EXTRACTABLES & LEACHABLES CORRELATION CLOSING THE GAP

PDA TRAINING COURSE

Sevilla

29 – 30 November, 2018

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1. INTRODUCTION

1. INTRODUCTION: WHY PERFORMING E&L-STUDIES?

- REGULATORY REQUIREMENT FOR SAFETY ASSESSMENT OF PHARMACEUTICAL CONTAINERS
  1999: FDA: "CONTAINER/CLOSURE SYSTEMS FOR PACKAGING HUMAN DRUGS AND BIOLOGICS"
  2005: EMEA: "GUIDELINE ON PLASTIC IMMEDIATE PACKAGING MATERIALS"

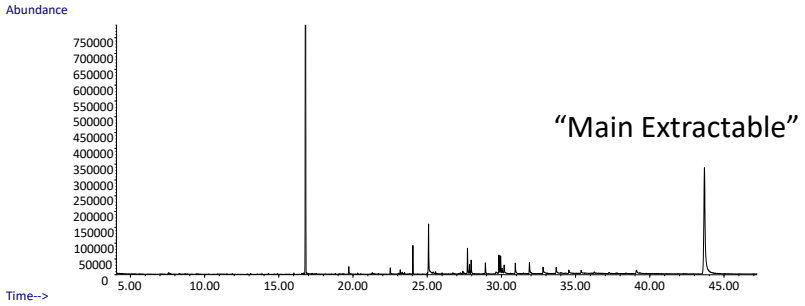
- TOXICITY OF IMPURITIES, LEACHING FROM CONTAINERS/CLOSURES

- May REACT with API, DRUG COMPONENTS

EXTRACTABLE PROFILE

*Purpose**: try to identify as many impurities as possible in the materials used for the manufacture of containers.***

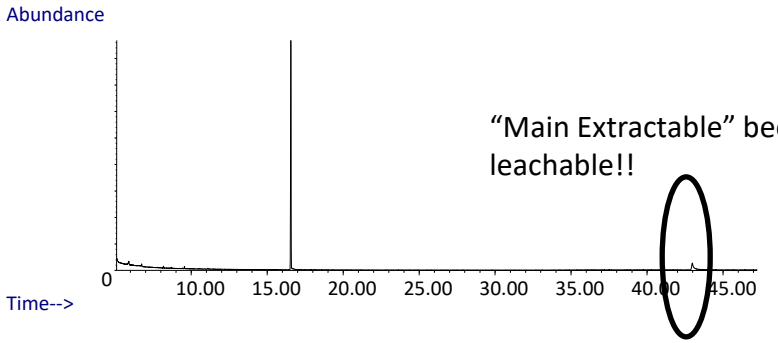
- *Aggressive extraction conditions*
- *Screening methods*



LEACHABLES PROFILE

*Purpose: **to identify impurities, leaching from the container into the actual drug product***

- *Simulated storage conditions (cfr. stability)*
- *Validated methods*



Extractables / Leachables Testing: a Relatively New Science!

- ✓ Regulatory Requirements are becoming more and more Stringent.
- ✓ This leads to more and more Testing.
- ✓ More Testing increases the Understanding of the Interaction of the Materials with the Drug Products
- ✓ In order to have a proper "*Risk Mitigation*" a good Understanding of what can happen is of premordial importance!

2. LEACHABLES: A SUBSET OF EXTRACTABLES?

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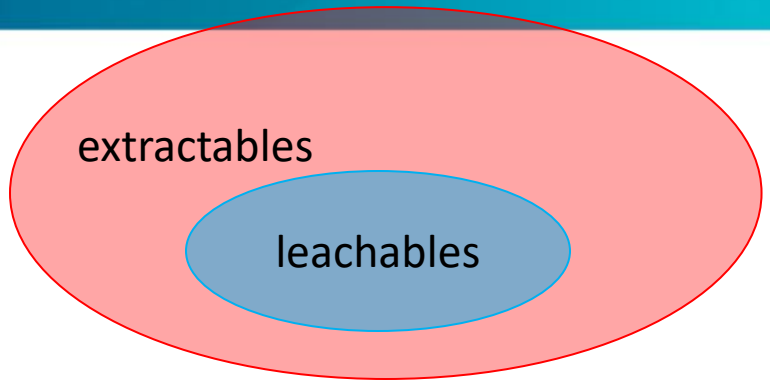
➔ THEORY:



In early stages of E/L research (5 – 10 years ago):

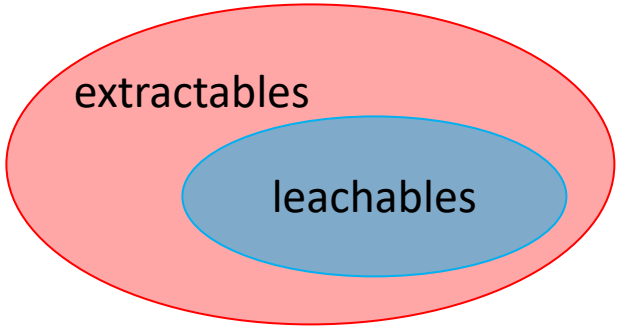
- *Consensus: Leachables are a subset of Extractables*
- *Extractable study should be designed to identify all potential leachables*

FDA and EMA also include this thinking in their Guidelines and Guidances

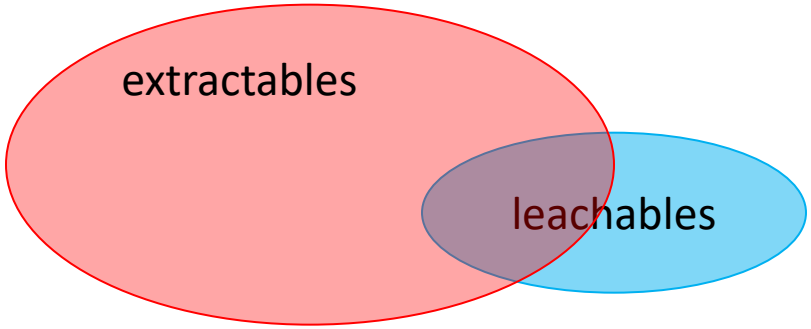
Migration studies may only be omitted if, based on the outcome of the extraction studies, the calculated maximum amount of individual leachable substance that may be present in the active substance/medicinal product leads to levels demonstrated to be toxicologically safe. When a migration study is not considered necessary and thus is not conducted, a justification should be provided.

2.LEACHABLES: A SUBSET OF EXTRACTABLES?

➔ THEORY:



➔ PRACTICE:



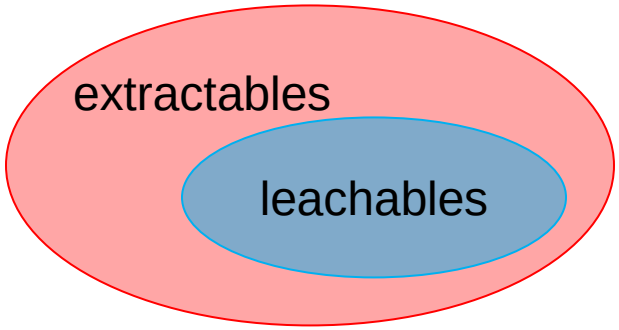
MIND THE GAP!

In the last 6-7 years, there is a growing consensus that – based upon experimental evidence – **Leachables are not always a subset of Extractables**!!

Yet, a lot of pharma companies adhere to the risk assessment of pharmaceutical containers and closures, solely based upon Extractables Data...

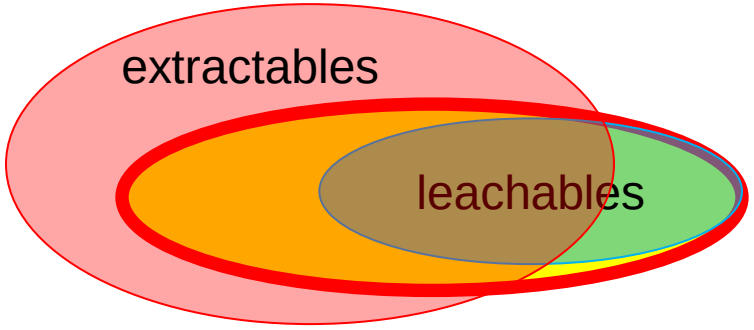
2.LEACHABLES: A SUBSET OF EXTRACTABLES?

➔ THEORY:



CLOSING THE GAP!!

➔ PRACTICE:



Additional Study Design

3. CONSIDER THE STERILIZATION

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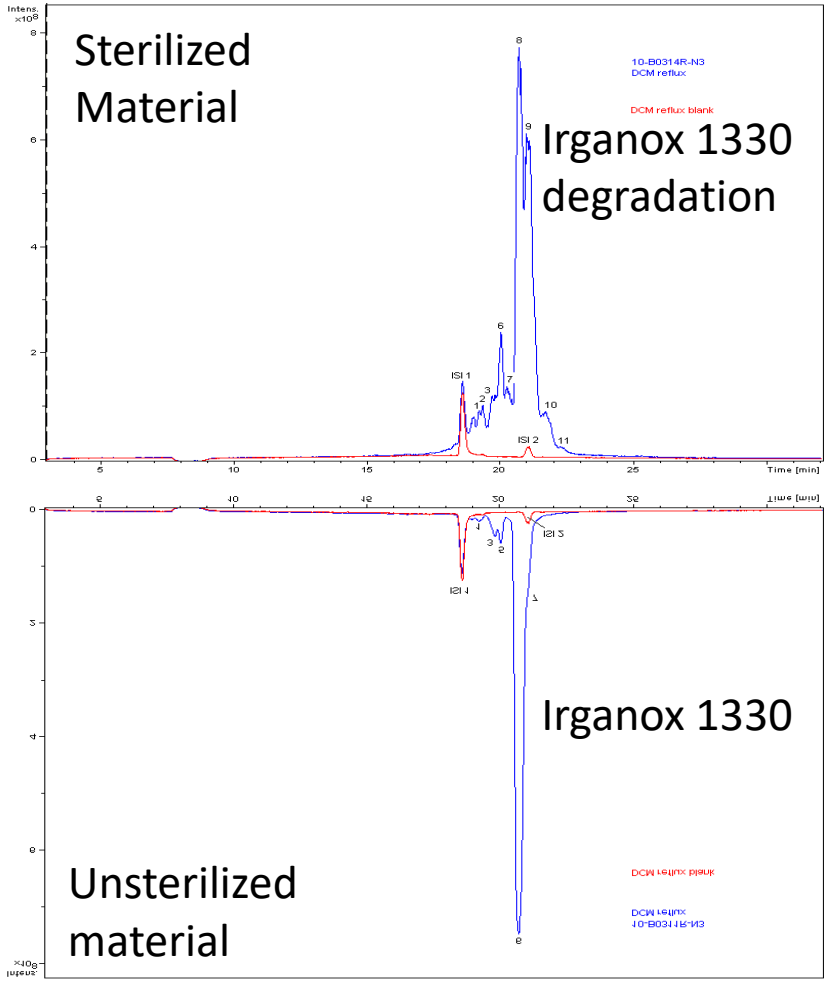
CASE STUDY

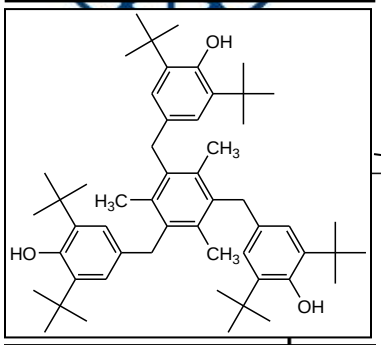
- Polypropylene Containers
- Before and after sterilization (25kGy Beta irradiation)
- Extracted with Dichloromethane
- Ratio: 1 g/ 10 mL, reflux for 8h
- Analysis (presented): LC/MS (APCI-)

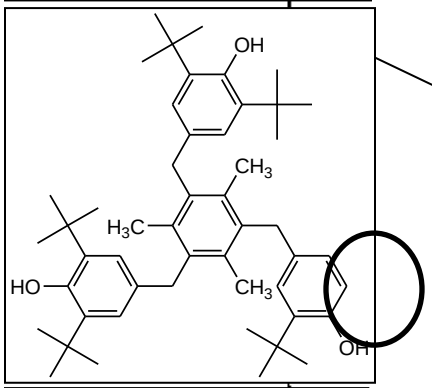


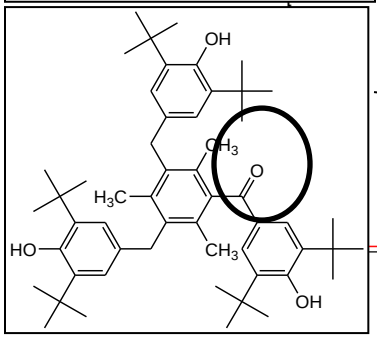
3. CONSIDER THE STERILIZATION

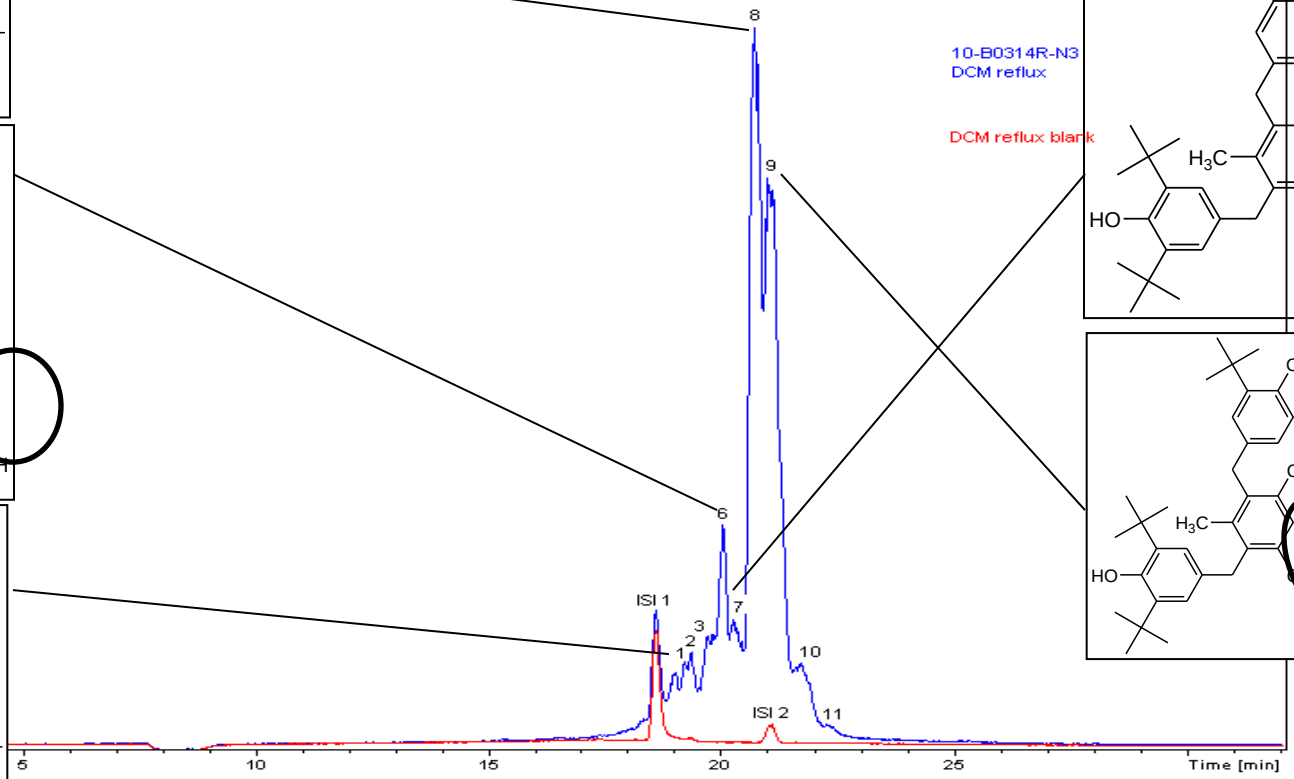
IRGANOX 1330

IRRADIATION STERILIZATION MAY LEAD TO DEGRADATION OF POLYMER ADDITIVES!!

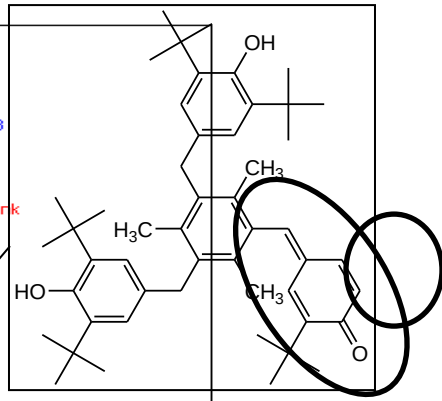






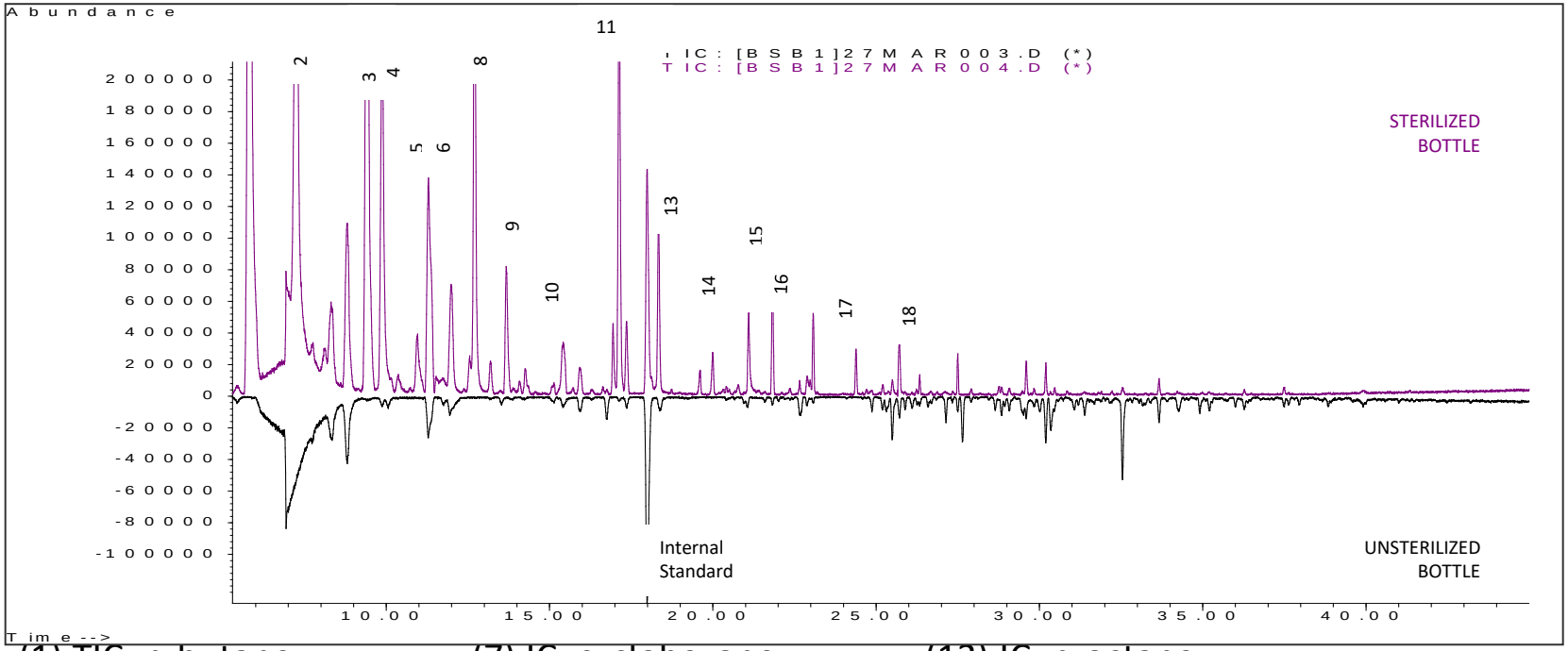


quinonemethide



3. CONSIDER THE STERILIZATION

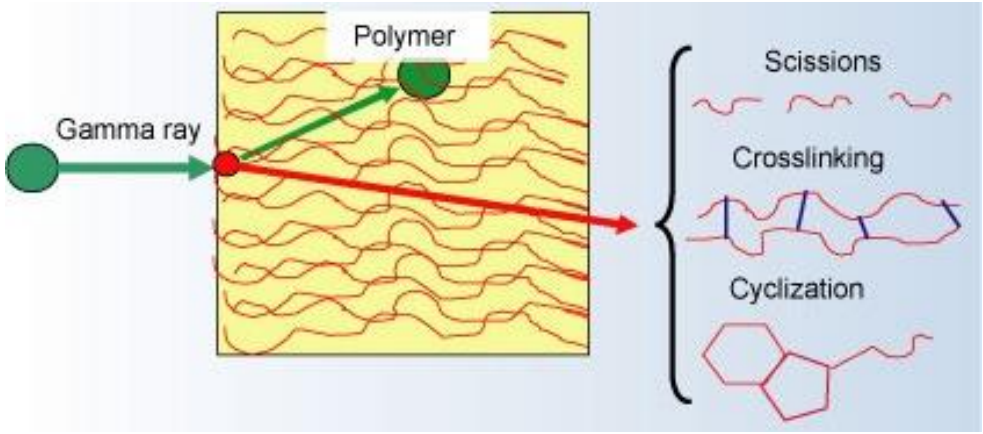
Sterilization of a Polyolefin: Polymer Degradation (Gamma Irratiation 50 kGy)



(1) TIC: n-butane
(2) IC: n-pentane
(3) IC: 3—methylpentane
(4) IC: n-hexane
(5) IC: butanal
(6)TIC: Hydrocarbon
(7) IC: cyclohexane
(8) IC: acetic acid
(9) IC: n-heptane
(10) IC: propanoic acid
(11) IC: 3-methylpentane
(12) TIC: Hydrocarbon
(13) IC: n-octane
(14) IC: 2-Hexanone
(15) IC: Butanoic acid
(16-18): TIC: HC

3. CONSIDER THE STERILIZATION

AGEING - STERILIZATION



POLYMER DEGRADATION (e.g. Scissions, Crosslinking, cyclization)

POLYMER ADDITIVE DEGRADATION (see example for Irganox 1330, but also the case study on biological reactivity (I168ox-diester)!)

CHANGES IN POLYMER CRYSTALLINITY

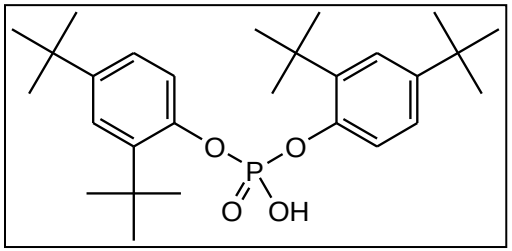
This will impact the: LEACHABLES SOLUBILITY

LEACHABLES MIGRATION

CONCLUSION: TEST FOR EXTRACTABLES AND LEACHABLES ON STERILIZED C/C SYSTEMS

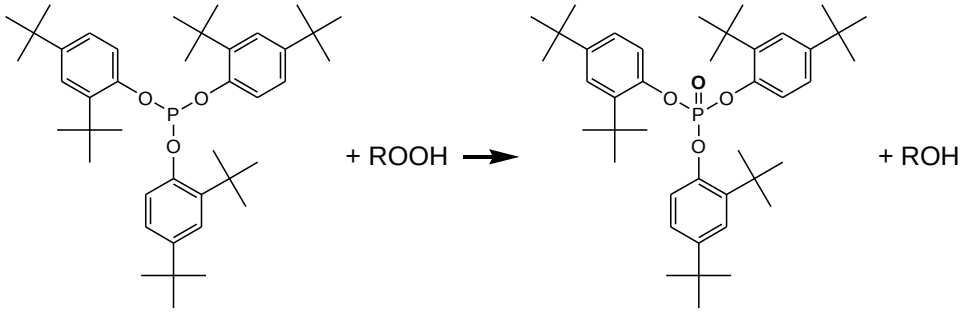
3. CONSIDER THE STERILIZATION

Biological Reactivity of I168ox-diester



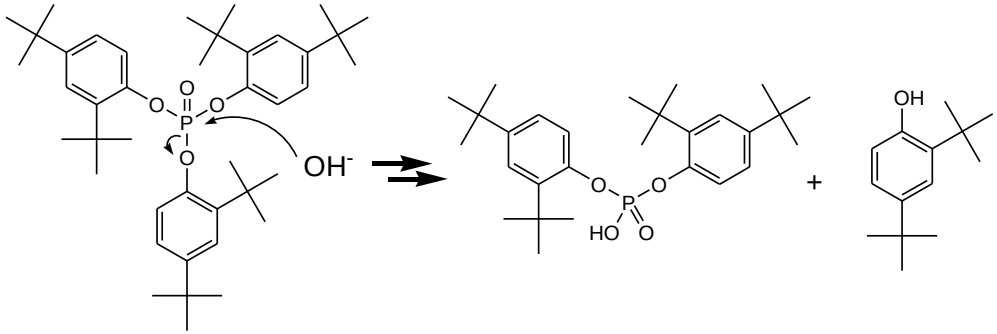
bDtBPP formation:

Step 1: Anti-oxidant I168 is oxidized to I168ox



Irgafos 168 Irgafos 168 Ox

Step 2: During γ-Irradiation: I168ox degrades to I168ox-diester (POTENTIAL DEGRADATION PATHWAY)



Irgafos 168 Ox bDtBPP

4. CONSIDER THE WHOLE DEVICE / ADMINISTRATION PROCEDURE

4. CONSIDER THE WHOLE DEVICE

Typical Cases:

- Connectors, Tubing of Administration Set (tubing), Ports, Filters in I.V. Bag applications (not only film!)
- Glue, Assembling aids, Lubricants
- Silicone Oil
- Integrated Filter in Sterile Administrations (e.g. Ophthalmic)
- Reconstituting Solution (WFI, 0.9% NaCl), stored in Separate Vial / Syringe
  (Case study: see part E/L for Lyo Products)
- Cross Contamination during Sterilization (e.g. Autoclaving)
- ....

5. CONSIDER THE SECONDARY PACKAGING

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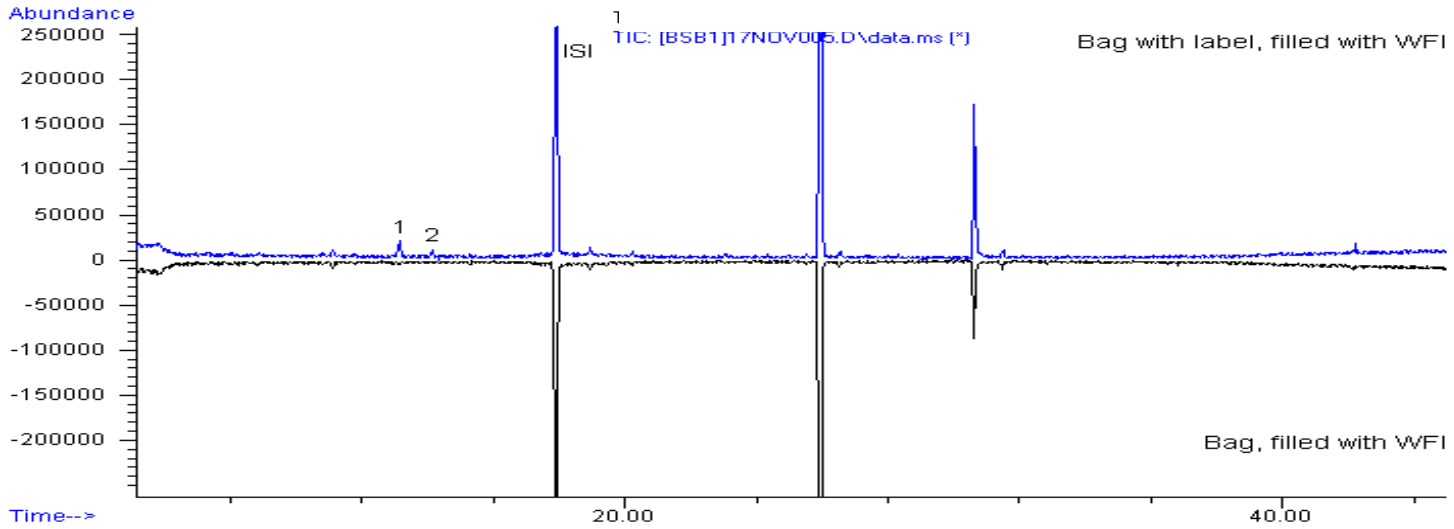
- Label
  - Adhesive
  - paper
  - Ink
  - Varnish
  - Typical extractable compounds:

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

5. CONSIDER THE SECONDARY PACKAGING

LABEL: Benzene formation/migration – Label/Ink

STUDY : Check the Migration of the Adhesive/Ink of the Label through the PVC layer of the Bag (results shown for *Headspace GC/MS*)

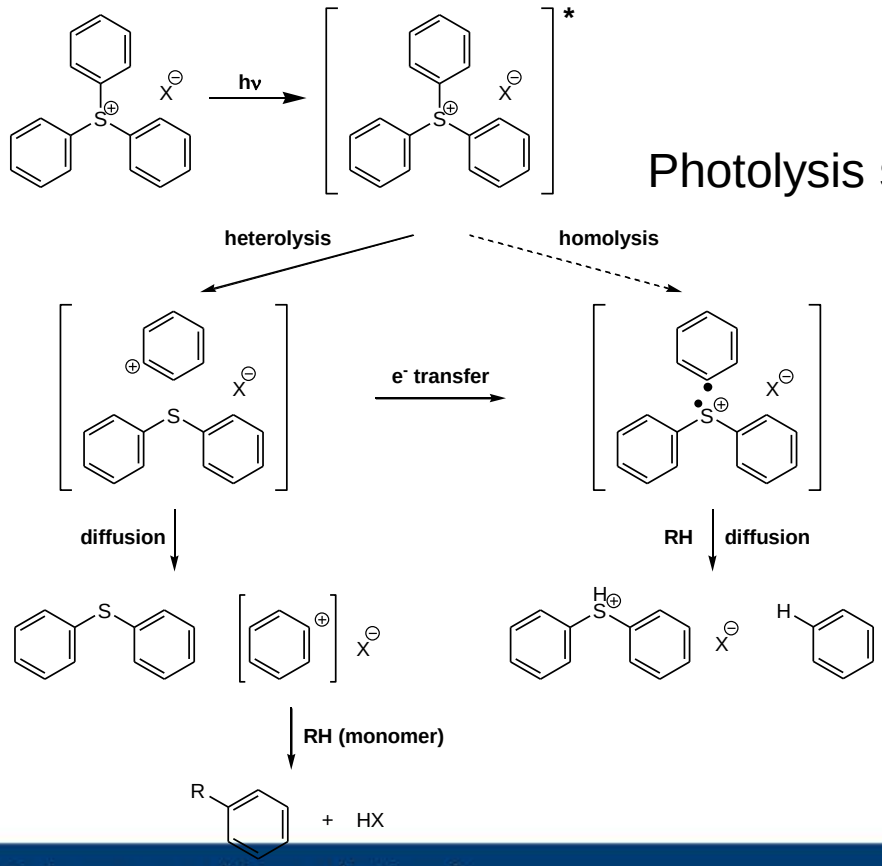


- **LABELED BAG vs. UNLABELED BAG – HS GC/MS**
  - **(1) IC: Benzene (5-10 µg/L)**
  - (2) IC: 1-butanol

5. CONSIDER THE SECONDARY PACKAGING

LABEL: Benzene Formation/Migration – Label/Ink

Triaryl sulfonium salts are photoinitiators for printing Inks



BENZENE FORMATION

Source: Presentation of A. Hauk at ECA E/L Seminar, 2011

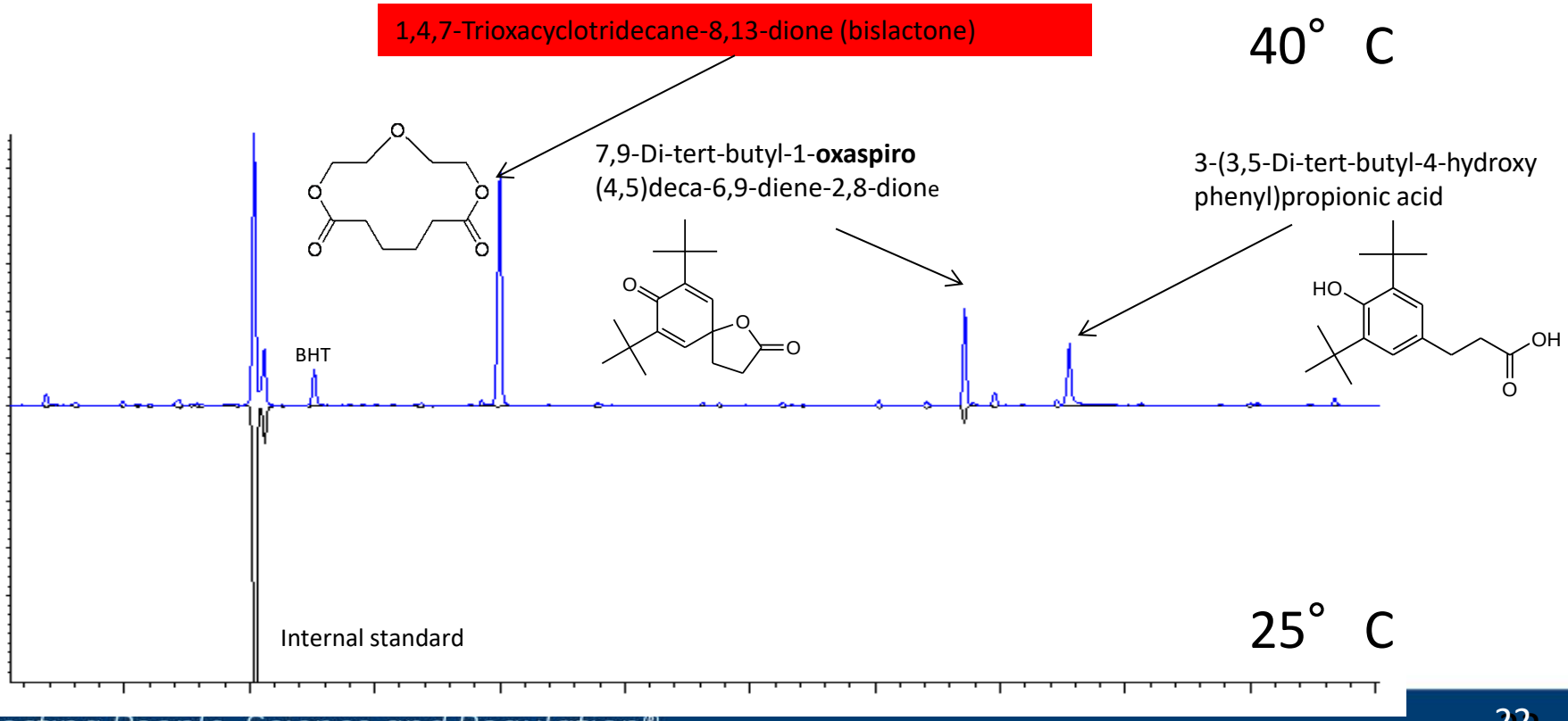
5. CONSIDER THE SECONDARY PACKAGING

Case study LEA: 100 mL flexible multi-layer bag containing a drug solution
ageing at 25° C and 40° C for 3 months
Results for S-VOC (Semi-Volatile Organic Compounds)

Conclusion:

1. MAIN Leachable: bislactone, from adhesive of ALUMINUM Multilayer overwrap!!

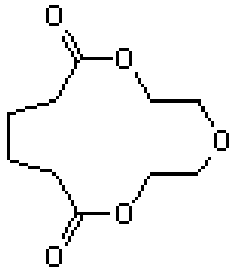
2. T increase leads to increased leaching behaviour of additives / degradation products



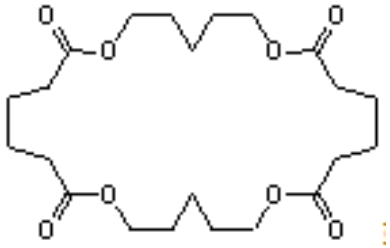
5. CONSIDER THE SECONDARY PACKAGING

- Overpouch
  - Multilaminated foils often containing Aluminium layer
  - Typical extractable compounds:

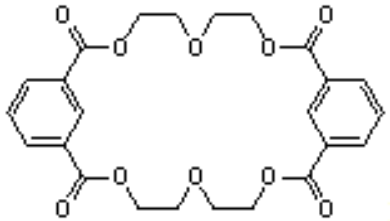
    Bislactone related compounds originating from polyurethane binding layers:



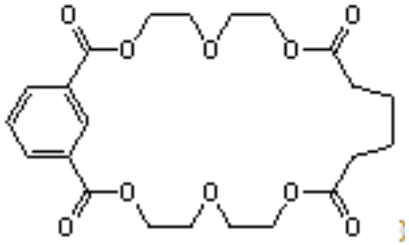
1,4,7-Trioxacyclotridecane-8,13-dione



Bislactone dimer



Heterodimer of Adipic acid di-glycol bis-lactone and Isophthalic acid di-glycol bis-lactone



Di-(Isophthalic acid di-glycol bis-lactone)

5. CONSIDER THE SECONDARY PACKAGING

Typical Cases:

- Overwrap (I.V.-Bags, Blow-Fill-Seal, ...)
- Label migration (Ophthalmic, I.V.-Bags, Polyolefin Containers)
- Ink Migration (I.V.-Bags, Blow-Fill-Seal)
- Needle Shield (Pre-Filled Syringe)

More delicate for semi-permeable Primary Packaging, made of materials with low barrier properties.

6. CONSIDER THE RIGHT EXTRACTION SOLVENT

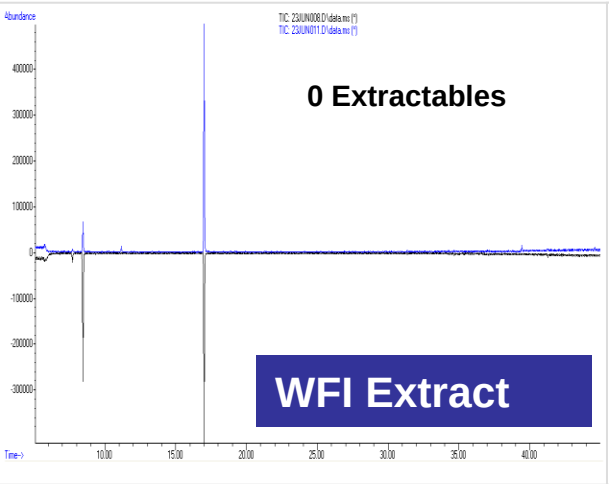
5. CONSIDER THE RIGHT SOLVENT

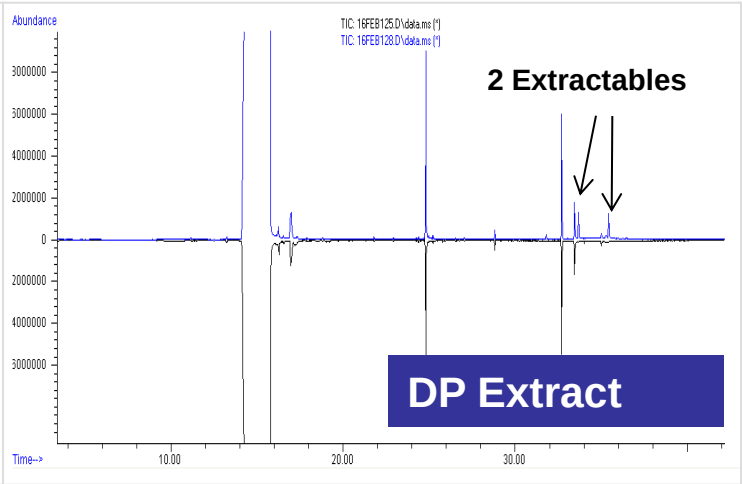
CASE STUDY: impact of contact solution on migration / extraction behavior

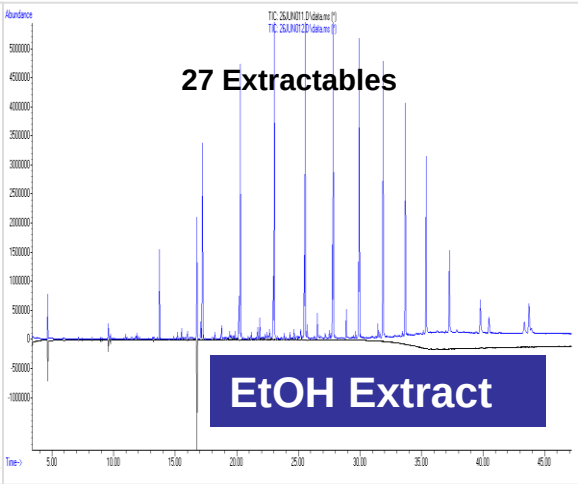
Extractable study of a POLYOLEFIN CONTAINER, using 3 solvents:

1. *Water for Injection (WFI)*
2. *Drug Product (containing 3% organic material)*
3. *Ethanol (96%)*

Identical extraction conditions for 3 experiments: refluxing for 8 h at 1 bottle/30mL ratio
Only results of GC/MS (semi-volatile compounds) is shown







Solubility of targets in WFI < Solubility of targets in DP << Solubility targets in EtOH

Interaction polymer-WFI < Interaction polymer-DP << Interaction polymer-EtOH

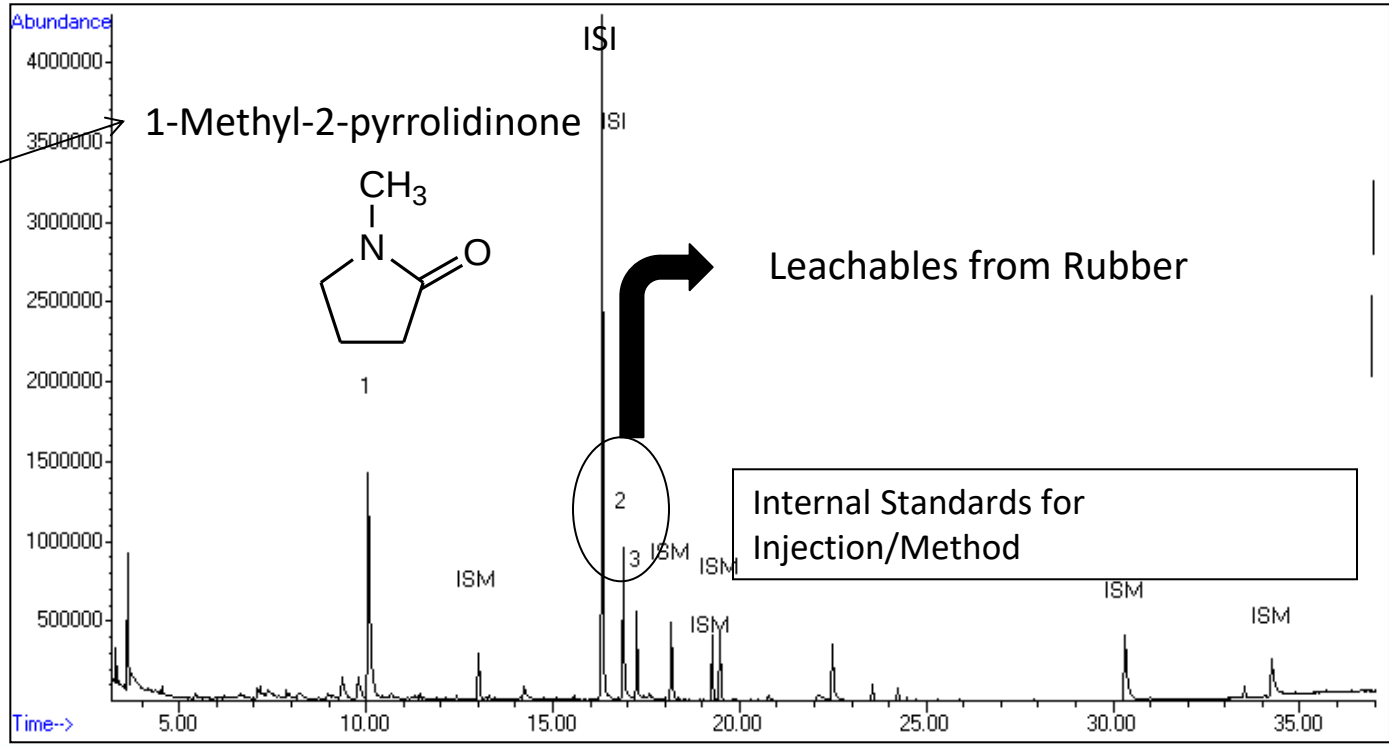
7. CONSIDER THE PROCESSING STEPS

4. CONSIDER THE PROCESSING STEPS

CASE STUDY: Leachable Study on a **vial system** (vial + rubber)
Using **Validated Methods** for Target Compounds, defined after Extractable Study + **Screening Method (**unexpected compounds)

RESULTS: 3 leachables were detected: 2 target compounds, 1 non-target compound (no increase in concentration over time)

Origin of non-target Compound:
Sterile Filtration prior to filling in the PFS!



4. CONSIDER THE PROCESSING STEPS

Typical Cases:

- Filtration
- Tubing for Filling
- Storage Containers of Excipients
- Intermediate Storage of API
- Lyophilization Equipment
- Cross Contamination during Sterilization (e.g. autoclaving)
- Inner/Outer layer cross contamination of Films.
- Diptubes in Storage Containers
- ....

8. EVEN THEN, THINGS CAN GO WONG!!

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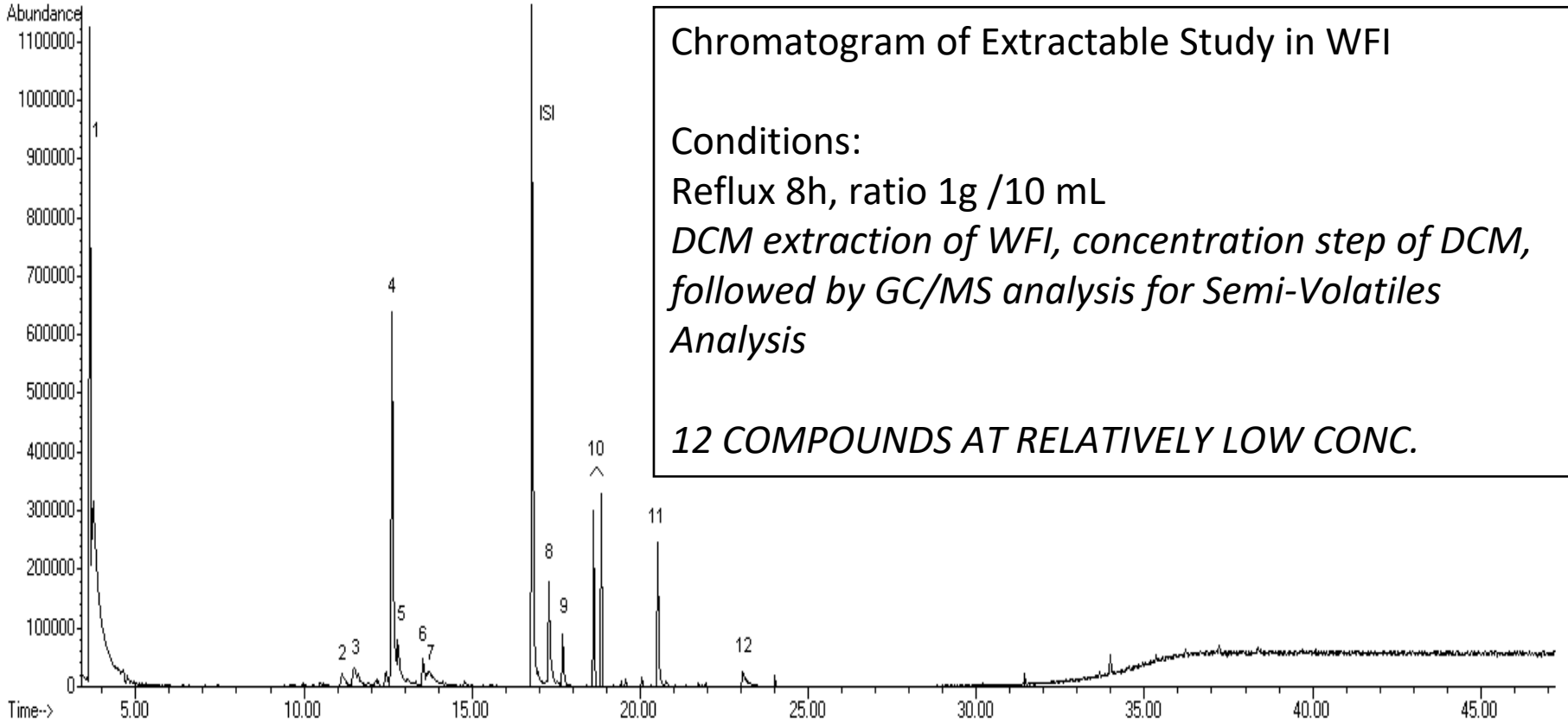
- Prefilled Glass Syringe
- Filled with WFI
- Stored for 3y at 25° C/60% R.H.
- Initial Extractables Study on Plunger (WFI, IPA)
- Leachables (Screening) Analyses after 3 years
  - Headspace GC/MS: Volatiles
  - DCM extraction + GC/MS: Semi-Volatiles
  - DCM extraction + LC/MS (APCI+/-): Non-Volatiles
- 6 different Combinations (Syringe/Plunger/Needle Shield) were tested.
- Results: for Semi-Volatiles, indicative for other groups of compounds

8. EVEN THEN, THINGS CAN GO WRONG

RESULT OF **WFI EXTRACTABLE STUDY** OF THE PLUNGER



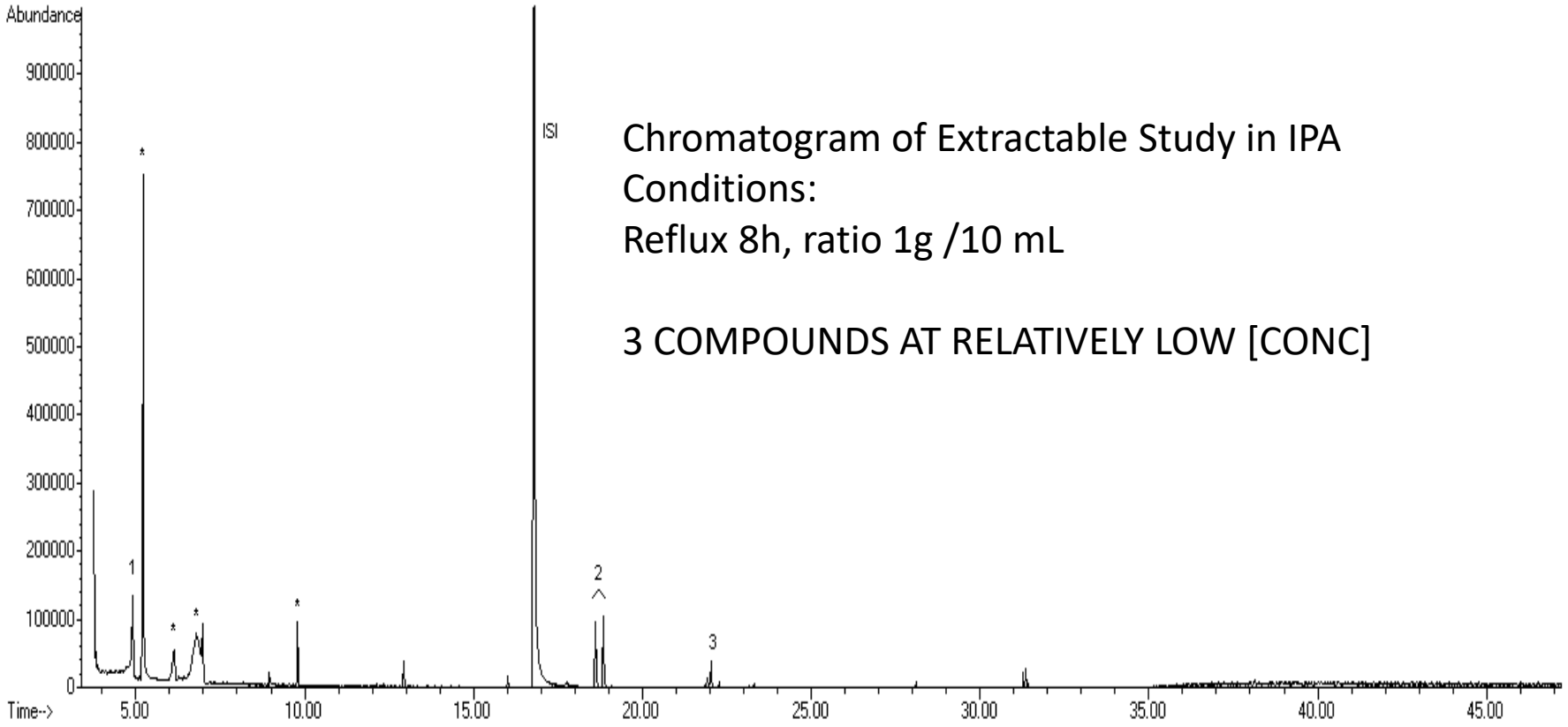
Chromatogram of Extractable Study in WFI

Conditions:
Reflux 8h, ratio 1g /10 mL
DCM extraction of WFI, concentration step of DCM, followed by GC/MS analysis for Semi-Volatiles Analysis

12 COMPOUNDS AT RELATIVELY LOW CONC.

8. EVEN THEN, THINGS CAN GO WRONG

RESULT OF **IPA EXTRACTABLE STUDY** OF THE PLUNGER



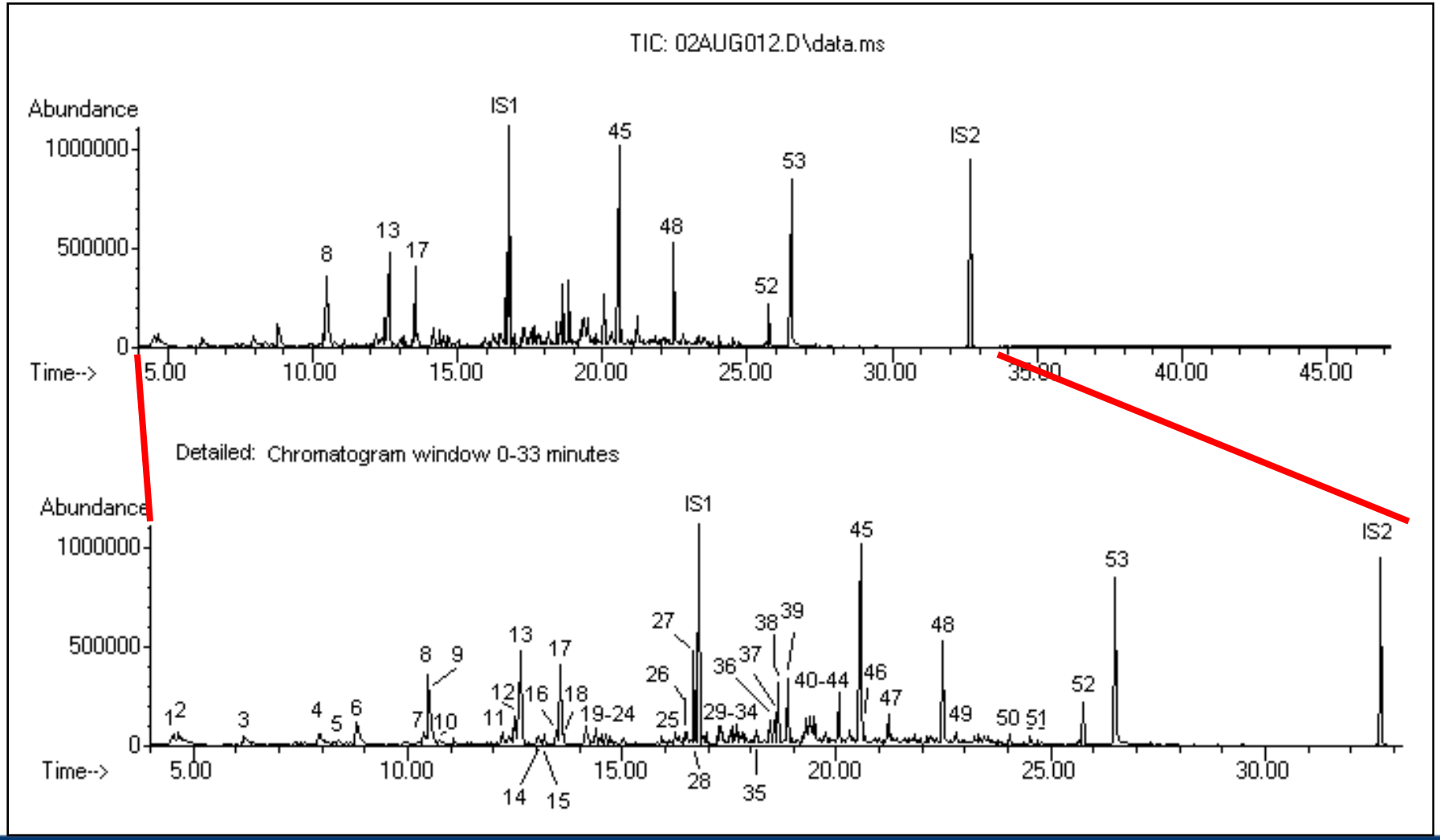
Chromatogram of Extractable Study in IPA
Conditions:
Reflux 8h, ratio 1g /10 mL

3 COMPOUNDS AT RELATIVELY LOW [CONC]

8. EVEN THEN, THINGS CAN GO WRONG

RESULT OF THE **LEACHABLE STUDY** OF THE **WFI- PREFILLED SYRINGE**

3 YEARS AT 25° C – 60% R.H.



8. EVEN THEN, THINGS CAN GO WRONG

LEACHABLES: compounds originating from:

1. **Rubber Plunger**
2. **Hydrolyzed** Compounds from Rubber Plunger
3. Compounds from **Needle Shield**
4. **Hydrolyzed/Oxidized** Compounds from Needle Shield
5. A lot of **"Unknown" Compounds**, both identity and origin is not clear
6. Results are **independent of Type of Rubber** / **Rubber Manufacturer** of the Rubber Plunger!!

Concentration range: from 10 µg/L to > 10 mg/L!

8. EVEN THEN, THINGS CAN GO WRONG

Observations when comparing the results of the Extractable Studies on the Rubber Plunger with the Leachable studies on the PFS system

- **Concentrations of Leachables was Higher** than the Extractables found with WFI as an Extraction Solvent

- Also for more **Aggressive solvents** (e.g. IPA), **not a good match** between Extractables and Leachables

- The observation was **independent of the type of rubber**

8. EVEN THEN, THINGS CAN GO WRONG

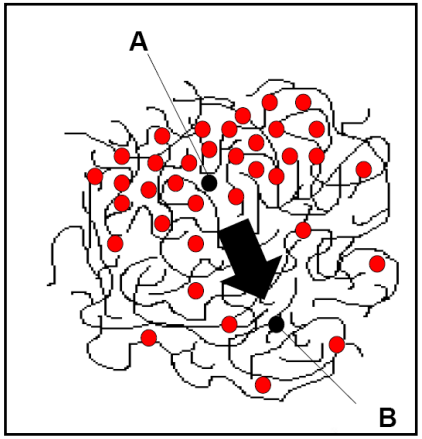
Extractable Studies: Temperature Dependence of Diffusion

By Heating up the material (boiling conditions), diffusion of extractables is increased

$$\frac{dC}{dt} = D \frac{d^2C}{dx^2}$$

With D = Diffusion coefficient

$$D = D_0 \exp(-E/RT)$$

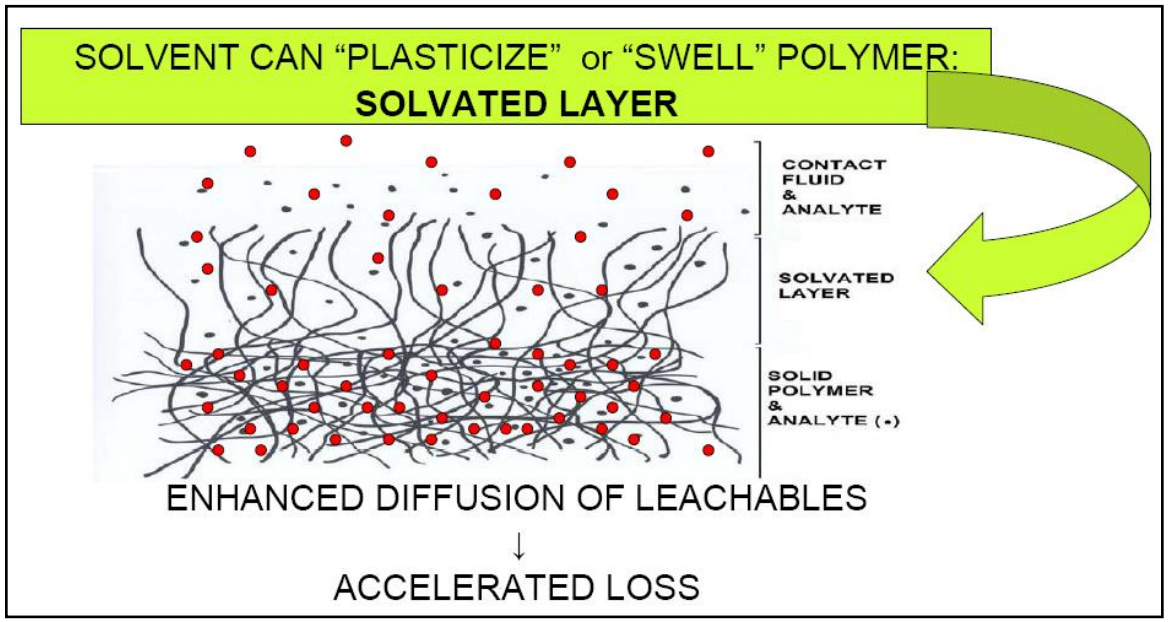


This means that a temperature increase from Room Temperature to solvent boiling point will lead to an increase of D of approx. 2 orders of magnitude *(reference for typical D values: H. Zweifel, « Plastic Additives »)*

Or Reflux extraction of 8h will mimic approx. 800h (=33d of R.T. contact)

8. EVEN THEN, THINGS CAN GO WRONG

Extractable Studies: Interaction between Solvent - Material



For Rubbers: Hexane, DCM and IPA will show enhanced diffusion because of the solvent-material interaction

Completeness of extraction can be checked via Asymptotic Extraction Behaviour

Not to the same extent for WFI!

8. EVEN THEN, THINGS CAN GO WRONG

What is not investigated (sufficiently) in an extractable study?

8.1 MATERIAL DEGRADATION (ageing)

8.2 The **REACTION** (WFI: hydrolysis / O_2: oxidation) **of the leachables with the Drug Product** (solution)

8. EVEN THEN, THINGS CAN GO WRONG

What is not investigated (sufficiently) in an extractable study?

1. MATERIAL DEGRADATION – ASTM 1980 – 02:

Material Degradation: In general ASTM 1980 can be a "general" guidance

$$AAF = Q_{10}^{[(T_{AA} - T_{RT})/10]}$$

AAF: Accelerated Aging Factor

Q_{10}: Aging factor (10° C increase in T)

T_{AA}: Accelerated Aging Temperature

T_{RT}: Room temperature

8h at 100° C (eg. Refluxing in WFI) represents 1440h (60 days) of RT ageing

8h at 80° C (eg. Refluxing in IPA) represents 15 days of RT ageing

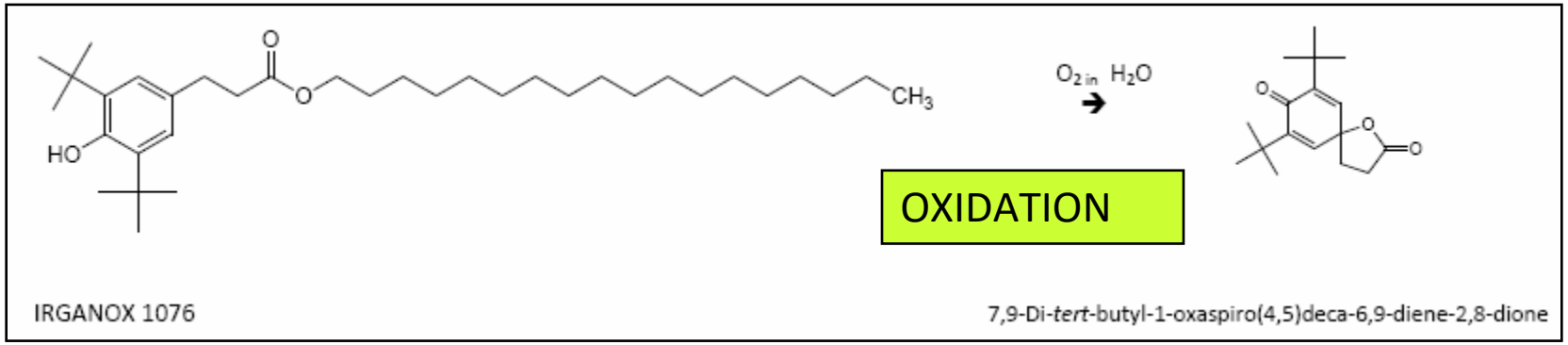
REMARK: Ageing of material is not always representative (Aqueous Environment versus Air (Oxygen!))

8. EVEN THEN, THINGS CAN GO WRONG

What is not investigated (sufficiently) in an extractable study?

2.REACTIVITY OF LEACHABLES

EXAMPLE 1 (Oxidation):



Dissolved Oxygen in WFI /DP(V) will Oxidize Irganox 1076 over time!

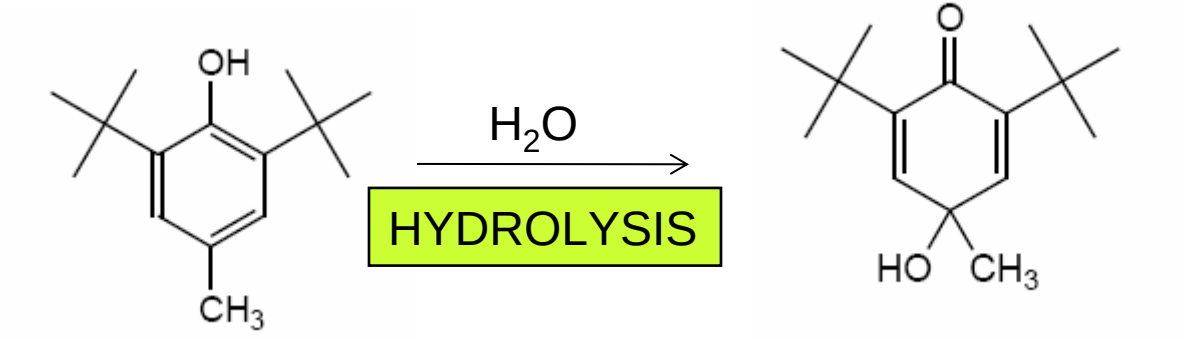
Occurrence of "oxaspiro" as a leachable is much more frequent than as an extractable!

8. EVEN THEN, THINGS CAN GO WRONG

What is not investigated (sufficiently) in an extractable study?

2.REACTIVITY OF LEACHABLES

EXAMPLE N° 2 (Hydrolysis):



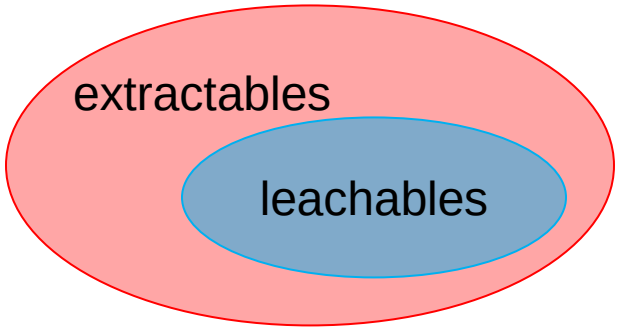
BHT

BHT-OH

BHT-OH is seldom seen as an extractable, but it is regularly seen as a leachable!

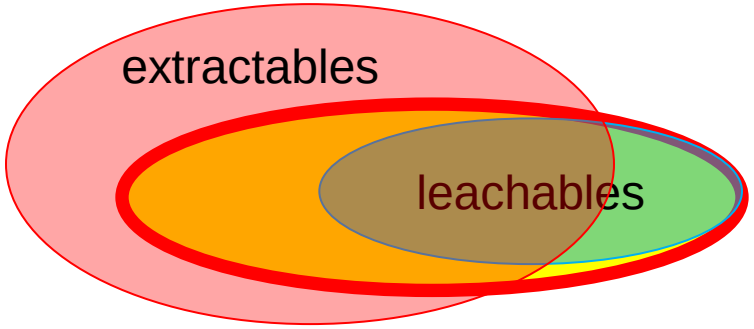
2.LEACHABLES: A SUBSET OF EXTRACTABLES?

➔ THEORY:



CLOSING THE GAP!!

➔ PRACTICE:



Additional Study Design

8. EVEN THEN, THINGS CAN GO WRONG

KINETICS OF	Extraction	Extraction	Accelerated Leachable St.	Real time/temp Leachable St.
	H_2O e.g. 8h reflux	DCM or IPA e.g. 8h reflux	e.g. 6 Mo, 40° C	e.g. 3 y at 25° C
EXTRACTION	SLOW – Incomplete no swelling/enhanced diffusion	FAST – complete Enhanced Diffusion Almost Asymptotic	Enhanced Diffusion controlled leaching is T-dependent $D = D_0 \exp(-E/RT)$	SLOW, but long term contact!
MATERIAL DEGRADATION	Slightly enhanced ASTM 1980: reflux at 100° C/8h: 60d at RT Even if they will be formed, will they come out?	Very Slightly enhanced ASTM 1980: (IPA) reflux at 80° C/8h: 15d at RT	Enhanced ASTM 1980: 6 Mo ageing at 40° C ≡ 17 Mo at 25° C	SLOW, but evaluated over LONG period! (e.g. 3y)
REACTION KINETICS • Dissolved O_2 in H_2O • Hydrolysis (H_2O) • Reaction with DP and leachates/materials • ...	Slightly enhanced Low $[extr]_{init}$ will limit the formation of reaction comp. (i.e. for slow reactions)	Not relevant!	Enhanced, $k = k_0 \exp(-\mathbf{E_a}/RT)$ E_a: Activation Energy, reaction dependent (Pseudo) first order kinetics	SLOW, but evaluated over LONG period! (e.g. 3y)

9. Lessons learned

9. LESSONS LEARNED

1. Consider All Components of the **Container Closure System**

2. Consider the Secondary Packaging, the Processing Conditions, the right set of Conditions to perform the Extractable Study

3. <u>Do not rely solely on Extractable Studies</u> to perform a risk assessment of your Containers/Closures

   Even if the Guidelines themselves suggest that this could be sufficient

FDA

Table 4
Information That Typically Should Be Submitted for Injectable or Ophthalmic Drug Products

Description	Overall general description of container closure system, plus: <u>For Each Packaging Component</u>: • Name, product code, manufacturer, physical description • Materials of construction (for each: name, manufacturer and product code) • Description of any additional treatments (e.g., procedures for sterilizing and depyrogenating packaging components)
Suitability	<u>Protection</u>: (By each component and/or the container closure system, as appropriate) • Light exposure, when appropriate • Reactive gases (e.g., oxygen) • Moisture permeation (powders) • Solvent loss (liquid-based dosage forms) • Sterility (container integrity) or increased bioburden • Seal integrity or leak testing of tubes (ophthalmics) <u>Safety</u>: (for each material of construction, as appropriate) • Chemical composition of all plastics, elastomers, adhesives, etc.[a] • For elastomeric closures: USP Elastomeric Closures for Injections testing • For glass components: USP Containers: Chemical Resistance — Glass Containers • For plastic components and coatings for metal tubes: USP Biological Reactivity Tests • If the extraction properties of the drug product vehicle may reasonably be expected to differ from that of water (e.g., due to high or low pH or due to a solubilizing excipient), then drug product should be used as the extracting medium. • If the total weight of extracts significantly exceeds the amount obtained from water extraction, then an extraction profile should be obtained. • For plastic or elastomeric components undergoing heat sterilization, it is current practice to request that the extraction profile be obtained at 121°C/1 hour using an appropriate solvent.

EMEA

Migration studies may only be omitted if, based on the outcome of the extraction studies, the calculated maximum amount of individual leachable substance that may be present in the active substance/medicinal product leads to levels demonstrated to be toxicologically safe. When a migration study is not considered necessary and thus is not conducted, a justification should be provided.

9. LESSONS LEARNED

3. If Safety Assessment is made on Extractables Results: check off with Leachable Studies!
   This will account for "unaccounted" leachables, such as polymer degradation, polymer additive degradants, process leachables, secondary packaging, or other extractables missed because of an ill designed study set-up

4. Consider – if possible – an additional **Accelerated Leachable study** (e.g. with screening methods) to verify the presence of "unexpected leachables"
   (as a step in between extractable studies and full leachable studies)

5. If the above is not possible: add a **screening step in the full leachable study**