SETTING UP EXTRACTABLE / LEACHABLE STUDIES

PDA TRAINING COURSE
EXTRACTABLES – LEACHABLES
Berlin
28 – 29 September, 2017

Dr. Piet Christiaens

Content

1. THE CHEMICAL ASSESSMENT TRIAD

The Chemical Assessment Triad

A General strategy for the chemical aspects of the safety assessment of extractables and leachables in Pharmaceutical Drug Products

Dennis Jenke
PDA J Pharm Sci and Tech 2012, 66 168-183

1. THE CHEMICAL ASSESSMENT TRIAD

Definitions E/L study

1. ***Donor phase*** : contact material
   E: **MAY BE** used to manufacture, store or deliver final drug product
   L: **IS** used to manufacture, store or deliver final drug product
2. ***Receiving phase***: contact solution
   E: extracting solvent
   L: Finished drug product
3. ***Migrant***: substance that migrates from the donor phase to the receiving phase as a result of contact between the two phases
   a)Active: e.g. solvation
   b)Passive: e.g. sorption

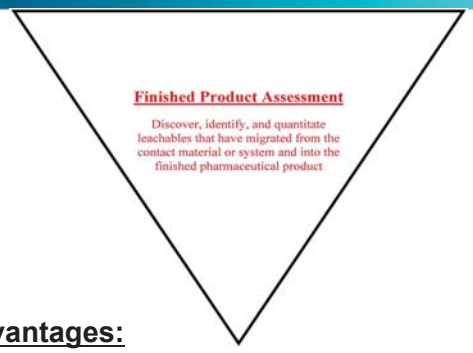
   Contact conditions:
   E: Laboratory conditions
   L: Actual use conditions

1. THE CHEMICAL ASSESSMENT TRIAD

- **Purpose**:
  - Which migrants will have a direct impact on patient safety?
  - Risk management
  - (Good) Quality by (good) Design
- **Necessary**: 1. Identification migrants
  2. Quantification migrants
  IN FINISHED DRUG PRODUCT

⇨ **Chemical Assessment Triad**
Efficient, effective and scientifically valid approach to develop safe packaging, manufacturing and delivery systems.

1. THE CHEMICAL ASSESSMENT TRIAD

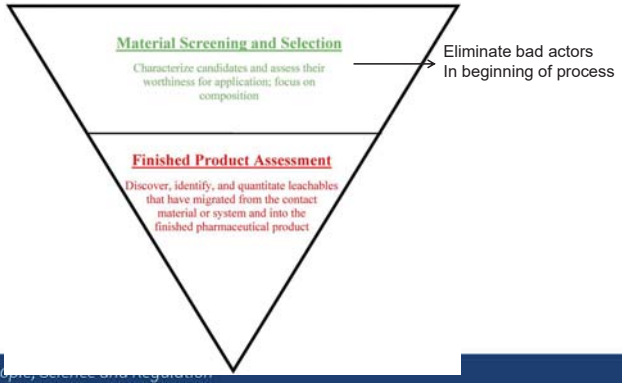


Disadvantages:

1. Performed in later stages of product development
2. Not consistent with QbD (Quality by Design)
   ⇨ Rarely applied

1. THE CHEMICAL ASSESSMENT TRIAD

- First step: Perform a screening of candidate materials
- Second step: migration / Leachable study



Eliminate bad actors
In beginning of process

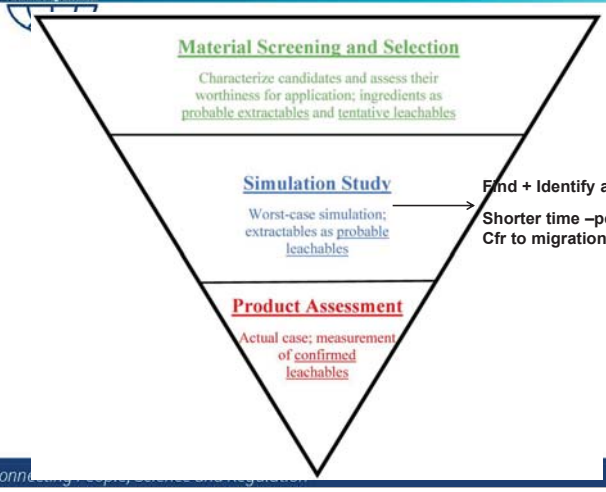
1. THE CHEMICAL ASSESSMENT TRIAD

- **Step 1: Material characterization**
  Early detection reduces risk on unfortunate outcome, BUT
  does not reflect actual use

- **Step 2: Migration study: in final drug product**
  What are all entities present in sample above certain concentration?
  Identification + Quantification in one step
  Problems: - complex matrices + low concentration of migrants
  - till end of shelf life
  - long time between step 1 and 2

⇨ Does the sample contain compound X above a certain conc.?
Two steps: First identification, then quantification

1. THE CHEMICAL ASSESSMENT TRIAD



Find + Identify all leachables

Shorter time –period
Cfr to migration study

1. THE CHEMICAL ASSESSMENT TRIAD

- **Purpose intermediate step**
- Find + identify extractables which are probable leachables
- Establish which extractables must be targeted in a migration study
  - screening
  - mimic circumstances of final drug product: acceleration, moderate exaggeration
  - worst case: sufficient amounts to identify
  - safety/ toxicological risk assessment to define target leachables

- Triad: three distinct phases:
  consistent with regulatory expectations + best demonstrated practice recommendations

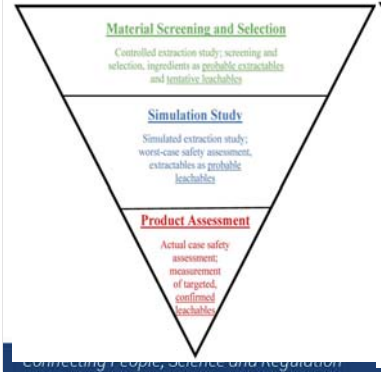
- BUT

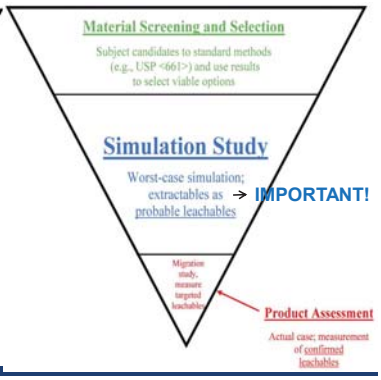
1. THE CHEMICAL ASSESSMENT TRIAD

BUT no standard approach, e.g. packaging↔manufacturing

Packaging:
- Controlled extraction study:
Characterize composition candidates

Manufacturing:
- Standard tests:
Potential to adversely affect safety





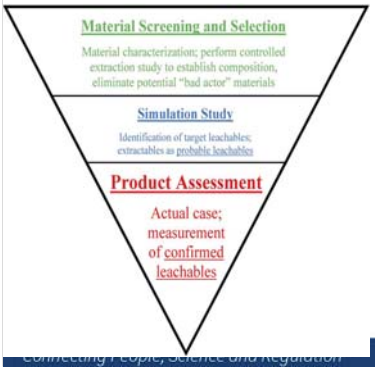
IMPORTANT!

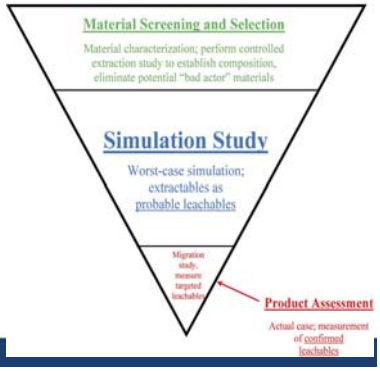
1. THE CHEMICAL ASSESSMENT TRIAD

- BUT no standard approach, e.g. simple ↔complex drug product

Simple drug:
- Simulation: early detection
- Migration: Important

Complex drug:
- Simulation is important
- Limited Migration study





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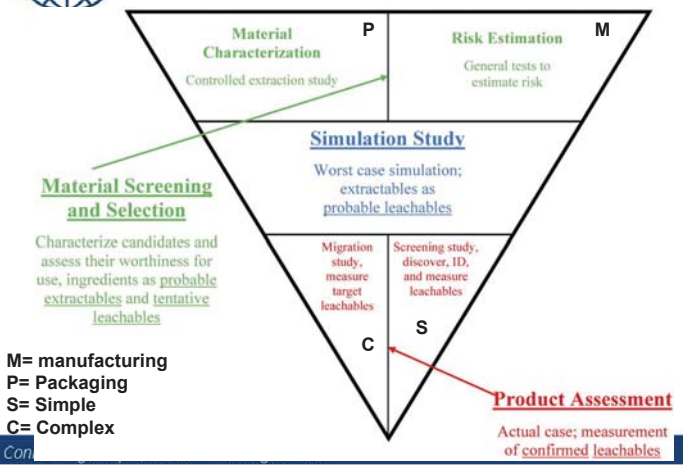
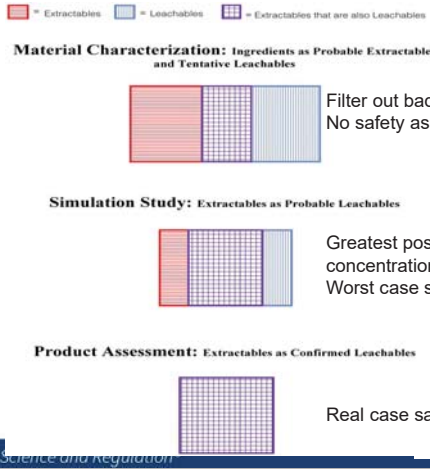


M= manufacturing
P= Packaging
S= Simple
C= Complex

1. THE CHEMICAL ASSESSMENT TRIAD



Filter out bad materials
No safety assessment

Greatest possible concentration
Worst case safety impact

Real case safety impact

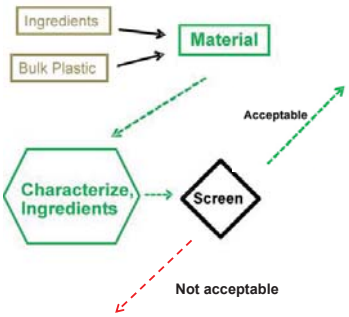
Threshold?

1. Material characterization: major compositional components
   - no safety assessment
   - 100 µg/g: typical ingredient concentration

2. Simulation study: worst-case safety risk assessment
   - AET = TTC or SCT: assume that compounds are carcinogenic
   - Result:
     > AET, but not carcinogenic: also above qualification threshold?
     > AET with toxicological risk:
     select as target compound for migration study
     < AET: probably also in migration study conc. < AET
   - Suggestion: only chemical + biological nature, not full identification
     Chemical: structural characterization (SAR)
     Biological: in vivo + in vitro tests for carcinogenicity

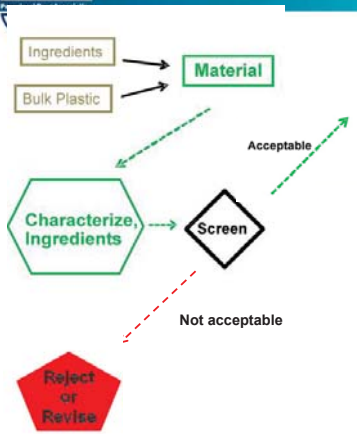
3. Migration study: focus on target compounds
   - ID is known: SCT and TTC are irrelevant, base on toxicological data
   - SCT or TTC only in case of insufficient toxicological data

1. THE CHEMICAL ASSESSMENT TRIAD



1. Material Characterization

1. THE CHEMICAL ASSESSMENT TRIAD



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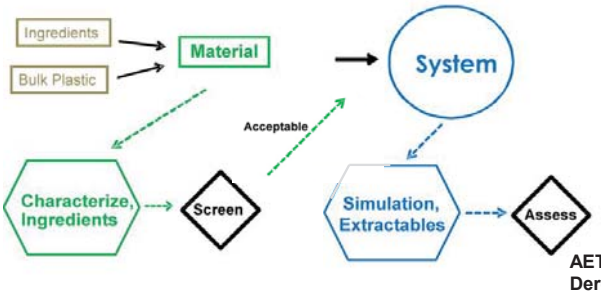
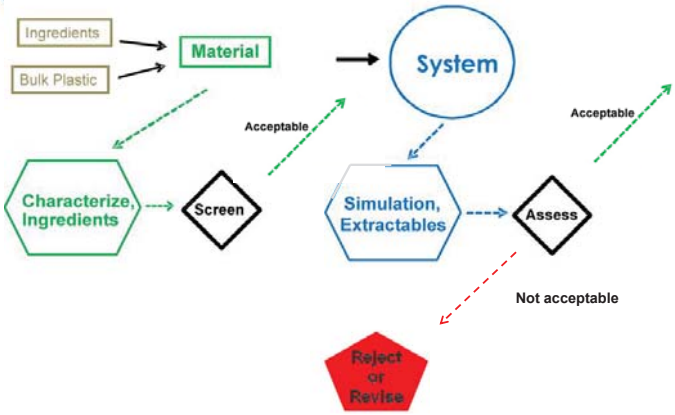
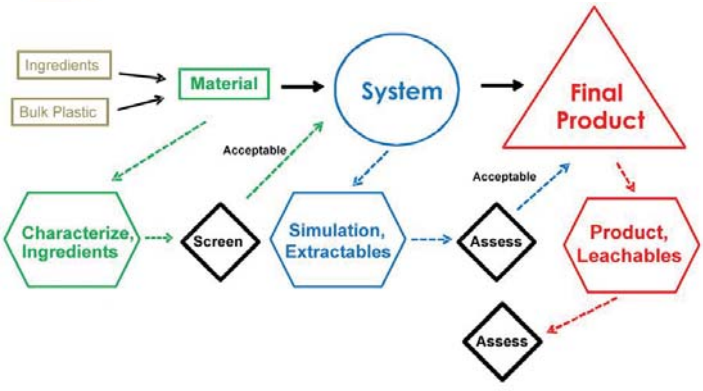


AET= TTC/SCT
Derek?

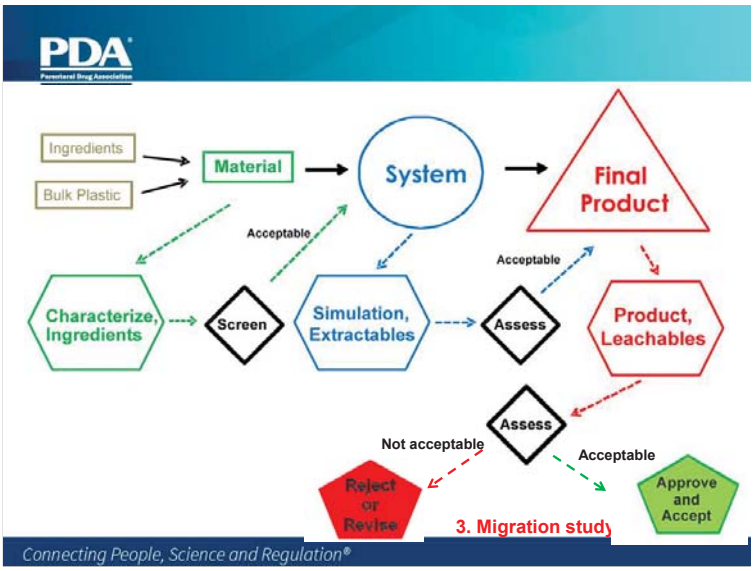
2. Simulation study

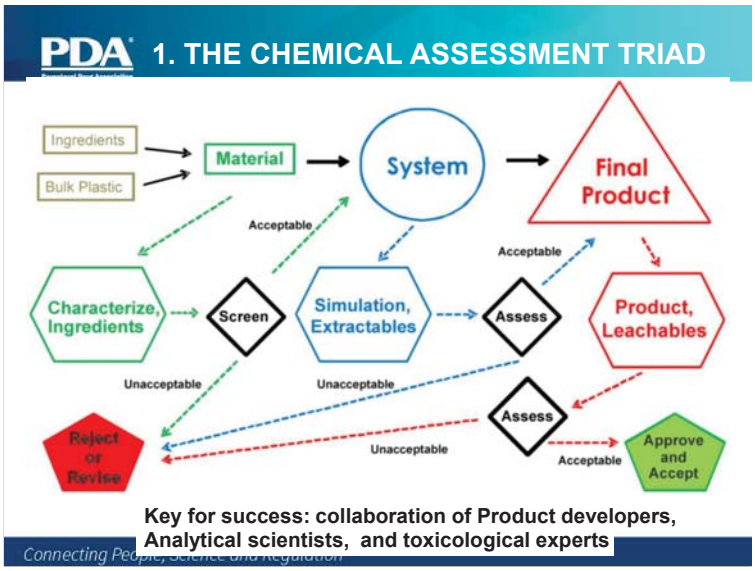


2. Simulation study



3. Migration study


Ingredients
Bulk Plastic
Material
System
Final Product
Acceptable
Characterize, Ingredients
Screen
Simulation, Extractables
Assess
Acceptable
Product, Leachables
Assess
Not acceptable
Acceptable
Reject or Revise
Approve and Accept
3. Migration study
Connecting People, Science and Regulation®


1. THE CHEMICAL ASSESSMENT TRIAD
Ingredients
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Product, Leachables
Unacceptable
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Assess
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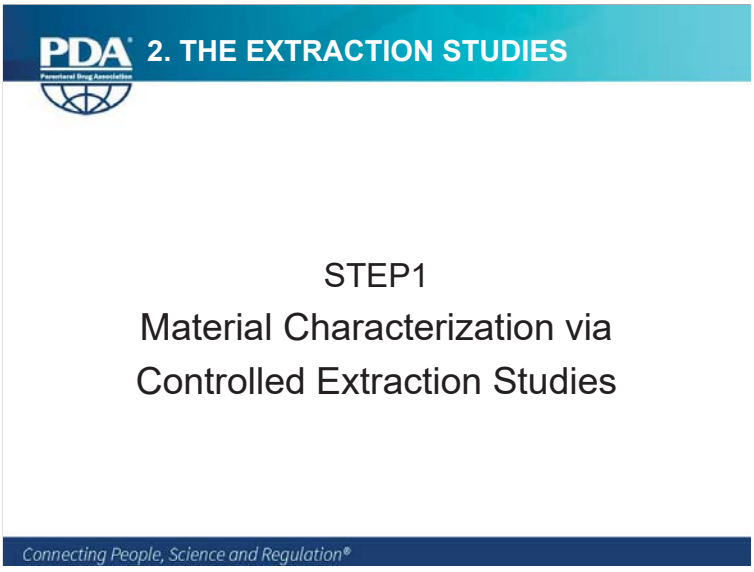
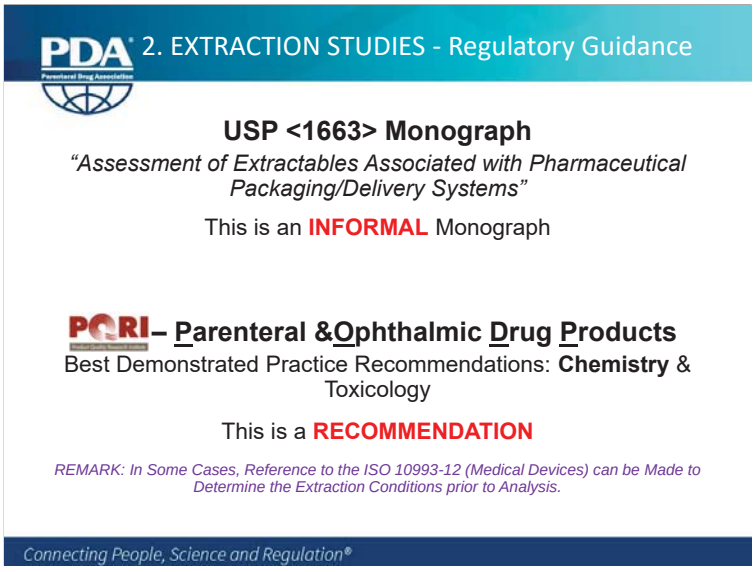
Acceptable
Approve and Accept
Key for success: collaboration of Product developers, Analytical scientists, and toxicological experts
Connecting People, Science and Regulation®


2. THE EXTRACTION STUDIES
STEP1
Material Characterization via Controlled Extraction Studies
Connecting People, Science and Regulation®


2. EXTRACTION STUDIES - Regulatory Guidance
USP <1663> Monograph
"Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems"
This is an INFORMAL Monograph
PQRI – Parenteral &Ophthalmic Drug Products
Best Demonstrated Practice Recommendations: Chemistry & Toxicology
This is a RECOMMENDATION
REMARK: In Some Cases, Reference to the ISO 10993-12 (Medical Devices) can be Made to Determine the Extraction Conditions prior to Analysis.
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2. EXTRACTION STUDIES - Regulatory Guidance

These Two Documents ar either **INFORMAL** or **RECOMMENDATIONS**

Allow Flexibility in Design

What is the *intent*? => **Strategy** of testing
How to design the study for the envisioned intent? => **Tactics**

However, Justification is Needed!

Both **Identifying the Necessity** for an Extraction Study, as well as **Justifying the Design**, is the responsibility of the Holder of the NDA.

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

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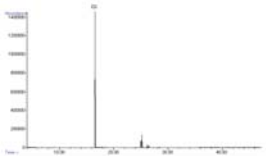
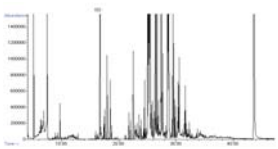
2. THE EXTRACTION STUDIES

DEPENDING UPON THE DESIGN OF E-STUDIES:

1. **LOW Nr** of extractables



2. **HIGH Nr** of extractables



HOW CAN THIS BE HARMONIZED?

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2. THE EXTRACTION STUDIES

What is the **PURPOSE** of an Extraction Study?

- Material Characterization of the Packaging Components
- "Impurities Profiling" of the Materials
  - Identify as Many Compounds as Possible
  - Identify "Bad Actors" in the Materials
- Early Risk Evaluation: Potential *Patient Exposure* to Chemical Entities
- Allows to establish Leachables – Extractable *correlations*
- In certain cases (more applicable to OINDP): Facilitates extractable specifications of *acceptance criteria*.
- Identify Compounds that may need to be Monitored as Leachable
  - Toxicity
  - Concentration in the Materials
  - Risk for Migration

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2. THE EXTRACTION STUDIES

What is the **PURPOSE** of an Extraction Study?

- Facilitates **"Timely Development"** of safet and effective C/C-systems
- Understand **the effects of various processes** on components
- Establish **worst case potential Leachables Profile**, when it is not scientifically possible to determine Leachables
- Use of **Extraction solutions** which are **"Compatible" with Screening** techniques: CLEAN SOLVENTS
- **Identify** Compounds that may need to be **Monitored as Leachable**
  - Toxicity
  - Concentration in the Materials
  - Risk for Migration
- Typically Not as a Final Step in the Safety Assessment!

2. THE EXTRACTION STUDIES

USEFUL DOCUMENTATION PRIOR TO E-STUDY

GENERAL INFORMATION

Product Name, Product N° , Type, Manufacturer, Physical properties…

CERTIFICATES of compendial tests

USP<381>, USP <87>, USP<88>, EP 3.2.9, JP<49>, ISO 8871

INGREDIENTS OF RUBBER

Very useful information, but this will not tell the complete E-story!!

EXTRACTABLES DATA FROM SUPPLIER

Highest Level of information !! *Check relevancy of technical and testing conditions!!*

2. THE EXTRACTION STUDIES

VARIABLES that may/will have an impact on the Study Design of an Extractable Study

- The **Classification & Specific Requirements** per Drug Product
  - Table 1 in FDA C/C-Guidance (1999)
  - Decision tree in the EMA-Guideline (2005)
- The **Composition of the DP**, in contact with the C/C system
- The **Type of contact** between the DP and the C/C system
  - Primary Packaging
  - Secondary Packaging (e.g. Needle Shield, Label,...)
- The **Types of Materials** used in te Manufacture of the C/C
  - E.g. Rubber versus Polyolefin for BFS
- The **Knowledge on the Composition** of Materials (from Vendor)
  - Additives, Catalysts, Oligomers, Colorants,...
- The **Use of the Data**
  - Only for this particular application, or also for other DP?
- Primary Packaging versus Manufacturing Equipment

2. THE EXTRACTION STUDIES

IF PROVIDED INFORMATION IS NOT AVAILABLE/SUFFICIENT:

SET-UP AN EXTRACTABLE STUDY

1. **DESIGN** YOUR E-STUDY, SO THAT IDEALLY:

"LEACHABLES ARE A SUBSET OF EXTRACTABLES"

2. **DO NOT ALLOW SURPRISES IN YOUR LEACHABLE / STABILITY STUDIES!!!**

E-study: Take worst case conditions compared to "real use"

2. THE EXTRACTION STUDIES

Parameters To be Considered for an Extraction Study

- ✓ Extraction **Solvents**
- ✓ Extraction **Techniques**
- ✓ Extraction **Conditions** (Temperature, time)
- ✓ Extraction **Ratio's - Stoichiometry**
- ✓ *Analytical **Techniques** (Different presentation)*
  - *Screening Techniques*
  - *Targeted analysis for specific compounds*

2. THE EXTRACTION STUDIES

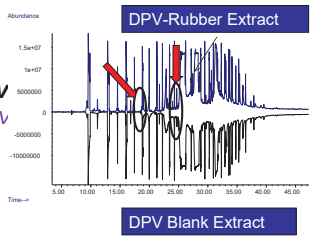
USP <1663> "Generating the Extract"

Chemical Nature of the Extracting Medium

If: PURPOSE: simulating worst case EXT-profile

- *Look for Similar or Greater Extraction Propensity*
- *That gives Similar Qualitative and Quantitative EXT-profile*

- ***Use Drug Product Formulation***
  - *May be complex or impractical*
- ***DPV/Placebo can be an Alternativ***
  - *REMARK: Extraction at High T with DP/DPV lead to degradation (eg Polysorbate)*



2. THE EXTRACTION STUDIES

THE CRITICALITY OF USING THE **DRUG PRODUCT (VEHICLE) (DP(V))** AS A SOLVENT

Perform E-study in Drug Product (Vehicle), suggested in:

FDA-Container/Closure Guidance (1999), (eg parenteral/Ophthalmic)

- 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.

EMEA-Guideline - immediate packaging (2005)

stress conditions to increase the rate of extraction. The solvent used for extraction should have the same propensity to extract substances as the active substance/dosage form as appropriate. In the case of medicinal products the preferred solvent would be the medicinal product or placebo vehicle. The

2. THE EXTRACTION STUDIES

THE CRITICALITY OF SELECTING **DP(V)** AS SOLVENT

ADVANTAGE: simulation of extractables behaviour in DP(V): same extraction propensity!

DISADVANTAGE: Risk of missing the presence of compounds

- *Matrix interference of DP(V) (see previous slide)*

Risk of misinterpretation of analytical data

- *DP(V) Matrix degradant may be misinterpreted as extractable!*

Risk of underestimating the concentration of compounds

- *Extraction conditions – may potentially be to mild*
- *Difficult to select the right set of extraction conditions (e.g. Extraction time, temperature!)*

2. THE EXTRACTION STUDIES

USP <1663> "Generating the Extract"

Chemical Nature of the Extracting Medium –

REMARKS WHEN CONSIDERING SELECTING DP/DPV

BETTER ALTERNATIVE:

SCREENING LEACHABLE STUDY

- *Use DP in the final Container/Closure System, stored in Stability*
- *Consider it as an **extra "Solvent"** in your Extractables Assessment*
- *Use same **Screening Methodologies** as you would do in an EXT Study*
- *This accounts for*
  - ***Unexpected Leachables** (due to ageing of Material, Hydrolysis, Oxidation,**Migrants** from Sec, Tertiary Packaging...)*
  - ***Reactive Leachables** (eg with API, other ingredients...)*
  - ***Accurate Prediction** of the Nature of the Leachables, and their Expected Levels*
  - *However:*
    - *Typically **not an End Point** in the Evaluation*
    - *Only a **"One Point Assessment"***
    - ***Not all DP** are Amenable to Screening*

2. THE EXTRACTION STUDIES

USP <1663> "Generating the Extract"

Chemical Nature of the Extracting Medium

If: PURPOSE: simulating worst case EXT-profile

If an Extraction Study needs a Simulating Solvent

Establish and Justify Composition of Simulating Solvent

Evaluate the PCHEM Properties of the Drug Product

- *pH*
- *Polarity (Polar, versus Non-Polar, or Intermediate Polarity)*
- *Stabilizers*
- *Solubilizing Agents*
- *Buffers*
- *Lipid containing solutions*
- *Biotech (proteins, peptides, blood derived products)*
- *Chelating Agent*
- *...*

REMARK: FOR **EXTRACTION STUDIES**: **NOT IDEAL** TO ONLY TAKE 1 EXTRACTION SOLVENT COULD BE CONSIDERED IF THE PURPOSE IS TO PERFROM A **SIMULATION STUDY**

2. THE EXTRACTION STUDIES

USP <1663> "Generating the Extract"

Chemical Nature of the Extracting Medium

If: PURPOSE: simulating worst case EXT-profile

If an Extraction Study needs MULTIPLE Simulating Solvents

Each Addressing 1 "Mechanism" that is relevant to the Drug Product

Is Consistent with the Industry "Best Practices" for High Risk Dosage Forms.

Also in Line with PQRI-Approach (see next slides)

***REMARK: PQRI:** proteins may be **more efficient** in **solubilizing leachables** due to abundance of **both hydrophilic** and **hydrophobic** sites**

In this case, an approach with multiple simulating solvents may be warranted.

** PQRI –PODP L/E Work Group: Outcomes and Practical Applications, D, Paskiet, Presentation at PEPTALK, 2016*

2. THE EXTRACTION STUDIES

USP <1663> "Generating the Extract"

Chemical Nature of the Extracting Medium

If: PURPOSE: Material Characterization

Use POWERFUL extraction Solvents

GOAL: to have an Efficient Quantitative & Qualitative Extraction

Powerful Extraction Solvents

- *Softening*
- *Swelling*
- *Dissolving*

EXAMPLES OF POWERFUL SOLVENTS:
Dichloromethane, Hexane, Isopropanol, Ethanol ...
Selection will also depend upon the Material

2. THE EXTRACTION STUDIES

Extraction Solvents

What do you want to learn from an Extraction Study?

"Impurities Profile" of a material- MATERIAL CHARACTERIZATION

Exhaustive Extraction Solvents

PQRI OINDP: Isopropanol
Hexane
Dichloromethane

BPSA: EtOH

Allows to determine the *"TOTAL POOL"* of Material Impurities

Risk Assessment of Total Conc. of Material Impurities
- More Complete
- More Challenging

Incorporate a level of "Simulation" already in the Extraction Study

Exaggerated Extraction Solvents

PQRI PODP: WFI pH 2.5
WFI pH 9.5
IPA/UPW 50/50

BPSA: UPW

BPOG: 0.5N NaOH
0.1M Phosphoric Acid
WFI (neutral)
5 M NaCl
EtOH/WFI 50/50
1% Tween

Risk Assessment is
- More Realistic wrt final Use
- Does not really assess "Total Pool"

2. THE EXTRACTION STUDIES

PQRI – **PODP** Best Demonstrated Practice Recommendations

UPW	UPW	UPW/IPA	IPA	HEXANE
pH 2,5	pH 9,5	(50/50)		
Acid Extractables	Base Extractables	Intermediate Polarity	→	Non-Polar

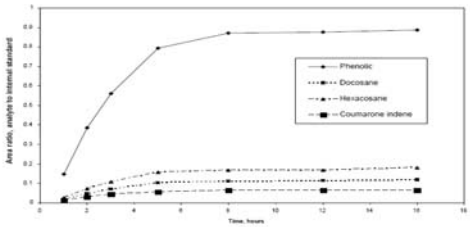
SIMULATION

MATERIAL CHARACTERIZATION & SIMULATION (NON AQUEUOUS DP)

REMARK: REMEMBER: THE PQRI-PODP DOCUMENT IS A RECOMMENDATION:
- *It is not Mandatory to ALWAYS include these 5 Extraction Solvents into the EXT Design*
- *Even the selection of solvents, or their PCHEM Properties may be Changed According to Actual Drug Product PCHEM Properties*
- *However, a Justification is always Necessary!!*

2. THE EXTRACTION STUDIES

Asymptotic Extraction Profile - Exhaustive Extractions:

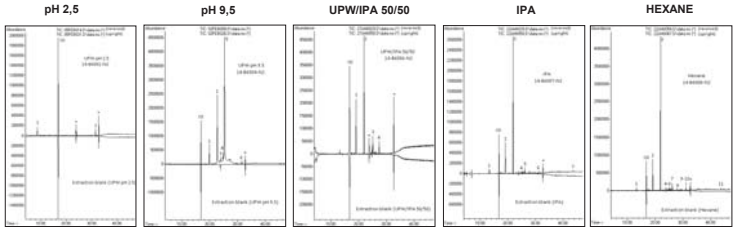


PQRI-Example: Test Article: Sulphur Cured Elastomer
Extraction: DCM – Soxhlet

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

2. THE EXTRACTION STUDIES

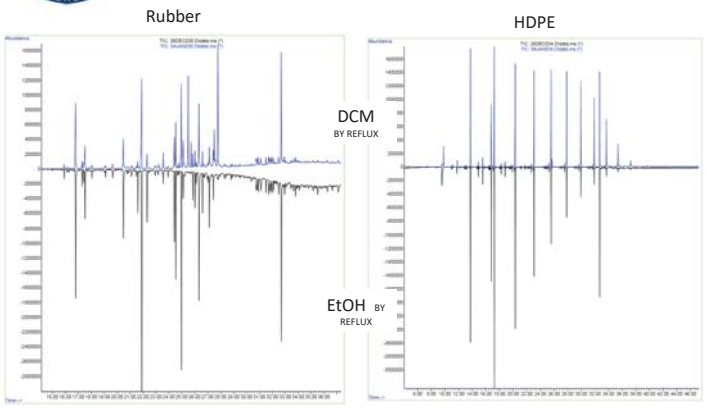
Example: *Extraction of a rubber component*
GC/MS Semi-Volatile Organic Compound "Profile"



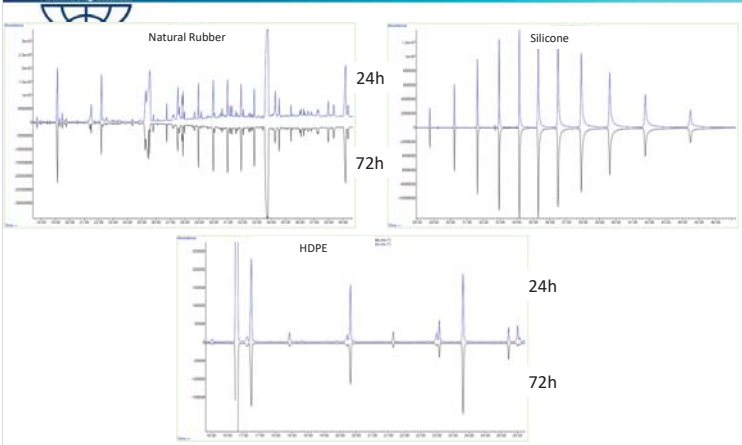
IS: Internal Standard for GC/MS
*: Internal Standard for LC/MS (not used in this GC/MS evaluation)

REMARK: Notice the Substantial "Visual" Difference in Extraction Profiles for the Different Extraction Solvents!

2. THE EXTRACTION STUDIES



2. THE EXTRACTION STUDIES



2. THE EXTRACTION STUDIES

USP <1663> "Generating the Extract"

Extraction Time & Temperature

The Combination of Extraction Time and Temperature establishes the Magnitude of the Driving Force & The Degree to which Equilibrium is Achieved.

In Extraction Studies, both the Temperature and Time of the Extraction are – in large part determined by the Extraction Technique that is selected

(This is different for simulation studies: see next presentation)

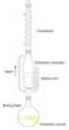
2. THE EXTRACTION STUDIES

USP <1663> "Generating the Extract"

Mechanism of Extraction – Extraction Technique

Reflux or Soxhlet Extractions

- Similar Extraction yields
- Reflux has shown - in limited cases - to introduce artefacts in extraction profile
  - Degradation of extractables during Relfux could occur



- Soxhlet has more practical implications
  - Takes longer (24h) to have the same extraction yields as reflux (8h)
  - Safety implications in Lab (24h extraction)
  - Less Practical for solvents with High Boiling Points
  - Less Practical for Aqueous Extraction Vehicles
  - Not to be used when *pH adjusted solvents* or *mixtures (e.g.IPA/UPW)* are used

2. THE EXTRACTION STUDIES

Sonication

- **Less Exhaustive** than Reflux & Soxhlet (PQRI)
- However, it may be **less detrimental to certain materials**
- Often used as the extraction technique for **Labels**
  - Avoids desintegration of Label, while extracting most relevant compounds
- Difficult to Control (see USP<1663>)

Sealed Vessel

- Closed vessel avoids loss of **VOLATILE Organic Compounds**
- Typically ISO 10993-12 Conditions can be Used (e.g. 50° C, 72h)
- In general, a **24h SV-extraction** at a temperature of **10° C below boiling** point is **equivalent in yields** to an **8h reflux** extraction

2. THE EXTRACTION STUDIES

Headspace Enrichment

- *Direct Analysis of the Material* using Headspace GC/MS
- Complete profile of **VOLATILE Organic Compounds**
- **Water Soluble** Compounds are **better detected** (often a problem for Headspace GC on aqueous extracts)

"In Situ" Extraction

- Container is filled with Extraction Solution, capped with Closure and Incubated.
- Allows **"One Sided Extraction"**
  - Coated Rubbers
  - Sealing Discs for Cartridges
  - Multi-Layer Foils
- Better Simulation, Less Exhaustive

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2. THE EXTRACTION STUDIES

"Static" versus "Dynamic" Extraction (not in USP <1663>)

- Consideration for "In-Situ" Extractions.
- Static Extraction: Pharmaceutical Packaging
- Dynamic Conditions, often considered for Production Items
  - *Tubings*
  - *Filters*
  - *Pump Systems (also for IV administrations)*
- Dynamic Extraction is a Better Simulation if the contact between the Components and the DP/DS is also dynamic,

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2. THE EXTRACTION STUDIES

Extraction Conditions - Temperature / Time

- For Reflux with Organic Solvents, typically:
  - Boiling Temperature, typically 8 h
- For Soxhlet with Organic Solvents, typically:
  - Boiling Temperature, typically 24 h
- For Sonication, typically:
  - Room temperature, typically ½ to 1h
- For Closed Vessel and "In Situ" Extraction, typically:
  - 50°C, 72 h (ISO 10993-12)
  - 24h below boiling point of extraction solvent = equivalent to 8h reflux
- For Headspace Enrichment:
  - 40 minutes, Temperature is selected based upon the type of material (from 70°C for LDPE upto 150° for Rubbers/Elastomeric Material)
- For Dynamic Extractions:
  - Extraction Conditions are determined based upon the conditions of use

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USP <1663> "Generating the Extract"

Extraction Stoichiometry

Stoichiometry: physical mass/surface area to volume

Can be based on

- *Known Chemical Ingredients in a Component/Material*
- *Safety based Thresholds for DP leachables*
- *Known Sensitivities of the Analytical Instrumentation*

Stoichiometry can be Manipulated to Produce a more conc. Extract

- *REMARK: beware of Solubility of Extractables in Extraction Medium when "Back Extrapolating" to Original Ratio's!*

Physical State can be Altered (Cut, Ground, Altered in Size...)

Extraction Stoichiometry

- Try to stay as close as possible to the ratio's of the actual use of the container
  - E.g. A rubber plunger for a 10 mL PFS could be extracted at a ratio of 1 plunger per 10 mL of solvent
- For Raw Materials, a reasonable, broadly accepted ratio is 1g/10mL
- For certain Container Closure systems (e.g. LVP), the Final AET levels that may need to be considered may have an impact on the extraction ratio's!

  EXAMPLE
  - For a 1 L bag (bag weighs 50g), Final AET in DP is at 1.5µg/L
  - This means that for the extraction study, 1.5µg/Bag(50g) or 30µg/g needs to be attained
  - With a ratio of 1Bag in 1L, this AET cannot be attained
  - Higher Material-to-Solvent Ratios will need to be considered

Analytical Techniques used to Characterize Extracts

- **PURPOSE**: Identify As many compounds as possible
- "SCREENING" Mode (see next slide)
- Broad Screening for Known & Unknown Compounds
- More Taylored Analyses for specific "known" Compounds, present in specific materials
  - Derivatisation GC/MS
  - S8 for (certain) rubbers
  - TMPTMA (HPLC) for adhesives
  - Acrylic Acid
  - Formaldehyde
  - ...

FRESHEN UP ANALYTICAL KNOWLEDGE – TECHNIQUES USED IN EXT ST

Anions	Fluoride, Acetate, Formate, Chloride Nitrite, Bromide, Nitrate, Sulphate, Phosphate	Ion Chromatography
Metals/Cations	Ag, Al, Ba, Ca, Cd, Co, Cr, Cu, Fe, In, K, Mg, Mn, Na, Ni, Pb, Si, Sr, Tl, Zn...	ICP-OES or ICP-MS
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 UPLC-HRAM **SCREENING**
Sulfur **Silicone Oil**	Cross Linking Lubrification	HPLC-UV GF-AAS

2. THE EXTRACTION STUDIES

Other Techniques & Methods used in Extractable Studies
USP <1663>: SCOUTING

NVR: Non-Volatile Residue
ROI: Residue on Ignition
FTIR: Characterization of NVR
UV: UV-Absorption of organic extractables
TOC: Total Organic Content: Sum of organic extractables in Aqueous Extracts
pH: Release of Acidic Alkalinic compounds in Aqueous Extracts
Conductivity: Release of Salts in Aqueous Extractrs
...

- *These Techniques and Methods only allow a limited identification (FTIR) or no Identification at all.*
- *TOC reconsiliation with Chromatographic Methods may be considered, but is always a Challenge.*

2. THE EXTRACTION STUDIES

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

2. THE EXTRACTION STUDIES

SCT: SAFETY CONCERN THRESHOLD

"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

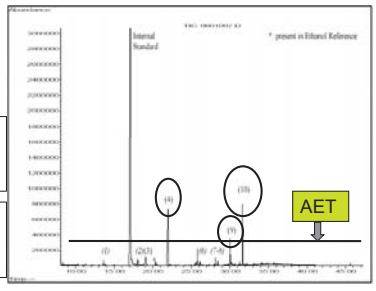
2. THE EXTRACTION STUDIES

AET: ANALYTICAL EVALUATION THRESHOLD

Translate SCT

into Analytical Thresholds
for Extractable Studies

Taking into account:
- *Total N° of doses / packaging*
- *Max. N° of doses administered / day*



2. THE EXTRACTION STUDIES

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

	Class I	Class II	Class III
Threshold Level (µg/day)	**50** (to be confirmed)	5	1.5

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.

2. THE EXTRACTION STUDIES

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**

2. THE EXTRACTION STUDIES

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
   - ...

2. THE EXTRACTION STUDIES

THRESHOLD APPROACH FOR LEACHABLE STUDIES

Could assist in reducing efforts in safety evaluation of Leachables

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

2. THE EXTRACTION STUDIES

AET: ANALYTICAL EVALUATION THRESHOLD

Example:

PFS Contains 1 dose
Maximum Daily Intake: 1 dose
Evaluation of Polymer Barrel (weight: 2 g)
Extraction ratio: 1 Barrel is extracted per 5 mL of Isopropanol
(exhaustive extraction)

EXTRACTABLES:
Threshold Class I: 50 µg/day: final AET level: 25 µg/Barrel
Threshold Class II: 5 µg/day: final AET level: 2.5 µg/Barrel
Threshold Class III: 1,5 µg/day: final AET level: 0,75 µg/Barrel

2. THE EXTRACTION STUDIES

AET: ANALYTICAL EVALUATION THRESHOLD

Formula used (see PQRI recommendations):

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

$$\text{Class I: Est. AET} = \frac{50\ \mu g / day}{1\,dose\ /\ day} \cdot \frac{1\,dose}{Barrel} = 50\ \mu g\ /\ barrel$$

$$\text{Final AET} = 25\ \mu g / Barrel$$

50% uncertainty for screening methods

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2. THE EXTRACTION STUDIES

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

	Threshold (µg/day)	Final AET (µg/barrel)	Final AET (mg/Kg)	Final AET (mg/L)
Class I	50	25	12	5
ClassII	5	2,5	1,2	0,5
Class III	1,5	0,75	0,37	0,15

Barrel weight: 2g

Extr. Ratio: 1barrel/5 mL

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2. THE EXTRACTION STUDIES

Typical Results for an Exhaustive Extraction on a Polymer Barrel

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

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2. THE EXTRACTION STUDIES

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

2. THE EXTRACTION STUDIES

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

STEP 2

SIMULATION STUDY

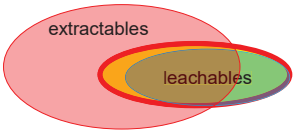
3. THE SIMULATION STUDIES

» **Purpose of Simulation Study – USP <1663>**

- Find + identify extractables which are **probable leachables**
- Establish which extractables must be targeted in a migration study
  - **Screening**
  - **mimic circumstances of final drug product:** acceleration, moderate exaggeration
  - **worst case:** sufficient amounts to identify
  - **safety/ toxicological risk assessment** to define target leachables

3. THE SIMULATION STUDIES

CLOSING THE GAP!!



Additional Study Design: SIMULATION STUDY

3. THE SIMULATION STUDIES

What SIMULANTS can be considered?

1. **Aqueous based solutions with organic solvent added** to mimic the extraction propensity of the actual DP
   - XX% Ethanol in UPW
   - XX% Isopropanol in UPW
2. The **Drug Product Vehicle**
   - When the DPV is not substantially different from the DP
3. The **Drug Product** itself *(see "Closing the Gap" presentation)*
   - "Screening Leachable Study"

3. THE SIMULATION STUDIES

Conditions of a Simulation Study:

1. Exaggerated & Accelerated Conditions:
   - Exaggerated: Composition of the Simulant
     Increased Surface area
     Underfilling (e.g. Bags)
   - Accelerated: temperature of Storage – Accelerated Ageing
2. Study the Complete Packaging System, not only the individual parts
3. Or, Study some parts of the Packaging System which are of Particular Interest

Example Novo Nordisk:

Carsten Worsoe, PDA Pre-Filled Syringes Conference

Exaggerated Exposure: Exposed Surface Area of Plungers 10x compared to reality Accelerated: 3 Months at 40° C Using DP

REMARK: Beware of Solubility of Extractables in Extraction Medium when "Back Extrapolating" to Original Ratio's!

3. THE SIMULATION STUDIES

Using a **SIMULANT** For SIMULATION Studies

Advantage

- Good solution if you have multiple DP using 1 C/C system
- Account for Unexpected Leachables
- Simulant allows to "screen"
- Allows to narrow down efforts in FORMAL Leachable Study
- Typically, not an end point in the E/L assessment. If considered as an end point, more documentation needs to be provided

Disadvantage

- Not Account for Reactive Leachables
- High Documentation Requirements
- Regulatoy Acceptance

Using a **DRUG PRODUCT** For SIMULATION Studies

Advantage

- Account for Unexpected Leachables
- Account for Reactive Leachables
- Allows to Predict Leachables very accurately
- Allows to narrow down efforts in FORMAL Leachable Study
- In some cases, it can be an end point

Disadvantage

- You ONLY have documentation of *"End of Shelf Life"* under accelerated conditions
- Not All DP can be used to "screen" for leachables

Regulatory Acceptance of SIMULATION Study

Think as a Regulator!

"Can you Prove that the Extraction Propensity of the Simulant is "worst case" compared to the Drug Product?"

e.g. 20% EtOH in UPW: More Documentation is needed
Simulant = DP: Yes

"Can you prove that there is no interaction between the leachables and the composing ingredients of a DP?"

e.g. 20% EtOH in UPW: No, needs to be studied
Simulant = DP: Yes

Regulatory Acceptance of SIMULATION Study

Can a SIMULATION study be considered as an alternative to a FORMAL LEACHABLE Study?

Using a Simulant like 20% EtOH/UPW:

- *A Lot of evidence will need to be provided to prove the Predictive Character of a Simulation Study.*
- *Secondary Leachables – Reaction products of leachables with DP – are not covered*
- *CONCLUSION: Risky!*
- ***The approach can be taken if a DP is Extremely Complex in its composition and no trace analysis is possible. However, the failed attempts should be documented to help justifying the alternative approach***

Using a the DRUG PRODUCT as a Simulant:

- *Some evidence will need to be provided to prove the Predictive Character of a Simulation Study, compared to a FORMAL LEACHABLE Study*
- *REMARK: a Screening approach does NOT work for ALL Drug Products*
- *Secondary Leachables – Reaction products of leachables with DP – are covered*
- *However: only the end point is tested, no across the whole shelf life...*
- *CONCLUSION: More Likely to be Accepted, but this cannot be generalized.*

CONCLUSION:

A Simulation Study

- Can help you to predict the "Probable" leachables
  - Narrow Down the long list of Extractables
  - Look at Unexpected leachables
  - Reactive Leachables
- Assist on reducing the efforts in "FORMAL" Leachable Study
- Considering a Simulation study as an End Point in E/L Qualification:
  - For Simulants: Be Careful!
  - For DP (Screening Leachable Study): yes in certain cases

STEP 3

MIGRATION / LEACHABLE STUDY

4. THE MIGRATION / LEACHABLE STUDIES

- TRYING TO ASSESS THE LEACHING BEHAVIOUR
- ASSESS POTENTIAL TOXIC CONSEQUENCES = **SAFETY**
- ASSESS IMPACT ON **DRUG PRODUCT QUALITY**
- FOCUS ON QUANTIFICATION OF **"TARGET" COMPOUNDS**
  - KNOWN POLYMER ADDITIVES USED
  - VALIDATION PACKAGE OF CONTAINER SUPPLIERS
  - EXTRACTABLES STUDY INFORMATION
- **"SIMULATED USE"** CONDITIONS
  - STORAGE TIME / TEMPERATURE / HUMIDITY
  - CONDITIONS: SIMILAR TO STABILITY STUDIES
  - PHARMACEUTICAL FORMULATION AS CONTACT SOLUTION
- **VALIDATED METHODS** (ICH Q2(R1))

4. THE MIGRATION / LEACHABLE STUDIES

USP <1664>: Leachable Studies can be used to

- Facilitate timely development of the C/C packaging Systems
- Establish Qual/Quant Correlations between Extractables & Leachables
- Establish Worst Case DP leachables profiles, Allowing a safety evaluation on the leachable compounds
- Establish Leachable accumulation levels in the Drug Product
- Facilitate the Change Control Process
- Facilitate Investigations into the origin of Identified Leachables that potentially may cause OOS for a marketed Drug Product

4. THE MIGRATION / LEACHABLE STUDIES

USP <1664>: Leachable Studies

- LEA studies are especially relevant
  - During **Late Stage product development**
  - During **formal product stability** assessment
- Should be **performed on the DP**, not on simulations thereof
- On **Registration Batches** of the DP during overall Stability assessments
- With the **actual C/C-system** that will be **commercialized**
  - Not with a prototype
  - Preferably on the same lots from the EXT study
- On the product, **MANUFACTURED** under conditions that reflect actual **commercial processes** of production
  - Fill & finishing
  - Sterilization
  - Distribution and storage
  - Clinical use

4. THE MIGRATION / LEACHABLE STUDIES

USP <1664>: Leachable Studies should be considered

- On **Real Time** Assessment (long term storage conditions)
  - Although accelerated ageing may be advantageous to better understand interactions
- For **"High Risk"** Dosage forms: In **Pre-Clinical Stage**
  - Facilitates the Selection of Packaging Components
  - Can be done with Placebo as simulant
- For **"High Risk"** Dosage forms: Leachable Characterization is RECOMMENDED for Test Article Batches in **CLINICAL STUDIES**
- **Post Market**, when there are changes to the Marketed DP
  - Supports the Change Control Process
  - Changes in Formulation
  - Changes in the Mfg. Process
  - Changes in Primary & Secondary Packaging OR Changes in the **MoC** of Components
- For **"Low Risk"** Dosage Forms: LEA studies are *not required "rigourously"*
  - However, it could be a "pro-active" excercise if an OOS would occur as a result of the contact between de DP and the C/C system

USP <1664>: The Design of Leachable Studies

- Will **depend upon the purpose and goals** of a Leachable Study
- However, they require **similar types of information**
  - Chemical Composition of Packaging
  - Details of Mfg. Process
  - Extractables Assessment
  - ALL potential sources should be assessed
    - Primary Packaging
    - Secondary Packaging (more important for semi-permeable containers)
- **Nature of Contact** : Direct versus Indirect contact *(Migration Mechanism)*
- **Time of contact**: Long Term versus Transient
- **Characteristics** of the **Drug Product Formulation**
  - E.g. Solid or Liquid? *(Migration Mechanism)*
- Compounds that may migrate from **Bulk Packaging**, may persist through the Mfg. Process end end up in the Final DP: **Should be treated as Leachables!!**

Typically, a **Leachable Study** is **looking at all DIFFERENTIAL peaks** in a **Comparative Assessment** between:

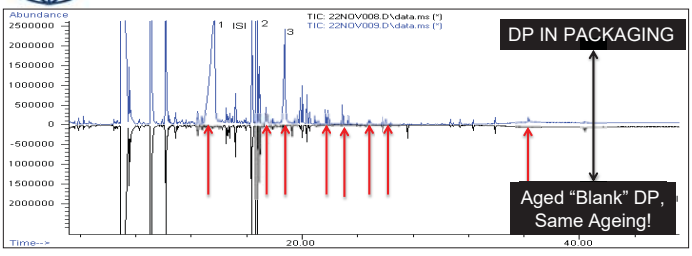
- *DP, aged in inert container (Aged Blank DP) (no contact with Packaging)*
- *The DP, aged in the Packaging System (Primary & Secondary Packaging)*

DP IN PACKAGING

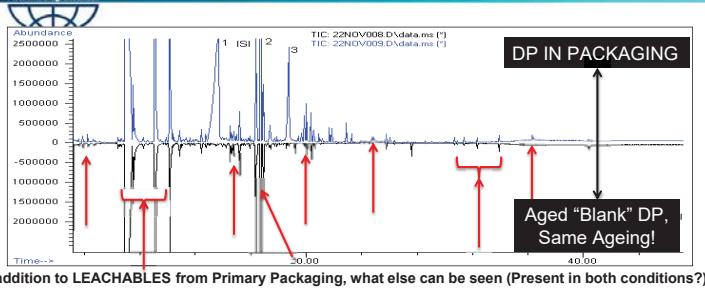
Aged "Blank" DP, Same Ageing!

Every Compound that is present in the DP, aged in the Packaging System But NOT in the DP, aged in inert container

CONSIDERED AS LEACHABLE



Differential peaks can be attributed to the interaction of the DP with the Packaging



In addition to LEACHABLES from Primary Packaging, what else can be seen (Present in both conditions?)

- *API, API degradants (expected & unexpected)*
- *Impurities from API (a.o. Genotoxic Impurities, residues from synthesis of API)*
- *DP ingredients + degradants*
- *Impurities from Ingredients (excipients, adjuvants, buffers,...)*
- *Leachables from processing materials (storage bags, filters, tubing materials...)*
- *Leachables from Intermediate Storage*
- *Secondary Leachables (reactive leachables)*
- *Leachables from the secondary packaging (label, ink, adhesive, overwrap, cardboard boxes…)*
- *in certain cases: batch cross contamination (traces)...*

USP <1664>: Methods for Leachable Studies

- **Nature of the Drug Product**
  - Aqueous or Non-Aqueous
  - pH
  - API concentration
  - Biologic (mAb, proteins, peptides...) vs Small Molecule
  - IgG, Albumin, Blood Products are challenging!
  - Other ingredients of the DP that could make the analytical development challenging
  - Tween, Castor Oil, Glycerine, Lipids, Squalene....
  - ...
- **Identities of the Leachables**
  - Volatile Organic Compounds
  - Semi-Volatile Organic Compounds
  - Non-Volatile Organic Compounds
  - Polar / Water Soluble Organic Compounds: special analytics (deriv. GC/MS, ESI LC/MS)
  - Pigments: often solubility problems of Analytical Standards
  - Metals
  - Ions / Small Acids / Dioic Acids...

PDA 4. THE MIGRATION / LEACHABLE STUDIES

USP <1664>: Methods for Leachable Studies

- **Expected Concentration Range of the Leachables**
  - What amounts were seen the components (MoC) during the EXT study?
  - What would this mean in Lea concentration if a certain % would leach out of the materials?
  - What is the likelihood of the compound leaching e.g.
    - BHT vs I-1010 in Aqueous DP
    - Pigments have typically a low solubility
    - Caprolactam has a very high solubility in aqueous DP: High accumulation level
    - DEHP has a very low solubility in e.g. 09% NaCl
- **What is the Evaluation Threshold of a Leachable?**
  - What is the SCT level (Class I, II or III), and corresponding AET levels?
  - Administration Volume and Administration Regimen will play a role
  - LVP versus SVP: LVP will be at much lower [LEA] in the DP

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PDA 4. THE MIGRATION / LEACHABLE STUDIES

USP <1664>: Methods for Leachable Studies

- **Capabilities of the Analytical Methods Employed**
  - Chromatographic Conditions
    - e.g. Non-Polar versus Polar Compounds
    - Alcohols, Amines, Acids, Dioic Acids
  - Detector Selection
    - E.g. MS selection for LC/MS: APCI +, APCI-, more non-polar compounds
      ESI+, ESI- : more polar / water soluble compounds
  - Adjustment of Sample Prep. based upon
    - Expected Concentration Range
    - Requested Evaluation Threshold
    - PCHEM conditions of Target Leachables versus DP-Composition

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PDA 4. THE MIGRATION / LEACHABLE STUDIES

CHALLENGES IN LEACHABLE STUDIES

LEACHABLE STUDIES ≡ STABILITY STUDIES

HOWEVER, THE **FOCUS** IS ON

1. *TRACE ANALYSES, LOW LEVELS*
2. *OF PACKAGING IMPURITIES*
3. *(OFTEN) IN COMPLEX MATRICES*
4. *USING OPTIMIZED METHODS*
   (HPLC-UV is not sufficient!!)

"...LEACHABLE STUDIES ARE OFTEN LIKE LOOKING FOR A NEEDLE IN A HAYSTACK..."

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CHALLENGES IN LEACHABLE STUDIES

METHOD DEVELOPMENT & VALIDATION: CHALLENGING BECAUSE OF THE

1. COMPLEXITY OF THE DRUG PRODUCT
2. REQUIRED LOW QUANTIFICATION LIMITS

METHODS SHOULD BE "SUFFICIENTLY QUANTITATIVE"

- Type of Drug Product – Route of Administration (From Inhalation to Oral)
- Primary Packaging versus Single Use Bioprocessing Equipment
- Administration Regimen ("*Daily, Chronic*" versus "*Once in a Lifetime*")
- Complexity of Drug Product Composition
  - ✓ *Can a Screening Methodology with Method Suitability Test be applied?*
  - ✓ *Analytical Interference: does a New Method need to be developed, specific for this DP?*
- Company Strategy for Compliance

"METHOD SUITABILITY TEST"

- Analytical Method used: Screening Method (also used for Extractables Testing)
- Spiking of Target Compounds
- Spiking at Relevant Levels (e.g. AET level)
- Only verifying if Screening Methodology works at relevant levels
- Can be considered as a "LIMIT TEST"
- Lower Cost, compared to Full Validation

"METHOD SUITABILITY TEST", Not suitable for:

- Inhalation DP (MDI), LVP and certain General Parenteral Applications
- DP which require a *Daily and/or Chronic Administration*
- Complex of Drug Products in their Composition
  - ✓ Screening Methodology with Method Suitability Test may not work
  - ✓ Potential Analytical Interference for certain DP
- Monitoring the leachables concentration over DP shelf life, rather it is considered as a "limit test"
- If the concentration is too close to critical safety levels

Validated Methods (ICH Q2(R1))

• Specificity - Identification	
• Range	
• Linearity of Method	r > 0.990
• Extraction Yields (when applicable)	
• Detection Limit	Application Specific
• Quantification Limit	
• Accuracy in low, mid and high range	100 ± 25%
• Precision in low, mid and high range	< 25%

Other: Intermediate Precision, Robustness...

For Validation of Analytical Methods for Trace Analysis other specifications apply than for API validation

CHALLENGES IN LEACHABLE STUDIES

DIVERSITY OF STABILITY CONDITIONS TO BE CONSIDERED:

SIMILAR TO WHAT NEEDS TO BE OFFERED FOR STABILITY STUDIES!!

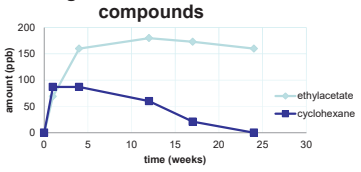
STABILITY CONDITIONS –CLIMATIC ZONES

General case	**25±2° C/ 60±5%RH**
	30±2° C/ 65±5%RH
	40±2° C/ 75±5%RH
DS intended for storage in refrigerator	5±3° C
	25±2° C/ 60±5%RH
DS intended for storage in freezer	-20±5° C
DP in semi-permeable containers	25±2° C/ 40±5%RH
	30±2° C/ 35±5%RH
	30±2° C/ 65±5%RH
	40±2° C/ 25±5%RH
Ultralow temperature for biotech products	-80° C

Case study LEA: 100 mL flexible multi-layer bag incl. Drug solution
ageing at 25° C for 6 months
VOC (Volatile Organic Compounds)
monitoring Ethylacetate and Cyclohexane

Conclusion: Ethylacetate: asymptotic behaviour
Cyclohexane: dissapears: worst case concentration is NOT ALWAYS AT THE END OF SHELF LIFE!!

leaching behaviour of two volatile compounds



CONCLUSION: LEACHABLES SHOULD BE STUDIED ACROSS THE SHELF LIFE OF A DRUG PRODUCT

Example Setup of the Study
Analytical Program for Leachable study of a Pre-Filled Syringe

Type of Solution	Storage Time (Months)				
	0	3	6	12	24
Pharmaceutical Matrix in Pre-filled Syringes (Test Item) at 5 ± 3 ° C	×	×	×	×	×
Pharmaceutical Matrix in Inert Containers (Blank) at 5 ± 3 ° C	×	×	×	×	×
Pharmaceutical Matrix in Pre-filled Syringes (Test Item) at 25 ± 3 ° C	-	×	×	-	-
Pharmaceutical Matrix in Inert Containers (Blank) at 25 ± 3 ° C	-	×	×	-	-
× = sampling time point					

4. THE MIGRATION / LEACHABLE STUDIES

Example Setup of the Study
Analytical Program for Leachable study of a Pre-Filled Syringe

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

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4. THE MIGRATION / LEACHABLE STUDIES

Analytical Techniques used for LEACHABLE

Similar Techniques as for Extraction Testing, only Quantitative:

- Headspace GC/MS
- GC/MS
- LC/MS
- ICP
- IC
- Other specific Methods for Specific Leachables...

If Possible – in addition to validated methods – always perform SCREENING also (see “Closing the Gap” Presentation):

- Account for Unexpected Leachables
- Reactive Leachables
- In General: look for Leachables, not reported as Extractables

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4. THE MIGRATION / LEACHABLE STUDIES

Analytical Techniques used for LEACHABLE

Specific Techiques for Monitoring Leachables at low levels:

- GC-QQQ
- LC-QQQ
  - Low Matrix Interference
  - Less extensive Sample Preparation
  - More “Robust” Methods

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Single Lot testing, versus testing of **Three Lots**

- There are no strict Guidelines/Guidances for this wrt Leachable testing
- In US – or - for **US Submissions**: there is more a *preference* to test **Three Lots**
- In EU, testing is *typically* performed on one **Single Lot**
- What kind of leachables concentrations do you expect – i.e. **How far from critical levels**?
- In General, one can say that it is **GOOD PRACTICE** to test three Lots, but it adds to the cost of a project

What if the DP is so Complex & Challenging in its Formulation that a normal Analytical Approach cannot be taken?

- Try to prove and document the analytical difficulties
- