Connecting People, Science and Regulation

E/L STUDIES FOR LYOPHILIZED/ FREEZE DRIED PRODUCTS

PDA WORKSHOP
EXTRACTABLES – LEACHABLES
Brussels
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Dr. Piet Christiaens

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PART 1

Introduction – Regulatory Requirements

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

Introduction

- **Extractables:**

  Extractables are compounds that migrate from the contact surface under ***more aggressive conditions*** such as elevated temperature, extended contact time, or aggressive solvent system. Any component that is added to the device or the materials used to make the device.

  What **CAN** come out.

- **Leachables:**

  Leachables are compounds that migrate from the contact surface under ***normal conditions*** of exposure. Leachables are usually a subset of extractables.

  What **DOES** come out.

D. Jenke (presentation at SmithersRapra, Providence, May 2013)

Introduction

The terms **extractable** and **leachable** provide clarity in terms of:

1. The **potential** versus the **actual** impact of the product on its user.

   * **Extractable** = potential impact: *what "could" come out*
   * **Leachable** = actual impact: *what "will" come out*

2. The object on which the testing is performed.

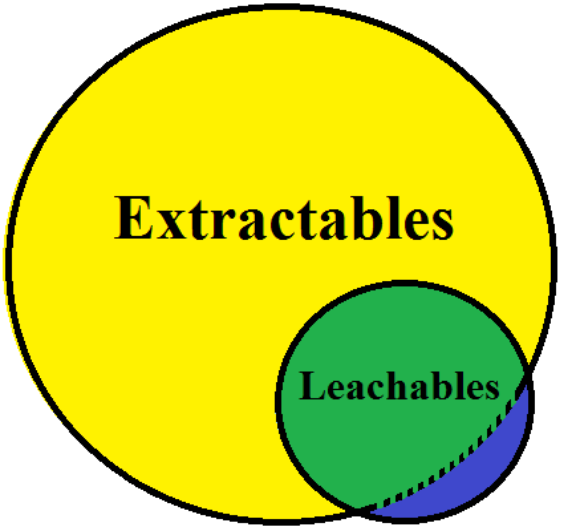
   * **Extractable** = test the **material**
   – **Leachable** = test the **finished product**

D. Jenke (presentation at SmithersRapra, Providence, May 2013)

Introduction

Extractables/Leachables

- **LEACHABLES** are *typically* a **SUBSET** of **EXTRACTABLES**



- **NOT ALL LEACHABLES are EXTRACTABLES**

Introduction

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

The FDA Guidance Document

"*Container Closure Systems for Packaging Human Drugs and Biologics*" of 1999

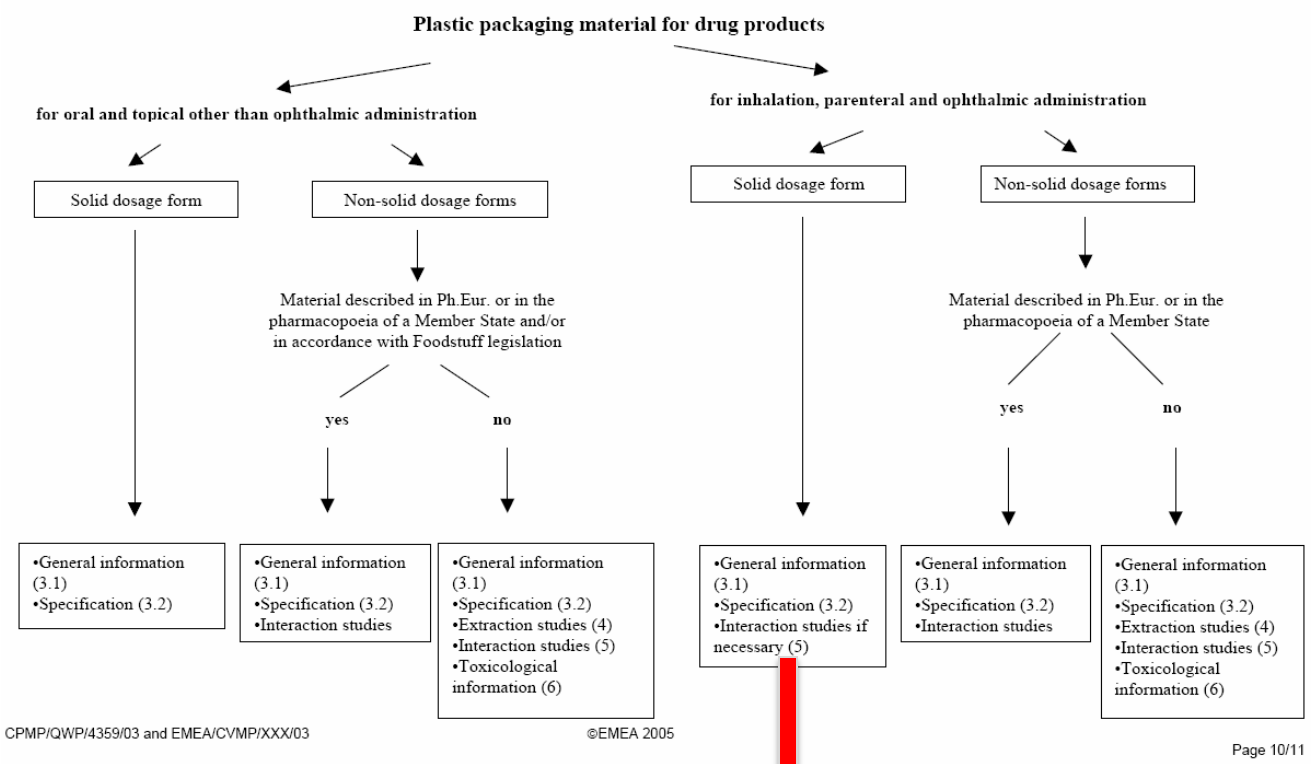
Introduction

The FDA Guidance Document
"*Container Closure Systems for Packaging Human Drugs and Biologics*" of 1999
may NOT reflect the current (2013) FDA requirements
for E/L Testing and Documentation:

- Requirements for Freeze Dried Products = Liquid Parenterals
- NOT ONLY EXTRACTABLES evaluation => Consider LEACHABLE STUDIES!
- Consider Lyo Container Parts,
  Reconstitution Solution Container Parts
  Administration Device/Set

Introduction

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



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

Introduction

The EM(E)A Guideline on
"*Plastic Immediate Packaging Materials*" of 2005
may NOT reflect the current (2013) European Regulatory Requirements
for E/L Testing and Documentation:

- Requirements for Freeze Dried Products = Liquid Parenterals

- Consider Lyo Container Parts,
  Reconstitution Solution Container Parts
  Administration Device/Set

Introduction

A lot of container/closure systems and devices for in the administration of Freeze Dried Products fall under the New Rule (*21CFR "Part 4"*) on Combination Products

Came into effect on July 22, 2013

Introduction

New Rule (*21CFR "Part 4")* on Combination Products

Came into effect on July 22, 2013

– **Single Entity**:

*"A **product comprised of 2 or more regulated components**, i.e. Drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically or otherwise **combined or mixed and produced as a single entity**"*

e.g. Dual Chamber vial

Pre-Filled Syringe

- **(Long Term) Stability Study of DP**
- **(Long Term) Leachable study , with multiple time points (cfr Stability Study)**

Introduction

New Rule (*21CFR "Part 4")* on Combination Products

Came into effect on July 22, 2013

– **Co-Packaged:**

"**…***2 or more* ***separate products packaged together in a single package*** *or as a unit and comprised of drug and device products, device and biological products, or biological and drug products..."*

e.g. Vial or Pre-Filled Syringe, containing Reconstitution Solution

e.g. Bag for Administration after Reconstitution

- **(Short Term) Stability Study of DP (e.g. Administration Set)**
- **Leachable study based upon the intended use – duration of contact and environmental conditions**

Introduction

New Rule (*21CFR "Part 4")* on Combination Products

Came into effect on July 22, 2013

– **Cross Labeled:**

"**…***A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g. To reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose..."*

e.g. Administration Pump

- **(Short Term) Stability Study of DP (e.g. Administration Pump)**
- **Leachable study based upon the intended use – duration of contact and environmental conditions**

Types of C/C for Lyo DP

PART 2

Container/Closure

& Administration Systems

for Freeze Dried Products

Types of C/C for Lyo DP

1. Lyo Cake Container:

- Glass Vial
- Rubber Stopper
- Dual Chamber Vial/Syringe *(single entity combination products)*

Types of C/C for Lyo DP

2. Container for Reconstitution Solution:

When marketed together with DP:
this becomes a COMBINATION PRODUCT

Vial + Rubber Stopper
+
Disposable Syringe
(Co- Packaged?)

Pre-Filled Syringe
(Single Entity)

Types of C/C for Lyo DP

3. Administration of Reconstituted DP:

When marketed together with DP:
this becomes a COMBINATION PRODUCT

Disposable Syringe
(Co-packaged?)

IV-Bag System
(+Administration Set)
(Co-packaged, Cross Labeled?)

Pump System
(Cross Labeled)

Types of C/C for Lyo DP

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!

PART 3

Designing Appropriate Extractable Studies Container-Closure & Administration Systems

Extractable Studies Design

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)
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) LC/MS **SCREENING**
Sulfur **Silicone Oil**	Cross Linking Lubrification	HPLC-UV GF-AAS

Extractable Studies Design

Questions for Container/Closure & Administration System, helping to **determine the EXTENT and DEPTH of the Extractable Study** Design for Lyo Applications:

- Length of Contact between Materials & Lyo DP
- Length of Contact between Materials & Reconstitution Solution
- Length of Contact between Materials & Reconstituted Drug Product
- Impact on DP Stability and Quality (Lyo or reconstituted)
- Risk to the patient
- ...

Extractable Studies Design

A. *Lyo-Cake Container* & *Container for Reconstitution* Solution

- **Lyo-Cake Container**: prolonged exposure of Lyo-Cake to the Vial and Rubber Stopper
- **Container for reconstitution**: prolonged exposure of Reconstitution Solution to Container materials (glass vial with rubber stopper or PFS parts)
- All released compounds (leachables) will be injected into the patient!
- Some compounds may represent a quality or performance issue for the DP!

CONCLUSION: HIGH RISK
IN DEPTH EXTRACTABLES & LEACHABLES ASSESSMENT

Extractable Studies Design

A.1 Lyo-Cake Container

- Sources of impurities, coming from packaging
  - **Glass**: Metals (may not be necessary to be studied in EXT Study, if glass composition is available, direct assessment in LEA study)
  - **Rubber Closure:**
    - ✓ **No Direct Contact** between DP and Closure (upright)
    - ✓ **HOWEVER:** Release of Volatile (VOC) and Semi-Volatile (SVOC) Compounds from the Rubber Closure vial desorption and subsequent adsorbtion of compounds onto Lyo-Cake!
    - ✓ **Lyo-cake acts as adsorbent for VOC and SVOC compounds! Released Compounds are concentrated over time onto the Lyo Cake**
    - ✓ **Regardless** if vial is in **upright or inverted** position (contact / no contact with DP)
    - ✓ VOC and SVOC may also be **Reactive** with DP (see case study): also potential Performance & Quality Issue!
    - ✓ Also NVOC, Metals and Ions need to be “checked off”, because of short term contact with Reconstituted DP.

Extractable Studies Design

A.1 Lyo-Cake Container

Potential set-up for an extraction study on the rubber closure of the Lyo-Cake Vial

TARGET COMPOUNDS	ANALYTICAL METHOD	**Rubber closure**		
		WFI	IPA	Neat
Volatile Organic Compounds (VOC)	Headspace- GC/MS	-	×	×
Semi-Volatile Organic Compounds (SVOC)	GC/MS	×	×	-
Non-Volatile Organic Compounds (NVOC)	LC/MS (APCI+)	×	×	-
Non-Volatile Organic Compounds (NVOC)	LC/MS (APCI-)	×	×	-
Sulfur (S_8)	LC/UV	×	×	-
Elements: Al, Ca, Fe, Mg, Si, S (total), Ti, Zn	ICP	×	-	-
Anions: Br^-, Cl^- and F	IC	×	-	-

Remark: also, other extraction vehicles can be considered

Extractable Studies Design

A.2 Container for Reconstitution Solution

- If it is a **GLASS VIAL with RUBBER CLOSURE:** Sources of Impurities, coming from packaging:
  - **Glass**: Metals (may not be necessary to be studied in EXT Study, if glass composition is available, direct assessment in LEA study)
  - **Rubber Closure:**
    - ✓ Typically, higher migration when solution is in contact (inverted)
    - ✓ Migration will be determined by:
      - Solubility of leachables in 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 & 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”...

Extractable Studies Design

A.2 Container for Reconstitution Solution

Potential set-up for an extraction study on the rubber closure of the **Vial** for Reconstitution Solution

TARGET COMPOUNDS	ANALYTICAL METHOD	**Rubber closure**		
		WFI	IPA	Neat
Volatile Organic Compounds (VOC)	Headspace- GC/MS	-	×	×
Semi-Volatile Organic Compounds (SVOC)	GC/MS	×	×	-
Non-Volatile Organic Compounds (NVOC)	LC/MS (APCI+)	×	×	-
Non-Volatile Organic Compounds (NVOC)	LC/MS (APCI-)	×	×	-
Sulfur (S_8)	LC/UV	×	×	-
Elements: Al, Ca, Fe, Mg, Si, S (total), Ti, Zn	ICP	×	-	-
Anions: Br^-, Cl^- and F	IC	×	-	-

Extractable Studies Design

A.2 Container for Reconstitution Solution

- If it is a **PRE-FILLED SYRINGE:** Sources of Impurities, coming from packaging:
  - **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 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”...

Extractable Studies Design

A.2 Container for Reconstitution Solution

- If it is a **PRE-FILLED SYRINGE:** Sources of Impurities, coming from packaging:
  - **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

A.2 Container for Reconstitution Solution

Potential set-up for an extraction study on the **rubber components** of the **Pre-Filled Syringe** for Reconstitution Solution

TARGET COMPOUNDS	ANALYTICAL METHOD	**Plunger**			**Needle shield**	
		WFI	IPA	Neat	IPA	Neat
Volatile Organic Compounds (VOC)	Headspace- GC/MS	-	×	×	×	×
Semi-Volatile Organic Compounds (SVOC)	GC/MS	×	×	-	×	-
Non-Volatile Organic Compounds (NVOC)	LC/MS (APCI+)	×	×	-	-	-
Non-Volatile Organic Compounds (NVOC)	LC/MS (APCI-)	×	×	-	-	-
Sulfur (S_8)	LC/UV	×	×	-	-	-
Elements: Al, Ca, Fe, Mg, Si, S (total), Ti, Zn	ICP	×	-	-	-	-
Anions: Br^-, Cl^- and F	IC	×	-	-	-	-

Extractable Studies Design

A.2 Container for Reconstitution Solution

Potential set-up for an extraction study on the **glass barrel** of the **Pre-Filled Syringe** for Reconstitution Solution

TARGET COMPOUNDS	ANALYTICAL METHOD	NH_3*	WFI	DCM	mix**	Hexane
Semi-Volatile Organic Compounds (SVOC) – Glue Residues	GC/MS	-	-	X	-	-
TMPTMA	LC/UV	-	-	-	X	-
Silicone oil	GF-AAS	-	-	-	-	X
Elements: Al, Ba, B, Ca, Cu, Fe, Mg, Mn, K, S(total), Na, Ti, W, Zn	ICP	-	X	-	-	-
Elements: W	ICP	X	-	-	-	-

*: 5 % NH_4OH in WFI; **: TFA/MeCN/WFI 0.2/30/70

Extractable Studies Design

A.3 Disposable Syringe for reconstitution (in case of vial container for reconstitution solution)

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

Extractable Studies Design

B.Container for Administration of Reconstituted Drug Product

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

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

Extractable Studies Design

B.Container for Administration of Reconstituted Drug Product

- If the Container for Aministration (e.g. Disposable Syringe, IV bag, Pump) falls under one of the definitions of a **COMBINATION PRODUCT** :
  - **Q: Can a Simulation study be an alternative for Leachable Studies?**
    Can be, however, preferably verify release of compounds in DP in a leachable study, where the administration procedure is incorporated in the study set-up.

Extractable Studies Design

B.Container for Administration of Reconstituted Drug Product

EXAMPLE: Potential set-up for an extraction study on a **IV-Bag** for Administration of the Reconstituted DP

TARGET COMPOUNDS	ANALYTICAL METHOD	**IV-Bags**			
		UPW	IPA	Hexane	Neat
Volatile Organic Compounds (VOC)	Headspace- GC/MS	-	×	-	×
Semi-Volatile Organic Compounds (SVOC)	GC/MS	×	×	×	-
Non-Volatile Organic Compounds (NVOC)	LC/MS (APCI+)	×	×	×	-
Non-Volatile Organic Compounds (NVOC)	LC/MS (APCI-)	×	×	×	-
Elements: Ag, Al, As, Ba, Ca, Cd, Co, Cr, Cu, Fe, K, Li, Mg, Mn, Mo, Ni, Pb, Pd, S, Si, Sr, Ti, V, Zn, Zr	ICP	×	-	-	-
Anions: Acetate, formate	IC	×	-	-	-

PART 4

How to Develop Leachable Studies for Lyo Drug Products

Critical Aspects

Leachables Study Design

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!

