Connecting People, Science and Regulation

EXTRACTABLE / LEACHABLE STUDIES FOR BLOW-FILL-SEAL APPLICATIONS

PDA WORKSHOP
EXTRACTABLES – LEACHABLES
Brussels
13-14 March, 2014

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Overview

1. What is Blow-Fill-Seal?

2. Regulatory Requirements

   - *Primary Packaging*
   - *Secondary Packaging*

3. Where could Extractables/Leachables come from for a Blow-Fill-Seal “System”?

4. Case Study 1:

5. Case Study 2

6 Conclusion

1. WHAT IS BLOW-FILL-SEAL?

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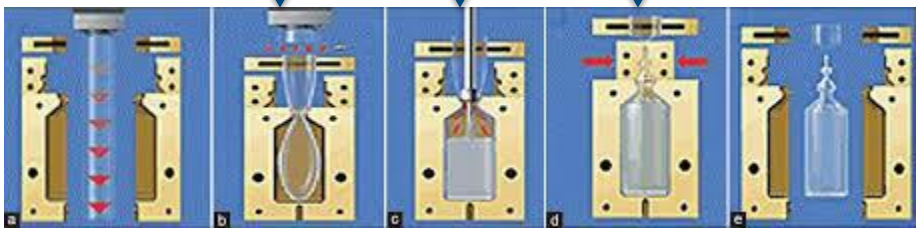
Blow - Fill - Seal: Principle

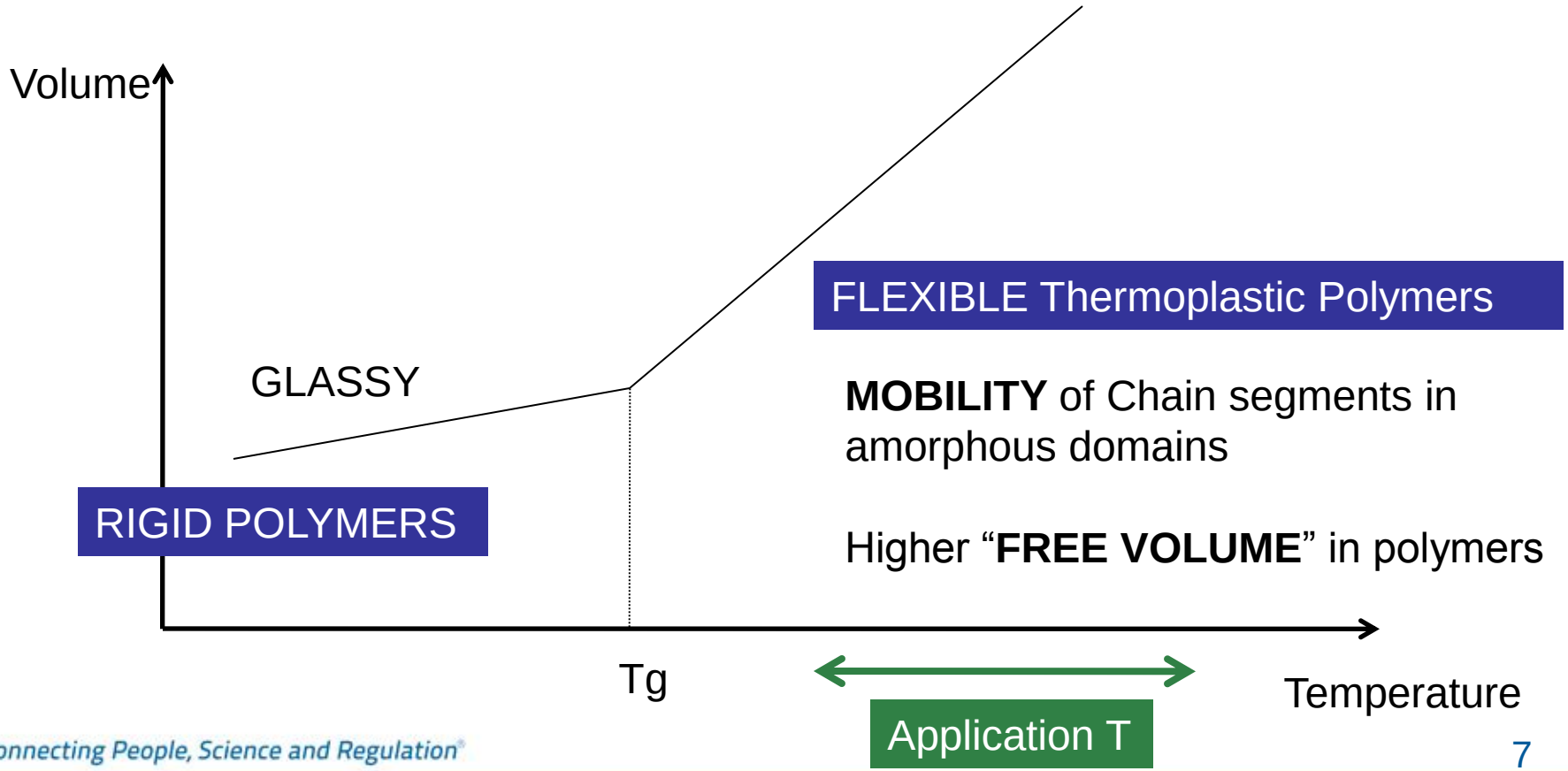


1. WHAT IS BLOW-FILL-SEAL?

B-F-S: Diverse types of containers

1. WHAT IS BLOW-FILL-SEAL?

WHAT IS FLEXIBLE PACKAGING (in General)?



1. WHAT IS BLOW-FILL-SEAL?

MATERIALS USED FOR FLEXIBLE PACKAGING?

- Low Density Polyethylene (LDPE)
- High Density Polyethylene (HDPE)
- Polypropylene (PP)
- PVC
- Multilayer films (PE, EVOH, Nylon, EVA, adhesive/tie layer...) for bag manufacturing

EXISTING TYPES OF FLEXIBLE PACKAGING?

- **Intravenous administration bags (I.V. Bags)**
  - Monolayers (e.g.PVC) versus Multilayer bags
  - Administration ports
  - Administration accessories
- **Blow-Fill-Seal Containers**
- **Tubes**
- …

1. WHAT IS BLOW-FILL-SEAL?

ROUTES OF ADMINISTRATION FOR DRUGS, STORED IN **BLOW-FILL-SEAL** PACKAGING?

- Respiratory
- Ophthalmic
- **Biologics**
- **Parenteral (I.V.-administration)**
- Oral
- Topical

Different routes of administration need different E/L-approaches!

2. Regulatory Requirements Extractables / Leachables for Blow-Fill-Seal

2. REGULATORY REQUIREMENTS B-F-S

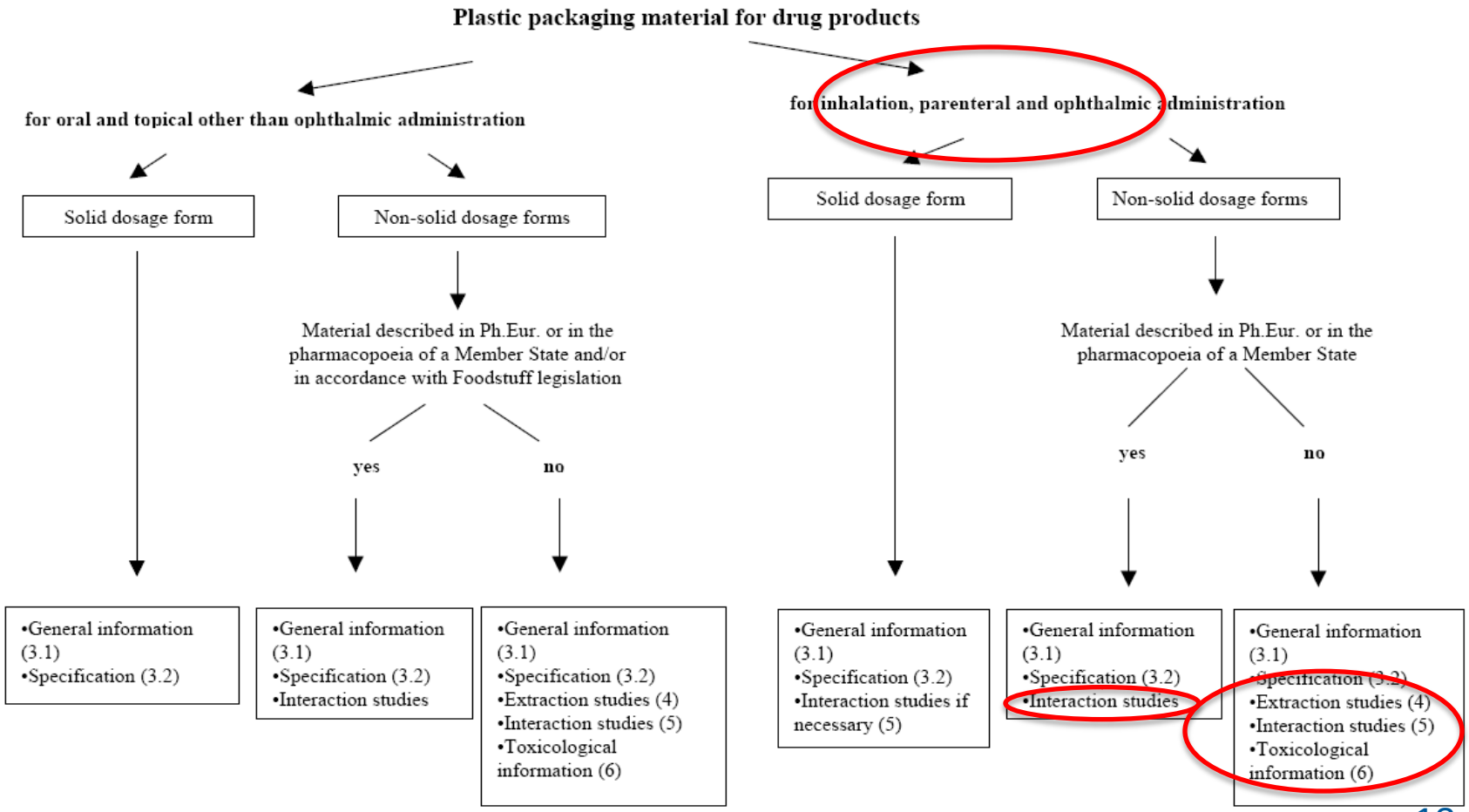
- FDA guidance document: 'Container Closure systems for Packaging Human Drugs and Biologics', 1999

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

2. REGULATORY REQUIREMENTS B-F-S

- EMA: 'Guideline on Plastic Immediate Packaging Materials', 2005



CPMP/QWP/4359/03 and EMEA/CVMP/XXX/03 ©EMEA 2005

2. REGULATORY REQUIREMENTS B-F-S

- SECONDARY PACKAGING: Regulatory requirements

  - FDA guidance document: 'Container Closure systems for Packaging Human Drugs and Biologics', 1999:

    "*if the packaging system is relatively permeable, the possibility increases that the dosage form could be contaminated by the migration of an ink or adhesive component…In such case the secondary packaging component should be considered a potential source of contamination and the safety of its materials of construction should be taken into consideration…*"

  - EMA: 'Guideline on Plastic Immediate Packaging Materials', 2005*:*

    "it should be scientifically demonstrated that no components of ink or adhesives, applied to the outer surface of the container closure system, will migrate into the medicinal product."

3. Where could the Leachables

(impurities from Container/Closure system)

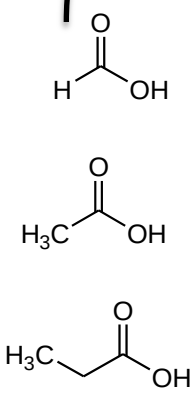
come from for Blow-Fill-Seal Systems”?

3.Where could Leachables come from in BFS?

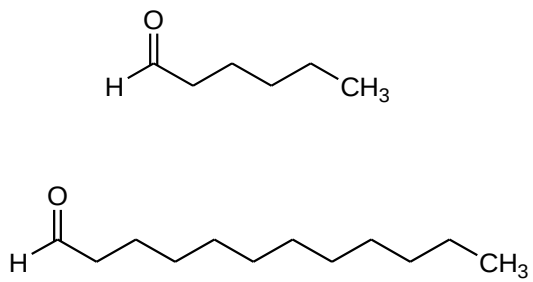
1. **From (Primary) Blow-Fill-Seal Containers**

- Typically, **"Virgin" Resins** are used (No/Low in Additives)
- **Low in Initial Impurities**
- However, Impurities in the polymer can be formed as a result of **Ageing** (and Sterilization)

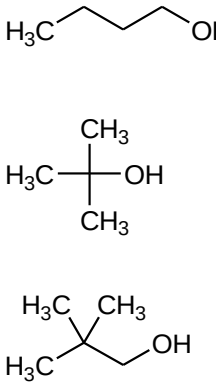
After Polymer Degradation / Ageing



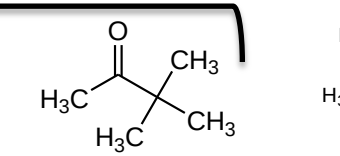
acids

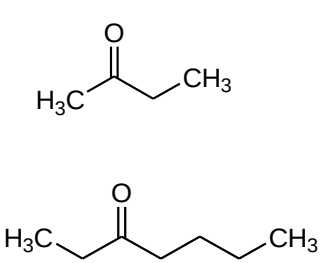


aldehydes

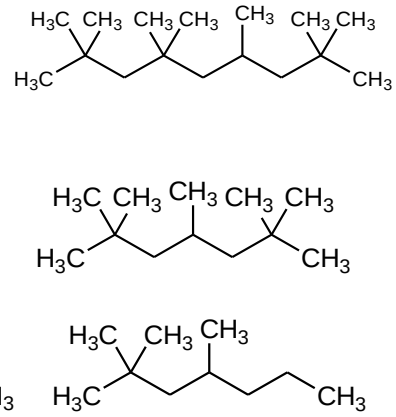


Alcohols





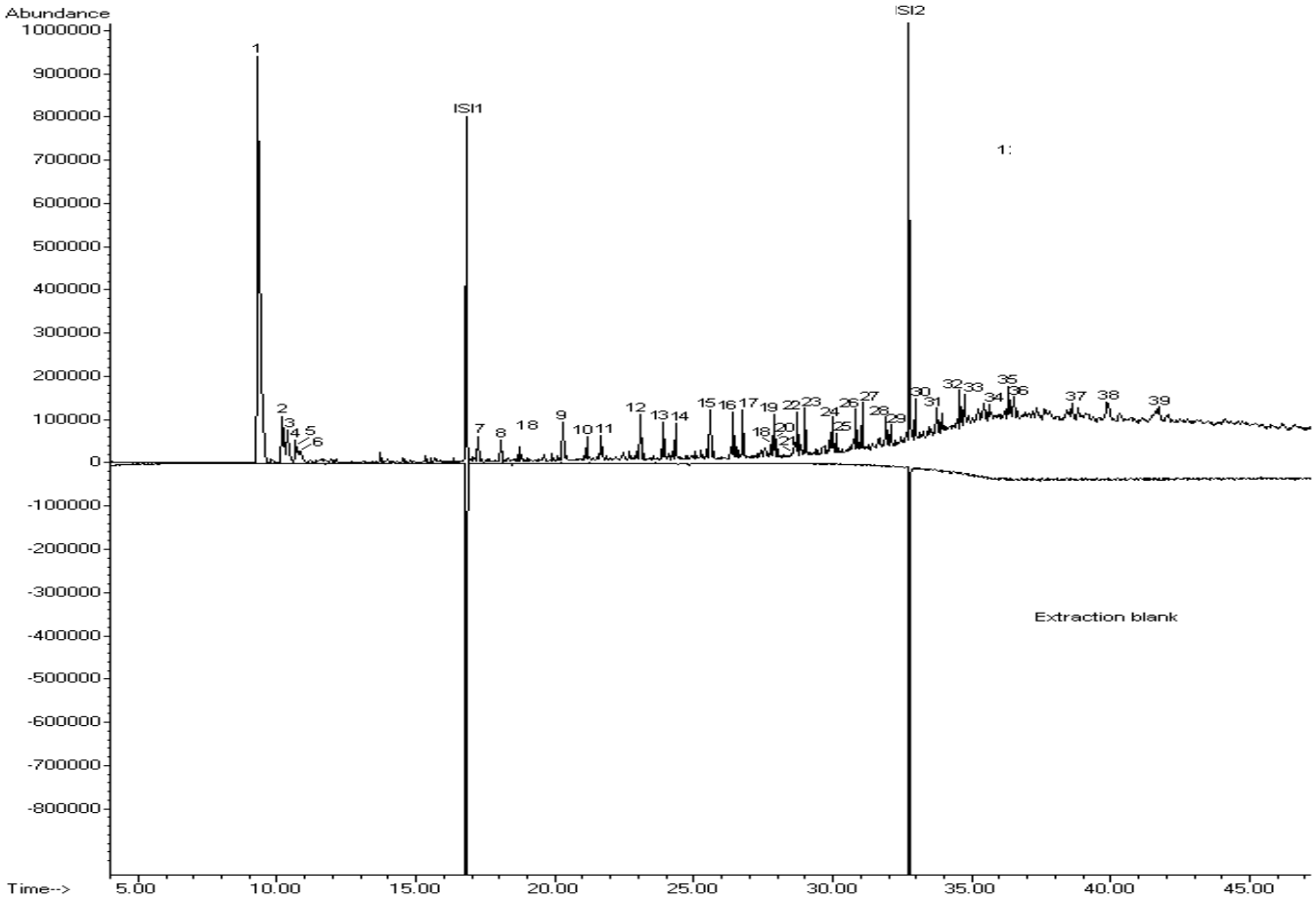
ketones



Olefin fragments / oligomers

3.Where could Leachables come from in BFS?

- Example Chromatogram of a "**Virgin Resin**"



Where could Leachables come from in BFS systems?

1. **From (Primary) Blow-Fill-Seal Containers**

- If Other than **Virgin Resins** are used:
- Polymer Additives e.g.
  - *Anti-Oxidants*
  - *Acid Scavengers*
  - *Clarifying/Nucleating Agents (PP)*
- Degradation Compounds of Polymer Additives

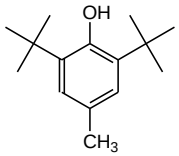
3.Where could Leachables come from in BFS?

Anti-Oxidants

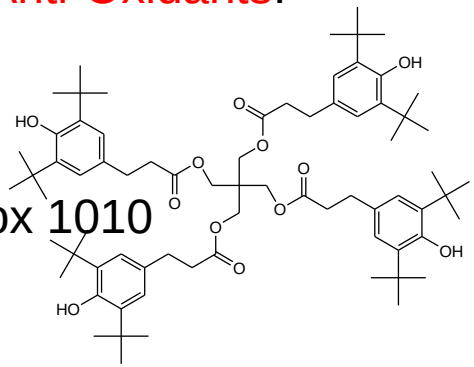
Function: assuring protection against thermal and oxidative degradation during processing and during shelf life of polymer
(*Sterically Hindered Phenols & Organic Phosphites/Phosphonates are mostly used*)

Some Examples of Anti-Oxidants:

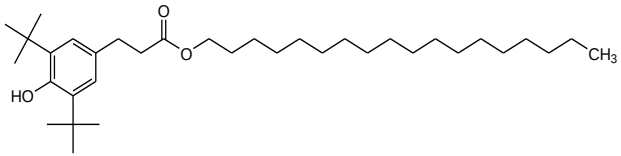
BHT



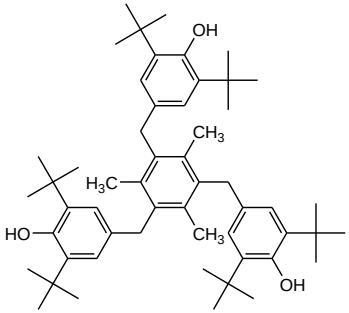
Irganox 1010



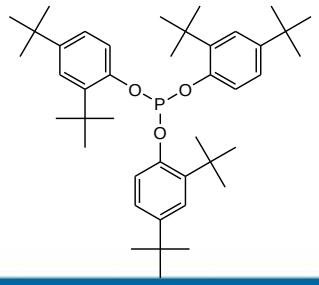
Irganox 1076



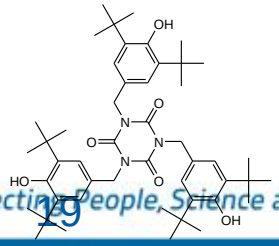
Irganox 1330



Irgafos 168



Irganox 3114



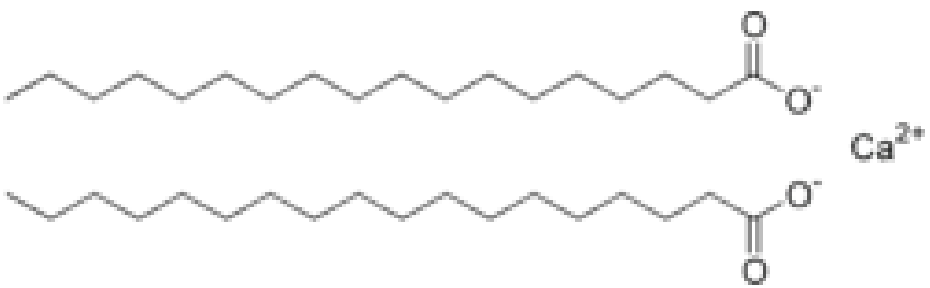
3.Where could Leachables come from in BFS?

Acid Scavengers

Function: Protects the polymer from “acid attacks” through conversion of strong acids (high degradation impact) to weak acids (low degradation impact)

Examples: $Ca(Stearate)_2 + 2HCl \rightarrow CaCl_2 + Stearic\ acid$

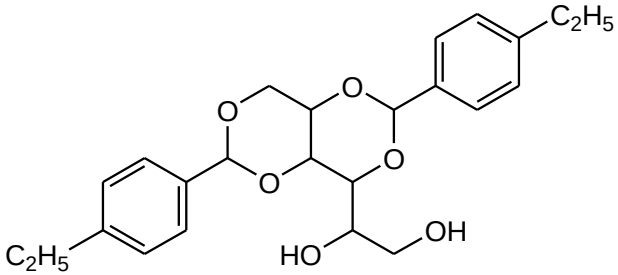
strong acid *weak acid*



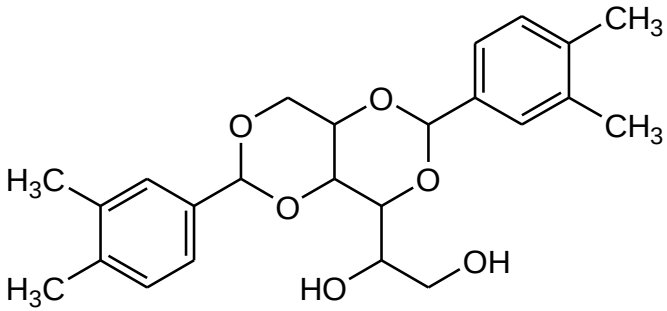
Clarifying Agents (Nucleating Agents)

Function: by controlling the crystallisation (nucleation) when cooling off PP, it becomes transparent.

NC-4



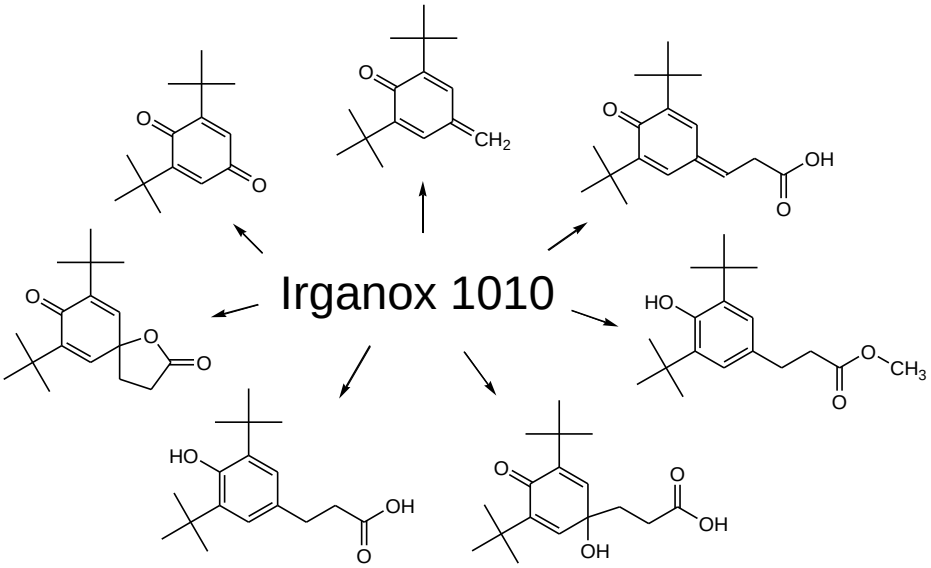
Millad 3988



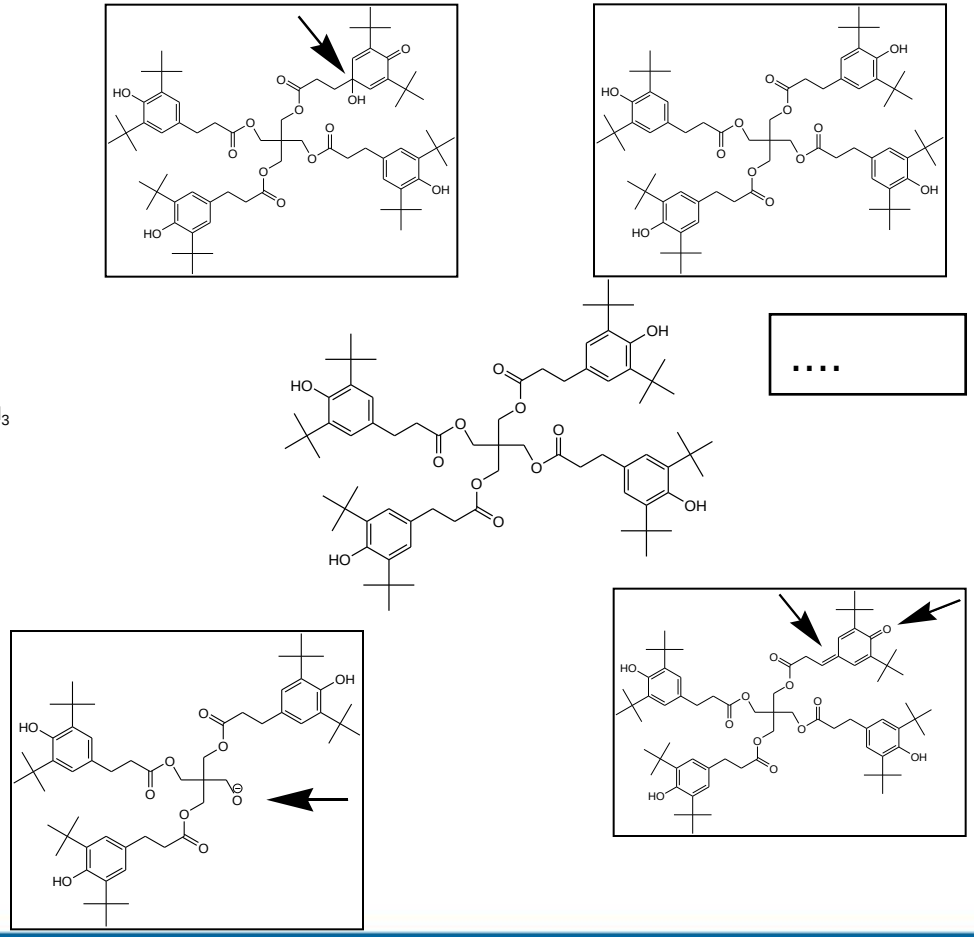
3.Where could Leachables come from in BFS?

Polymer Additive Degradation Compounds: Example for **Irganox 1010**

SMALL degradation Compounds



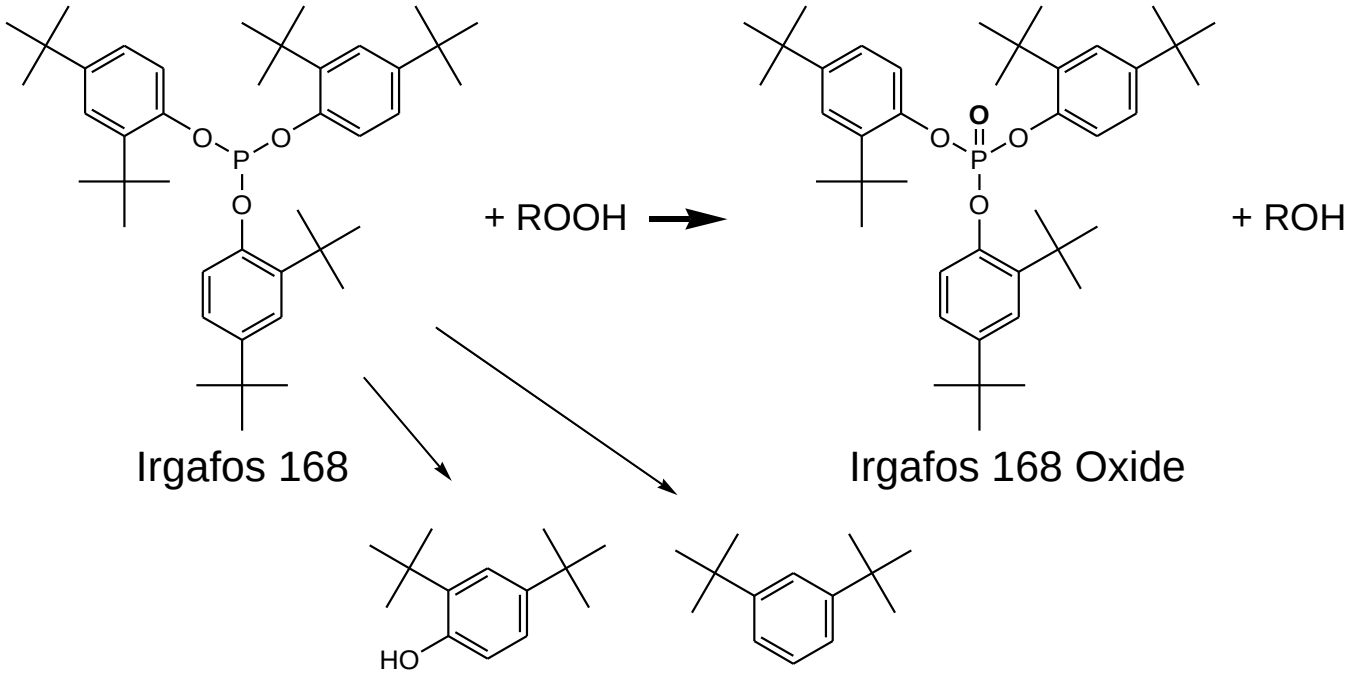
LARGE degradation Compounds



3.Where could Leachables come from in BFS?

- EXAMPLE: Degradation of Irgafos 168

  (also other degradation compounds for Irgafos 168 are known)



3.Where could Leachables come from in BFS?

Where could Leachables come from in BFS systems?

2. **From the Labels on the BFS containers**

- Label
  - Adhesive
  - paper
  - Ink
  - Varnish

Typical extractable compounds:

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

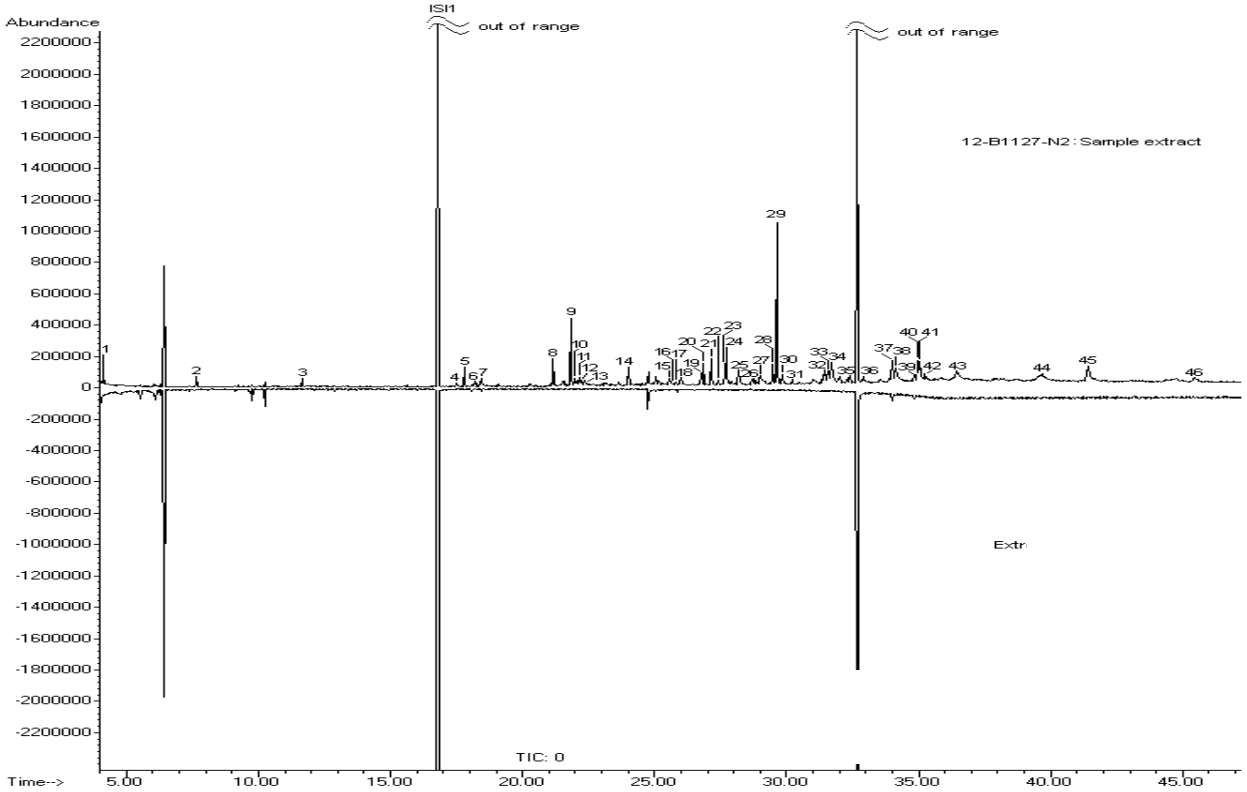
Solvent residues (e.g.Toluene, acetone)

Adhesive residues (e.g. Acrylates)

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

3.Where could Leachables come from in BFS?

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



Where could Leachables come from in BFS systems?

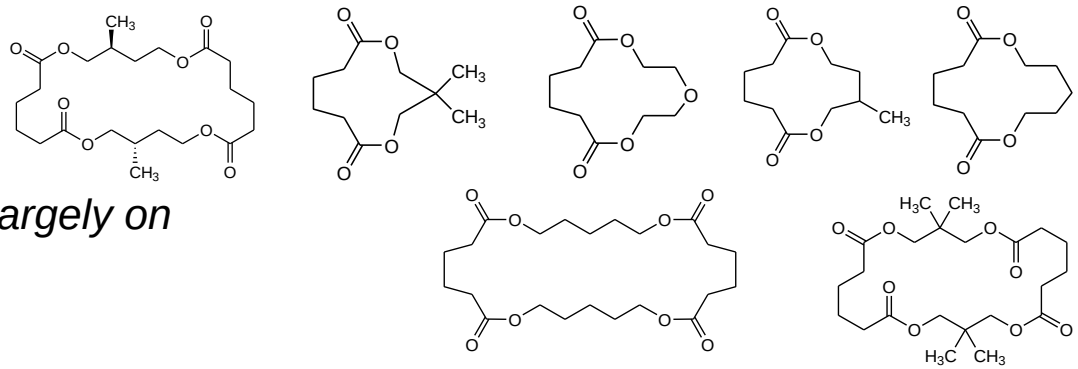
3. From the Overwrap on the BFS containers

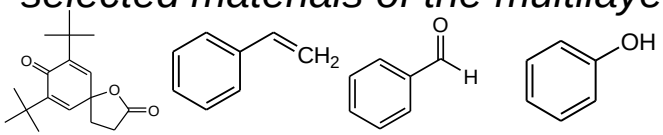
- Overwrap
  - Multilayer System
  - Aluminum as barrier layer
  - Tie-layers to keep the different layers together

Typical extractable compounds:

Bislactone Compounds from Tie-layer

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





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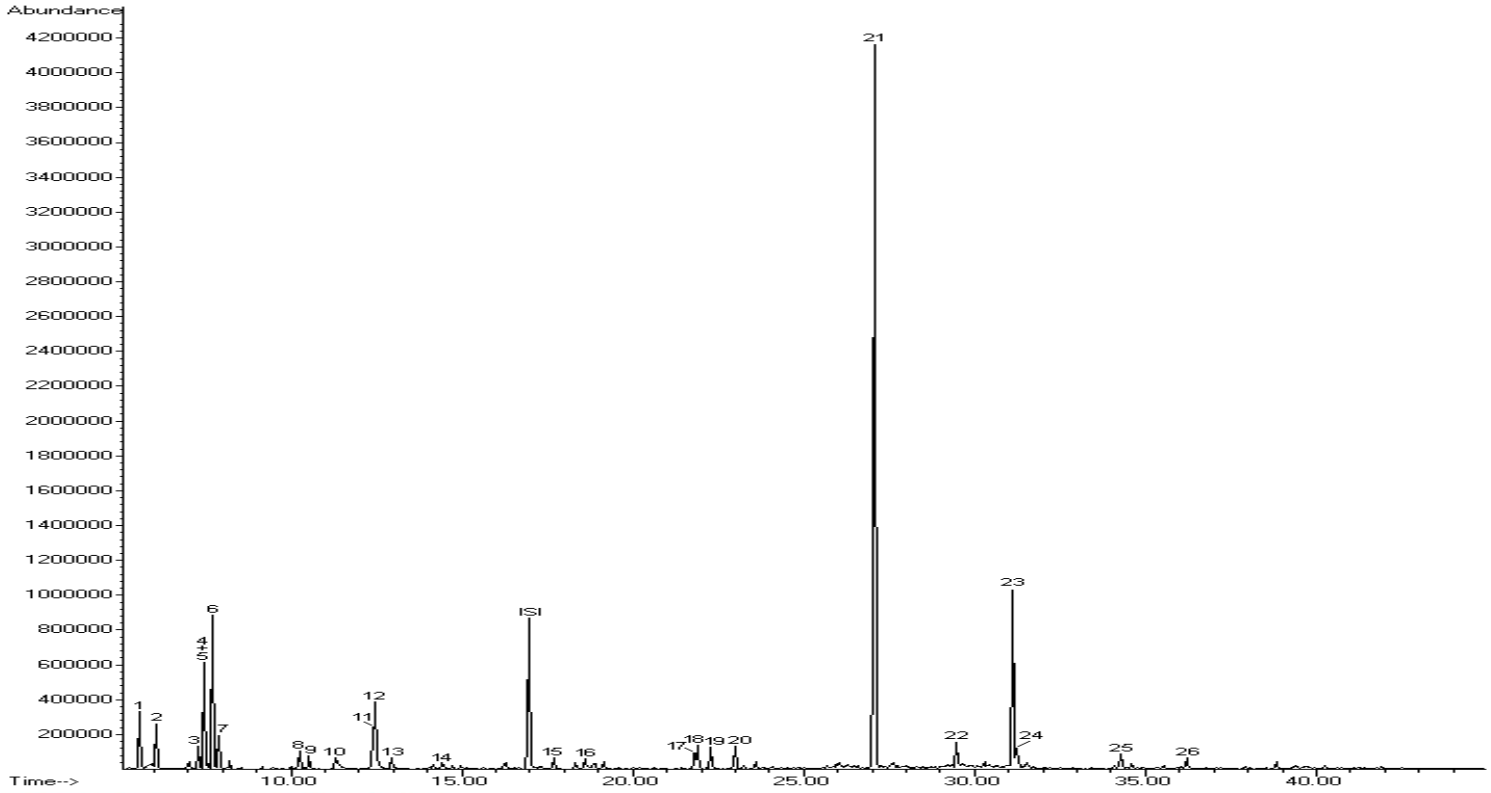
3.Where could Leachables come from in BFS?

Example GC/MS Chromatogram of an Aluminum Overwrap

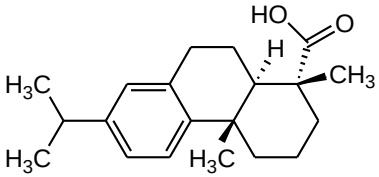


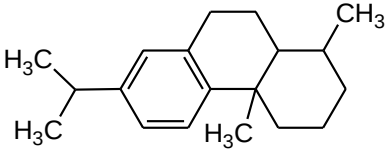
3.Where could Leachables come from in BFS?

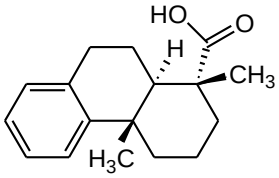
Where could Leachables come from in BFS systems?

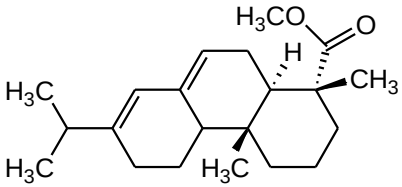
4. From the Carton Box, containing the BFS containers

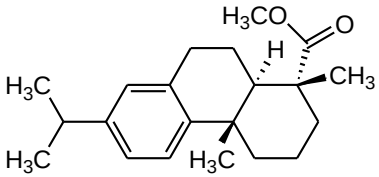
- Carton / Paper: Example Structures Of abietic acids / abietates (& Vanillin)

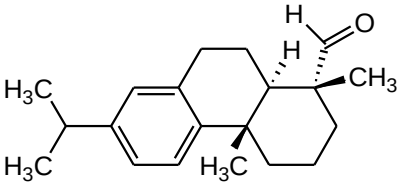


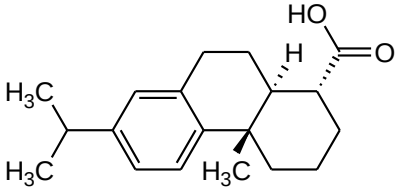


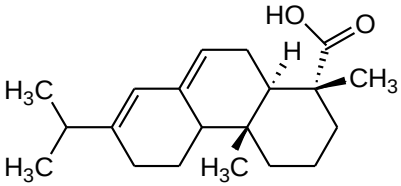


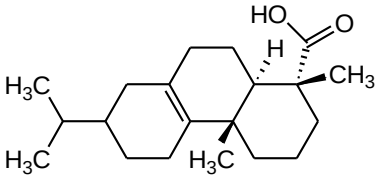


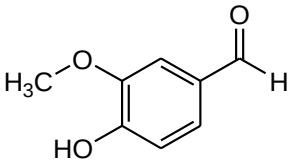












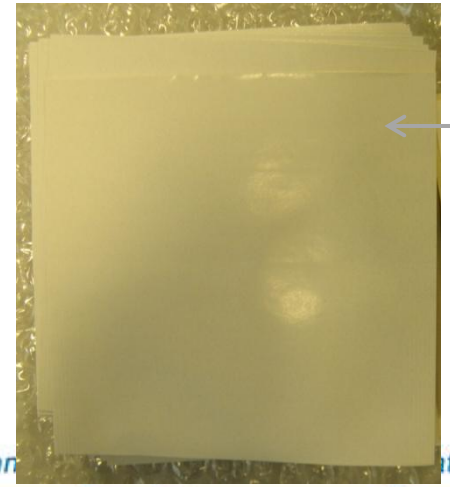
4. Case Study 1

4. Case Study 1

Extractables study on a Blow Fill Seal (BFS) Eye Dropper system

The container closure system consists of :

- BFS Eye droppers (primary packaging)
- Labels (secondary packaging)
- Multi-layer pouch (secondary packaging)



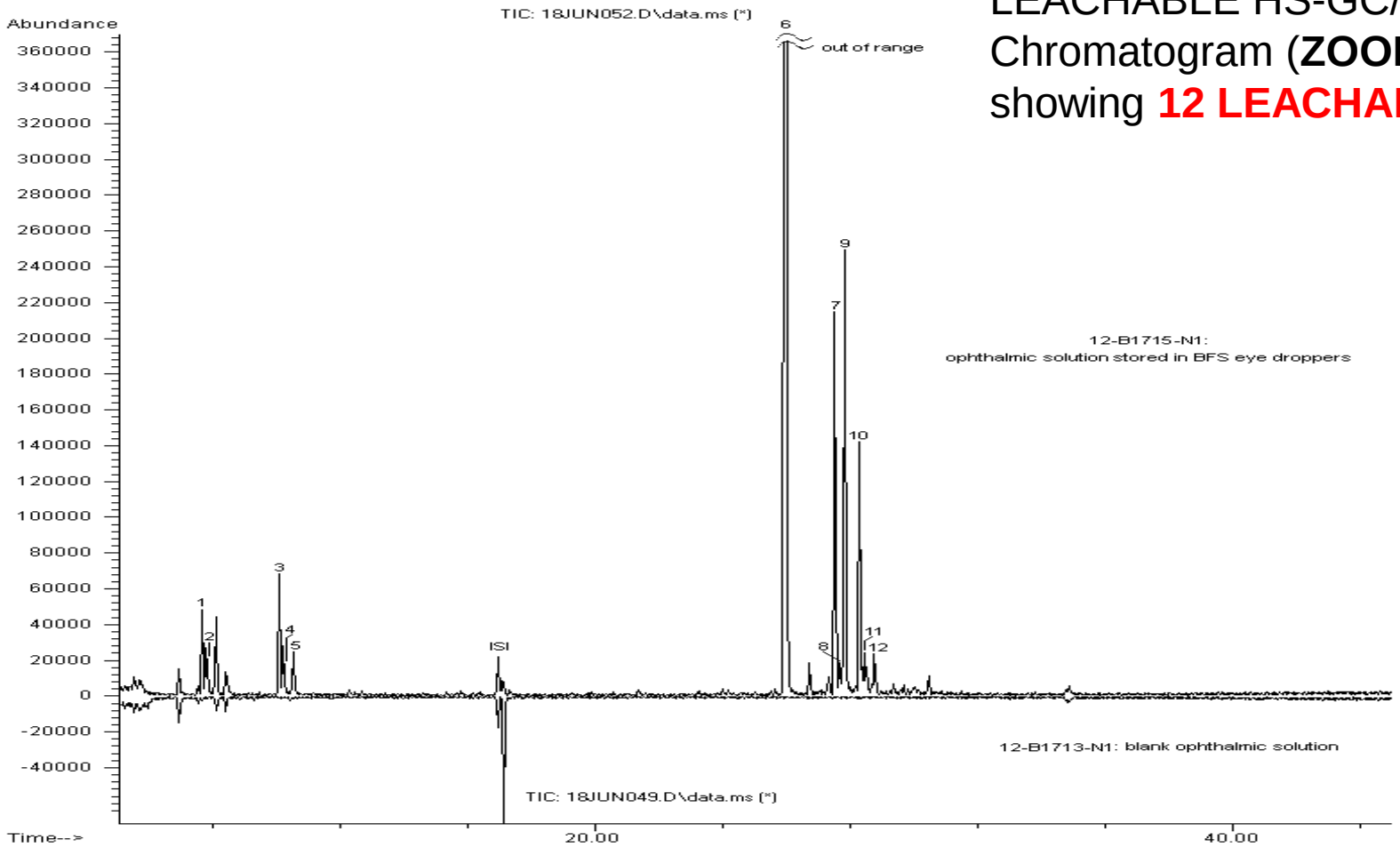
pouch

dropper

label

4. Case Study 1

LEACHABLE HS-GC/MS Chromatogram (**ZOOMED**) showing **12 LEACHABLES**



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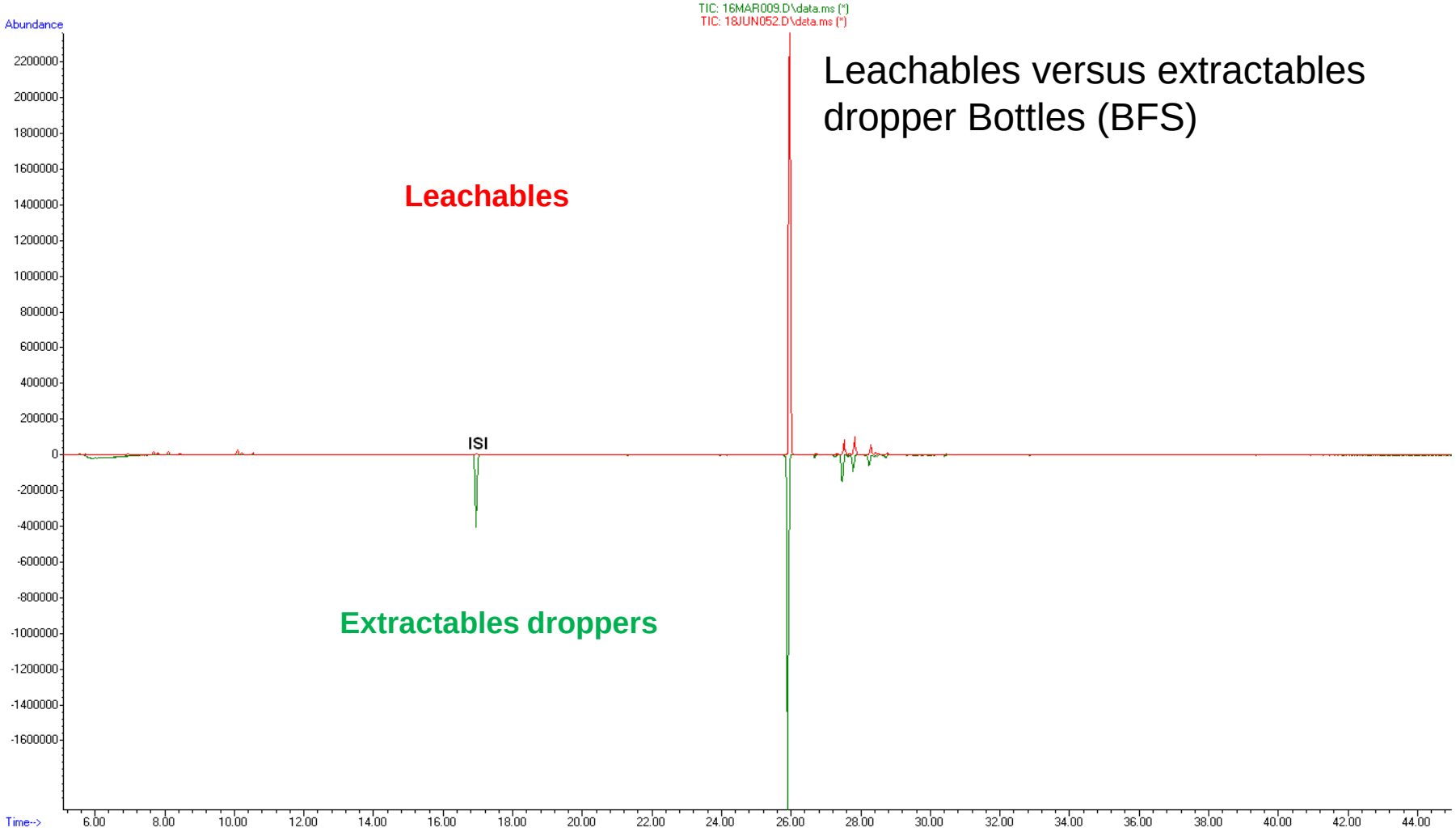
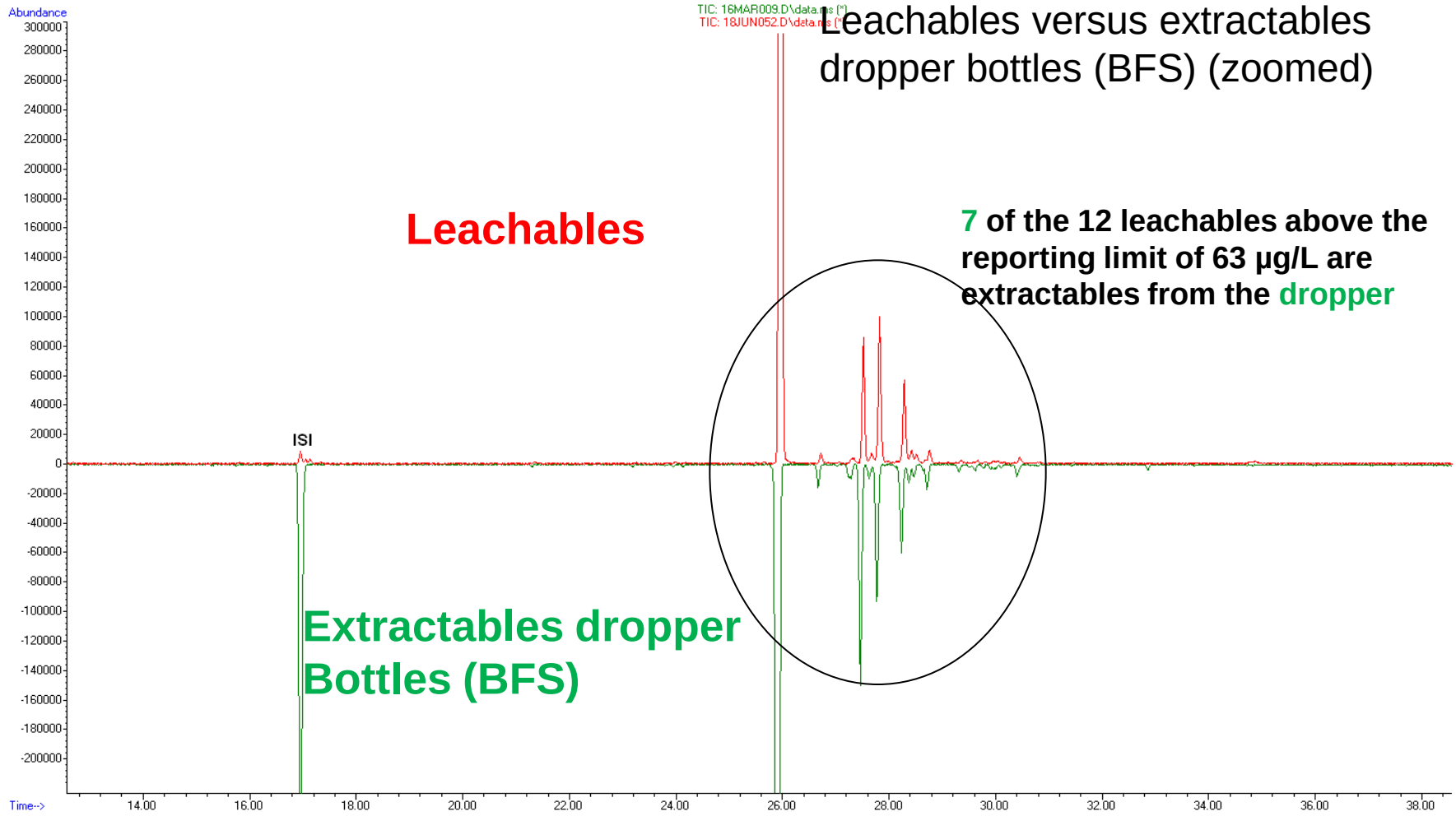


Leachables versus extractables dropper Bottles (BFS)

4. Case Study 1

Leachables versus extractables dropper bottles (BFS) (zoomed)



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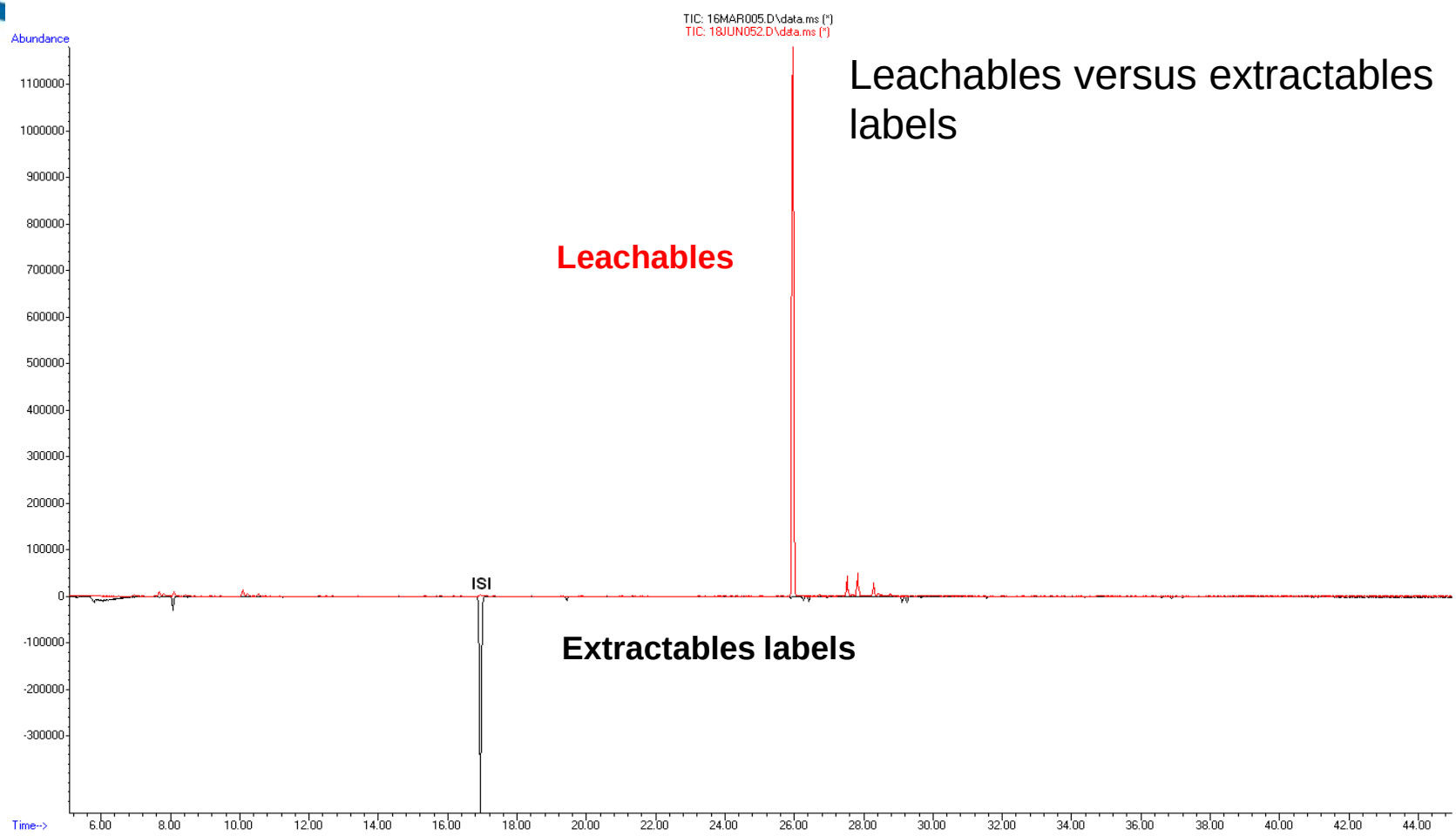
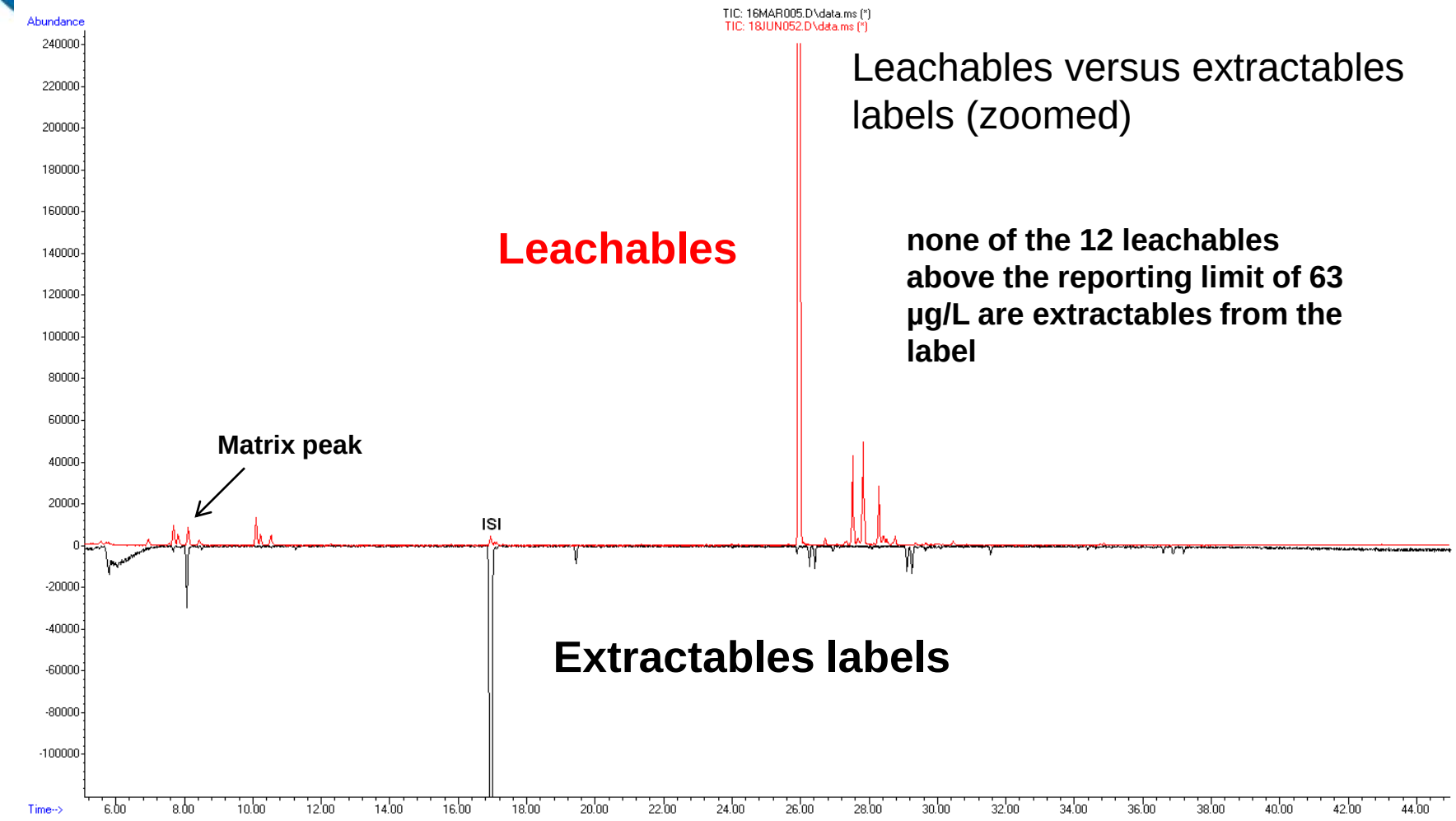


Leachables versus extractables labels

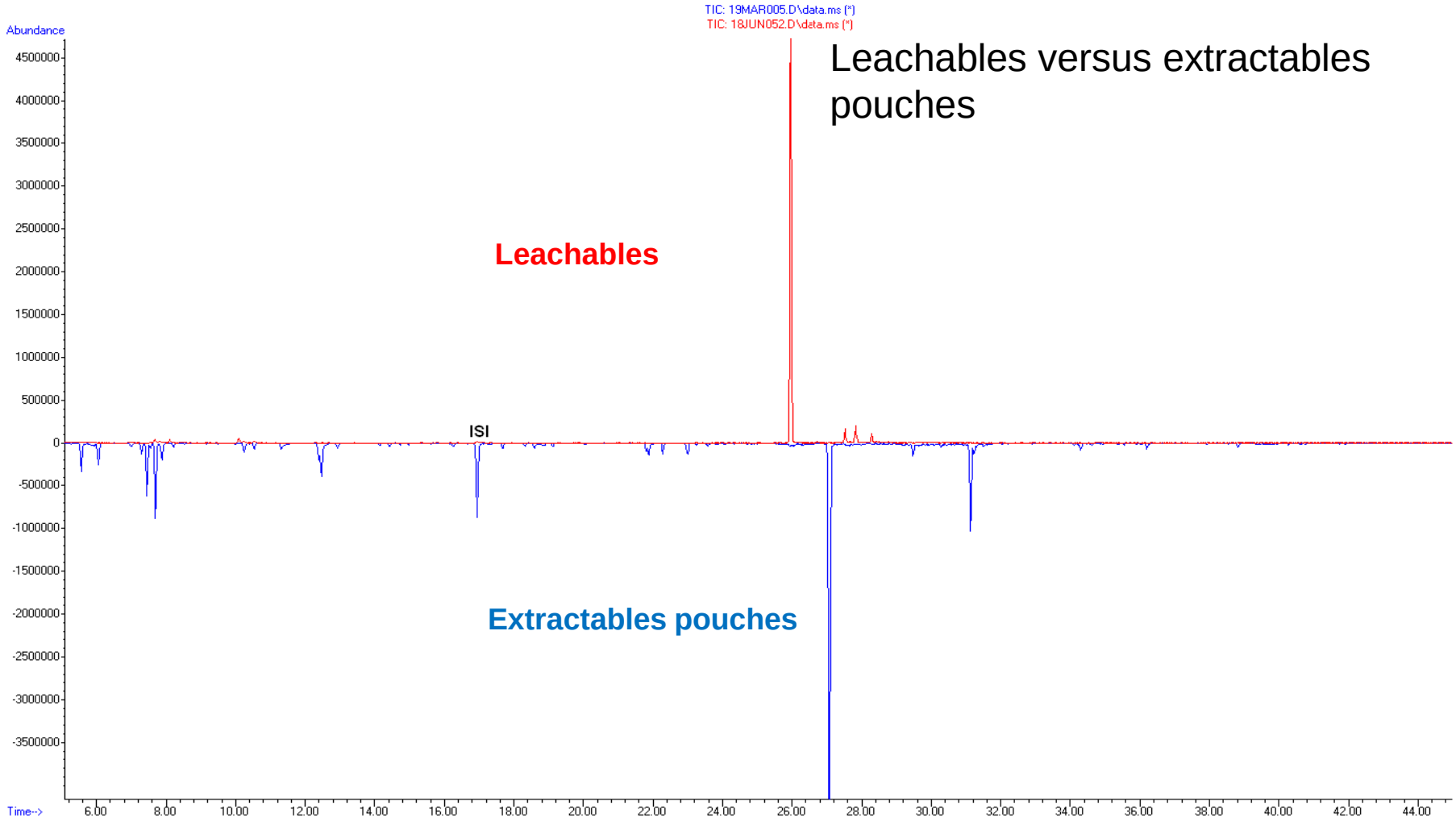
4. Case Study 1



Leachables versus extractables labels (zoomed)

none of the 12 leachables above the reporting limit of 63 µg/L are extractables from the label

4. Case Study 1



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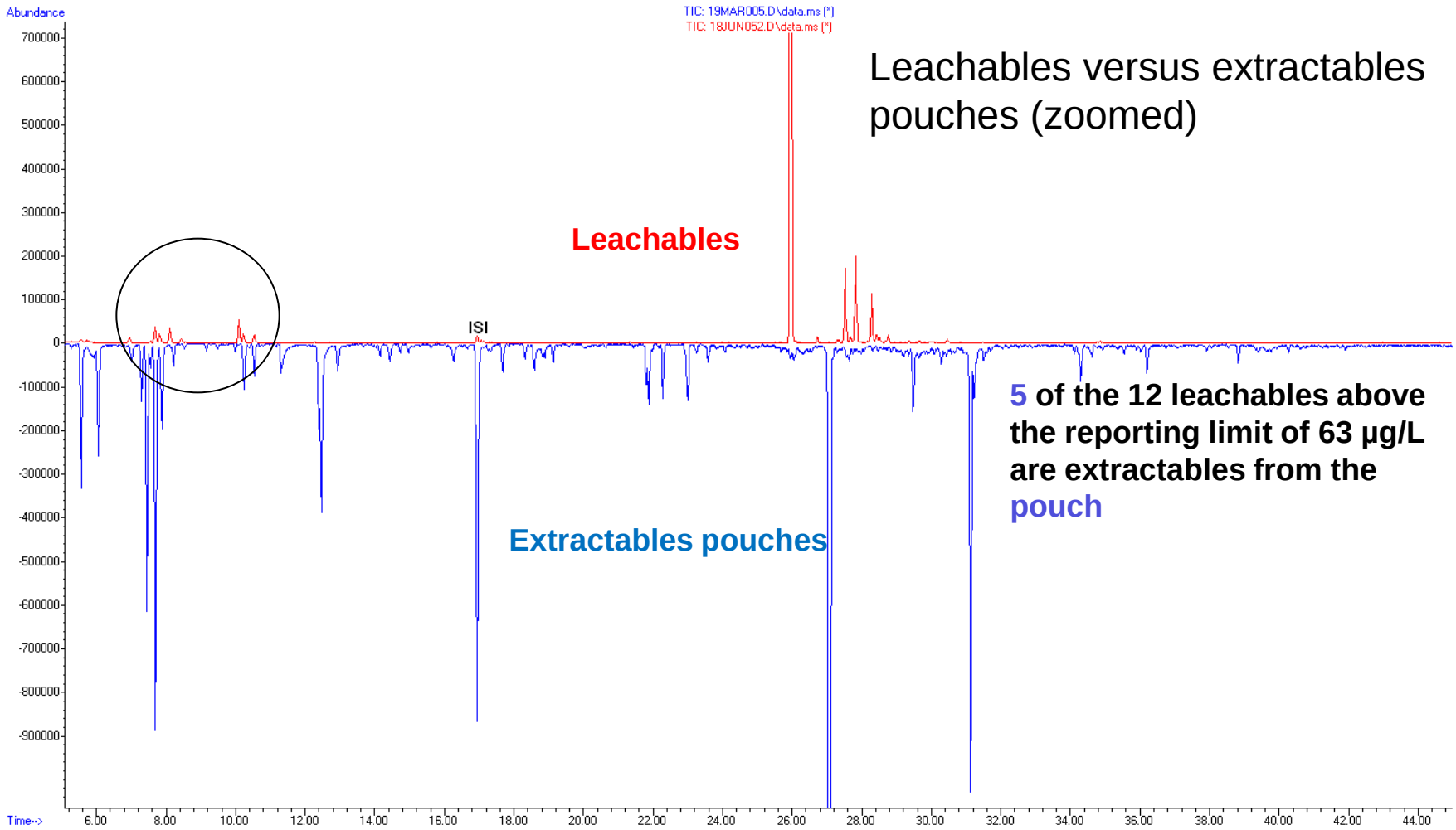


Leachables versus extractables pouches (zoomed)

5 of the 12 leachables above the reporting limit of 63 µg/L are extractables from the pouch

4. Case Study 1

(SCREENING) LEACHABLE STUDY: HS-GC/MS

Pharmaceutical matrix: ophthalmic emulsion

Origin leachable compounds:

Dropper Bottle – label - pouch

n°	ID Level	VOLATILE COMPOUND	CAS-No.	MS Fit (%)	Retention Time (min)	Test result (µg/L)
1	IC	Acetone	67-64-1	-	7.69	150
2	IC	Isopropanol	67-63-0	-	7.82	100
3	IC	Trimethylsilanol	1066-40-6	-	10.10	200
4	IC	Butanal	123-72-8	-	10.23	85
5	IC	2-Butanone	78-93-3	-	10.53	82
6	IC	2,2,4,6,6-Pentamethylheptane	13475-82-6	-	25.96	17000
7	TIC	Aliphatic Hydrocarbon	-	-	27.52	570
8	TIC	Aliphatic Hydrocarbon	-	-	27.68	67
9	TIC	Aliphatic Hydrocarbon	-	-	27.82	740
10	TIC	Aliphatic Hydrocarbon	-	-	28.29	430
11	TIC	Aliphatic Hydrocarbon	-	-	28.42	76
12	TIC	Aliphatic Hydrocarbon	-	-	28.76	63

IC: Identified Compound; TIC: Tentatively Identified Compound;
Reporting limit: 63 µg/L.

5. Case Study 2

5. Case Study 2

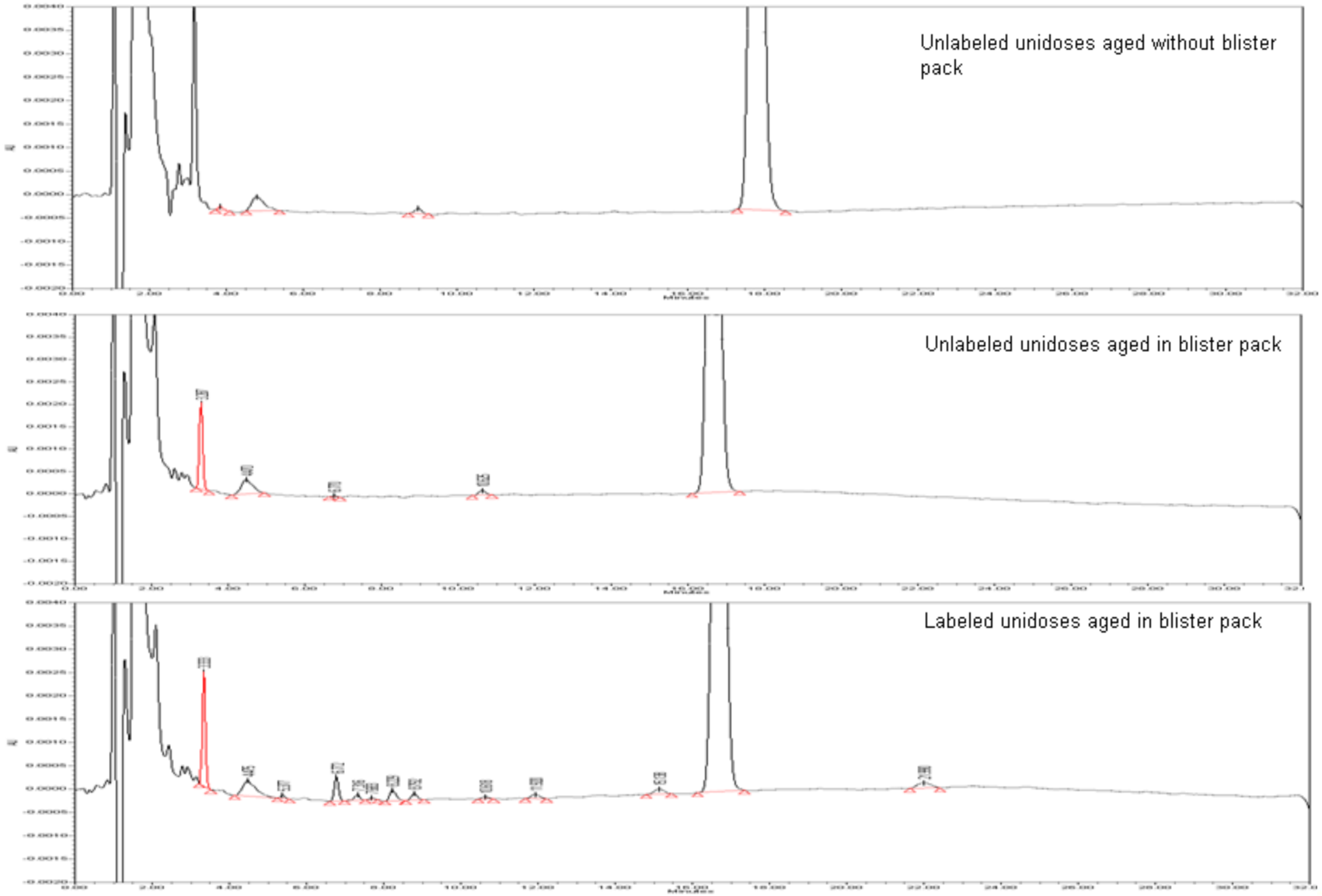
- Secondary packaging has a high impact on the leachables profile of BFS:
  - Primary Containers mainly consist of semi-permeable materials, such as LDPE.
  - Typically a High surface-to-volume ratio (for small containers (Ophthalmic, Inhalation))

⇨ Evaluation of secondary packaging components at early stage of drug product development is essential!

5. Case Study 2

- Case study
  - Unidose presentation: blister pack containing 5 unidoses (5x0.2mL) with label on the tail.
  - No extractables testing performed
  - Stability study: several impurities showed up which could not be linked to the active substance
  - A primary evaluation was performed by the customer to identify the source of the impurities:
    - Labeled unidoses aged in blister pack
    - Unlabeled unidoses aged in blister pack
    - Unlabeled unidoses aged without blister pack

5. Case Study 2



Con

5. Case Study 2

- Label
  - Adhesive
  - paper
  - Ink
  - Varnish
  - Typical extractable compounds:

    curing agents (e.g. Benzophenone, Irgacure 184), solvents (e.g.Toluene, acetone), residual monomers (e.g. Acrylates)

5. Case Study 2

AET: ANALYTICAL EVALUATION THRESHOLD

Example Ophthalmic DP:

- LDPE bottle with white masterbatch
- Natural colored LDPE dropper
- PP cap with pink masterbatch
- Printed label
- Available information:
  - MD: 4 eye drops per day, 1 eye drop = 0.03 mL
    4 x 0.03 mL = 0.12 mL, for both eyes: 0.24 mL
  - Filling volume: 8 mL => ER: 1 test item / 8 mL

EXTRACTABLES:

Identification Threshold (Class III): 1,5 µg/day:

final AET level: 6.25 µg/mL in Bottle of 8 mL

5. Case Study 2

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

Formula used (see PQRI recommendations):

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

$$\text{Class III: Est. AET} = \frac{1{,}5\ \mu\text{g / day}}{8\ \text{dose / day}} \cdot \frac{266\ \text{doses}}{\text{Bottle}} = 50\ \mu\text{g / bottle (8mL)}$$

$$\text{Final AET} = 3.12\ \mu\text{g / mL}$$

50% uncertainty for screening methods

5. Case Study 2

- Real use conditions and/or accellerated conditions
- In parallel with stability study
- Including all secondary packaging components
- Quantification of target compounds
- If target compound present at or above the AET level
  - ⇨ Toxicological assessment
- Screening analyses for unexpected leachables

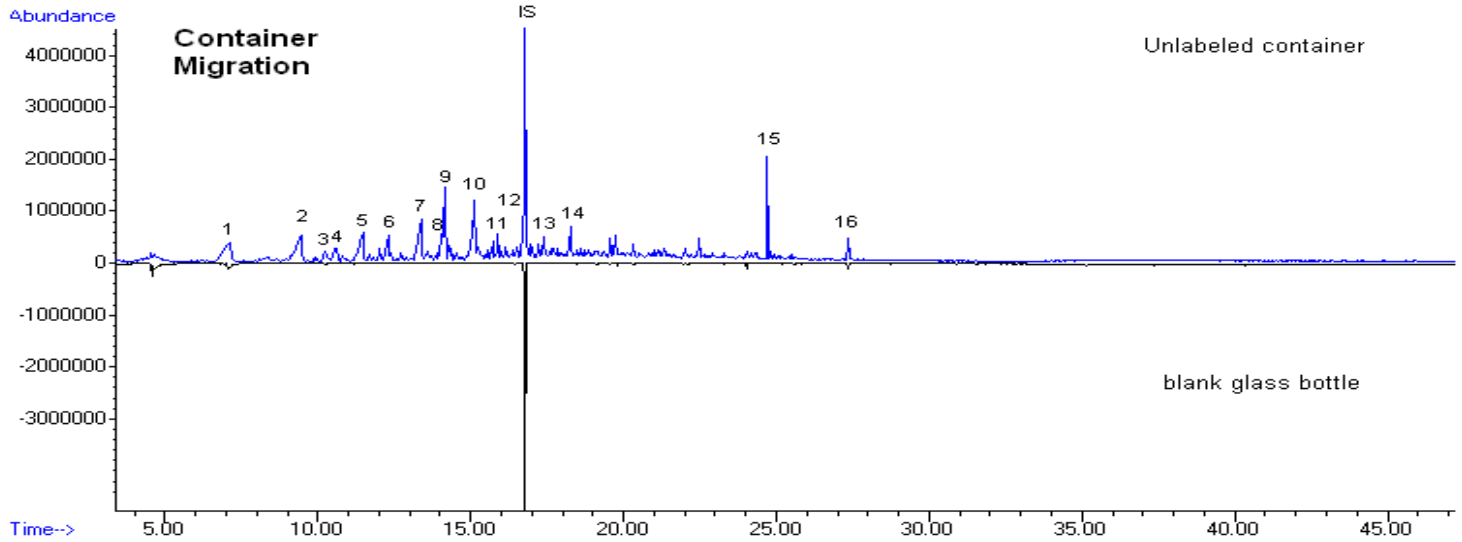
5. Case Study 2

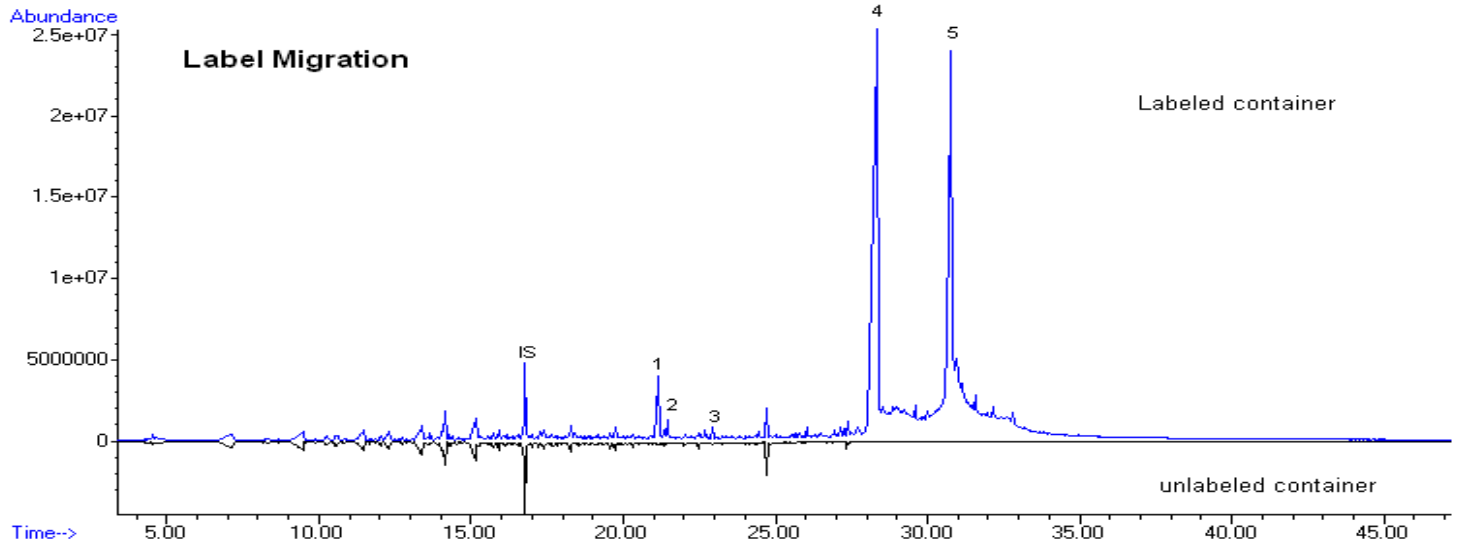
- Labeled and unlabeled containers filled with ophthalmic solution stored for 3 months at accelerated conditions
  - Analysed by *"Screening Methodology"*
  - Container migration:

    Unlabeled containers compared to blank ophthalmic solution
  - Label Migration:

    Labeled containers compared to unlabeled containers

5. Case Study 2





5. Case Study 2

- Container migration:

n°	Ident. Level	Semi-Volatile Organic Compounds	CAS-Number/ MS spectrum	Retention Time (min)	Test result (µg/L)
1	MPC	Pentanoic acid	109-52-4	7.14	80
2	MPC	Hexanoic acid	142-62-1	9.47	80
3	TIC	2,2-Diethyl-butanoic acid	813-58-1	10.23	16
4	IC	1-Methyl-2-Pyrrolidinone	872-50-4	10.53	12
5	IC	Heptanoic acid	111-14-8	11.48	55
6	IC	2-Ethylhexanoic acid	149-57-5	12.32	35
7	IC	Octanoic acid	124-07-2	13.38	66
8	U	Main masses: 69, 83, 98, 99, 111, 87, 57	-	14.02	11
9	IC	2-Phenoxyethanol	122-99-6	14.15	67
10	IC	Nonanoic acid	112-05-0	15.14	72
11	TIC	4-Methylnonanoic acid	45019-28-1	15.90	11
12	IC	Decanoic acid	334-48-5	16.75	37
13	U	Main masses: 156, 141, 57, 41, 109, 81	-	17.39	11
14	IC	Undecanoic acid	112-37-8	18.26	16
15	MPC	7,9-Di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione	Irganox 1010 degradation product		
16	U	Main masses: 224, 127, 141, 82, 182	-	27.36	13

IC: Identified Compound, MPC: Most Probable Compound, TIC: Tentative Identified Compound, U: Unidentified

5. Case Study 2

➢ Label Migration:

n°	Ident. Level	Semi-Volatile Organic Compounds	CAS-Number/ MS spectrum	Retention Time (min)	Test result (µg/L)
1	U	Main masses: 173, 146, 117, 131, 206, 91	-	21.16	160
2	U	Main masses: 131, 146, 117, 191, 206, 91, 173	-	21.46	20
3	MPC	4a-Methyl-1-methylene-1,2,3,4,4a,9,10,10a-octahydrophenanthrene	53084-68-7	22.94	15
4	MPC	Podocarpa-8,11,13-trien-19-oic acid (Dehydroabietic acid related compound)	4586-72-5	28.36	3200
5	MPC	Dehydroabietic acid	1740-19-8	30.78	3600
MPC: Most Probable Compound, U: Unidentified					

To Assess E/L from Blow-Fill-Seal "Systems"

1. Evaluate which Polyolefin grades are suitable wrt E/L
2. Perform an Extraction study on All components of the BFS "System"
   - BFS containers (after processing)
   - Labels
   - Overwrap
   - Carton box (if necessary)
3. Select the Target Compounds for a leachable study
   - **PQRI Threshold** evaluation
   - Accelerated Screening Leachable study: understand interaction!
4. Perform a "Formal" Leachable Study
5. Final Toxicological/Safety Assessment

ANY QUESTIONS?

For further questions, please contact:
piet.christiaens@toxikon.be

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