, containing large amounts of organic material (excipients, buffers, solvents...)
- Lyophilized Drug Products
- Coming out of Needle Shields
- Aqueous long term contact (limited)
- Gaskets of administration pumps

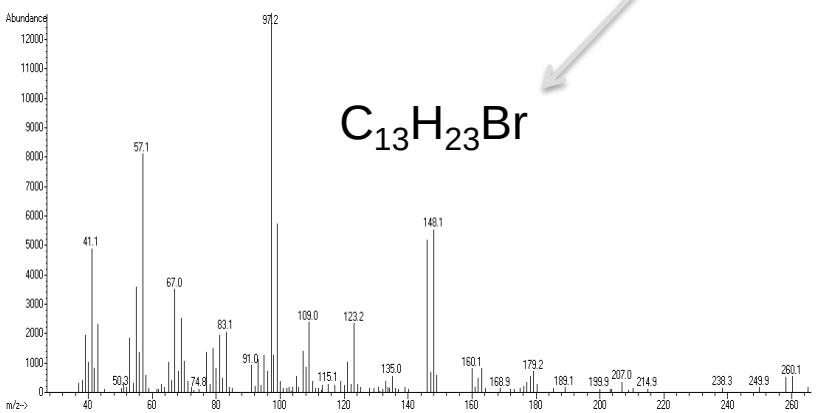
3. RUBBER OLIGOMERS

Headspace GC/MS on Bromobutyl Rubber Closure:





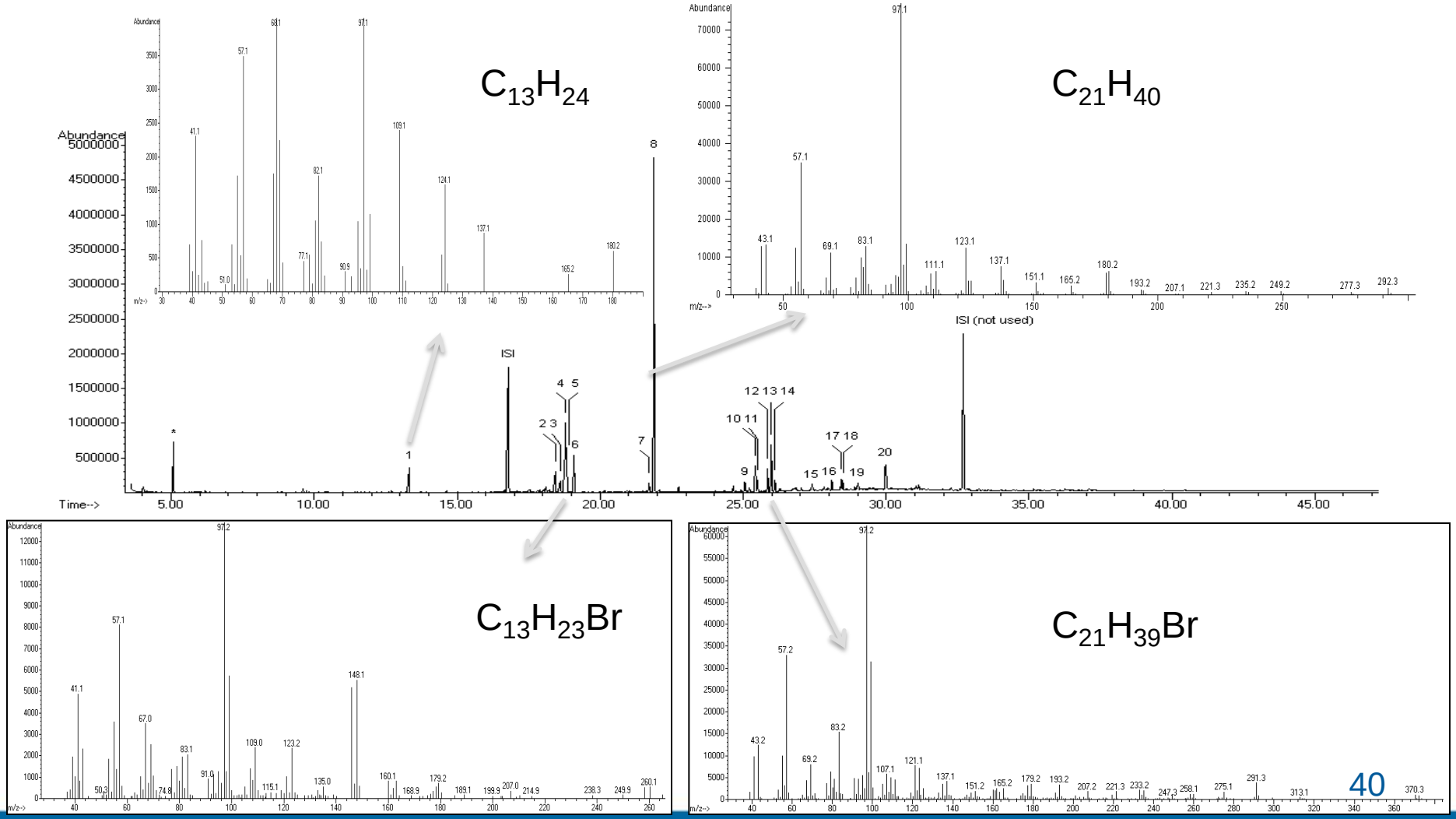
$C_{13}H_{24}$



$C_{13}H_{23}Br$

3. RUBBER OLIGOMERS

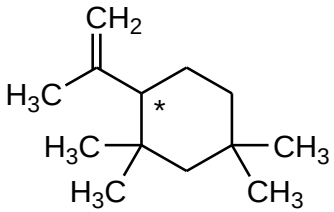
GC/MS on IPA extract of Bromobutyl Rubber Closure:

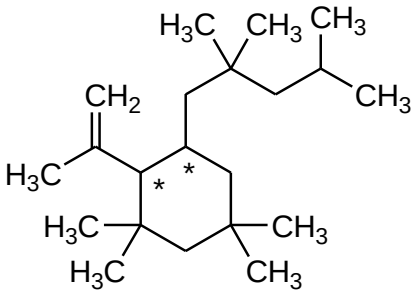


STRUCTURE ELUCIDATION

Structure Characteristics of $C_{13}H_{24}$ / $C_{21}H_{40}$ Rubber Oligomers

(After obtaining the Compounds via Isolation)





$C_{13}H_{24}$ Oligomer:

- cyclohexyl core
- 1 isopropenyl substituent
- 4 methyl substituents at the ring

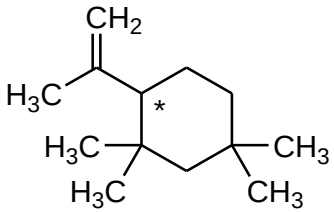
- 1 chiral center
  => 1 pair of enantiomers

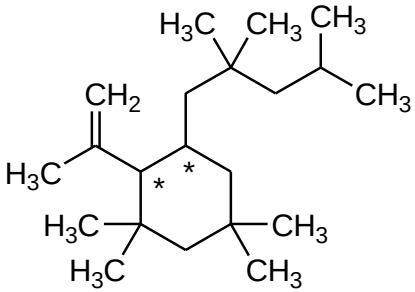
$C_{21}H_{40}$ Oligomer:

- cyclohexyl core
- 1 isopropenyl substituent
- 4 methyl substituents at the ring
- 1 additional alkyl substituent
- 2 chiral centers
  => 2 pairs of diastereomeric enantiomers

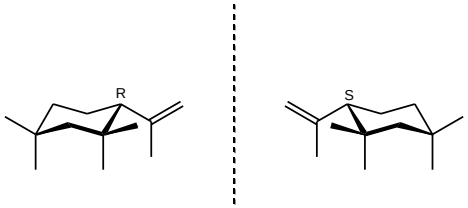
3. RUBBER OLIGOMERS

Structure Characteristics of $C_{13}H_{24}$ / $C_{21}H_{40}$ Rubber Oligomers

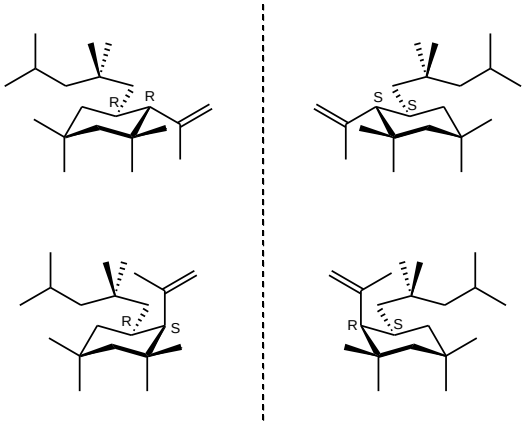




$C_{13}H_{24}$ Oligomer:
=> 1 pair of enantiomers



$C_{21}H_{40}$ Oligomer:
=> 2 pairs of diastereomeric enantiomers

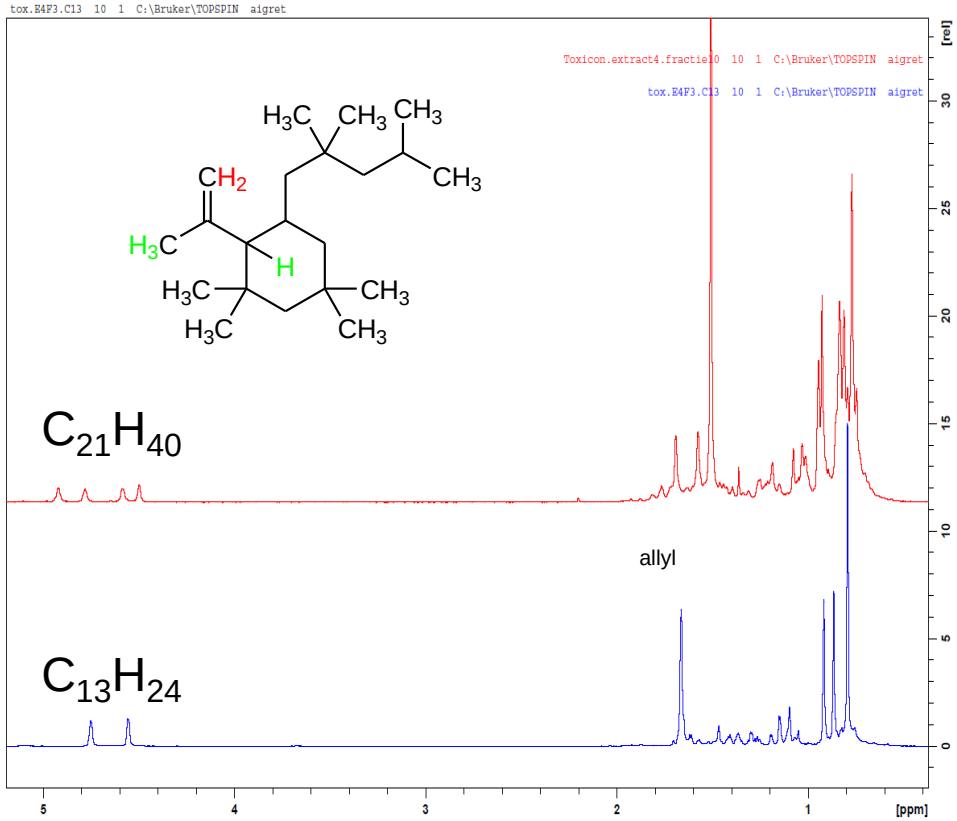


NMR Spectrum obtained from the isolated Oligomers

Characteristic peaks:

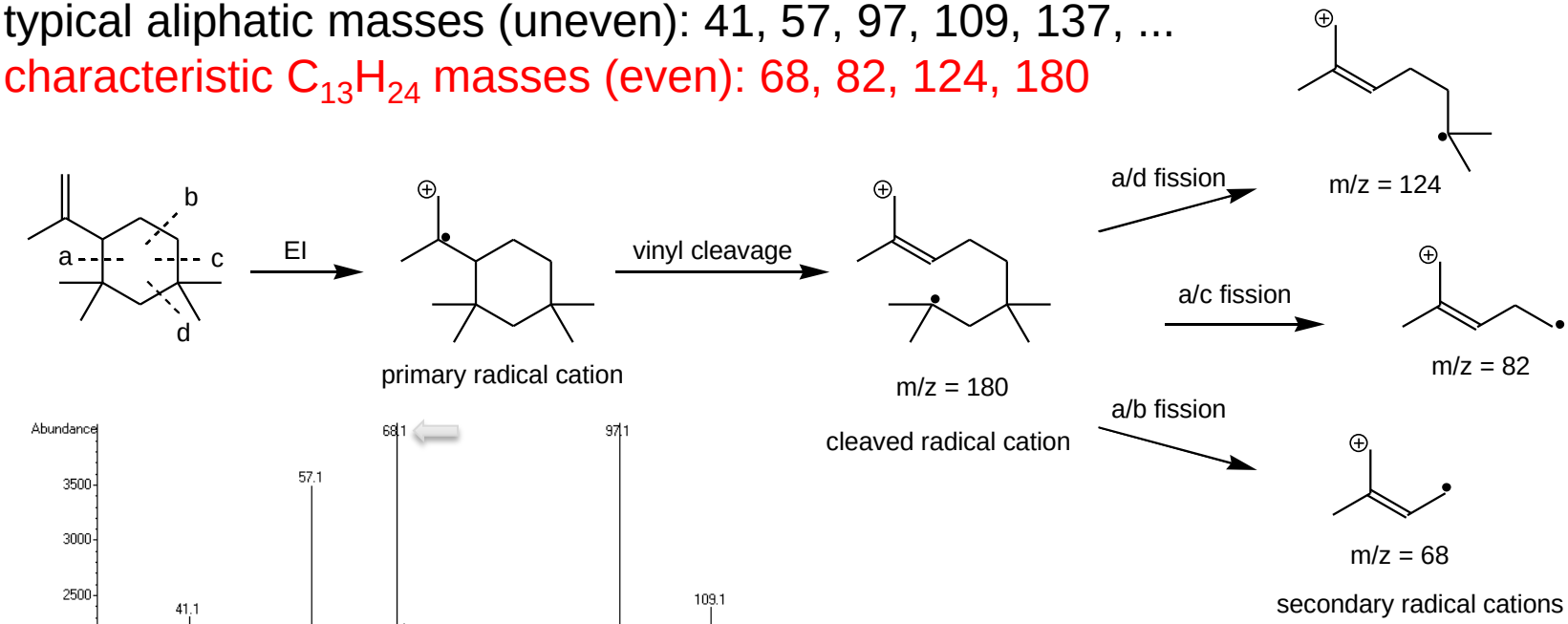
- ~4.7 ppm: 2 vinyl protons
- ~1.6 ppm: allyl protons
  (3 methyl & 1 tertiary)
- <1.0 ppm: 4 ring-methyl groups
  (4 additional methyl groups for $C_{21}H_{40}$)

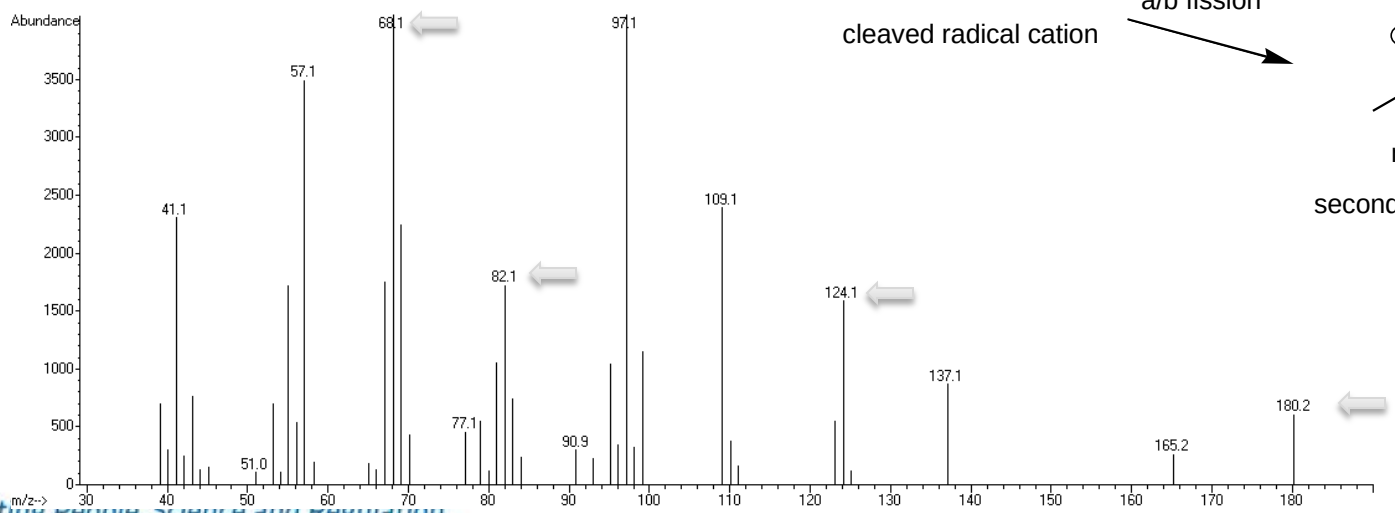
➢ NOTE: ALL PEAKS ARE DOUBLED FOR THE $C_{21}H_{40}$ DUE TO THE OVERLAY OF THE SPECTRA OF THE 2 DIASTEREOMERS



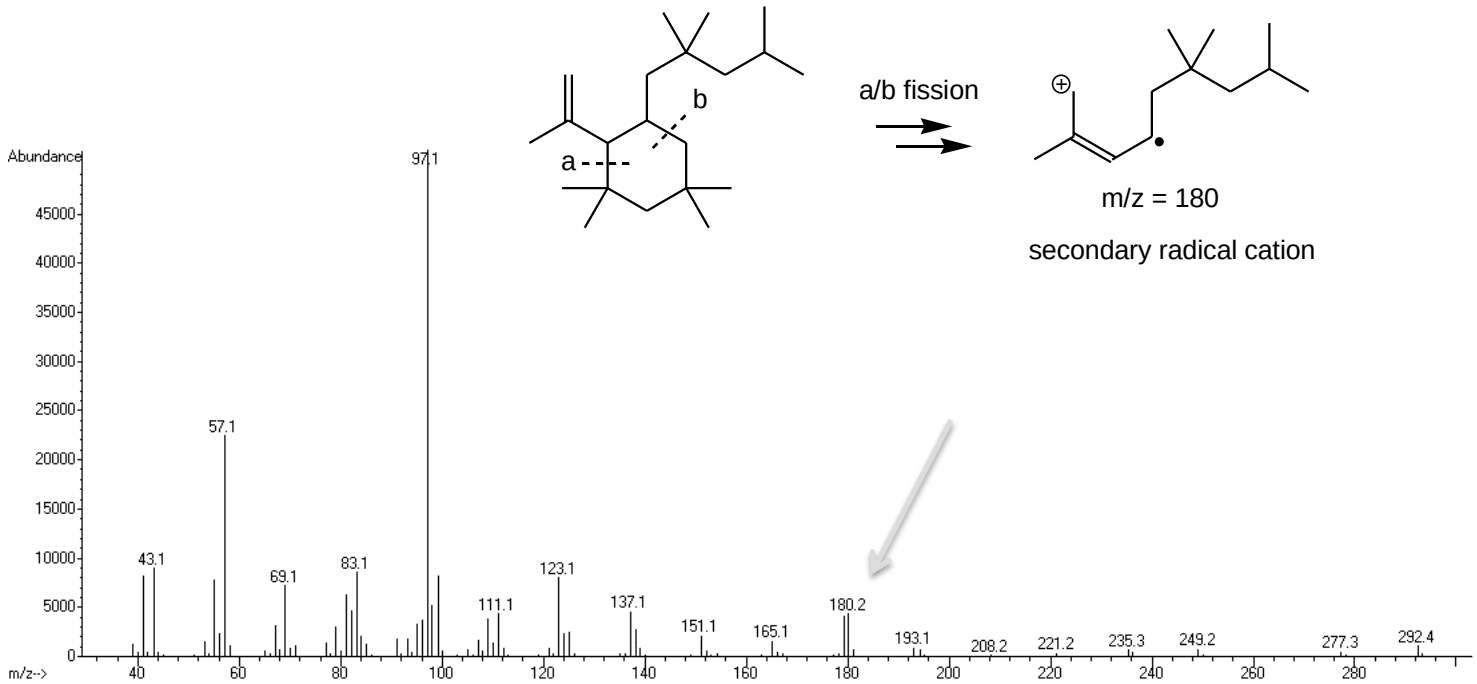
GC/MS Mass Spectrum of the $C_{13}H_{24}$ Oligomer

- typical aliphatic masses (uneven): 41, 57, 97, 109, 137, ...
- characteristic $C_{13}H_{24}$ masses (even): 68, 82, 124, 180



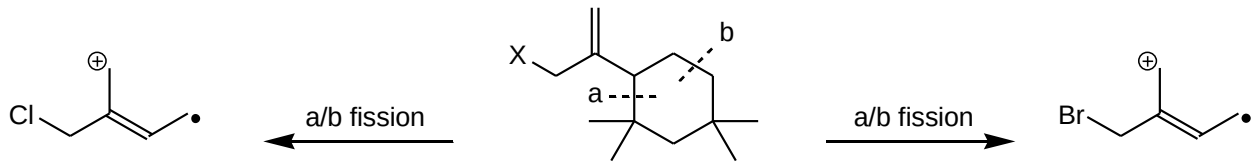


GC/MS Mass Spectrum of the $C_{21}H_{40}$ Oligomer



3. RUBBER OLIGOMERS

GC/MS Mass Spectrum of the $C_{13}H_{23}Cl$ and $C_{13}H_{23}Br$ Oligomer



m/z = 102/104

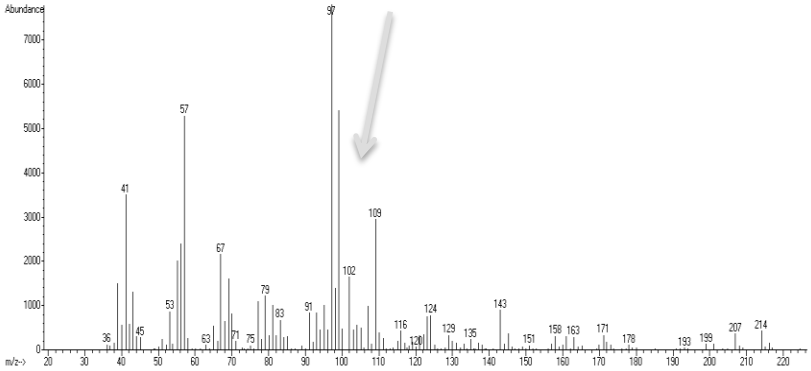
chlorinated secondary radical cation

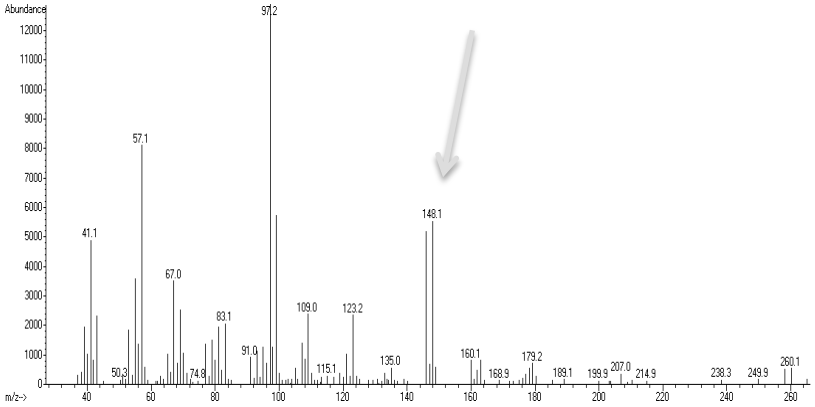
m/z = 214/216 (Cl); 258/260 (Br)

Halobutyl oligomer (X=Cl,Br)

m/z = 146/148

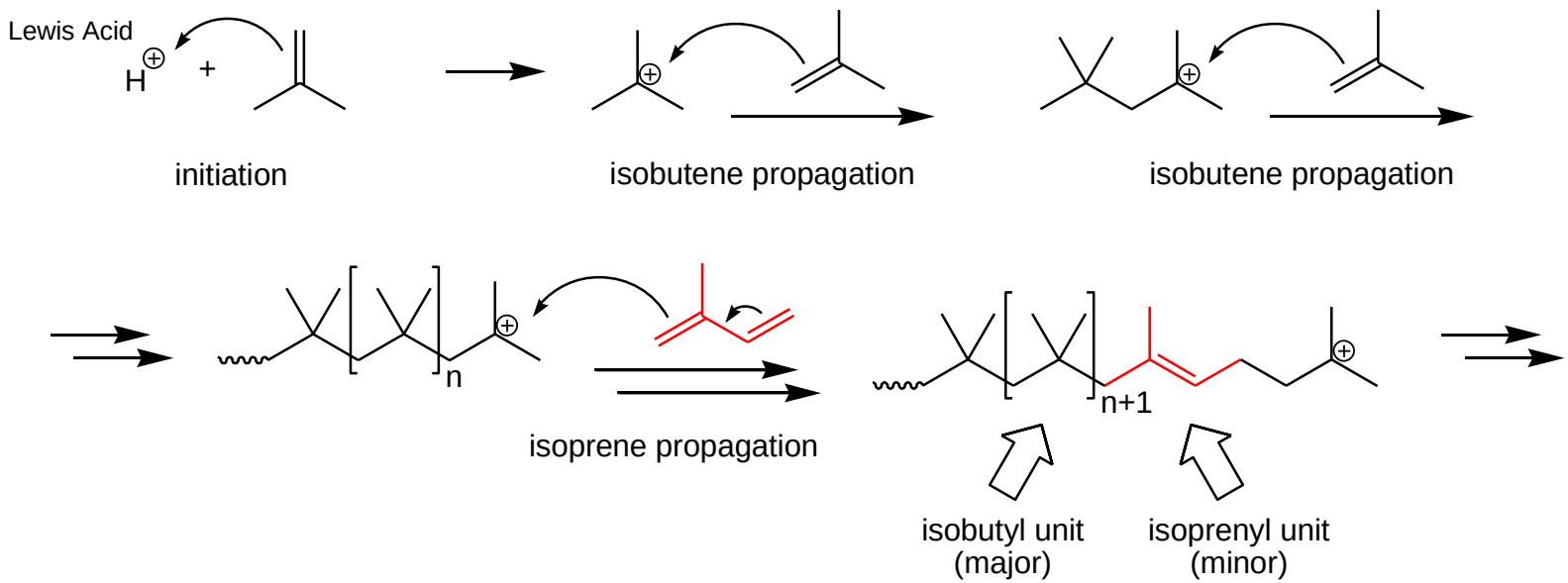
brominated secondary radical cation





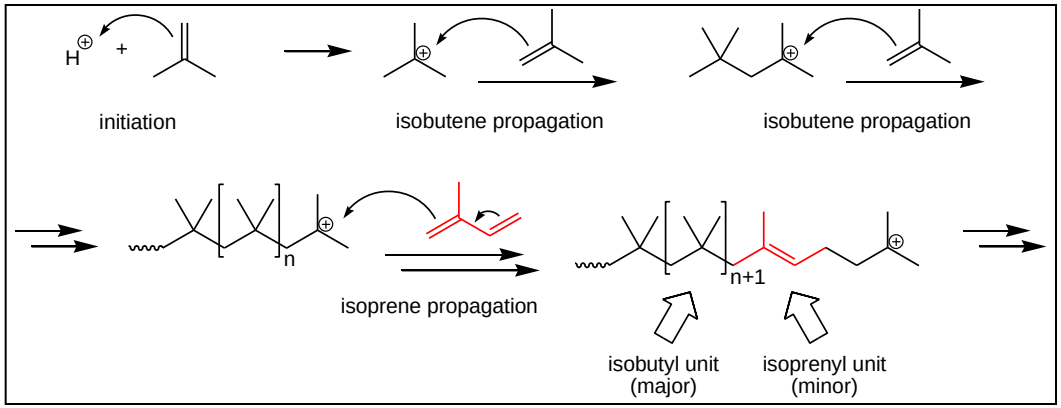
FORMATION OF OLIGOMERS

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*

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



- *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:

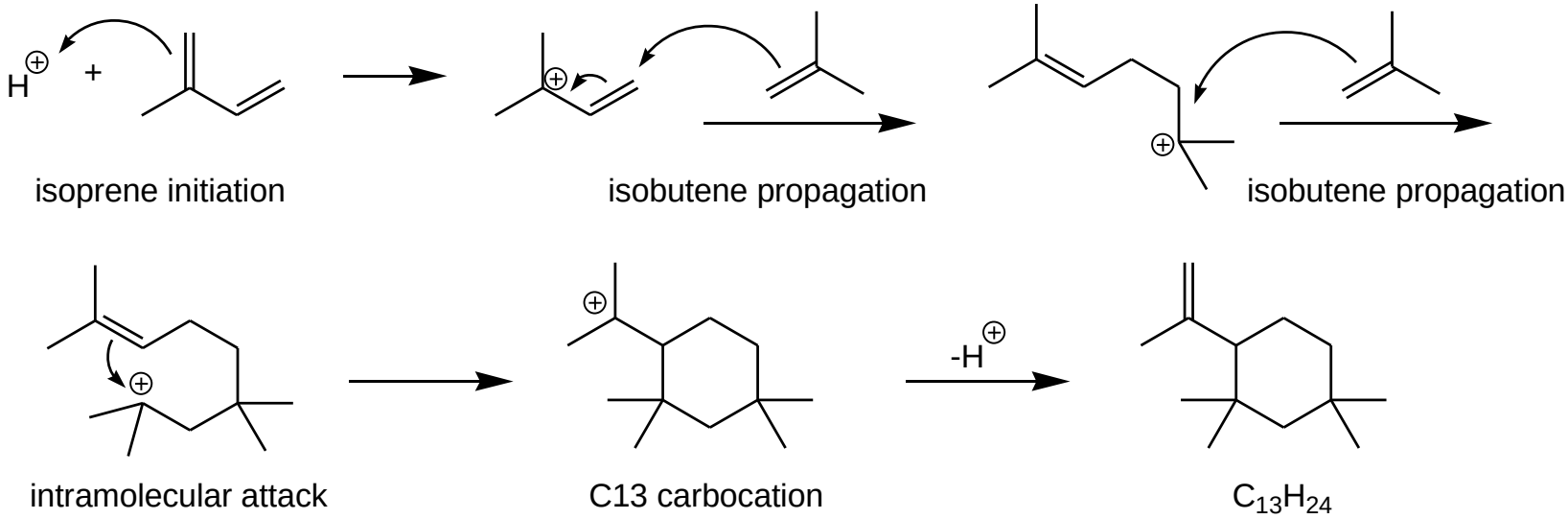
*Butyl Elastomer (IIR) is **less prone to Oxidation***

*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)

Formation of the $C_{13}H_{24}$ Oligomer:

One of the postulated Routes of Formation

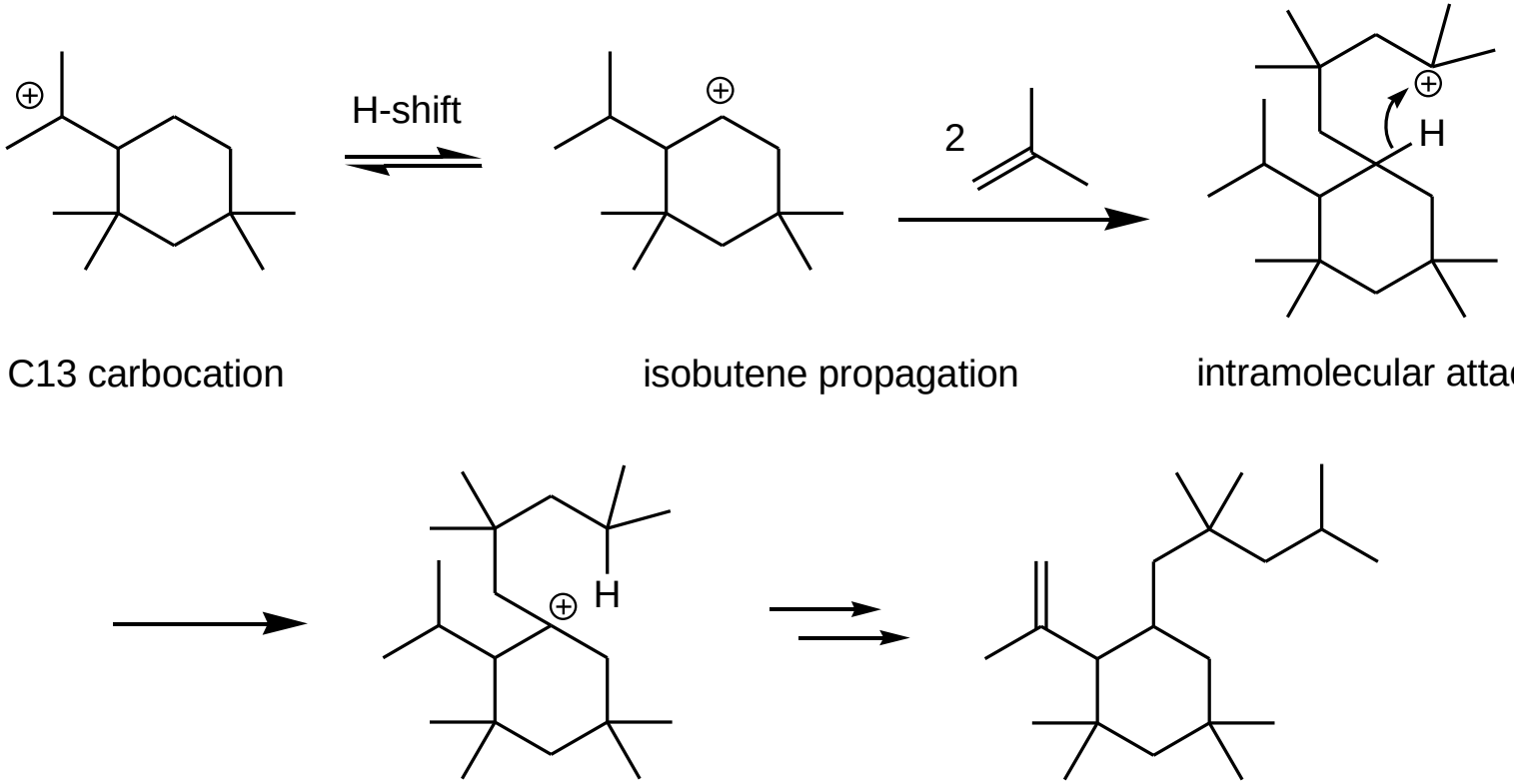


Backbite reaction

- Note: the polymerization starts with an isoprene unit which provides the double bond which is necessary for the intramolecular ring formation

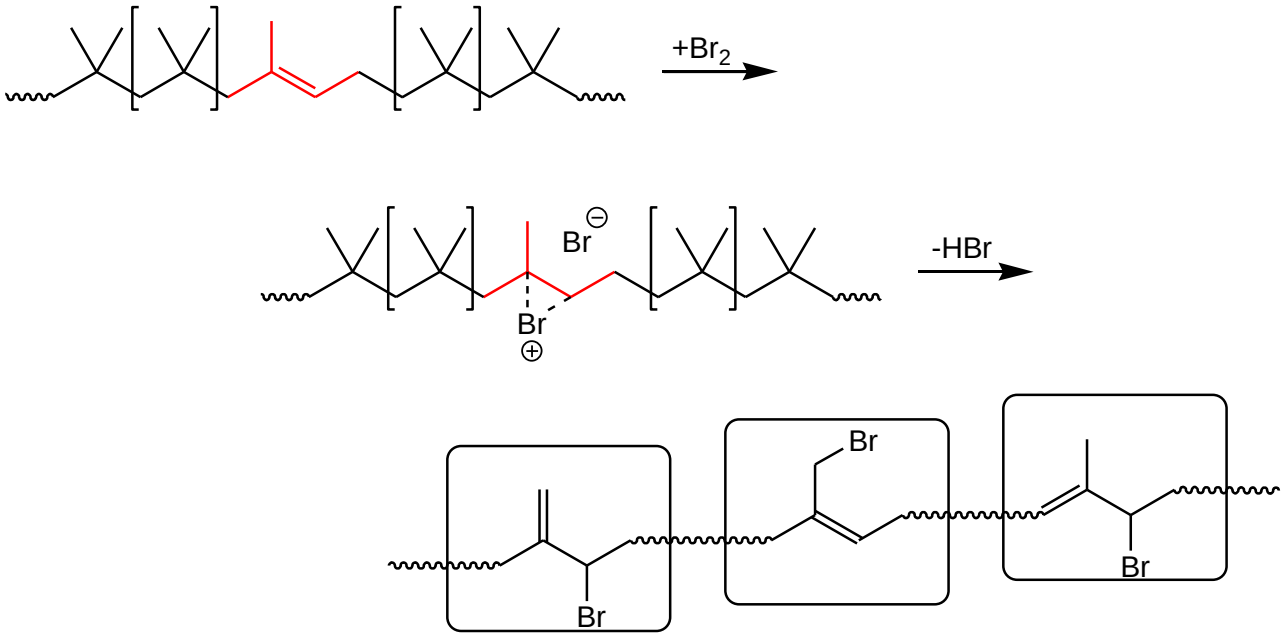
Ref. 2, 3

Formation of $C_{21}H_{40}$ Oligomer:



Ref. 2, 3

Bromination of a Butyl Elastomer (BIIR)



Type 1 Type 2 Type 3

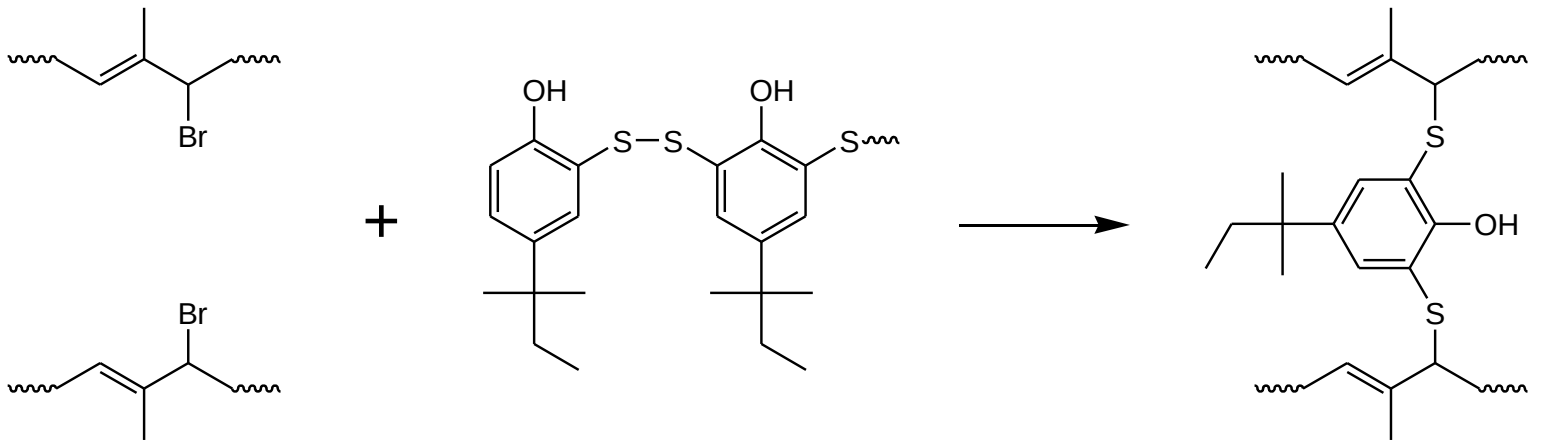
Bromination of the Backbone makes Elastomer

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

more reactive in vulcanization/cross linking

Ref. 9

Vultac Curing of (Halobutyl) Elastomers



Amyl Disulfide Polymer

Phenol Sulfide Crosslink

Bromide: good leaving group!

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

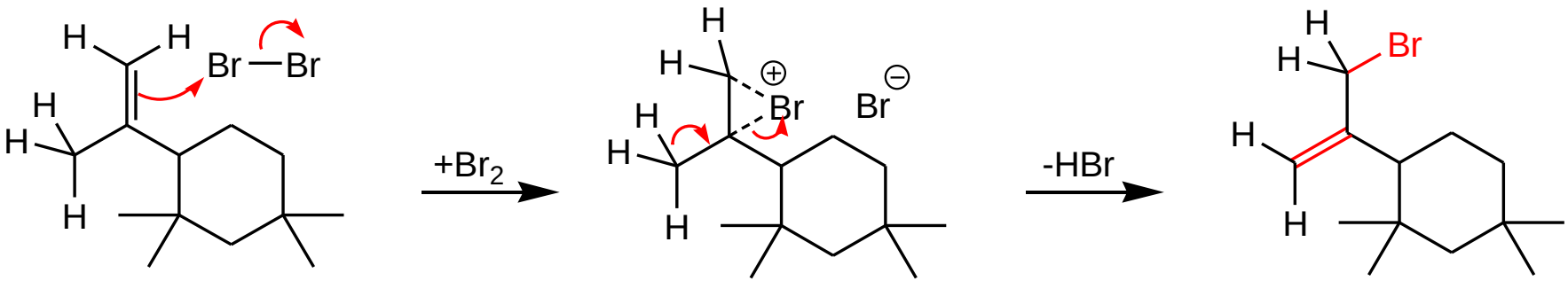
Explains Br^- release from bromobutyl rubbers

Ref. 8

3. RUBBER OLIGOMERS

Formation of $C_{13}H_{23}Br$, $C_{13}H_{23}Cl$, $C_{21}H_{39}Br$ & $C_{21}H_{39}Cl$:

side reaction in the production of halobutyl elastomer (halogenation of butyl elastomer)



$C_{13}H_{24}$ Bromonium intermediate $C_{13}H_{23}Br$

➢ Note: the halogenation occurs according to classical rubber halogenation chemistry by the substitution of one of the allylic hydrogen atoms

4. DESIGNING EXTRACTABLE STUDIES FOR INJECTABLES

4. Designing Extractable Studies

EXTRACTABLE STUDIES

- Increase **KNOWLEDGE** About Qualitative Composition of Materials, used in PFS Manufacture
- Focus: IDENTIFICATION of Extractables
- ADDS TO INFORMATION Provided by either Raw Material Suppliers or C/C Manufacturers
- Extractables List: FOCUS for Leachable Study
- In Some Cases: QUANTITATIVE Extractable Studies (using Validated Methods)

4. Designing Extractable Studies

VARIABLE 1: TYPE OF SOLVENTS / EXTRACTION VEHICLES

PQRI: combination of POLAR and NON-POLAR solvents
Isopropanol, Hexane, Dichloromethane, WFI

OTHER: acidified WFI (e.g. pH 2.5)
alkaline WFI (e.g. pH 9.5)
saline/buffered WFI
WFI/EtOH-mix *(e.g. to mimic Organic content)*
Drug Product Vehicle (in FDA-Guidance, PQRI)

4. Designing Extractable Studies

VARIABLE 2: MATERIAL-TO-SOLVENT RATIO - during extraction

DO NOT USE FIXED RATIO's LIKE:

- 2 g / 250 mL (e.g. EP 3.1.3, sample prep for quant analysis of AO's)
- 1 g / 10 mL
- ...

RATHER:

Adjust the M-t-S Ratio to the "*Real Use of the Prefilled Syringe*" (e.g. Extract a 10 mL Syringe in 10 mL of solvent)

OR

Adjust the extraction ratio's in order to *attain the "IDENTIFICATION THRESHOLD" Level* (See Part 5 of this presentation)

4. Designing Extractable Studies

VARIABLE 3: EXTRACTION TIMES

Difficult parameter to extrapolate from "real use"

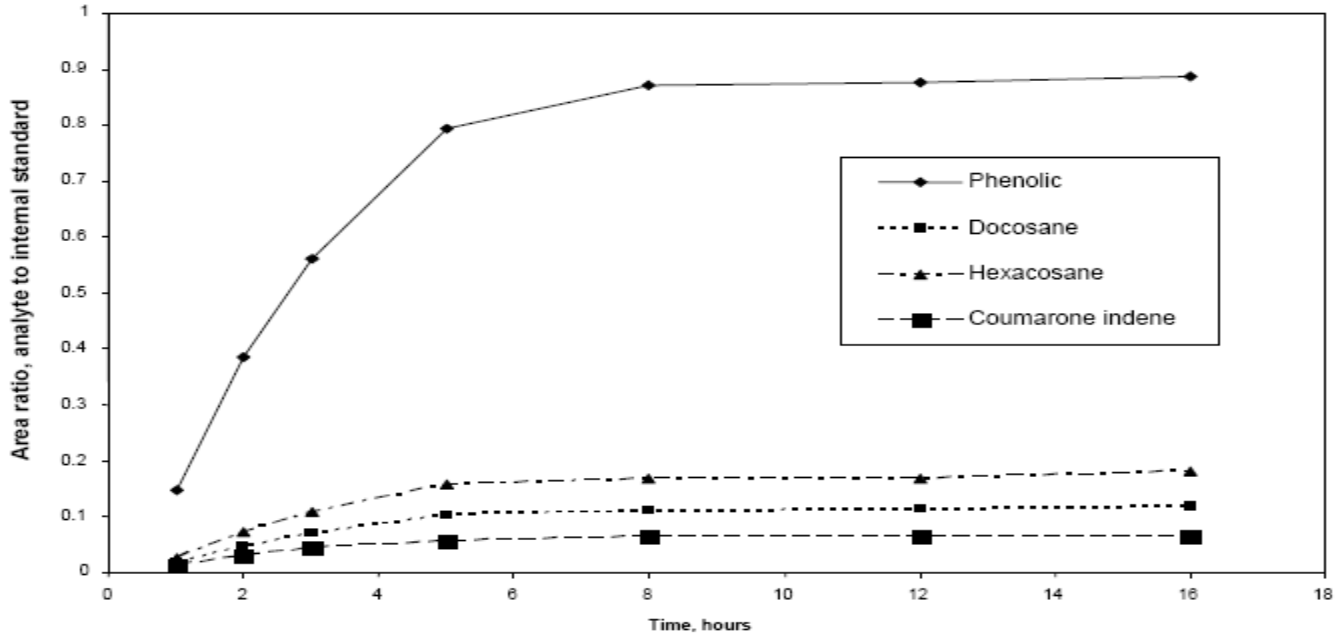
EXAMPLE: for WFI – does 8 hour reflux mimic a 3 year shelf life?

for IPA – does 1 hour reflux reflect a "worst case"?

Alternative Approach: PQRI (OINDP):

"Determine Asymptotic Extraction Profile"

4. Designing Extractable Studies



PQRI-Example: Test Article: Sulphur Cured Elastomer
Extraction: DCM – Soxhlet

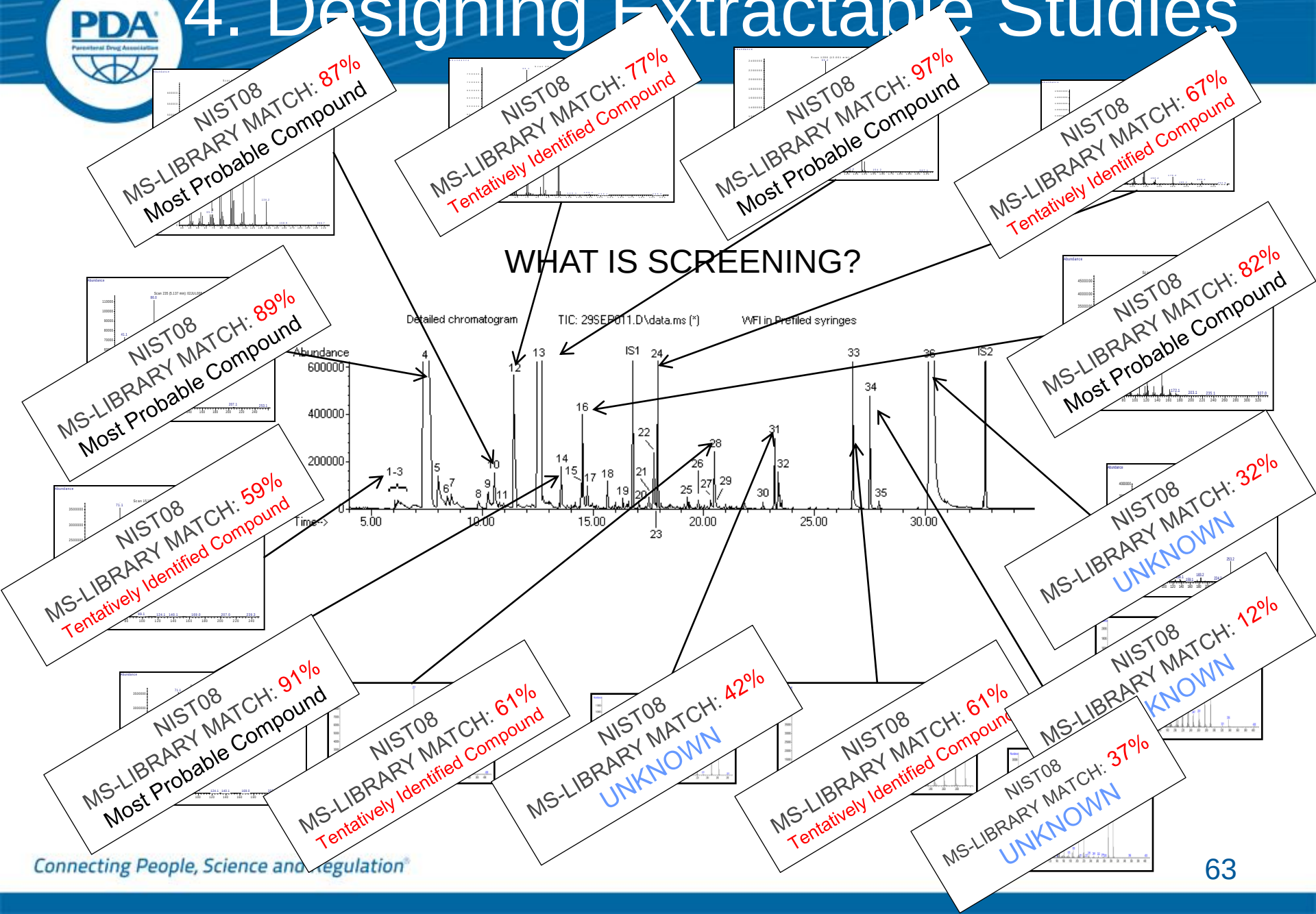
CONCLUSION: Extraction conditions on the 'plateau'-regime
= "MAXIMUM RISK"

4. Designing Extractable Studies

FRESHEN UP ANALYTICAL KNOWLEDGE – TECHNIQUES USED IN EXT STUDY

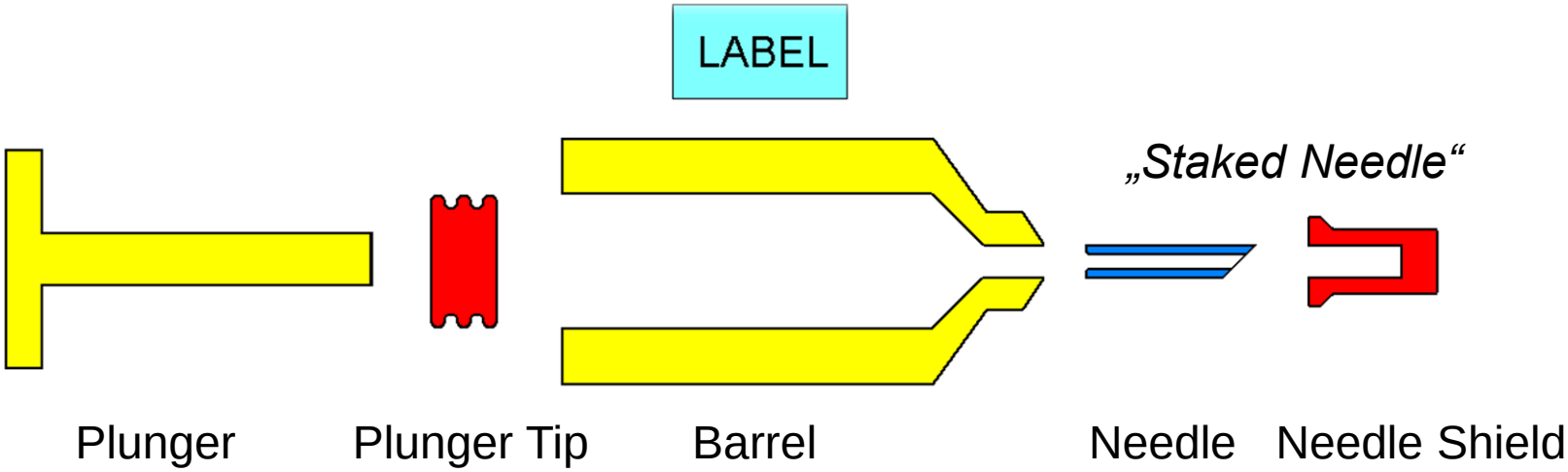
Anions	Fluoride, Acetate, Formate, Chloride Nitrite, Bromide, Nitrate, Sulphate, Phosphate	Ion Chromatography (Validated Method)
Metals/Cations	Ag, Al, Ba, Ca, Cd, Co, Cr, Cu, Fe, In, K, Mg, Mn, Na, Ni, Pb, Si, Sr, Tl, Zn	ICP-OES (Validated Method)
Volatile Organic Compounds (VOCs)	Monomers, solvents, polymer treatment residues, smaller polymer breakdown products	Headspace GC/MS **SCREENING** (semi-quantitative)
Semi-Volatile Organic Compounds (SVOCs)	Lubricants, Plasticizers, anti-oxidants, polymer degradation products	GC/MS **SCREENING** (semi-quantitative)
Semi-Volatile POLAR Organic Compounds (Polar-SVOCs)	Organic Compounds, with a Polar Functional Group (e.g. Acids, Alcohols, Amides, Amines...)	DERIVATISATION GC/MS (semi-quantitative)
Non-Volatile Organic Compounds (NVOCs)	Polymer additives: anti-oxidants, nucleating agents, UV-stabilizers, fatty acids, waxes, Polymer Degradation Products	LC-UV LC/MS (Validated Method) UPLC/HRAM MS **SCREENING**
Sulfur	Cross Linking	HPLC-UV
Silicone Oil	Lubrification	GF-AAS

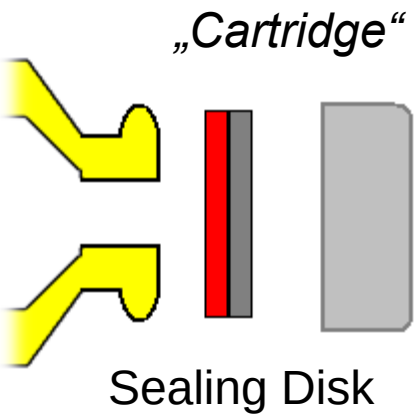
4. Designing Extractable Studies

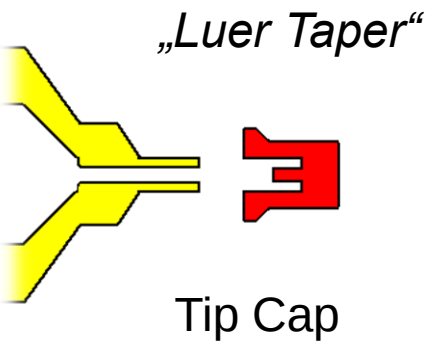


4. Designing Extractable Studies

PRE-FILLED SYRINGE: COMPOSING PARTS



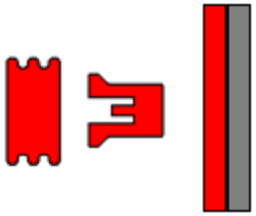




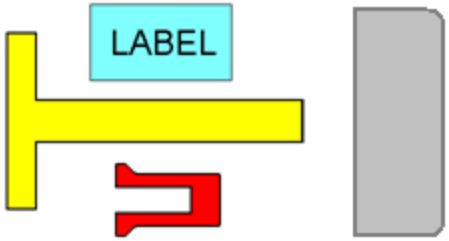
4. Designing Extractable Studies

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, ...

Barrel Materials

Polypropylene (PP)

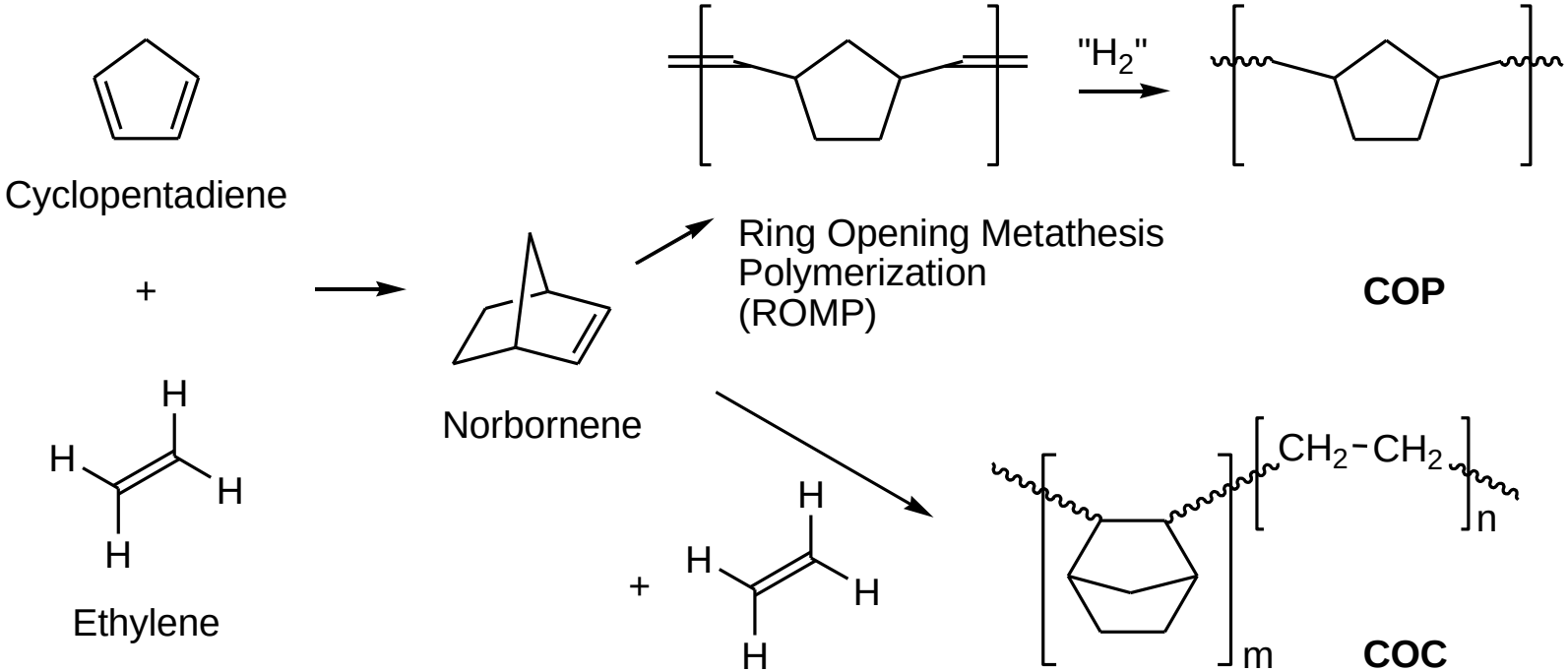
Cyclic Olefin (Co-)Polymer COC/COP

Glass

4. Designing Extractable Studies

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



4. Designing Extractable Studies

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*

4. Designing Extractable Studies

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!*

4. Designing Extractable Studies

Glass as Barrel Material

Surface treatment (dealkalization) to obtain Type II glass (out of Type III):

Exchange of Na^+ with H^+ :

Injected before annealing

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

$$2Na^+ \text{ (Glass)} + (NH_4)HSO_4 \rightarrow Na_2SO_4 + NH_3 + 2H^+ \text{ (Glass)}$$

Removed by rinsing

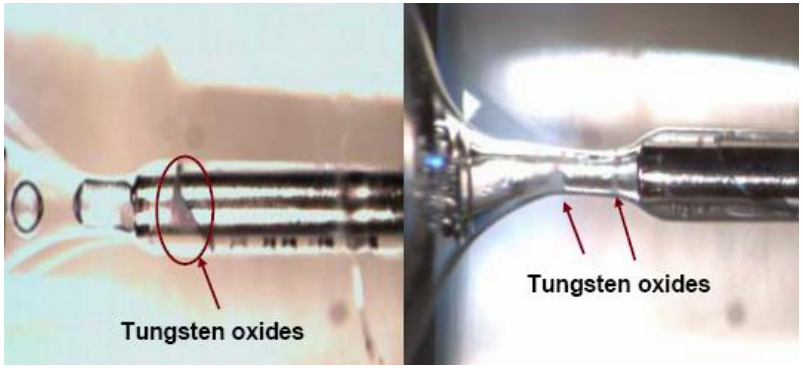
4. Designing Extractable Studies

Glass as Barrel Material

EXTRACTABLES RELATED TO GLASS BARRELS:

TUNGSTEN RESIDUES

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



4. Designing Extractable Studies

Glass as Barrel Material

EXTRACTABLES RELATED TO GLASS BARRELS:

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)

4. Designing Extractable Studies

Glass as Barrel Material – Related Compound

1. PRODUCT AND COMPANY IDENTIFICATION

Product name: **Loctite 3345**
Product type: Ultraviolet adhesive

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

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

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

3. COMPOSITION / INFORMATION ON INGREDIENTS

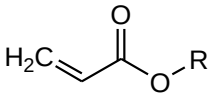
Hazardous components	CAS NUMBER	%
Polyurethane Methacrylate Resin	Proprietary	30 - 60
Tetrahydrofurfuryl methacrylate	2455-24-5	10 - 30
Hydroxyalkyl methacrylate	27813-02-1	10 - 30
Acrylic acid	79-10-7	5 - 10
High boiling methacrylate	7534-94-3	5 - 10
Propylidynetrimethyl trimethacrylate	3290-92-4	1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

Glass as Barrel Material – Related Compounds

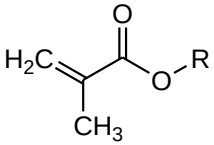
EXTRACTABLES RELATED TO GLASS BARRELS:

GLUE RESIDUES

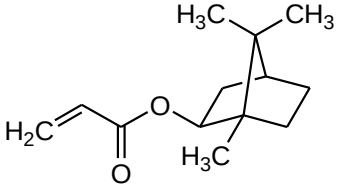
Base Polymer



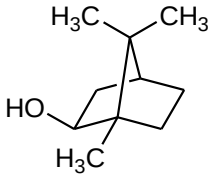
Acrylate



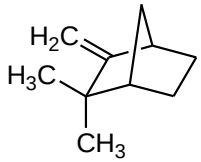
Methacrylate



Isobornyl acrylate

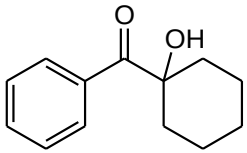


Isoborneol

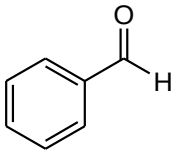


Camphene

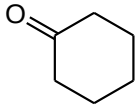
UV curing / activation



Irgacure 184



Benzaldehyde



Cyclohexanone

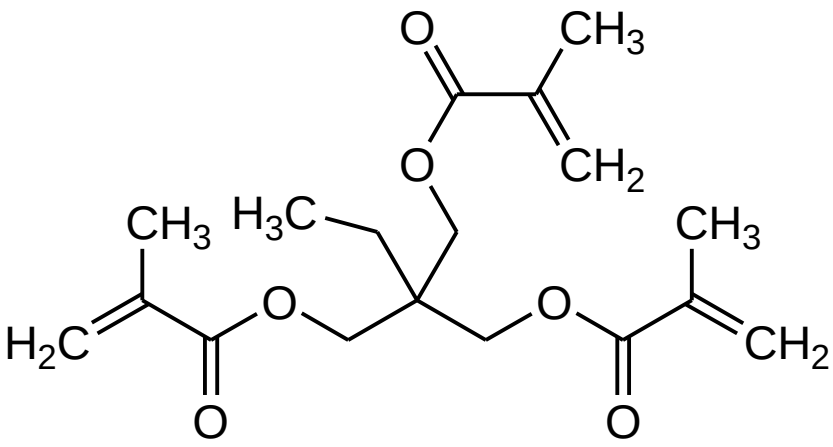
4. Designing Extractable Studies

Glass as Barrel Material – Related Compounds

EXTRACTABLES RELATED TO GLASS BARRELS:

GLUE RESIDUES

The key indicator compound TMPTMA



Glass as Barrel Material – Related Compounds

EXTRACTABLES RELATED TO GLASS BARRELS:

SILICONE OIL RESIDUES

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

4. Designing Extractable Studies

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:**
  - ✓ 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 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”...

4. Designing Extractable Studies

Pre-Filled Syringes

- **GLUE for staked needle**: Metals (may not be necessary to be studied in EXT Study, if glass composition is available, direct assessment in LEA study)

- **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.

Extractable Studies Design

VIAL: Container for Liquid Drug Products

- 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** with reconstituted DP: also potential Performance & Quality Issue!
    - ✓ Also, Ions may need to be “checked off”...

Designing Extractable Studies

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”...

4. Designing Extractable Studies

Cartridges

- **Sealing Disc:**
  - ✓ 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. Designing Extractable Studies

Ports in I.V. Administration Systems

- **Ports:**
  - ✓ Relatively “lower grade” rubbers (e.g. PolyIsoprene)
  - ✓ Only Small Surface Area is exposed to the DP
  - ✓ The migration of Rubber Impurities is dependent upon the composition of the DP
    - *For Aqueous Solutions, potential migration will be low*
    - *For Solutions, highly loaded with Organic material, the potential migration will be high!*
  - ✓ Include the port in the Assessment!

5. DESIGNING LEACHABLE STUDIES

5. DESIGNING LEACHABLE STUDIES

ANALYTICAL CHALLENGE

- Looking for trace impurities in often very complex matrices!!
- Analytical Methods for Stability Testing are often NOT suited/optimized for detection of Leachables
  - Historically: if no additional peaks (impurities) were found in the HPLC/UV chromatogram, no leachables
  - However: HPLC/UV is optimized for stability/QC testing on API. HPLC/UV is NOT optimized for the detection of trace impurities originating from the primary packaging!

5. DESIGNING LEACHABLE STUDIES

ANALYTICAL CHALLENGE

- Use dedicated and optimized analytical tools for leachables analysis, e.g.:
  - Headspace GC/MS: volatile compounds
  - Sample prep. + GC/MS or GC/QQQ: semi-volatile compounds
  - Sample prep. + LC/MS or LC/QQQ: non-volatile compounds
  - ICP: metals
  - IC: ions
  - ...
- PQRI- threshold considerations for leachables

5. DESIGNING LEACHABLE STUDIES

- "Simulated Use" Conditions

  Storage Time / Temperature / Humidity

  Conditions: Similar to Stability Studies

  Pharmaceutical Formulation As Contact Solution

5. DESIGNING LEACHABLE STUDIES

IF POSSIBLE, CONSIDER A 2 STEP APPROACH FOR LEACHABLE STUDIES

1. Screening "*Semi-Quantitative*" Leachable Study (e.g. Accelerated Conditions)

2. A "Formal" *Quantitative* Leachable Study

5. DESIGNING LEACHABLE STUDIES

1. "Screening Leachable Study"

- As a **Step in between an Extractable Study and a "FORMAL" Leachable study**
- **Understanding the "Long Term" Interaction** between the Container/ Closure System and the Drug Product.
- **Screening Methodology** to verify:
  - The Extractables that have become Leachables
  - Leachables From Secondary Packaging e.g**. Label Migration**
  - Unexpected Leachable Compounds
  - Allows to narrow down the list of relevant compounds for a leachable study
- With the **same techniques as** were selected for the **Extractables Study**
- **Easy if some DP is already available in ongoing stability studies** (e.g. Accellerated Conditions)
- For **Large Volume Parenterals**: Further **Narrowing down** the list of target compounds for a Formal Leachable Study

5. DESIGNING LEACHABLE STUDIES

1. "Screening Leachable Study"

- **Feasibility** of a Screening Leachable Study **depends largely on the complexity of the DP** (the DP should allow screening methodologies)

- Screening Leachable Study is typically "semi-quantitative" in nature (no validated methods

- Could be performed in a more quantitative way by adding a **Method Suitability Check** for certain target compounds.
  - To verify if the screening methodology is capable of picking up certain target compounds at relevant concentrations in the DP

- If the purpose would be to verify if there are no unexpected leachbles (leachables that were not detected as extractables):
  - Adding a screening mode study in the Formal leachable study could help to address this issue

5. DESIGNING LEACHABLE STUDIES

2. "Formal Leachable Study"

- Quantification of "Target" Compounds
  - ✓ **Extractables Study** Information
  - ✓ Targets, Identified after **Threshold Evaluation**
  - ✓ ***Screening Leachable*** *Information*
  - ✓ Composition of Raw Materials/Compounds
  - ✓ Validation Binder of Container/Closure Manufacturer

- Validated Methods (ICH Q2(R1))
  - ✓ **Specificity** - Identification
  - ✓ **Range** and **Linearity** of Method
  - ✓ **Extraction Yields** (when applicable)
  - ✓ **Detection Limit** and **Quantification Limit**
  - ✓ **Accuracy** and **Precision** in low, mid and high concentration range

  Other: Intermediate Precision, Robustness...

- Other Conditions
  - ✓ ***Long Term*** Ageing Conditions
  - ✓ ***Accelerated*** Ageing Conditions can be considered, in support of LT Ageing
  - ✓ At different ***time points***
  - ✓ Add ***Screening*** Methods (semi-quantitative), to pick up unexpected leachables

EXAMPLE OF ANALYTICAL PACKAGE FOR A FULL LEACHABLE STUDY

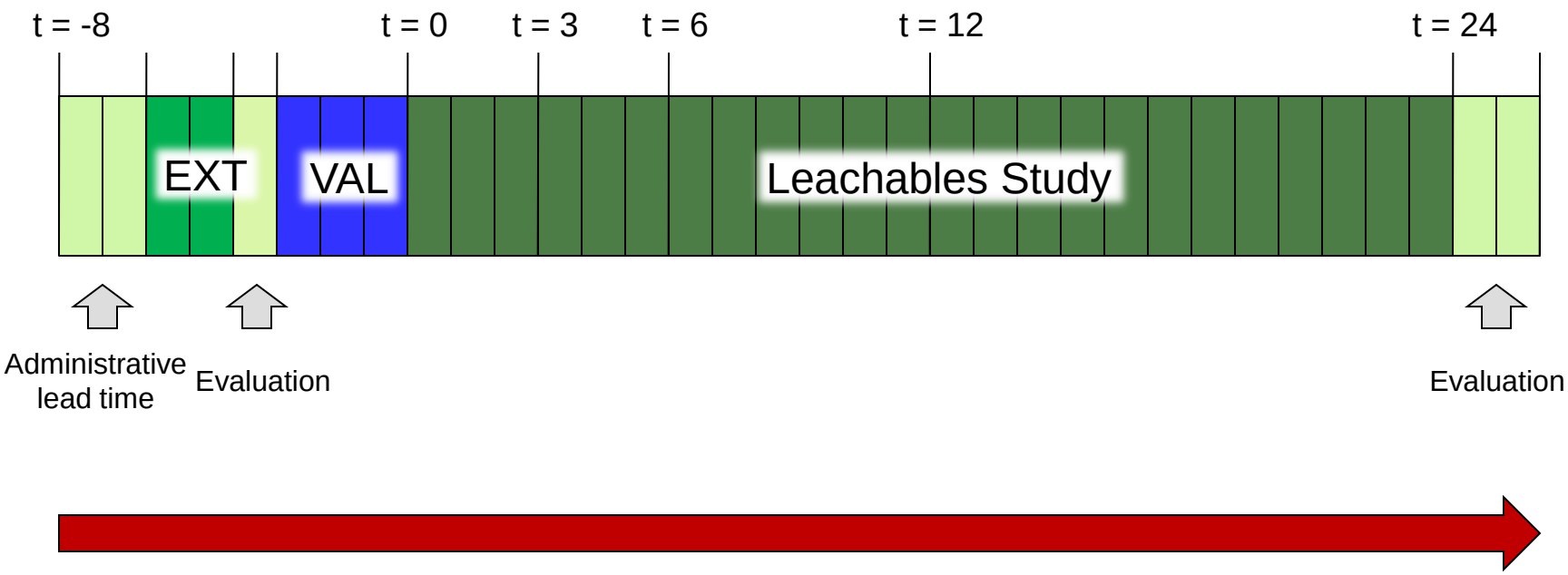
TARGET COMPOUNDS	ANALYTICAL METHOD
VALIDATED METHOD	Headspace GC/MS
Volatile Organic Compounds (VOC) SCREENING	
VALIDATED METHOD	GC/MS
Semi-Volatile Organic Compounds (SVOC) SCREENING	
VALIDATED METHOD	LC/MS
Non-Volatile Organic Compounds (NVOC) SCREENING	
Element Analysis	ICP
Anions: fluoride, chloride, and bromide	IC
Sulfur (S_8)	LC/UV

EXAMPLE OF FULL TIME TABLE LEACHABLE STUDY

Type of Solution	Storage Time (Months)				
	0	3	6	12	24
Drug Product in Rubber Sealed Vials (Test Item) at 5 ± 3 °C	×	×	×	×	×
Drug Product in Inert Containers (Blank) at 5 ± 3 °C	×	×	×	×	×
Drug Product in Rubber Sealed Vials (Test Item) at 25 ± 3 °C	-	×	×	-	-
Drug Product in Inert Containers (Blank) at 25 ± 3 °C	-	×	×	-	-
× = sampling time point					

5. DESIGNING LEACHABLE STUDIES

EXAMPLE OF FULL EXTRACTABLE&LEACHABLE STUDY



Total = 34 months

6. Safety Evaluation of Results:

Learning from the PQRI PODP Threshold Approach

6. PQRI PODP Threshold Approach

INITIAL PQRI EFFORTS: ESTABLISH SAFETY THRESHOLDS FOR OINDPs – 2006

- Toxicologists: acquired data through extenensive literature and database searches and analyses
- Chemists: acquired data by conducting extractions studies and placebo LEA studies
- Assess data and reach consensus
- Develop L & E Recommendations Document
  Submitted to FDA in 2006 for consideration in support of Regulatory Submission
- Recommendations widely used in Industry
  Not a policy/regulatory document

In 2008, PQRI started a similar approach for Parenteral & Ophthalmic DP. Expected to be finalized in 2014.

Information, from presentation D. Paskiet, CPhI Pharma Extractables & Leachables, November 29,2012, Hyderabad.

6. PQRI PODP Threshold Approach

SCT: **S**AFETY **C**ONCERN **T**HRESHOLD

"Threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and non-carcinogenic toxic effects"

PQRI for **OINDP's**: SCT = 0,15 µg/day

The SCT is not a Control Threshold, it is not a TTC

6. PQRI PODP Threshold Approach

AET: **A**NALYTICAL **E**VALUATION **T**HRESHOLD

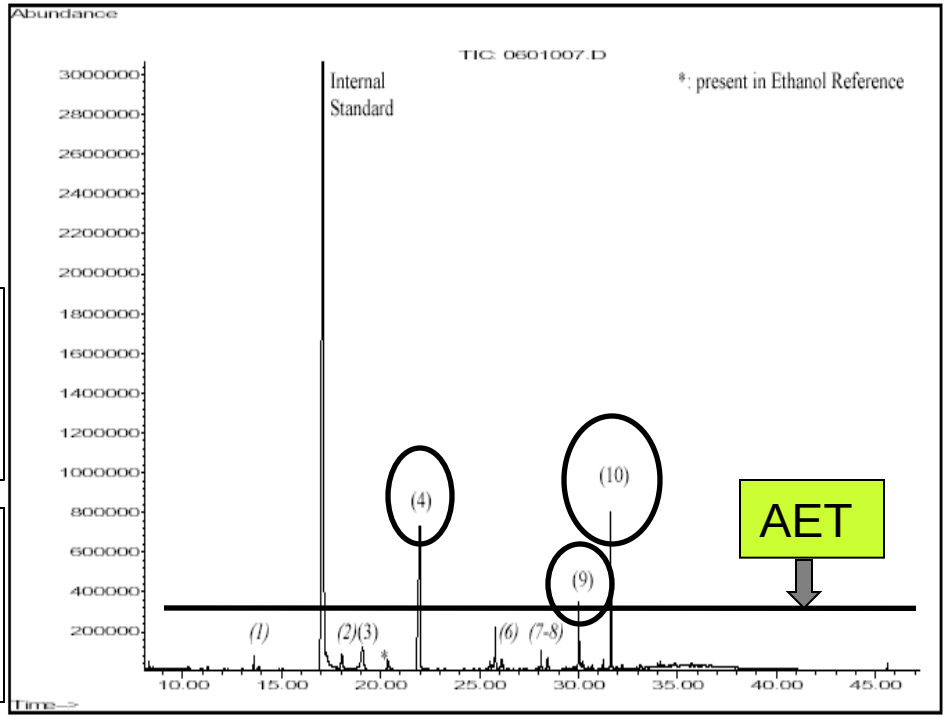
Translate SCT

into Analytical Thresholds

for Extractable Studies

Taking into account:

- *Total N° of doses / packaging*
- *Max. N° of doses administered / day*



6. PQRI PODP Threshold Approach

PQRI: SUGGESTED THRESHOLDS FOR **PARENTERAL** & OPHTHALMIC APPLICATIONS – current status

	Class I	Class II	Class III
Threshold Level (µg/day)	150 (to be confirmed)	5	1.5 - tbd

Class I: class of compounds which are **no** sensitizers, irritants, genotoxicants or carcinogens.
Class II: class of compounds which are known or expected to have sensitizing or irritating properties, but do not have any indications of genotoxicity or carcinogenicity.
Class III: class of compounds which are known or expected to be genotoxic or carcinogenic.

6. PQRI PODP Threshold Approach

THRESHOLD APPROACH CAN BE USED AT 2 DIFFERENT LEVELS

1. Safety Evaluation on results of an **Extraction Study**
2. Assisting in a Safety Evaluation on the results of a **Leachable Study**

6. PQRI PODP Threshold Approach

THRESHOLD APPROACH FOR EXTRACTION STUDIES

1. Facilitates the safety qualification of the (parts) of a Primary Packaging

2. Threshold approach could assist in a better determination of the steps to be taken in a subsequent leachable study

   - Selected Target Compounds for Quantitative LEA Study (i.e. Targets for validation)
   - Additional efforts in identification of compounds
   - In some cases, additional efforts in a safety evaluation of compound/part of a CCS
   - Expected concentration range to validate
   - ...

6. PQRI PODP Threshold Approach

THRESHOLD APPROACH FOR LEACHABLE STUDIES

Could assist in reducing efforts in safety evaluation of Leachables

- Leachables, detected below their respective threshold may not need further individual safety evaluation
- Only Leachables, detected at a level above their respective threshold, will need a more in depth chemical and risk assessment

6. PQRI PODP Threshold Approach

AET: **A**NALYTICAL **E**VALUATION **T**HRESHOLD

Example:

PFS Contains 1 dose

Maximum Daily Intake: 1 dose

Evaluation of Polymer Barrel (weight: 2 g)

Extraction ratio: 1 Barrel is extracted per 5 mL of Isopropanol (exhaustive extraction)

EXTRACTABLES:

Threshold Class I: 150 µg/day: final AET level: 75 µg/Barrel

Threshold Class II: 5 µg/day: final AET level: 2.5 µg/Barrel

Threshold Class III: 1,5 µg/day: final AET level: 0,75 µg/Barrel

6. PQRI PODP Threshold Approach

AET: **A**NALYTICAL **E**VALUATION **T**HRESHOLD

Formula used (see PQRI recommendations):

$$\text{Est. AET} = \frac{\text{Threshold}}{\text{dose/day}} \cdot \frac{\text{total dose}}{\text{PFS}}$$

$$\text{Class I: Est. AET} = \frac{150\ \mu\text{g / day}}{1\text{dose / day}} \cdot \frac{1\text{dose}}{\text{Barrel}} = 150\ \mu\text{g / rubber}$$

$$\text{Final AET} = 75\ \mu\text{g / Barrel}$$

50% uncertainty for screening methods

6. PQRI PODP Threshold Approach

Further Calculations will give the following AET levels for the respective Classes:

	Threshold (µg/day)	Final AET (µg/barrel)	Final AET (mg/Kg)	Final AET (mg/L)
Class I	150	75	37	15
ClassII	5	2,5	1,2	0,5
Class III	1,5	0,75	0,37	0,15

Barrel weight: 2g

Extr. Ratio: 1barrel/5 mL

6. PQRI PODP Threshold Approach

Typical Results for an Exhaustive Extraction on a Polymer Barrel

	EXT result mg/L extract	EXT result mg/Kg Barrel	EXT result µg/Barrel
COMPOUND #1	0,1	0,25	0,5
COMPOUND #2	0,2	0,5	1
COMPOUND #3	1,25	3,13	6,3
COMPOUND #4	2	5	10
COMPOUND #5	0,4	1,0	2,0
COMPOUND #6	0,25	0,63	1,3
COMPOUND #7	13	32,5	65
COMPOUND #8	0,1	0,25	0.5
COMPOUND #9	27	67,5	135
COMPOUND #10	0,4	1	2
COMPOUND #11	0,1	0,25	0,5
COMPOUND #12	5,5	13,8	27,5
COMPOUND #13	32,5	81,3	163
COMPOUND #14	1,2	3	6
COMPOUND #15	0,35	0,88	1,8

6. PQRI PODP Threshold Approach

EXAMPLE OF GC/MS RESULTS FOR EXTRACTABLE STUDY

	EXT result mg/L	Class	Threshold for Class (µg/day)	AET for Class (mg/L)
COMPOUND #1	0,10	Class I	75	15
COMPOUND #2	0,20	Class I	75	15
COMPOUND #3	**1,25**	**Class III**	**0,75**	**0,15**
COMPOUND #4	2,00	Class I	75	15
COMPOUND #5	0,40	Class II	2,5	0,5
COMPOUND #6	0,25	Class I	75	15
COMPOUND #7	**13,00**	**Class II**	**2,5**	**0,5**
COMPOUND #8	0,10	Class III	0,75	0,15
COMPOUND #9	**27,00**	**Class I**	**75**	**15**
COMPOUND #10	0,40	Class II	2,5	0,5
COMPOUND #11	0,10	Class III	0,75	0,15
COMPOUND #12	5,50	Clas I	75	15
COMPOUND #13	**32,50**	**Class III**	**0,75**	**0,15**
COMPOUND #14	1,20	Class I	75	15
COMPOUND #15	0,35	Class II	2,5	0,5

6. PQRI PODP Threshold Approach

Conclusion of the Threshold Evaluation:

- ❑ Exhaustive Extraction Results indicate that – if all would come out – these compounds would be detected as leachable above their respective threshold level

- ❑ Were Compounds 3, 7, 9 and 13 identified?
  In some cases, furthe attention to additional identification needs to be given

- ❑ Analytical methods for compounds 3, 7, 9 and 13 will need to be validated for the subsequent leachable study

- ❑ The validation range will be different for the 4 compounds as a result of:
  - ➢The concentration level of the compound, found in the rubber
  - ➢The different classess for the respective compounds:
  - ➢The validation range should always include the AET level for the respective compound, as a minimum

- ❑ Presence of other compounds may be monitored (semi-quantitatively) in Leachable Study, using screening methodology

Conclusion

7. CONCLUSION

- ✓ STEP 1: COLLECT INFORMATION ON MATERIALS USED
- ✓ STEP 2: CAREFULLY PLAN, PERFORM AND EVALUATE EXTRACTABLE STUDY
- ✓ STEP 3: SELECT TARGET COMPOUNDS AMENABLE TO LEACHABLE STUDY
- ✓ STEP 4: CARRY OUT LEACHABLES STUDY UNDER "SIMULATED USE CONDITIONS"
- ✓ STEP 5: CARRY OUT TOXICOLOGICAL ASSESSMENT ON LEACHABLES RESULTS

ANY QUESTIONS?

For further questions, please contact:

piet.christiaens@toxikon.be

http://www.toxikon.be/extractables-leachables-parenteral-injectables.html