Connecting People, Science and Regulation

EXTRACTABLES & LEACHABLES FOR INJECTABLES

PDA Post-Conference E/L-Workshop
06-07 November, 2014

Dr. Piet Christiaens
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

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...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

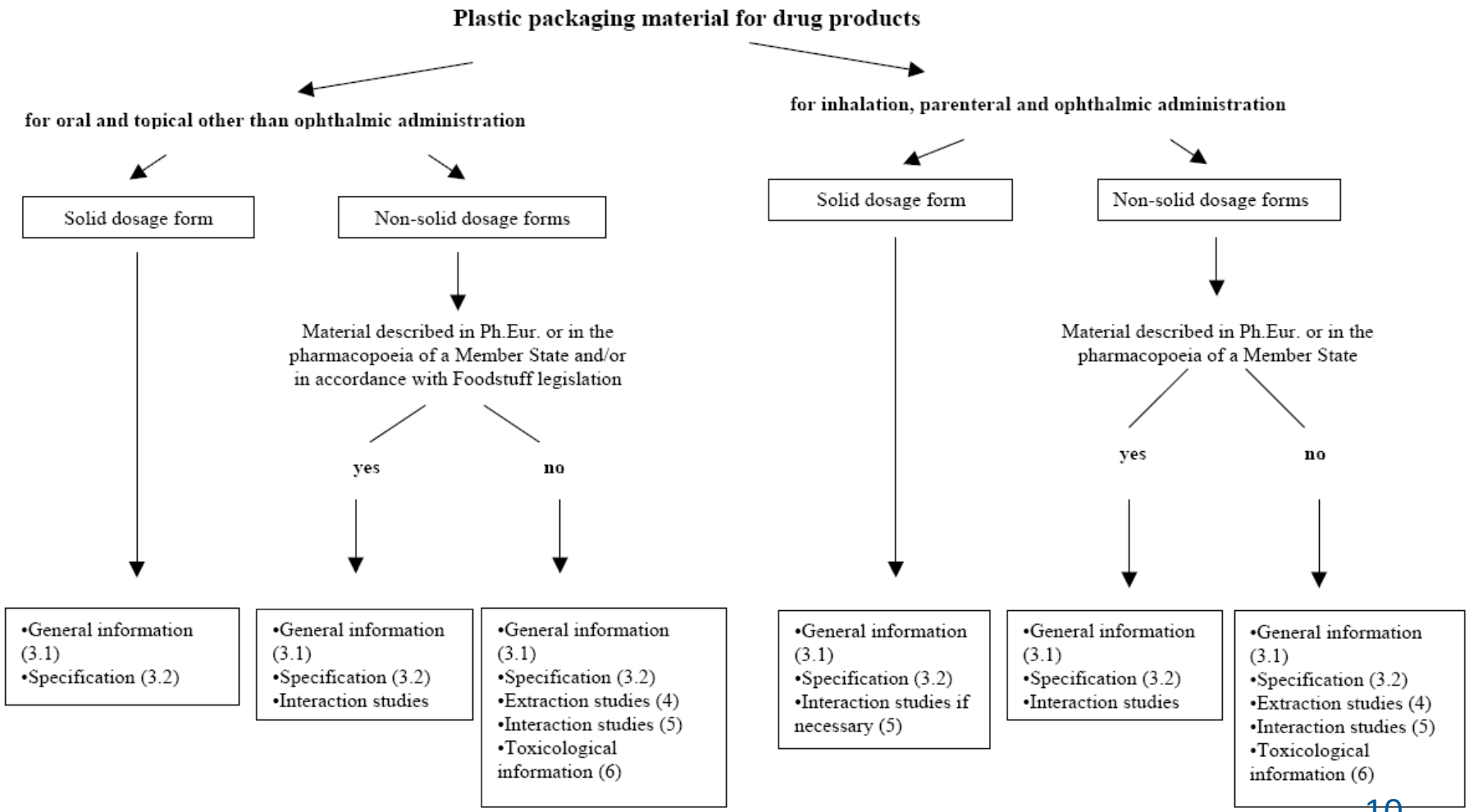
REMARK:

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*

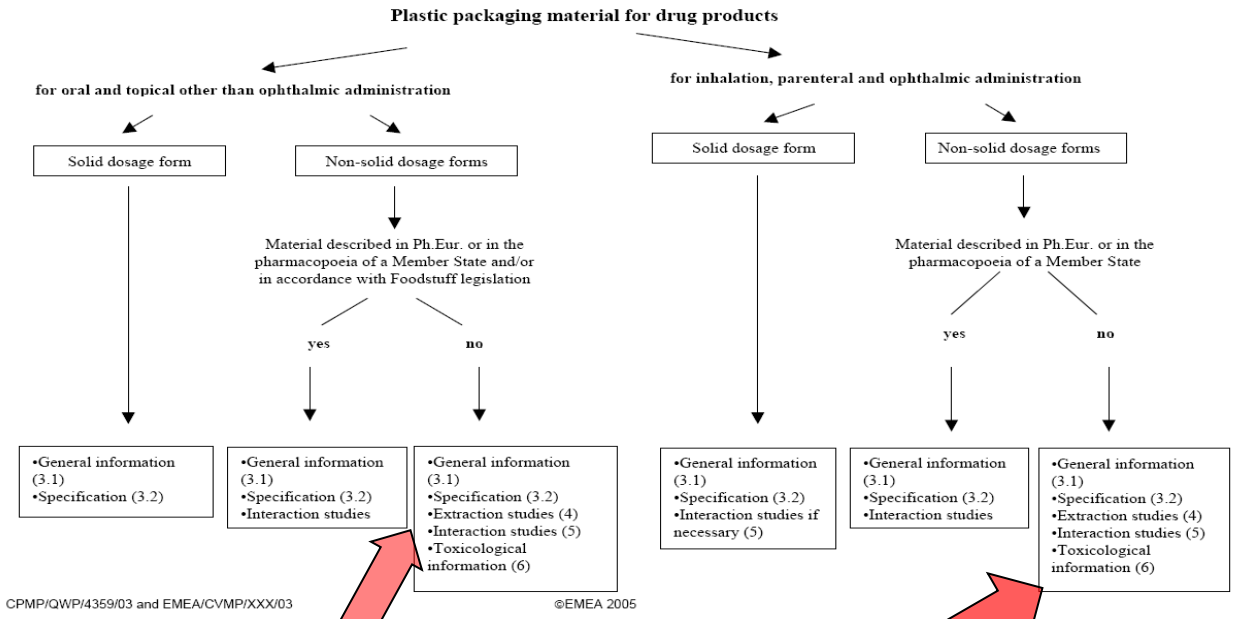


CPMP/QWP/4359/03 and EMEA/CVMP/XXX/03

©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!

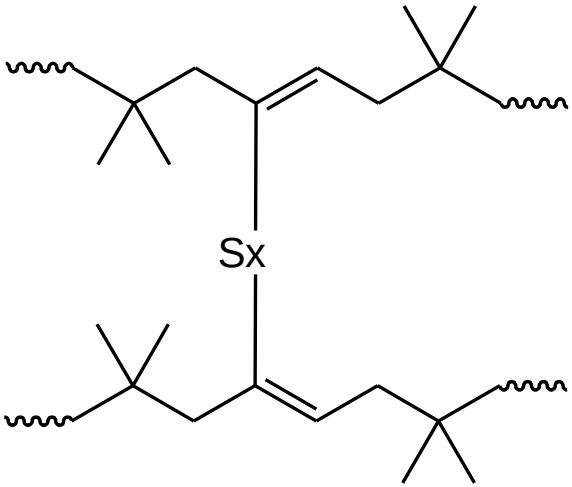
Rubber Sealings

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)***

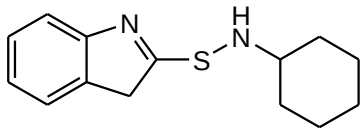
2. TYPES OF ELASTOMERIC CLOSURES

Rubber Curing / Vulcanization:

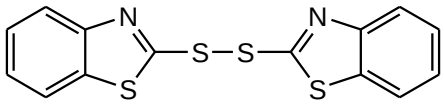


Rubber crosslinking requires S-Donors, activators, accelerators
Activator: ZnO / Stearic acid

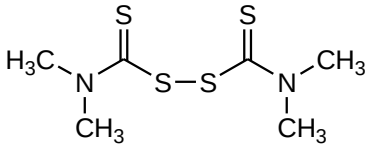
Rubber Curing - Accelerators:



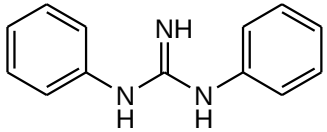
Cyclohexyl benzothiazole sulfenamide



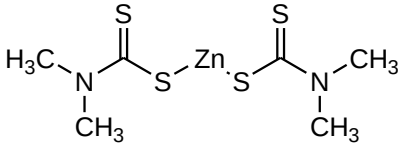
Mercaptobenzothiazole disulfide



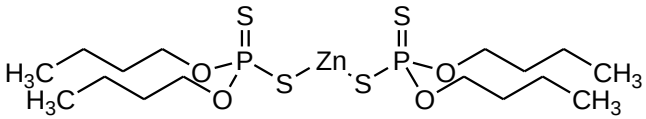
Tetramethylthiuram disulfide(TMTD)



Diphenyl guanidine



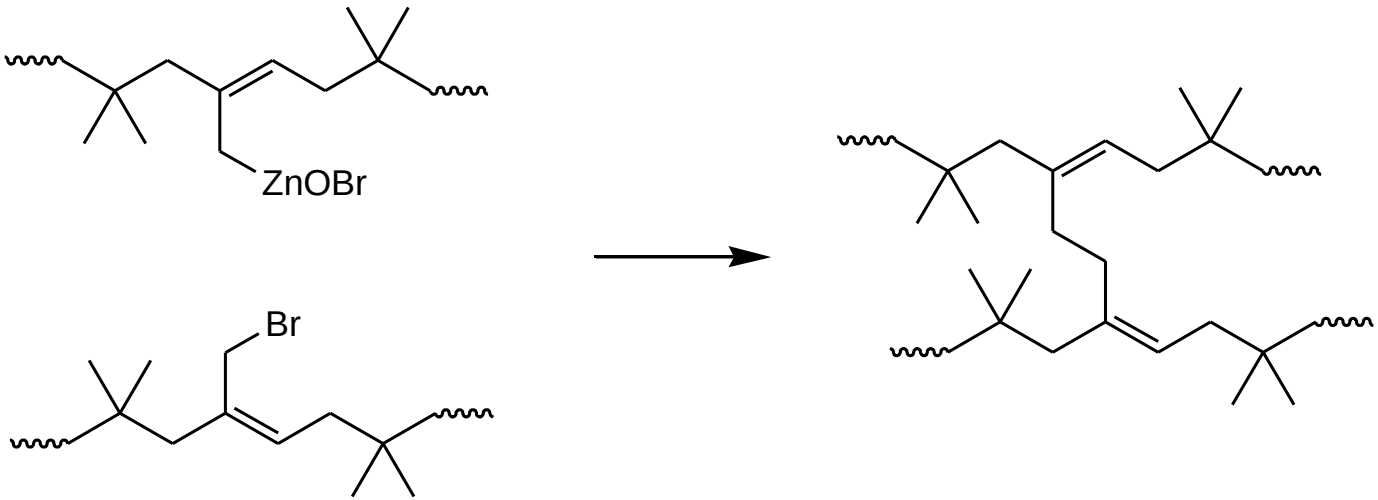
Zinc dimethyldithiocarbamate



Zinc dibutylphosphorodithiate

2. TYPES OF ELASTOMERIC CLOSURES

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…

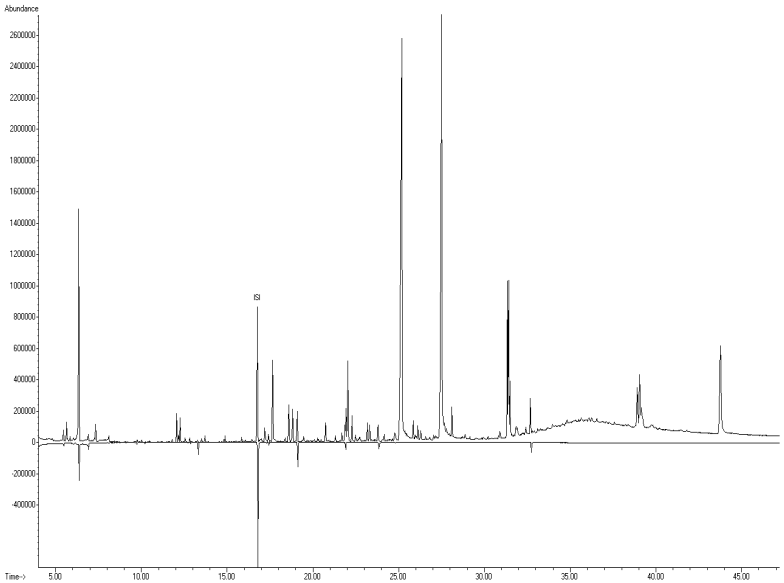
2. TYPES OF ELASTOMERIC CLOSURES

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*)

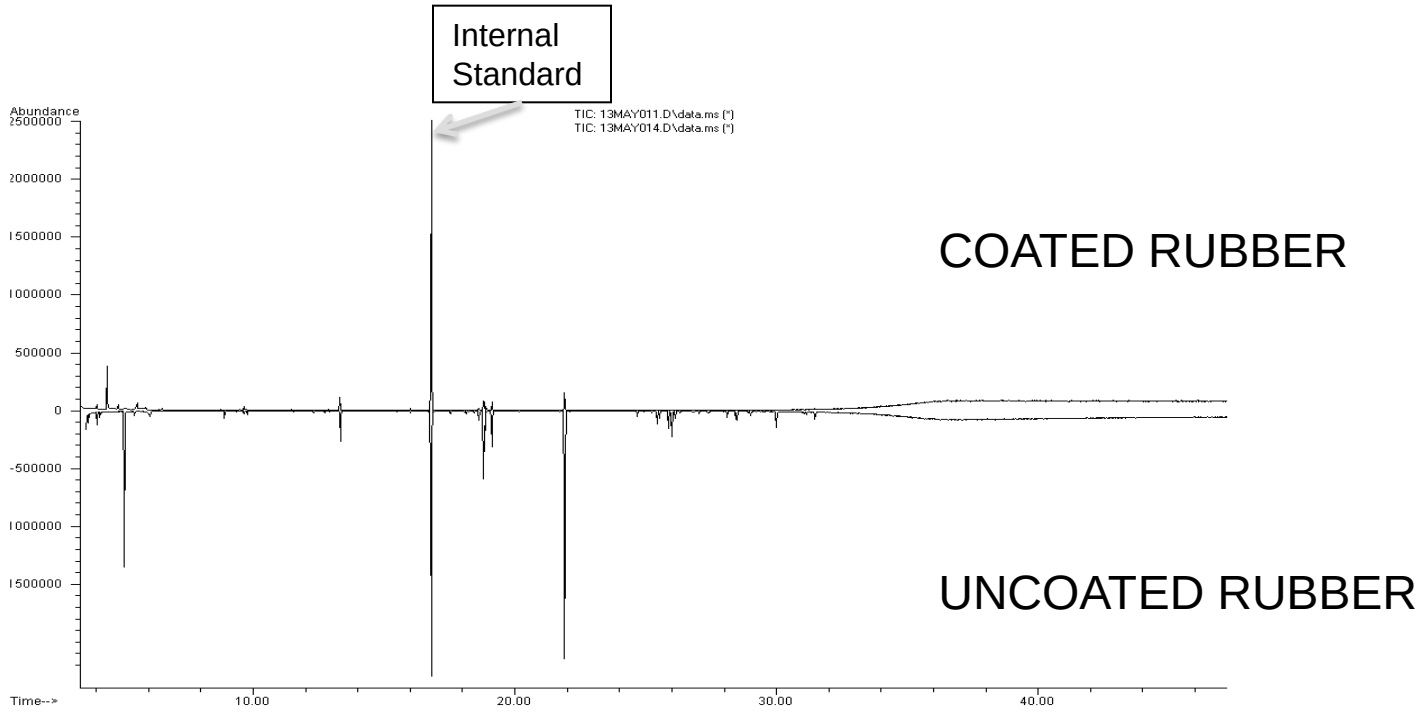


“OLD” RUBBER

“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

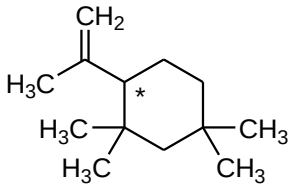
3. RUBBER OLIGOMERS

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

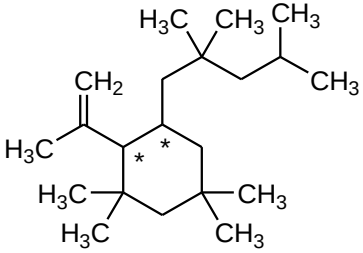
- Considered as
  - Cyclic aliphatic hydrobarbon compounds
  - One double bond

- 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)

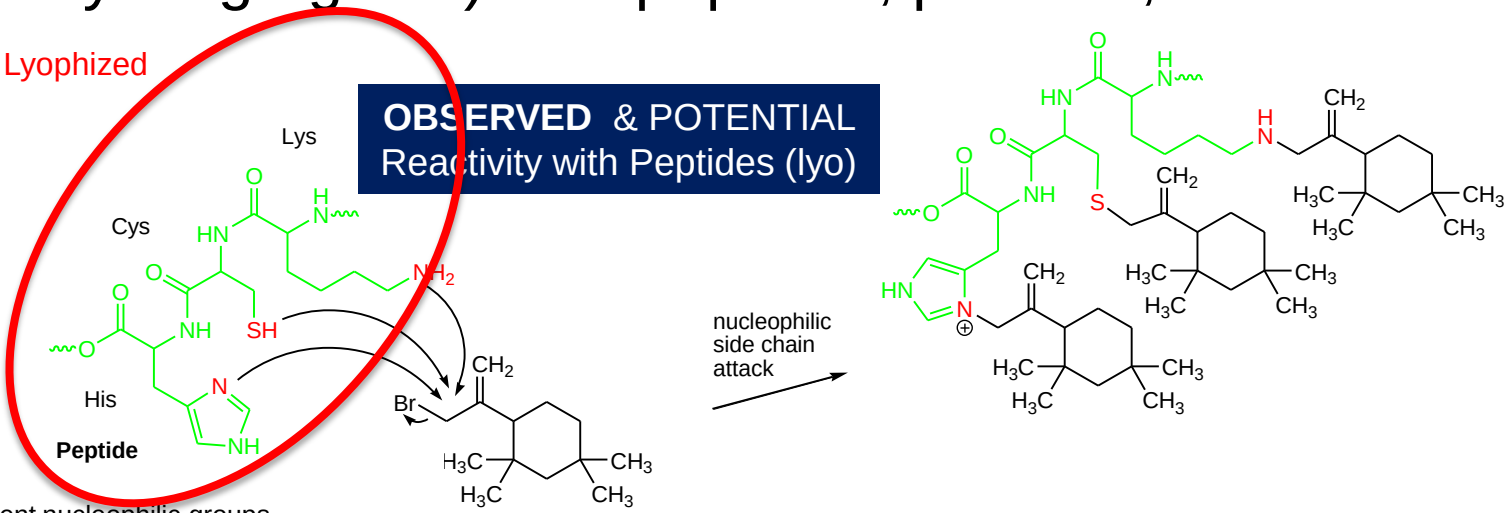
The low SCT/TTC levels for the Halogenated Oligomers mean:

- 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



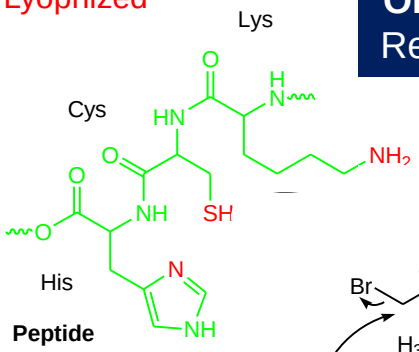
With different nucleophilic groups

Ref. 7

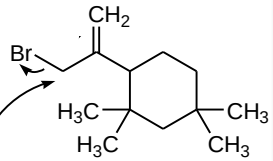
Observed Reactivity of $C_{13}H_{23}Br$ and $C_{21}H_{39}Br$ (as alkyating agents) with peptides, proteins, c acids

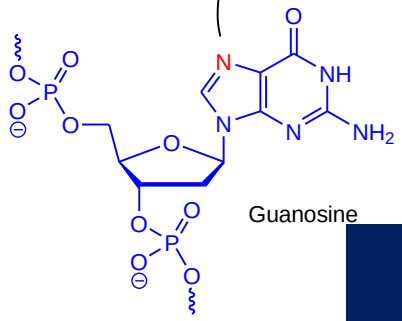
Example of Lyophized peptide

OBSERVED & POTENTIAL Reactivity with Peptides (lyo)



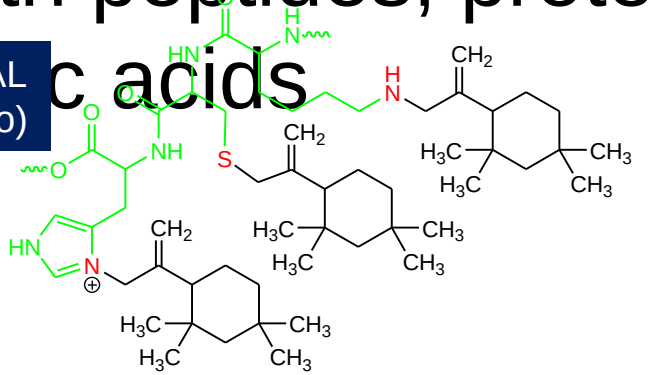
With different nucleophilic groups





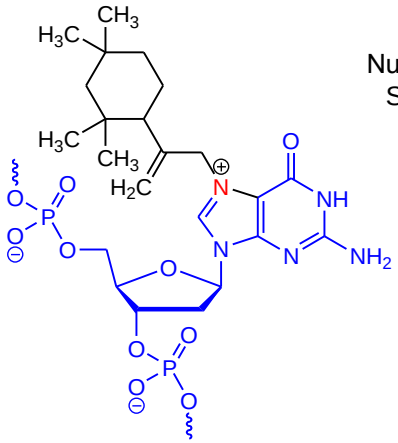
DNA

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

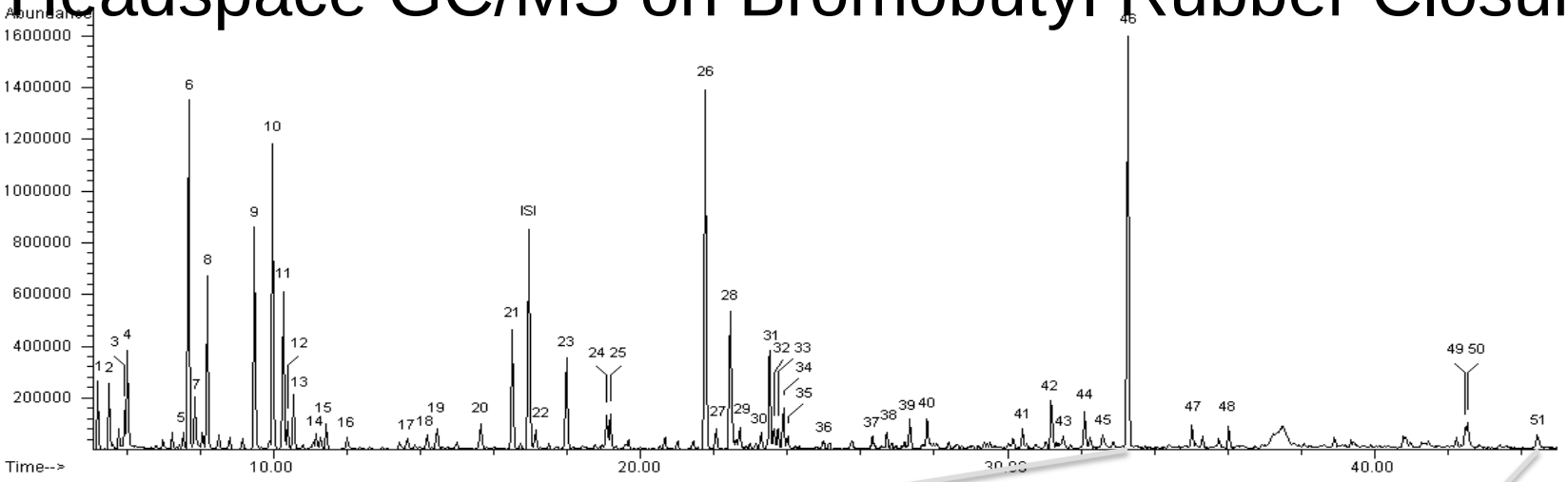
3. RUBBER OLIGOMERS

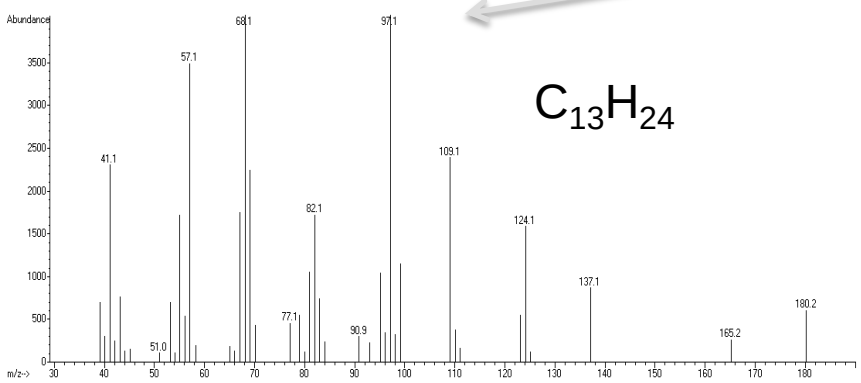
Cases where Rubber Oligomers have been detected as LEACHABLES:

- 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

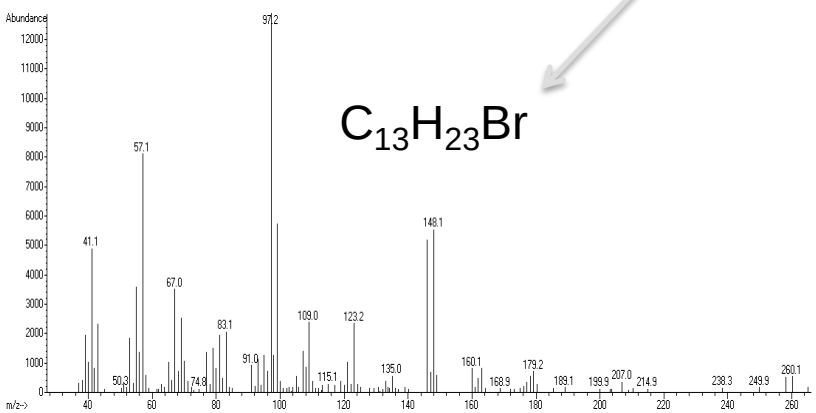
3. RUBBER OLIGOMERS

Headspace GC/MS on Bromobutyl Rubber Closure:





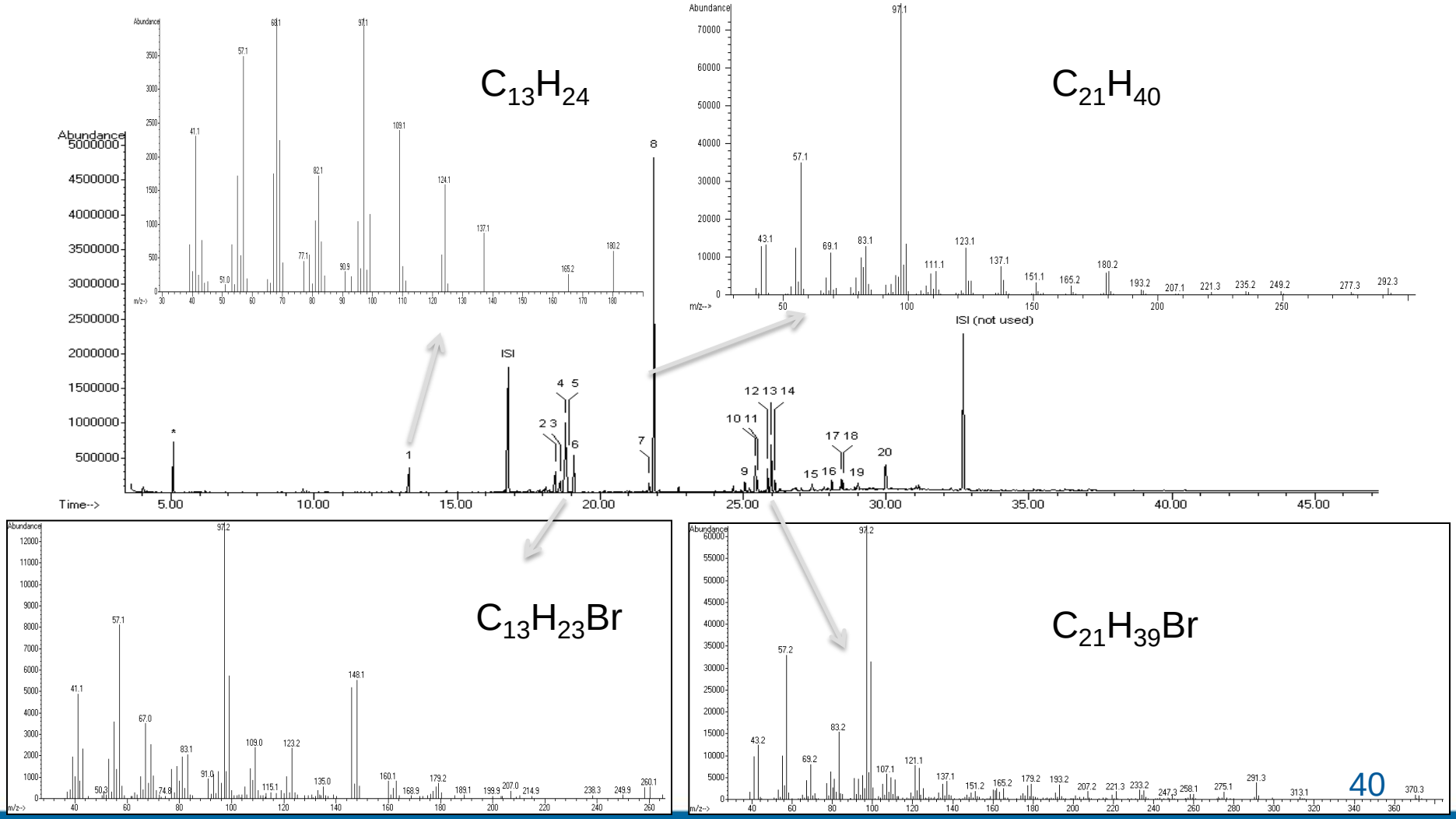
$C_{13}H_{24}$



$C_{13}H_{23}Br$

3. RUBBER OLIGOMERS

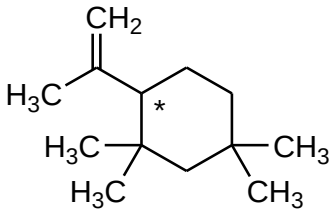
GC/MS on IPA extract of Bromobutyl Rubber Closure:

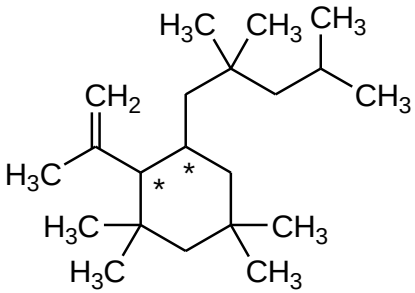


STRUCTURE ELUCIDATION

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

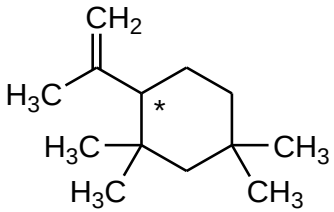
- 1 chiral center
  => 1 pair of enantiomers

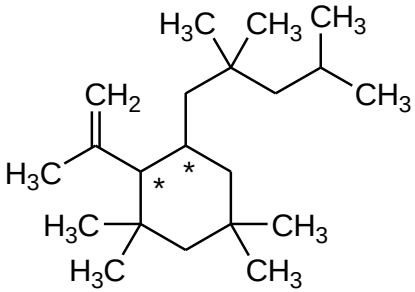
$C_{21}H_{40}$ Oligomer:

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

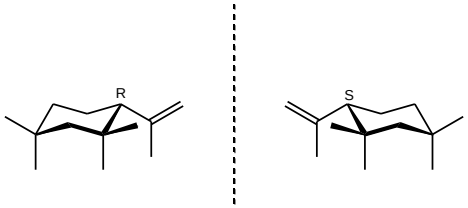
3. RUBBER OLIGOMERS

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

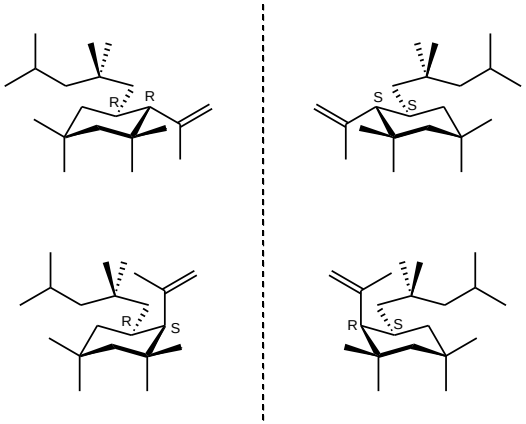




$C_{13}H_{24}$ Oligomer:
=> 1 pair of enantiomers



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

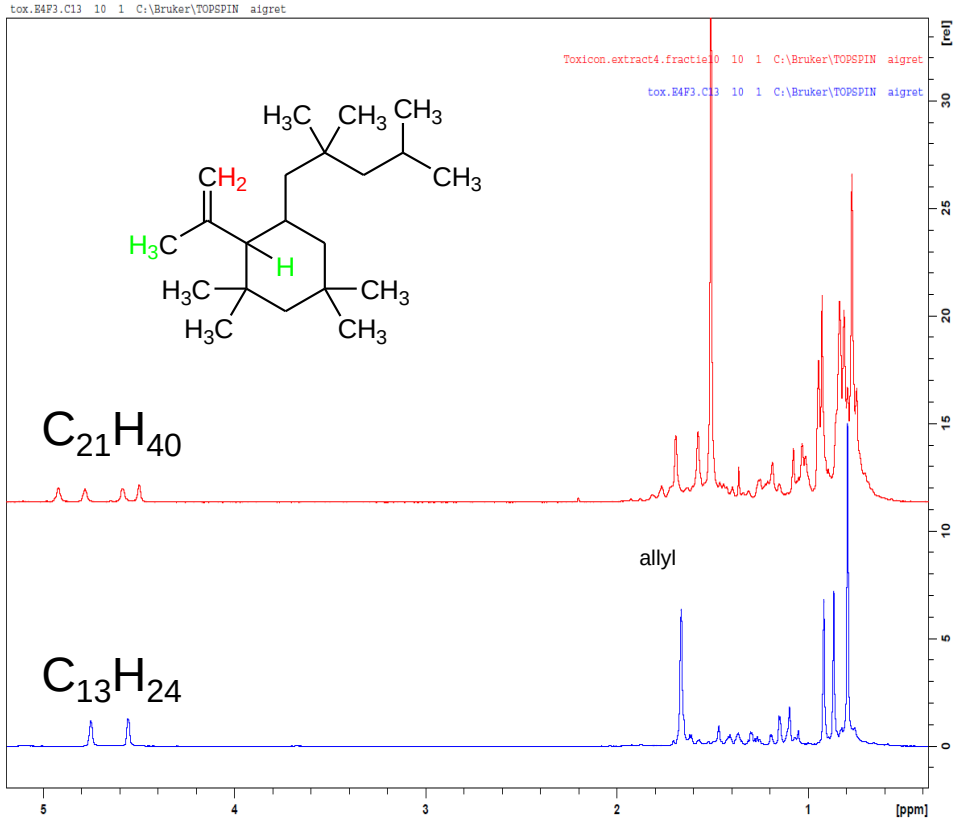


NMR Spectrum obtained from the isolated Oligomers

Characteristic peaks:

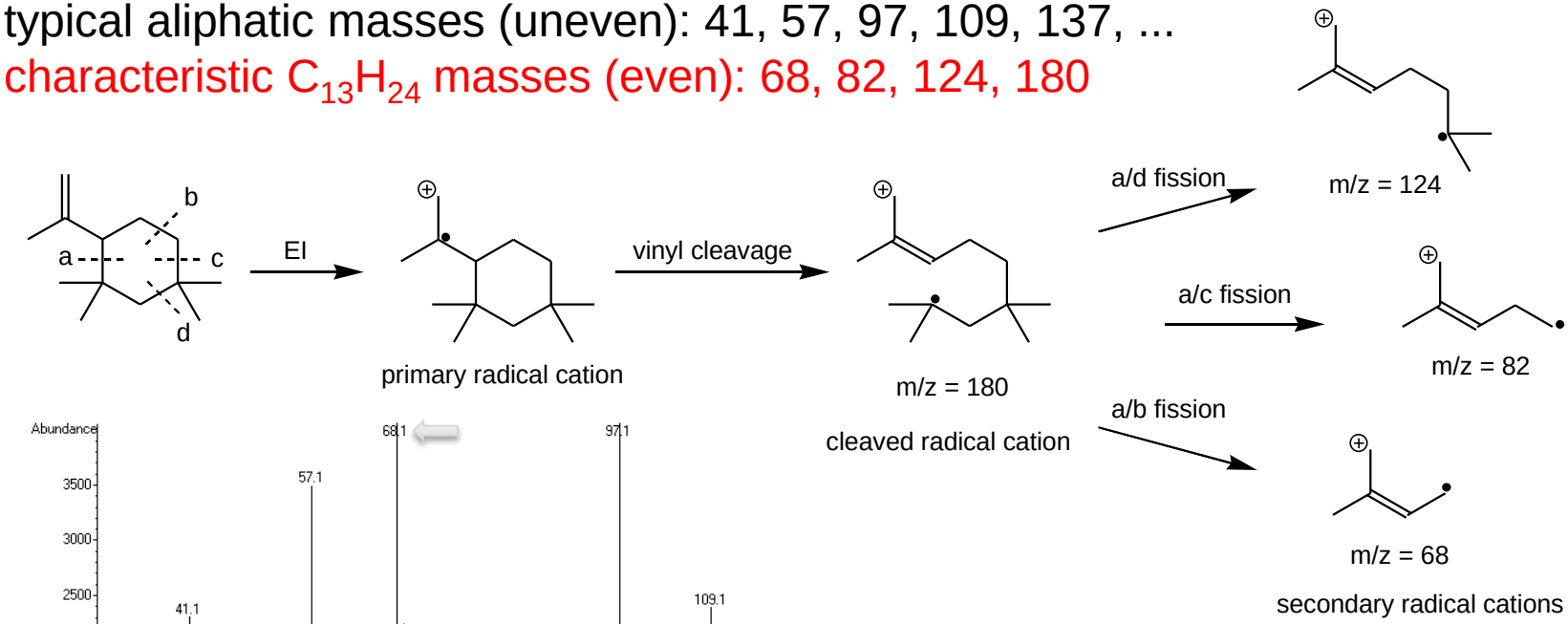
- ~4.7 ppm: 2 vinyl protons
- ~1.6 ppm: allyl protons
  (3 methyl & 1 tertiary)
- <1.0 ppm: 4 ring-methyl groups
  (4 additional methyl groups for $C_{21}H_{40}$)

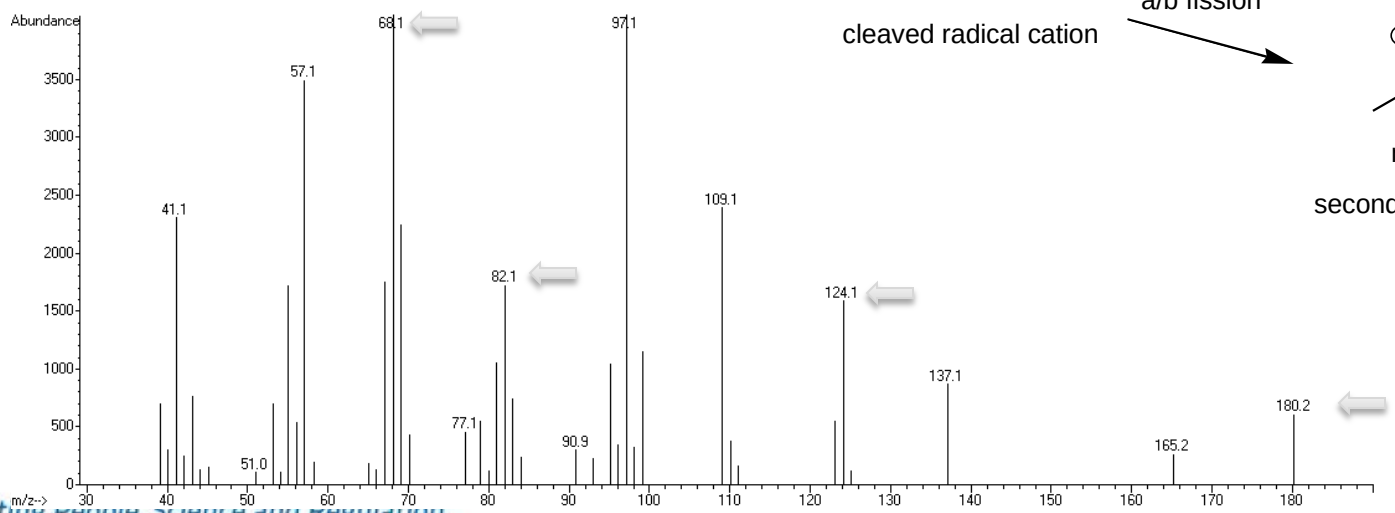
➢ NOTE: ALL PEAKS ARE DOUBLED FOR THE $C_{21}H_{40}$ DUE TO THE OVERLAY OF THE SPECTRA OF THE 2 DIASTEREOMERS



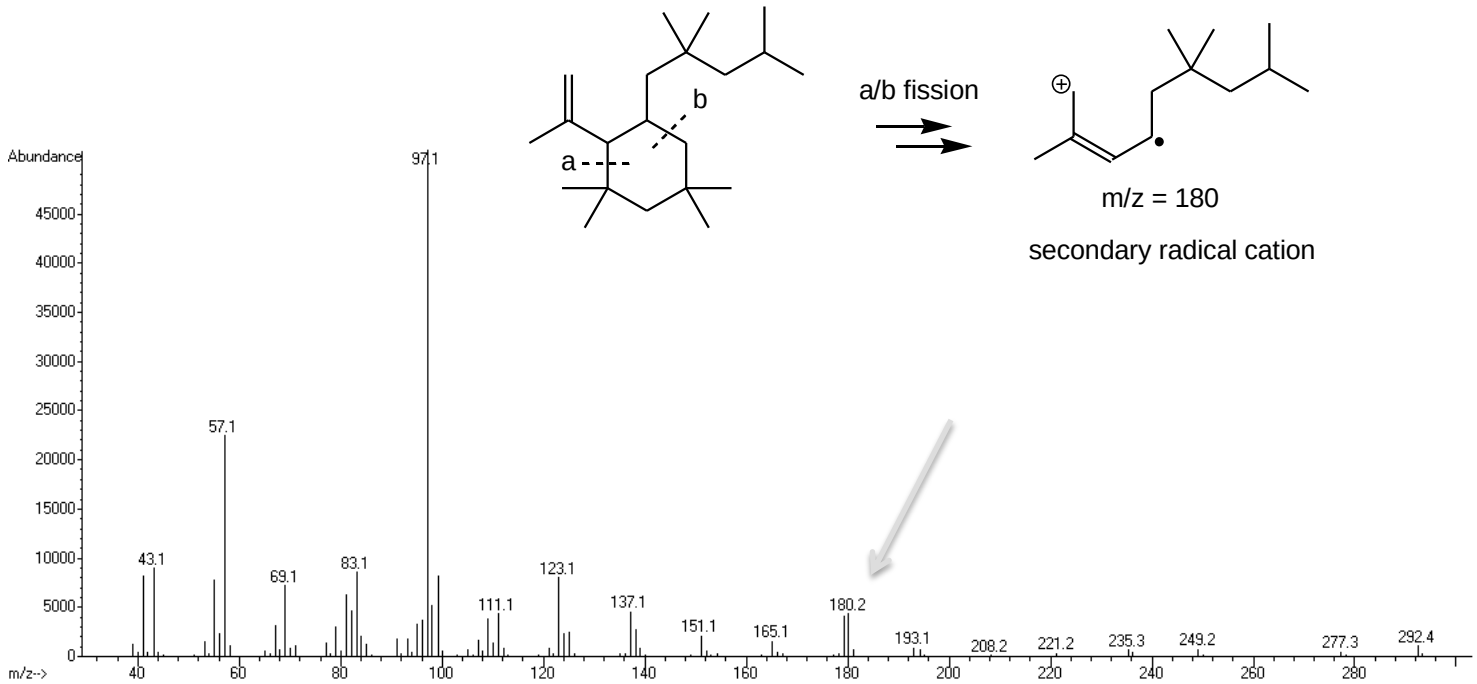
GC/MS Mass Spectrum of the $C_{13}H_{24}$ Oligomer

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



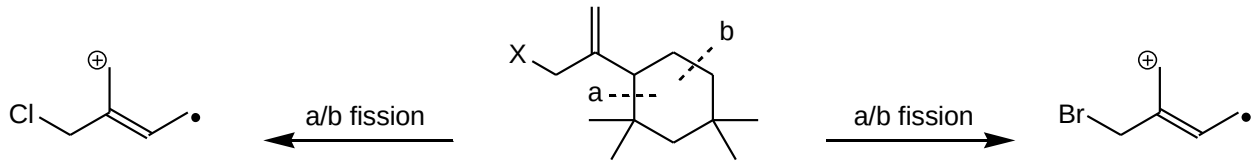


GC/MS Mass Spectrum of the $C_{21}H_{40}$ Oligomer



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

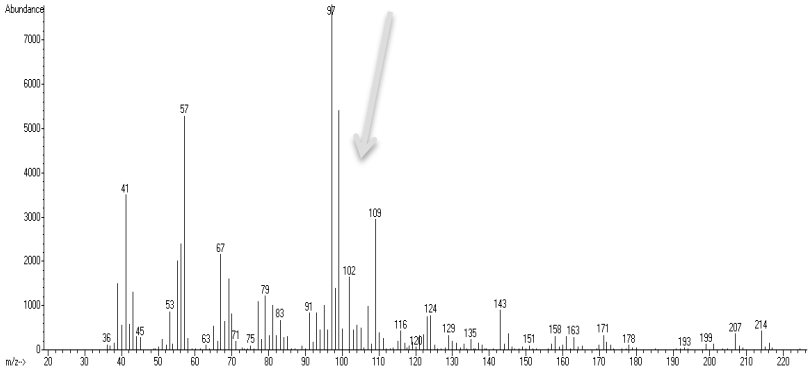
chlorinated secondary radical cation

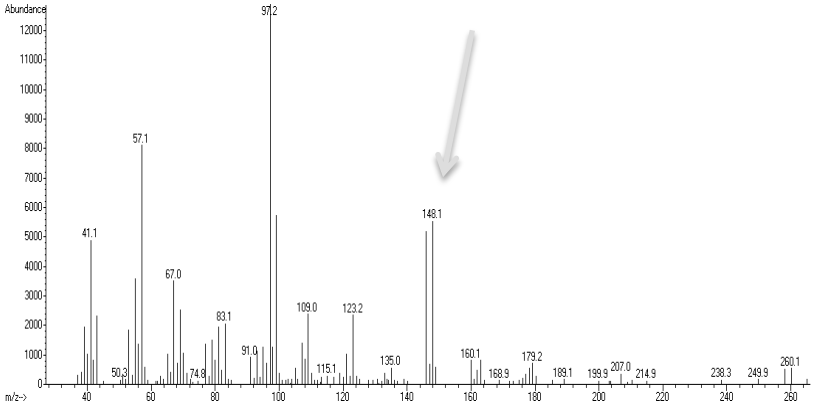
m/z = 214/216 (Cl); 258/260 (Br)

Halobutyl oligomer (X=Cl,Br)

m/z = 146/148

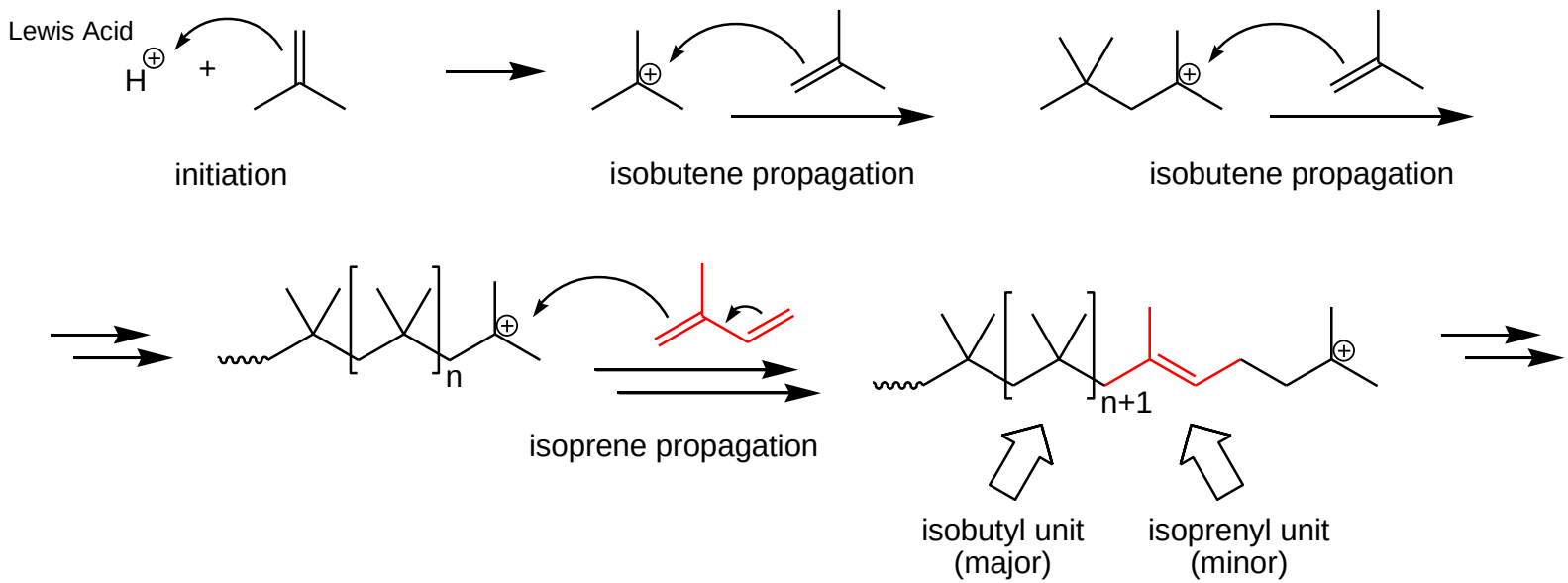
brominated secondary radical cation





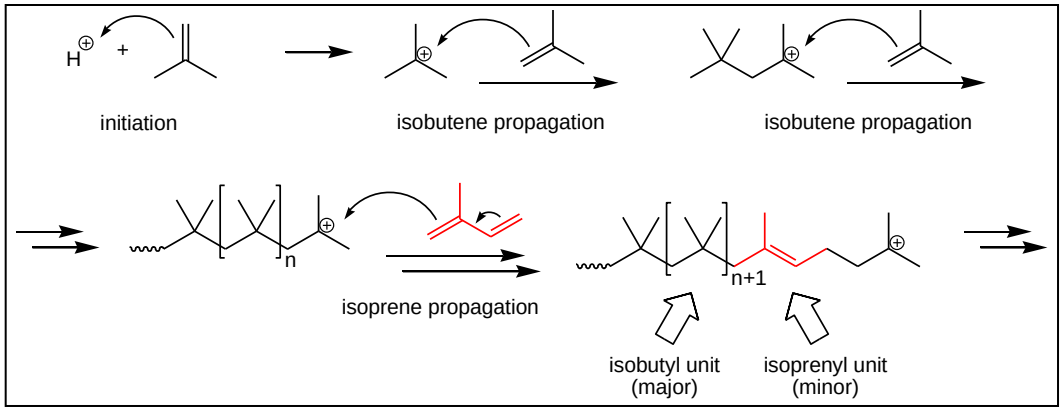
FORMATION OF OLIGOMERS

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:

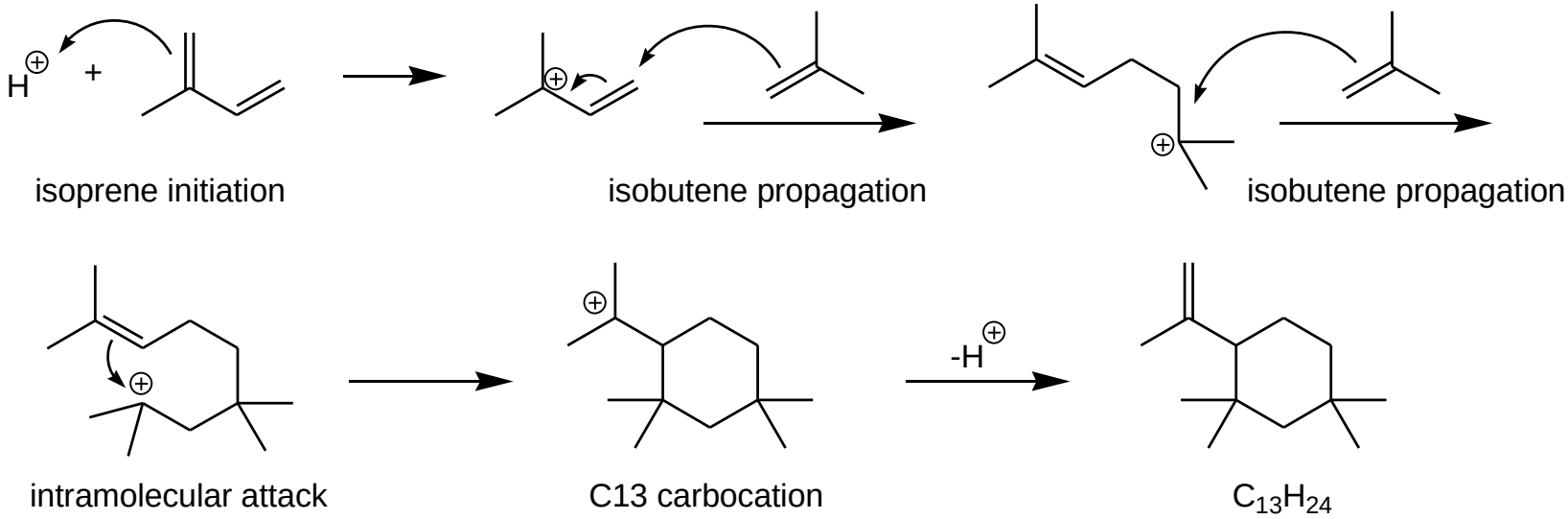
*Butyl Elastomer (IIR) is **less prone to Oxidation***

*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

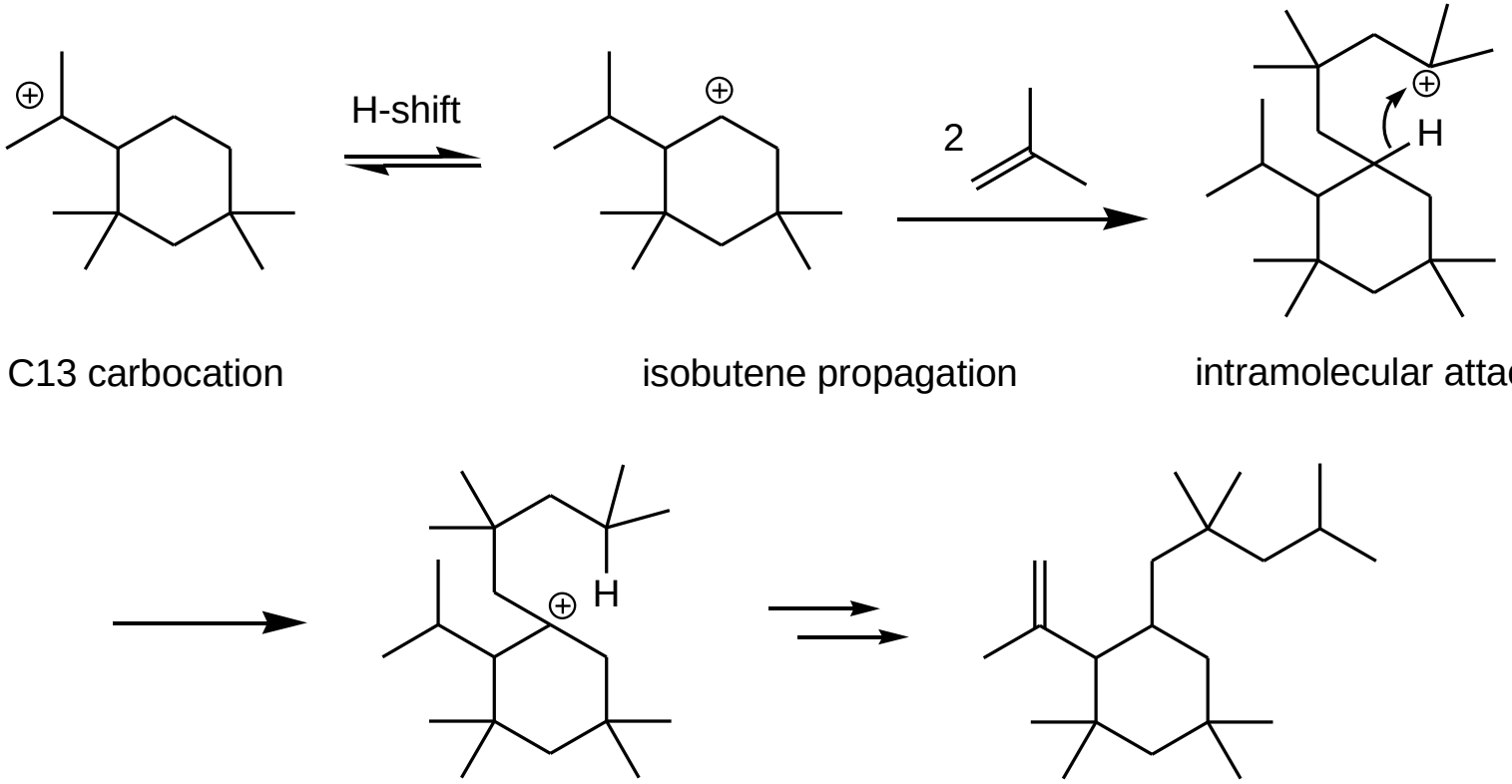


Backbite reaction

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

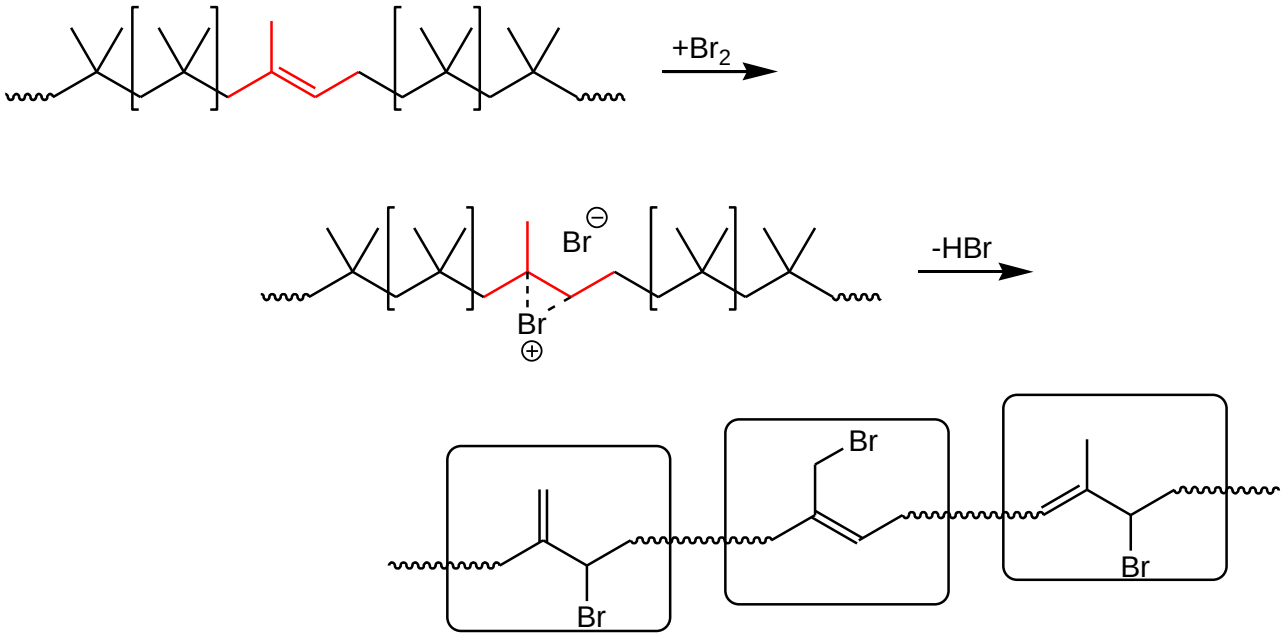
Ref. 2, 3

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



Ref. 2, 3

Bromination of a Butyl Elastomer (BIIR)



Type 1 Type 2 Type 3

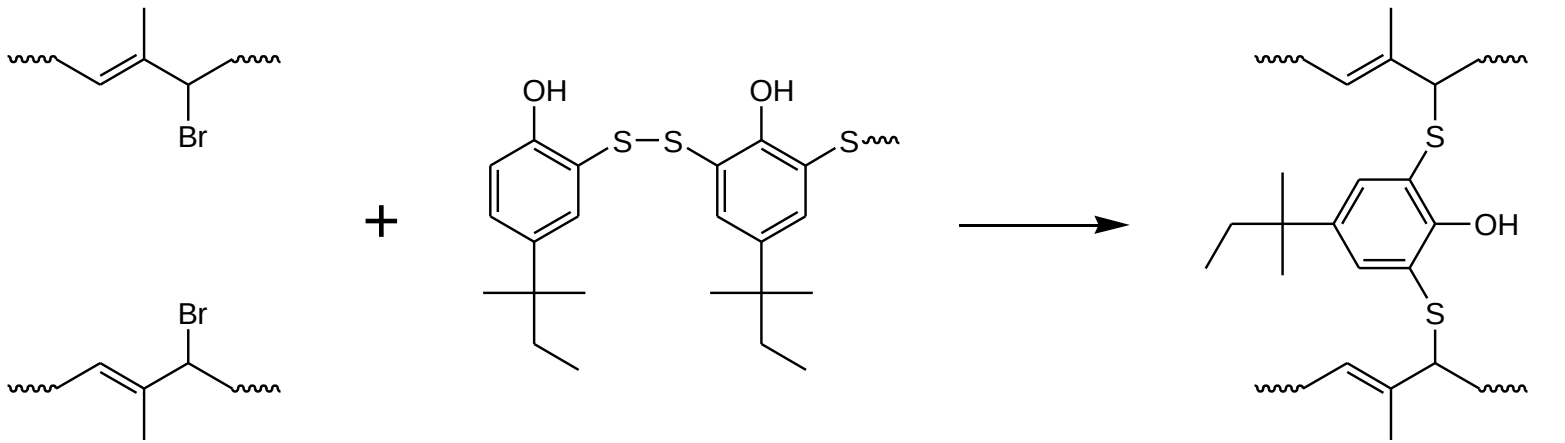
Bromination of the Backbone makes Elastomer

(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

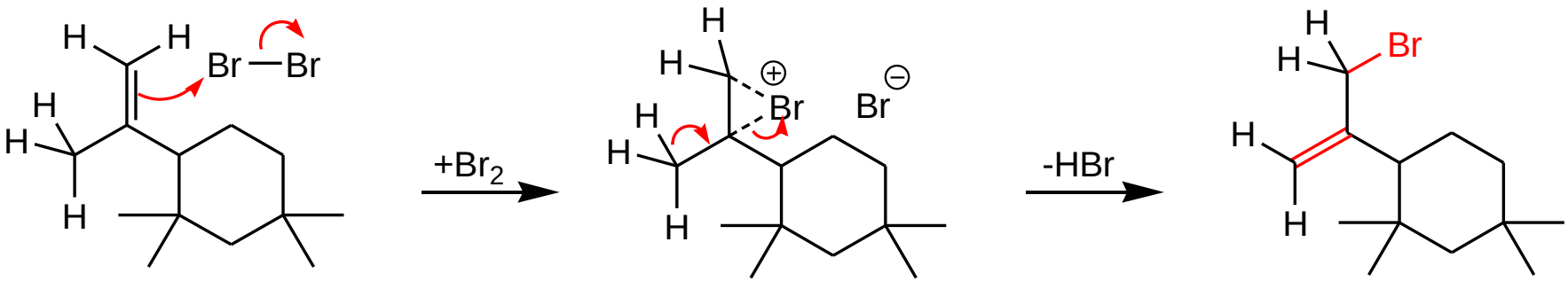
Explains Br^- release from bromobutyl rubbers

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

Note: a lot of valuable information on how to develop a scientific protocol for Parenteral / Ophthalmic DP can also be found in the following documents from the PQRI-PODP workgroup

PQRI
Product Quality Research Institute

Parenteral and Ophthalmic Drug Products Leachables and Extractables Working Group

Issued and Effective
September, 2011

Study Protocol – Stage 1
Amendment #1

Experimental Protocol for Qualitative Controlled Extraction Studies on Material Test Articles Representative of Prefilled Syringe (PFS) and Small Volume Parenteral (SVP) Container Closure Systems

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"

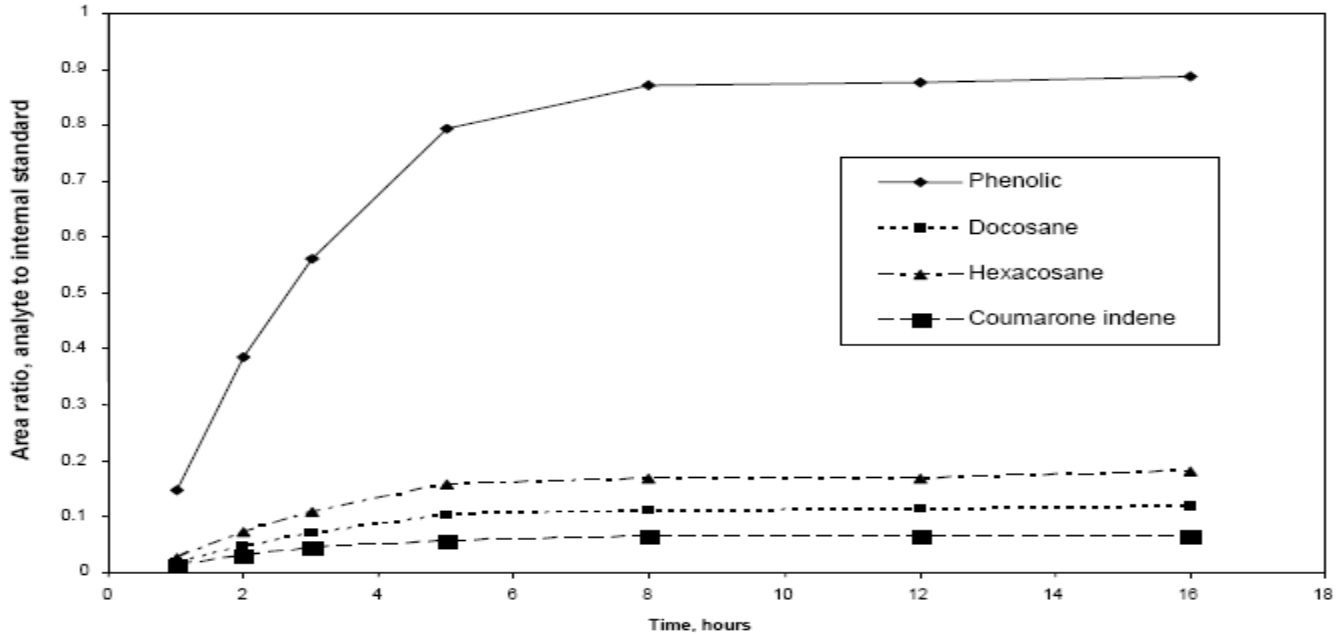
EXAMPLE: for WFI – does 8 hour reflux mimic a 3 year shelf life?

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"

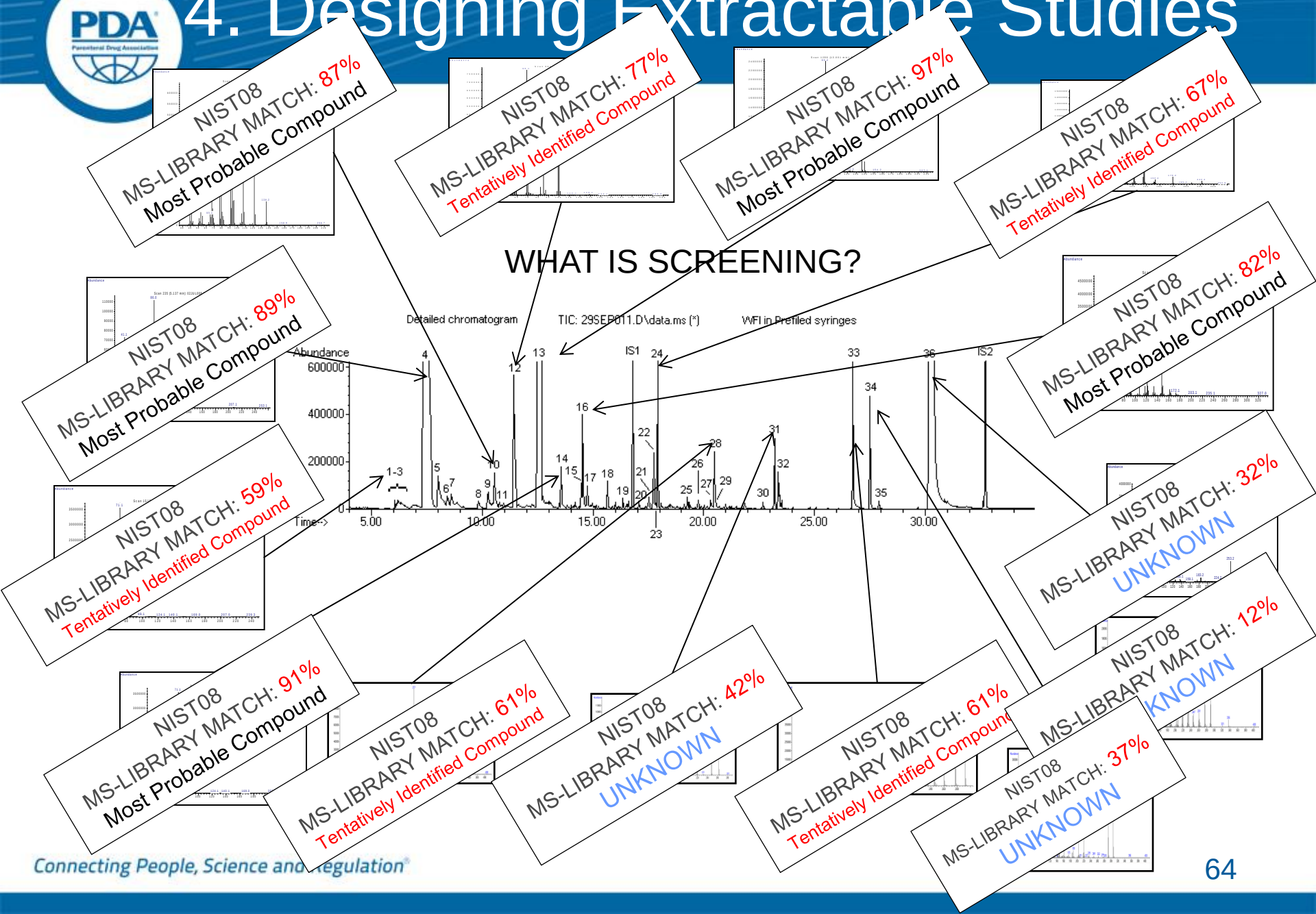
4. Designing Extractable Studies

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

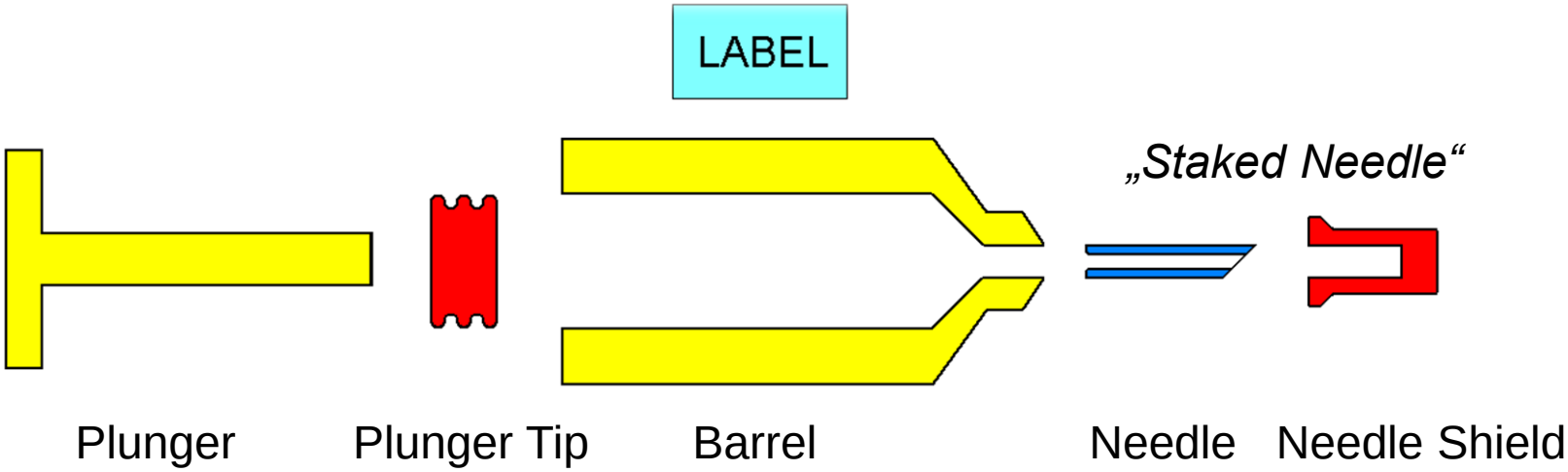
4. Designing Extractable Studies

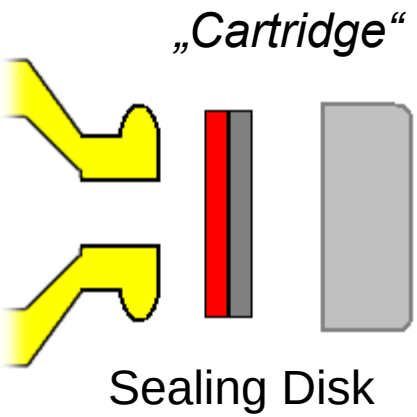
WHAT IS SCREENING?

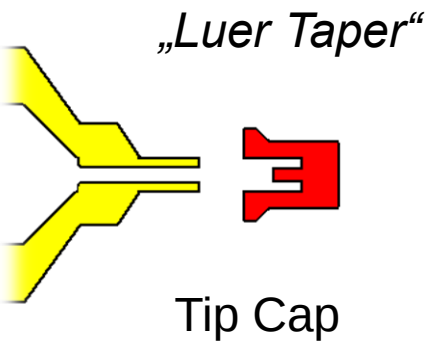


4. Designing Extractable Studies

PRE-FILLED SYRINGE: COMPOSING PARTS



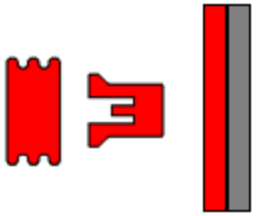




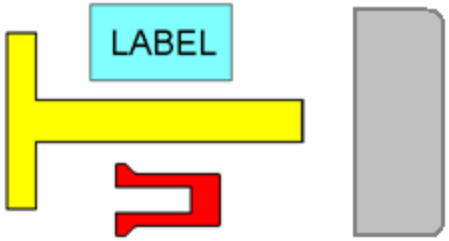
4. Designing Extractable Studies

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)

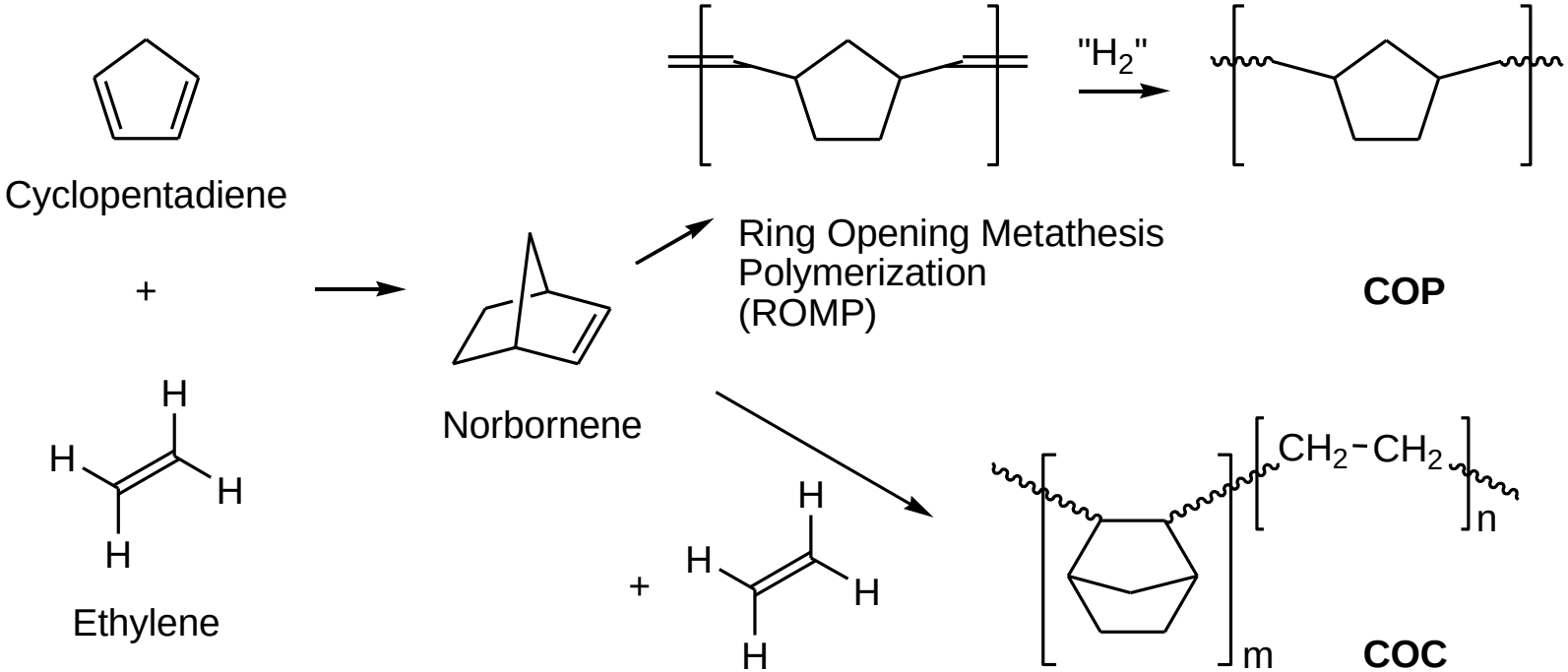
Cyclic Olefin (Co-)Polymer COC/COP

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

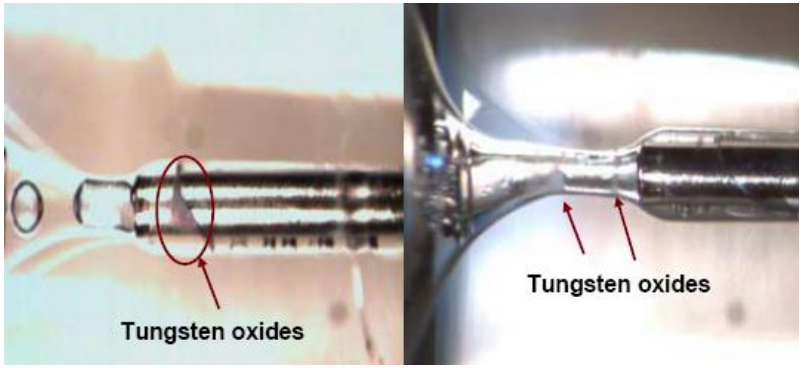
4. Designing Extractable Studies

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

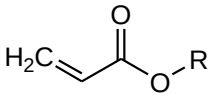
4. Designing Extractable Studies

Glass as Barrel Material – Related Compounds

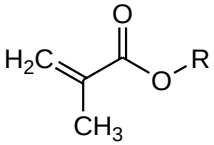
EXTRACTABLES RELATED TO GLASS BARRELS:

GLUE RESIDUES

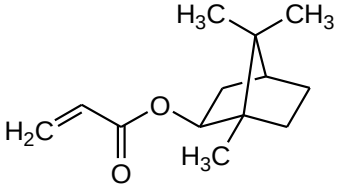
Base Polymer



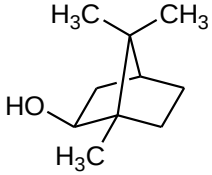
Acrylate



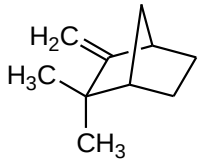
Methacrylate



Isobornyl acrylate

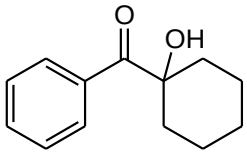


Isoborneol

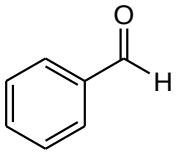


Camphene

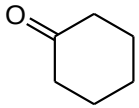
UV curing / activation



Irgacure 184



Benzaldehyde



Cyclohexanone

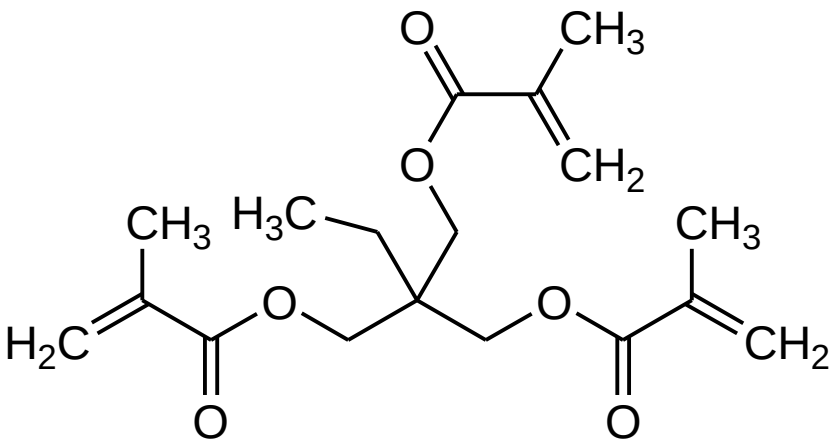
4. Designing Extractable Studies

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

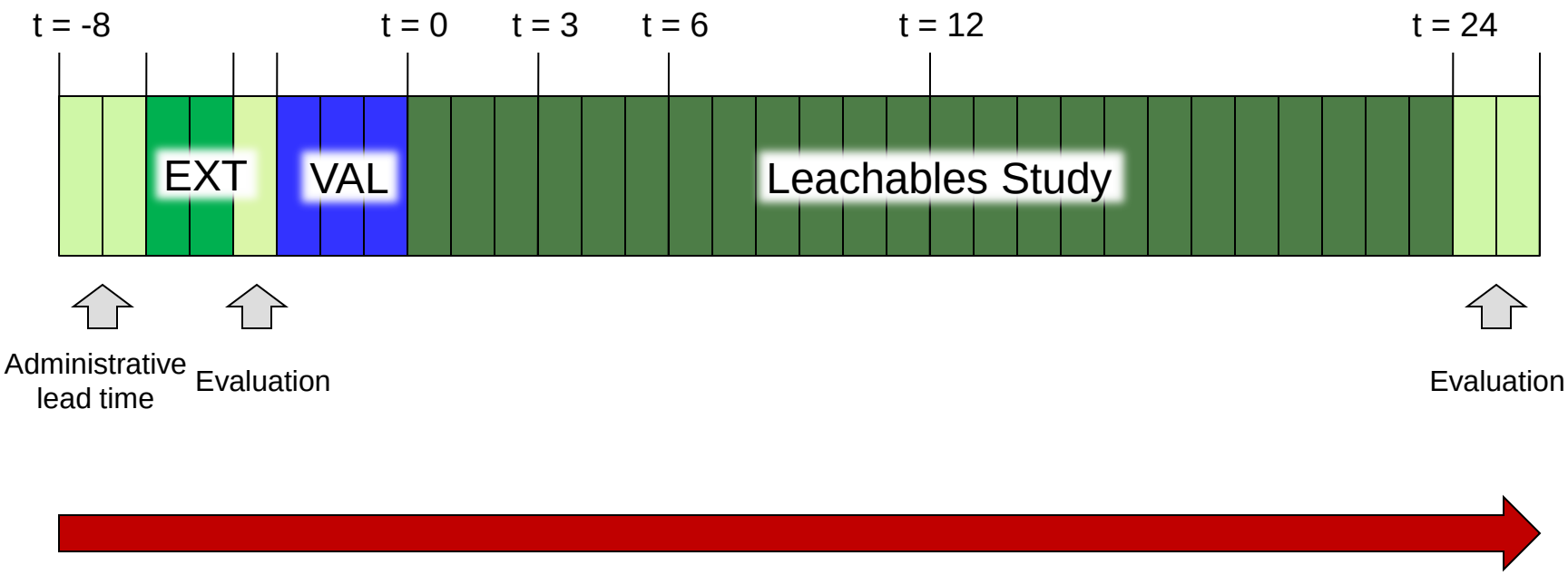
EXAMPLE OF ANALYTICAL PACKAGE FOR A FULL LEACHABLE STUDY

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					

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

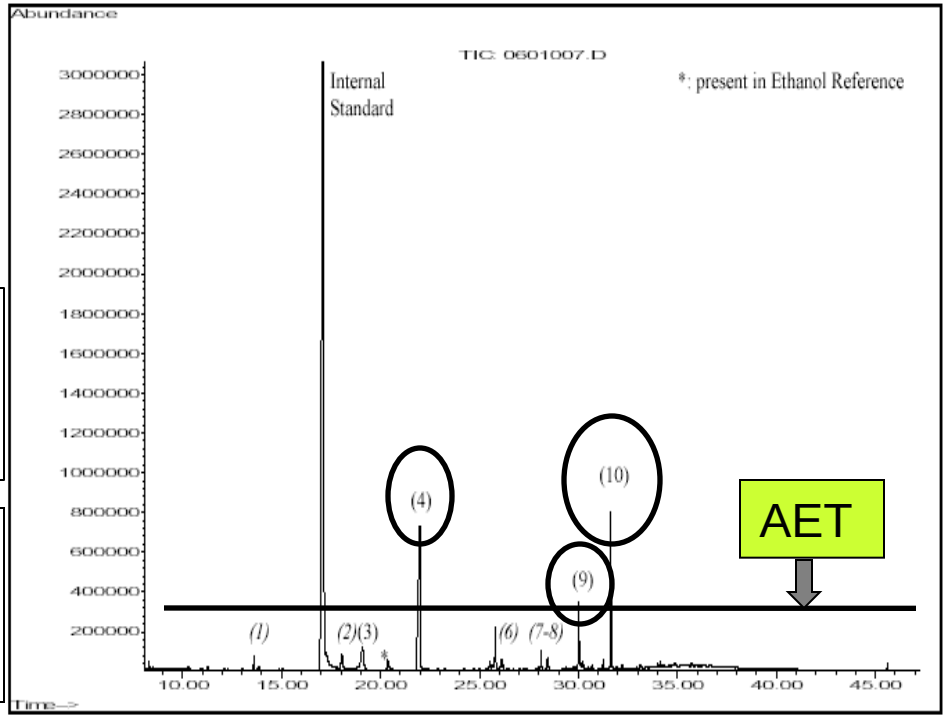
Translate SCT

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