Leachables Study Design

ANALYTICAL CHALLENGE

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

Leachables Study Design

- Assess potential Toxic Consequences

  For Toxicological assessments, reliable analytical data are needed. Therefore, consider:

- Validated Methods (ICH Q2(R1))

- "Simulated Use" Conditions

  Storage Time / Temperature / Humidity

  Conditions: Similar to Stability Studies

  Pharmaceutical Formulation As Contact Solution

- Quantification of "Target" Compounds

  Extractables study information

Leachables Study Design

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

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

FULL LEACHABLE STUDY

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

Leachables Study Design

EXAMPLE OF 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

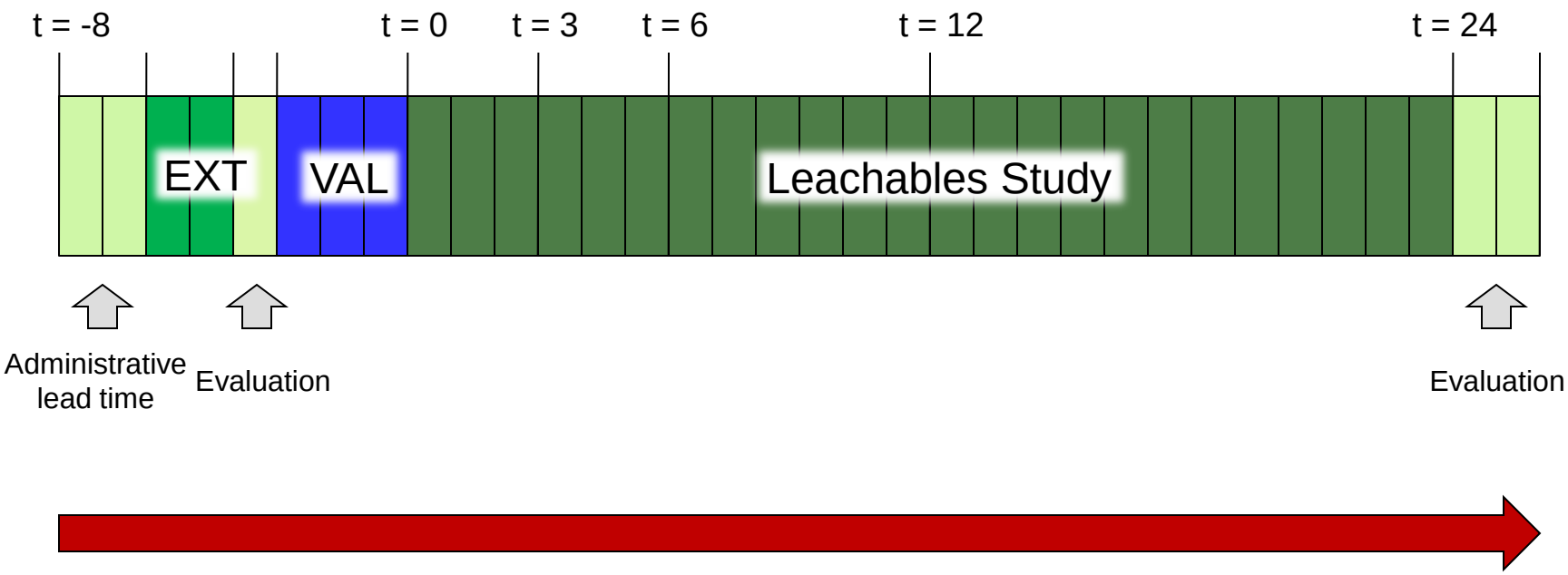
Leachables Study Design

EXAMPLE OF FULL 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					

Leachables Study Design

EXAMPLE OF FULL EXTRACTABLE&LEACHABLE STUDY



Total = 34 months

Leachables Study Design

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

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

LIMITED LEACHABLE STUDY

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

At least, check of the following:

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

Leachables Study Design

Conclusion for SHORT TERM EXPOSURE containers

- Perform the Full Leachable Study as requested for the containers/closures with long term contact.
- Add the Procedure for Reconstitution (when disposable syringe is used)
- Add the Procedure for Administration.
- In Certain Cases: in addition to quantitative analysis of target compounds for LT C/C:
  - add certain targets for Administration Devices in quantitative assessment, **or**
  - Perform a semi-quantitative assessment of impurities from administration devices
  - For at least 2 time points (early and late time point), to cover the ageing of Device.

Leachables Study Design

WHAT ABOUT THE BLANK "REFERENCE" MEASUREMENTS FOR LYO DP?

Typically, a **leachable** study is a **"differential assessment"**

- Impurities detected in the DP after contact with the Container/Closure
- Impurities detected in DP with NO CONTACT with Container/Closure
- For each time point (exclude degradation of DP)

Less Critical for Validated Methods => Target Compounds are assessed

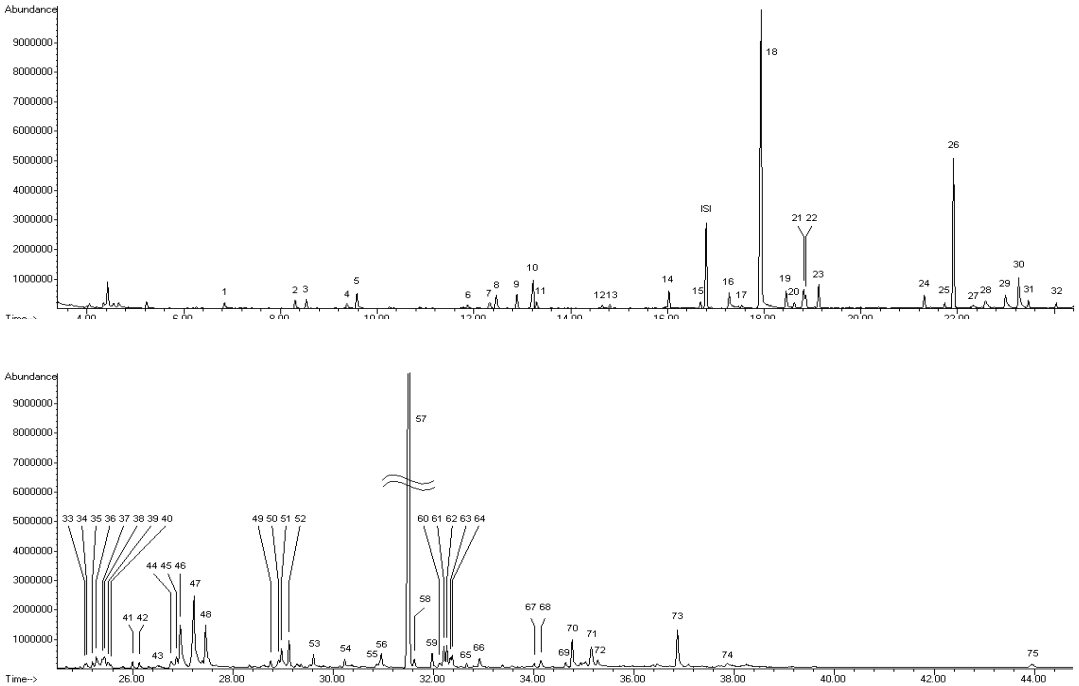
More Critical for Screening Methods!!

Looking at each compound that is present in the Drug Product with C/C contact, which are not present in the Drug Product without C/C Contact

Especially Critical for evaluation of Short Term Contact Containers/Closures!

Leachables Study Design

Example GC/MS chromatogram of a Lyo DP, after reconsitution & Sample prep



74 Compounds, detected in GC/MS. Which one is a leachable??

Leachables Study Design

Observed Potential Solutions for Unavailability of the Blank DP

1. Consider **t = 0 as blank baseline** throughout the complete study

   Disadvantage:

   - Some Compounds may already be present after a short term contact
   - Stability / Degradation of DP is not accounted for

2. Use **upright position as a "reference"** for inverted position **=> NOT AN OPTION**

   Disadvantage:

   - *Migration Mechanism* is not based upon material contact, rather based upon headspace release of VOC/S-VOC into headspace of vial with subsequent adsorption onto the lyo cake

3. Use **"Lab Prepared & Freshly Prepd DP",** containing all the ingredients of the DP

   Disadvantage:

   - Some volatile impurities may be present in "Prepared DP" but not in DP in contact with material
     (lyophilization also removes a lot of VOC/S-VOC impurities)
   - Degradation of DP may/will be different in solution compared to Lyophilized

Leachables Study Design

Potential Solutions

- ❑ Report all compounds (=> impurities profiling)
- ❑ Select target compounds to be monitored, even for screening in Semi-Quantitative analysis
- ❑ Evaluate the leachable results, along with the EXT results of every device / container.
- ❑ Use quantitative methods, even for short term contact containers.
- ❑ Use blank type N°3 (of previous slide), knowning the disadvantages.

PART 5

Safety Evaluation of Results: Learning from the PQRI PODP Threshold Approach

The PQRI PODP Thresholds

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.

The PQRI PODP Thresholds

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

The PQRI PODP Thresholds

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

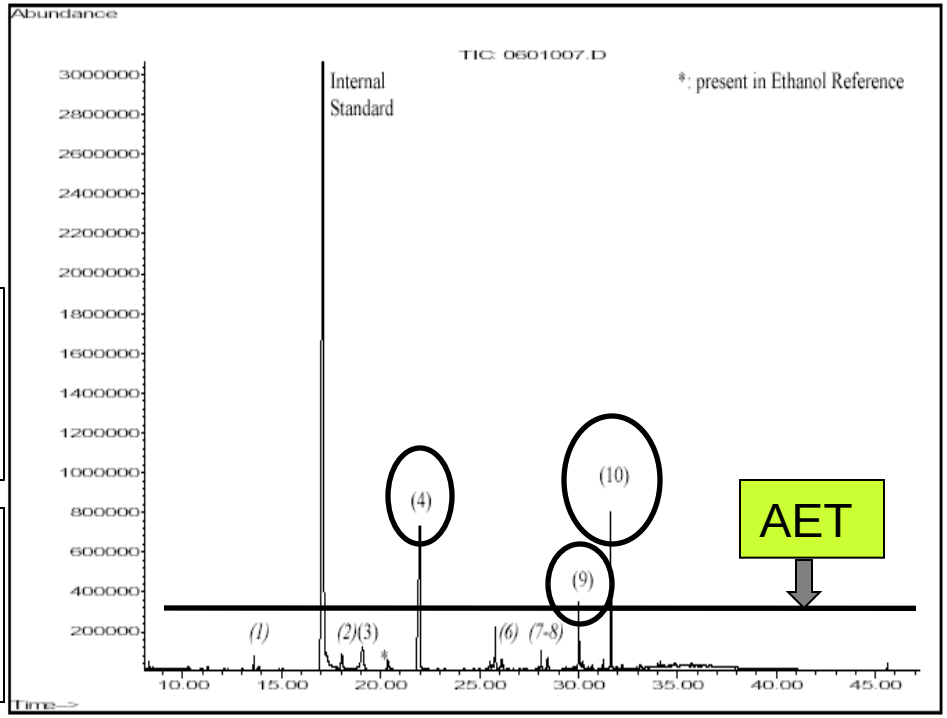
Translate SCT

into Analytical Thresholds

for Extractable Studies

Taking into account:

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



The PQRI PODP Thresholds

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

	Class I	Class II	Class III
Threshold Level (µg/day)	150	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.

The PQRI PODP Thresholds

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**

The PQRI PODP Thresholds

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
   - ...

The PQRI PODP Thresholds

THRESHOLD APPROACH FOR LEACHABLE STUDIES

1. 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

The PQRI PODP Thresholds

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

Example:

Lyo DP, 3 doses in vial

Maximum Daily Intake: 1 dose

Evaluation of rubber closure (weight: 2 g)

Extraction ratio: 1 rubber is extracted per 10 mL of Dichloromethane (exhaustive extraction)

EXTRACTABLES:

Threshold Class I: 150 µg/day: final AET level: 225 µg/rubber closure

Threshold Class II: 5 µg/day: final AET level: 7.5 µg/rubber closure

Threshold Class III: 1,5 µg/day: final AET level: 2.25 µg/rubber closure

The PQRI PODP Thresholds

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

Formula used (see PQRI recommendations):

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

$$\text{Class I: Est. AET} = \frac{150\ \mu\text{g / day}}{1\,\text{dose / day}} \cdot \frac{3\,\text{doses}}{\text{vial (rubber)}} = 450\ \mu\text{g / rubber}$$

$$\text{Final AET} = 225\ \mu\text{g / rubber}$$

50% uncertainty for screening methods

The PQRI PODP Thresholds

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

	Threshold (µg/day)	Final AET (µg/rubber)	Final AET (mg/Kg)	Final AET (mg/L)
Class I	150	225	112,5	22,5
ClassII	5	7,5	3,75	0,75
Class III	1,5	2,25	1,125	0,23

Rubber weight: 2g

Extr. Ratio: 1rubber/10 mL

The PQRI PODP Thresholds

Typical Results for an Exhaustive Extraction on a Rubber

	EXT result mg/L extract	EXT result mg/Kg rubber	EXT result µg/Rubber
COMPOUND #1	0,1	0,5	1
COMPOUND #2	0,2	1	2
COMPOUND #3	1,25	6,25	12,5
COMPOUND #4	2	10	20
COMPOUND #5	0,5	2,5	5
COMPOUND #6	0,25	1,25	2,5
COMPOUND #7	13	65	130
COMPOUND #8	0,2	1	2
COMPOUND #9	27	135	270
COMPOUND #10	0,4	2	4
COMPOUND #11	0,15	0,75	1,5
COMPOUND #12	5,5	27,5	55
COMPOUND #13	32,5	162,5	325
COMPOUND #14	1,2	6	12
COMPOUND #15	0,35	1,75	3,5

The PQRI PODP Thresholds

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	150	22,5
COMPOUND #2	0,20	Class I	150	22,5
COMPOUND #3	**1,25**	**Class III**	**1,5**	**0,23**
COMPOUND #4	2,00	Class I	150	22,5
COMPOUND #5	0,50	Class II	5	0,75
COMPOUND #6	0,25	Class I	150	22,5
COMPOUND #7	**13,00**	**Class II**	**5**	**0,75**
COMPOUND #8	0,20	Class III	1,5	0,23
COMPOUND #9	**27,00**	**Class I**	**150**	**22,5**
COMPOUND #10	0,40	Class II	5	0,75
COMPOUND #11	0,15	Class III	1,5	0,23
COMPOUND #12	5,50	Clas I	150	22,5
COMPOUND #13	**32,50**	**Class III**	**1,5**	**0,23**
COMPOUND #14	1,20	Class I	150	22,5
COMPOUND #15	0,35	Class II	5	0,75

The PQRI PODP Thresholds

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

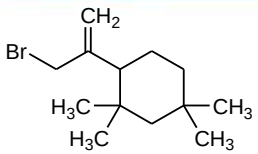
- ❑ The validation range will be different for the 4 compounds as a result of:
  - ➢The concentration level of the compound, found in the rubber
  - ➢The different classess for the respective compounds:
  - ➢The validation range should always include the AET level for the respective compound, as a minimum

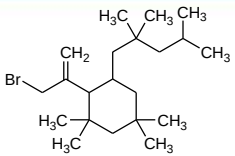
- ❑ Presence of other compounds may be monitored (semi-quantitatively) in Leachable Study, using screening methodology

PART 6

Case Studies

Case Studies





CASE 1:

Interaction of Rubber Extractables $C_{13}H_{23}Br$ or $C_{21}H_{39}Br$ with Lyo DP

- Rubber Oligomers, formed during polymerisation of the Elastomer, with subsequent Bromination Step
- Compounds are fairly volatile, will be released from the rubber stopper, adsorbed onto lyo-cake
- For uncoated rubbers, potentially the problem is larger!
- Considered as
  - **HALOGENATED** Cyclic Aliphatic Hydrobarbon compounds (Allyl Halide)
  - **Alkylating Agents: reactive compounds towards 1. DNA**
    2. Lyo-Product
  - One double bond
- Structure Activity Relationship (SAR) Assessment:

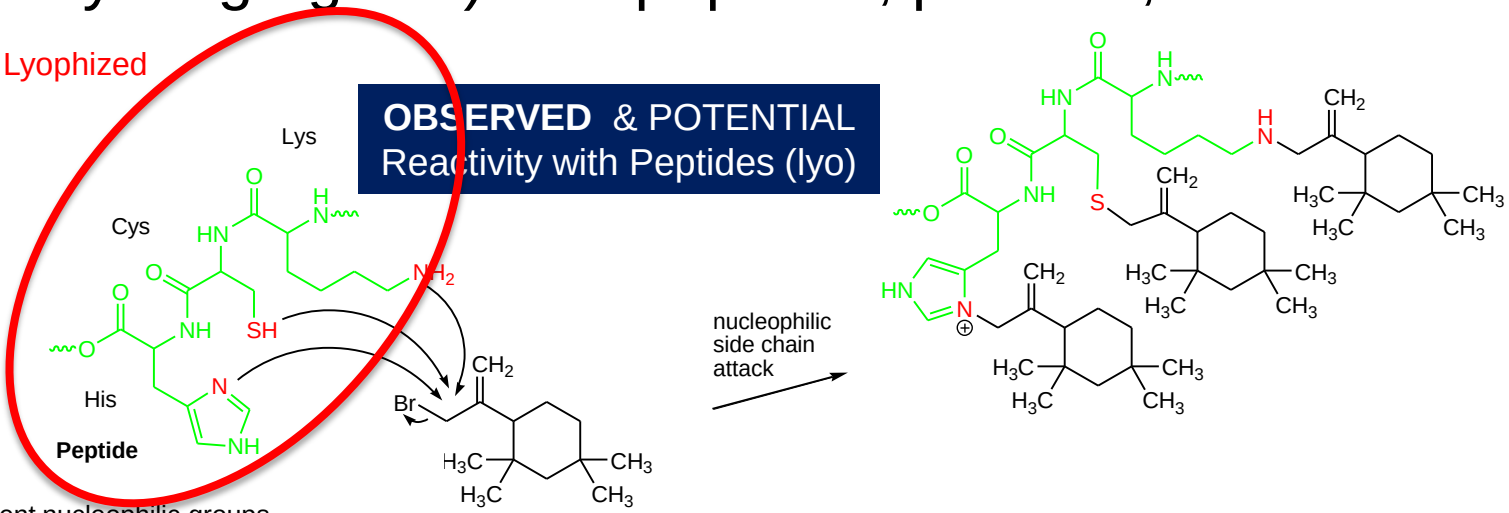
CARCINOGENICITY IN HUMANS IS PLAUSIBLE

Case Studies

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

Example of Lyophized peptide

OBSERVED & POTENTIAL
Reactivity with Peptides (lyo)

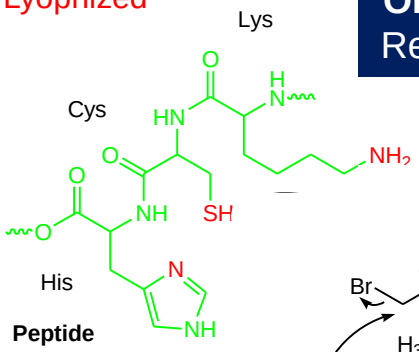


With different nucleophilic groups

Case Studies

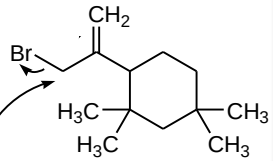
Observed Reactivity of $C_{13}H_{23}Br$ and $C_{21}H_{39}Br$ (as alkyating agents) with peptides, proteins, and nucleic acids

Example of Lyophized peptide

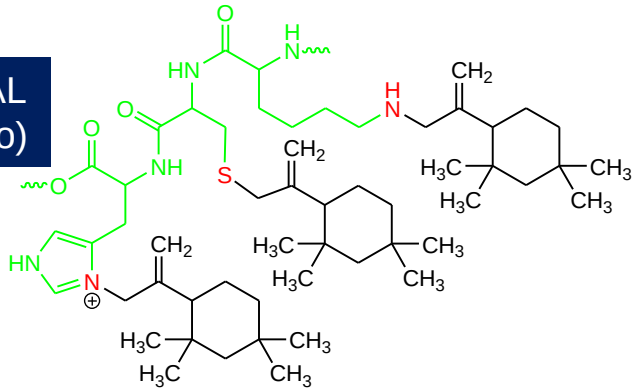


With different nucleophilic groups

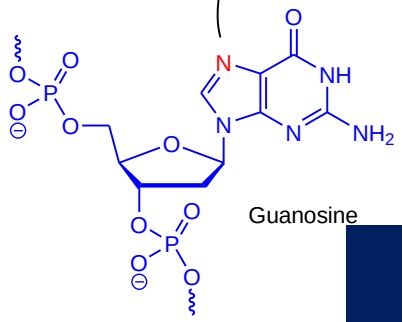
OBSERVED & POTENTIAL
Reactivity with Peptides (lyo)



nucleophilic side chain attack

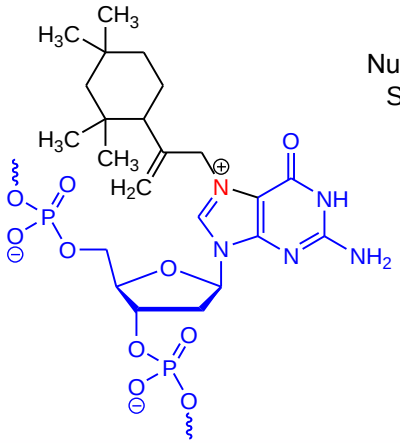


DNA



"N7" attack

Most nucleophilic site



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

POTENTIAL
Reactivity with DNA

Ref. 7

Case Studies

CASE 2:
Leachable Study on Reconsituted Lyo DP after Administration Procedure

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

Purpose of Study:

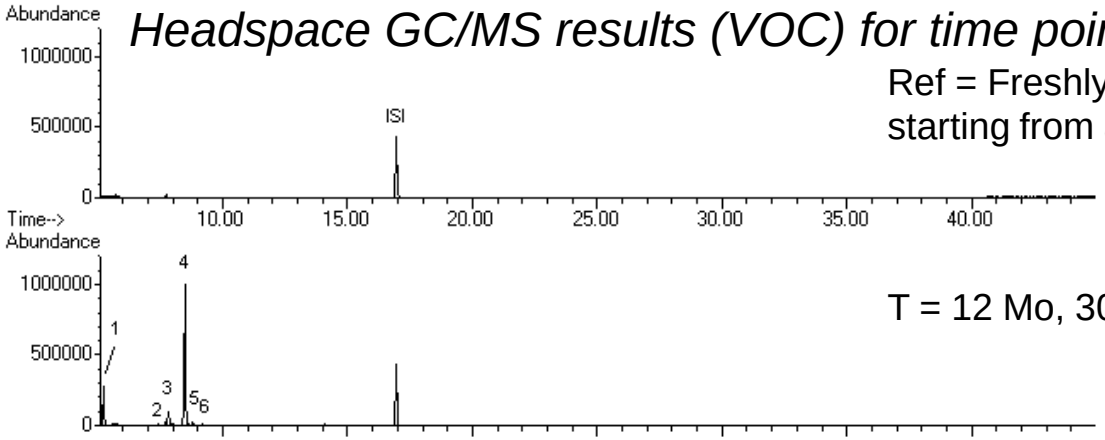
- Impact of Rubber Closure on Leachable Profile of Lyo Powder (long term)
- Impact of Length of Storage of reconstituted DP in I.V.-Bag (short term)
  1 Day storage in Bag at 5°C versus
  2 Day Storage in Bag at 5°C
  3 Day Storage in Bag at 5°C
  - Allows to define the Worst Case condition
- Impact of the I.V. Set on Leachable Profile during Administration (short term)

Case Studies

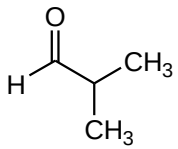
1. Drug Product: Lyo DP, Stored in Vial with Rubber Stopper

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

Ref = Freshly prepd lyo soln, starting from all ingredients



T = 12 Mo, 30°C, 75%RH



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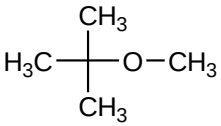

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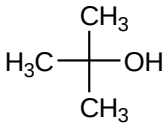

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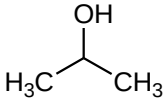

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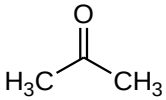

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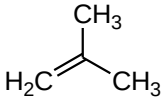
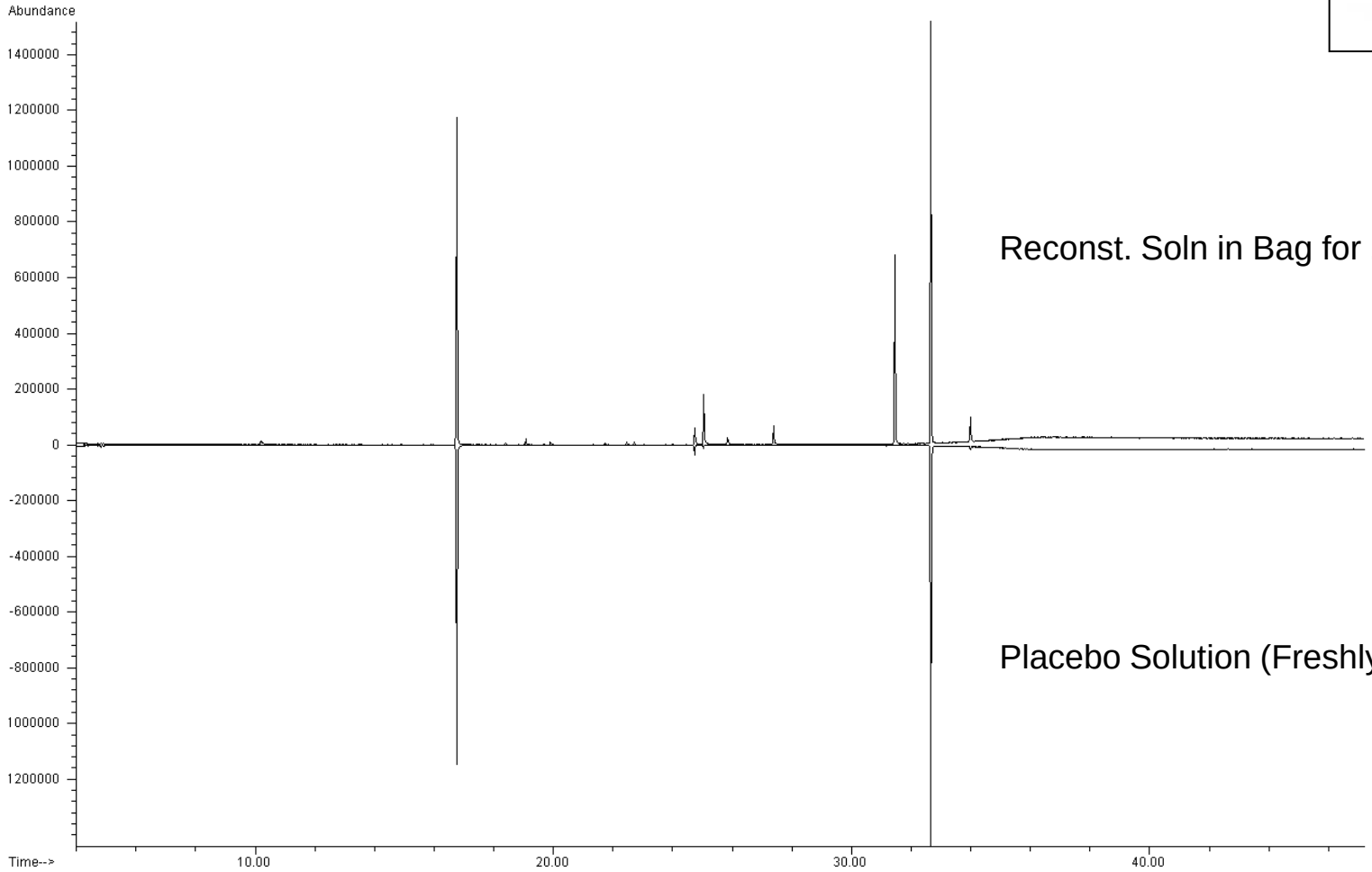


6

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

Case Studies

2. Administration: I.V. Bag

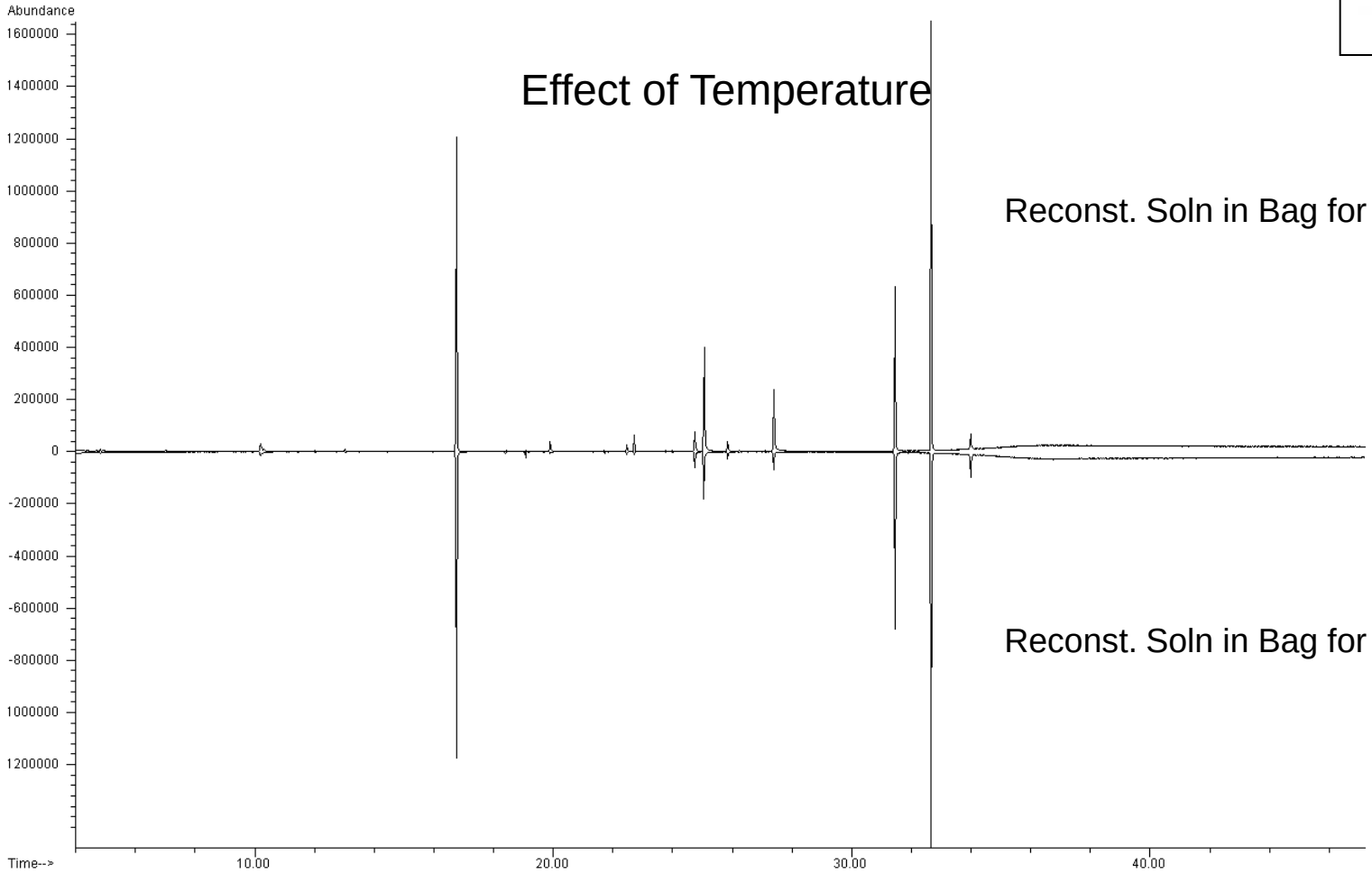


Reconst. Soln in Bag for **1 day** at **5°C**

Placebo Solution (Freshly Prepared)

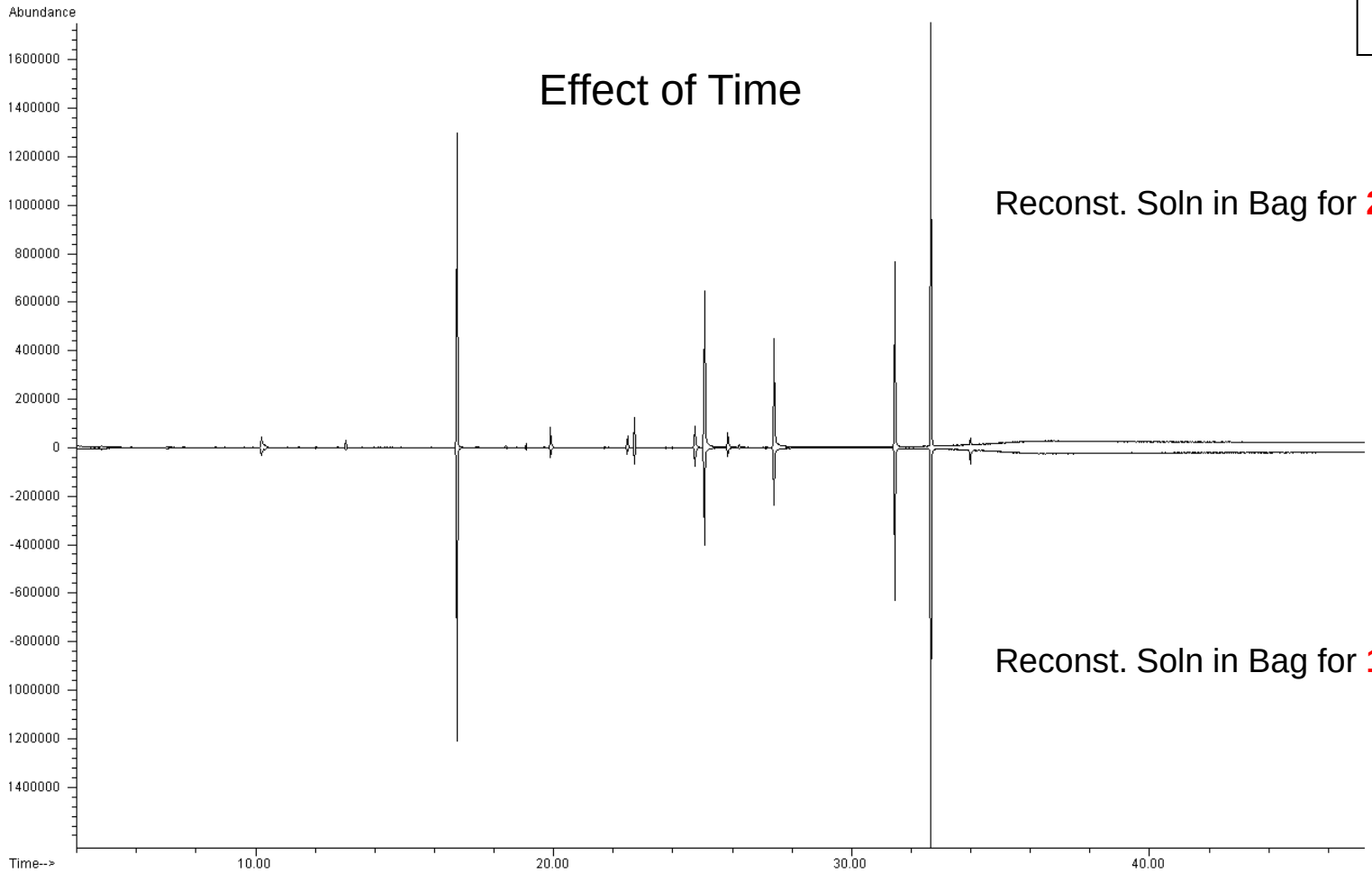
Case Studies

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



Case Studies

2. Administration: I.V. Bag

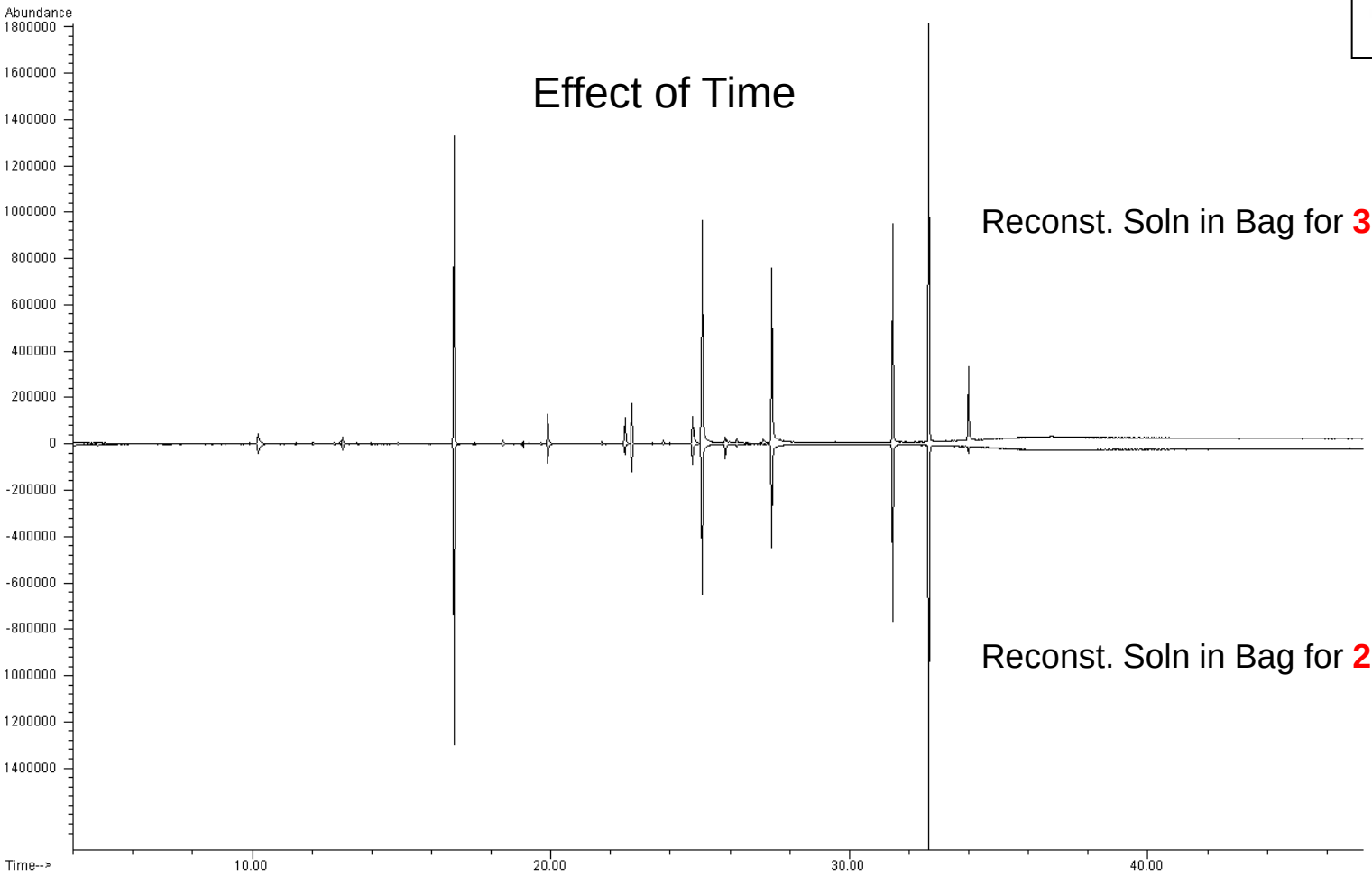


Reconst. Soln in Bag for **2 days** at **25°C**

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

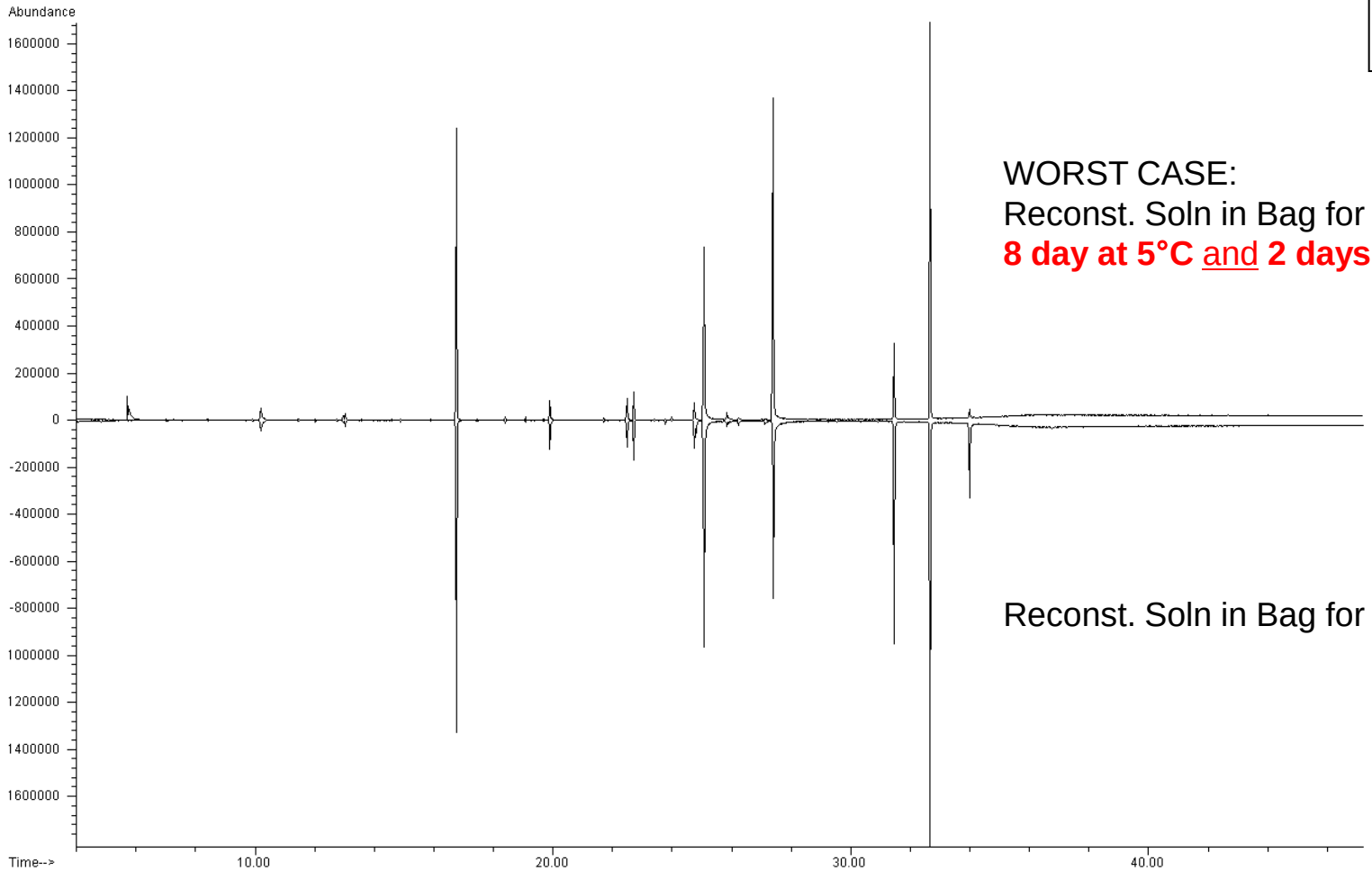
Case Studies

2. Administration: I.V. Bag



Case Studies

2. Administration: I.V. Bag

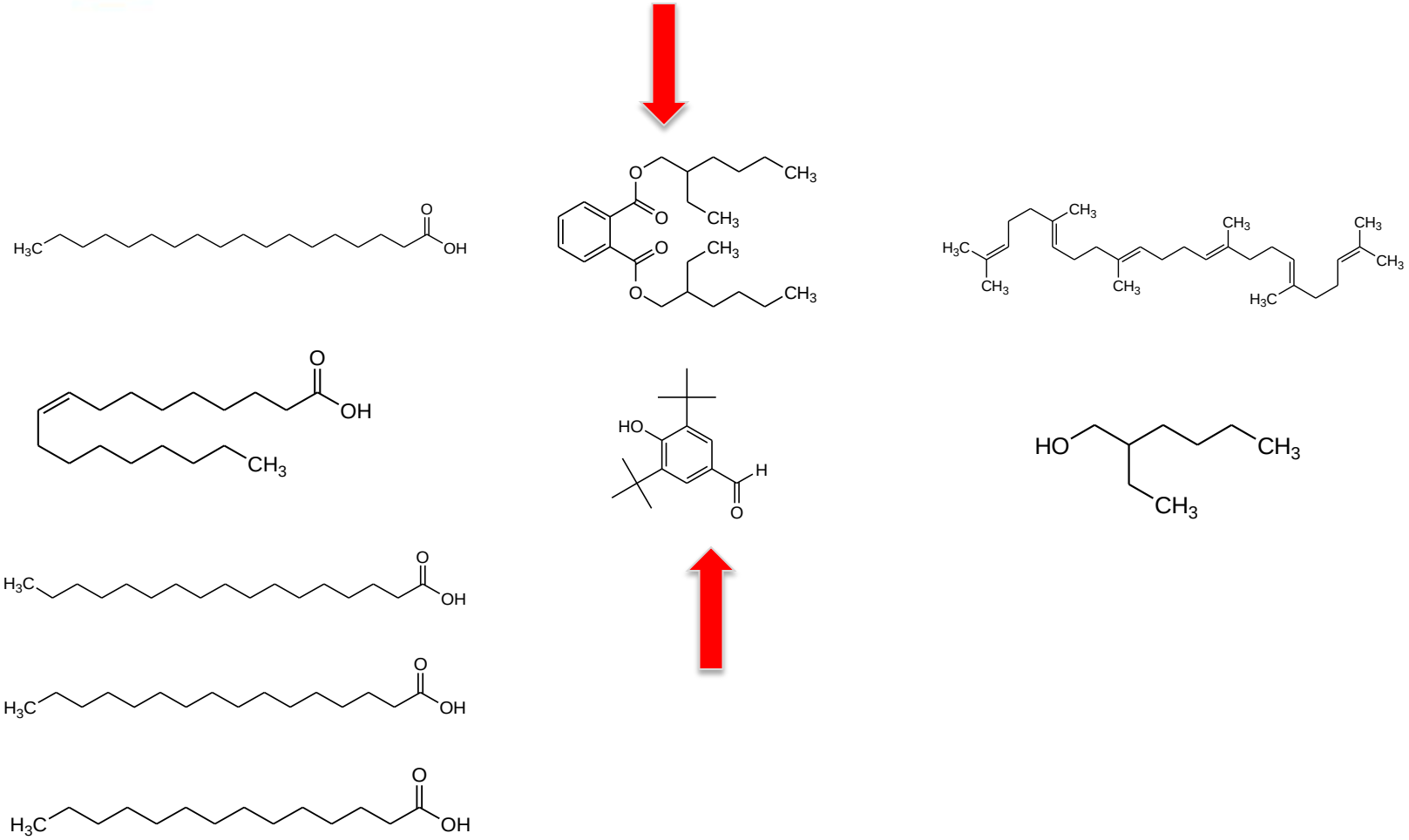


WORST CASE:
Reconst. Soln in Bag for
8 day at 5°C and **2 days at 25°C**

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

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

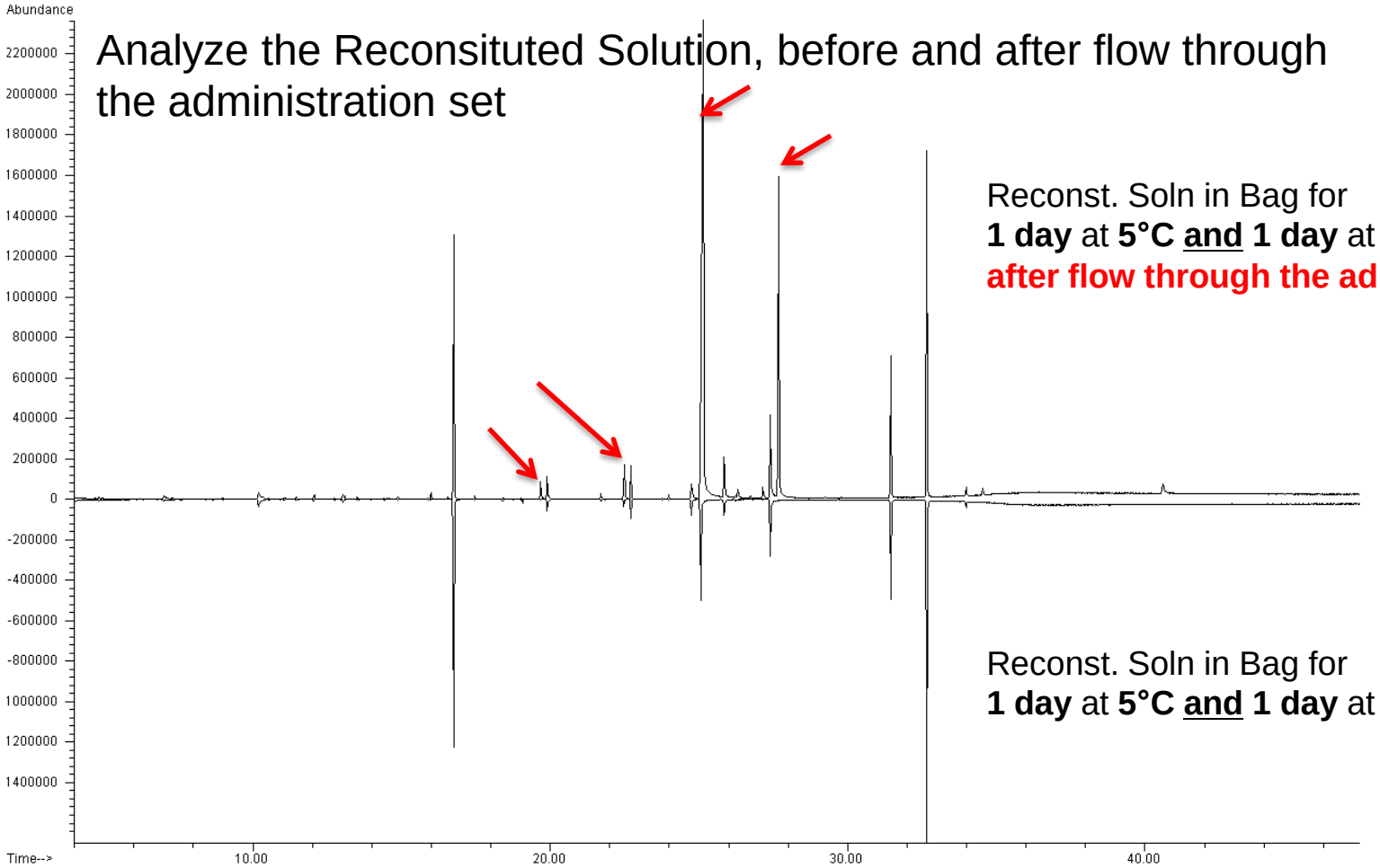
Case Studies



Case Studies

3. Administration: Contribution of Administration Set

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

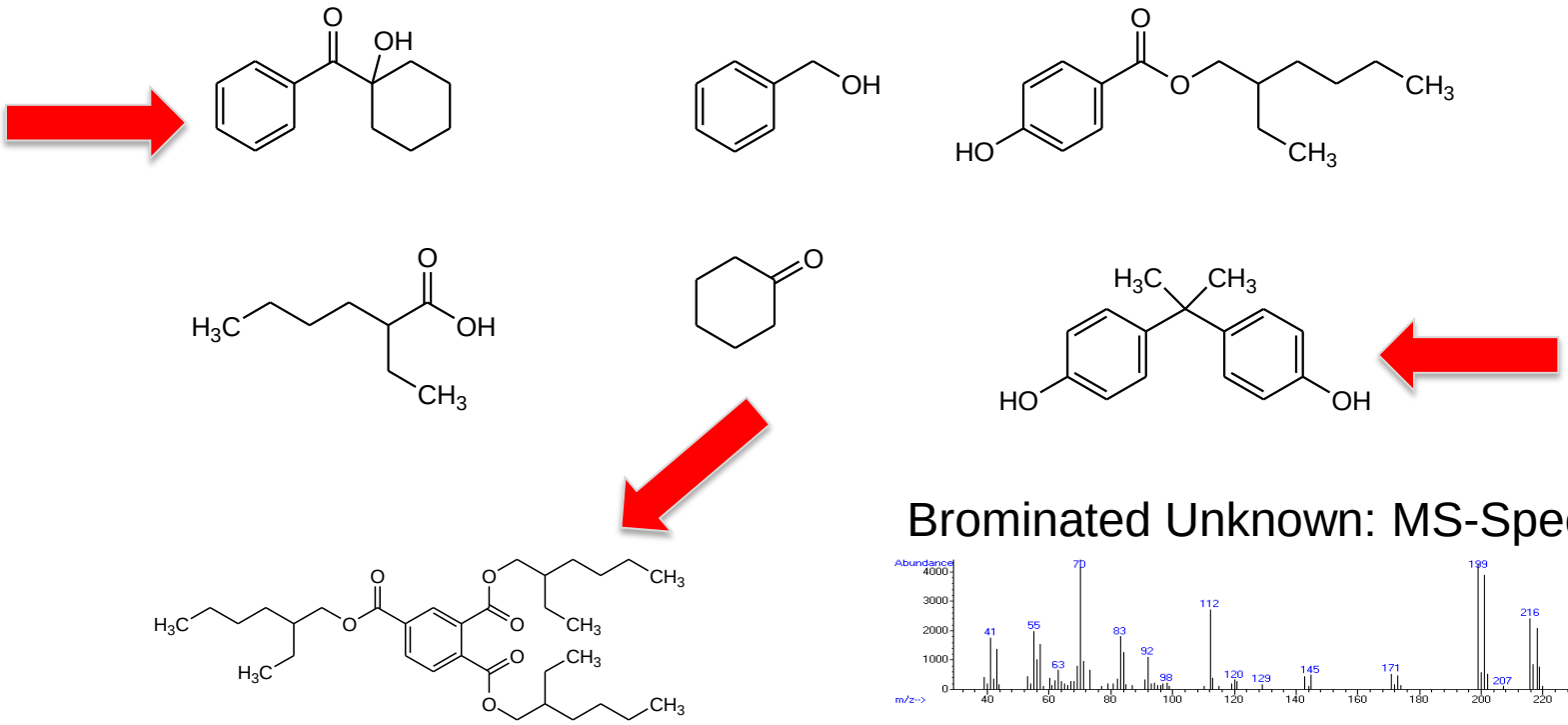


Reconst. Soln in Bag for
1 day at **5°C** **<u>and</u>** **1 day** at **25°C**
after flow through the administration set

Reconst. Soln in Bag for
1 day at **5°C** **<u>and</u>** **1 day** at **25°C**

Case Studies

3. Administration: Contribution of Administration Set



Brominated Unknown: MS-Spectrum

PART 7

Conclusion

Conclusions

1. Verify the Regulatory Requirements for Lyophilized DP
   - FDA
   - EMA
   - Are there any parts of the reconstitution or administration procedure that falls under the “Combination Products” Rule

2. Plan an Extraction Study (using optimized protocols) for each C/C system or Device that will be used for either long term storage or for reconstitution / administration set.

3. Risk Evaluation of the Results (e.g. according to PQRI PODP)

4. Perform a Formal Leachable Study
   - Long term Contact between Lyo DP and Container
   - Long term Contact between Reconstitution Solution and Container
   - Short term Contact between Reconstituted Drug Product and administration device

5. Safety Toxicological Evaluation of Leachables Data

ANY QUESTIONS?

For further questions, please contact:

piet.christiaens@toxikon.be

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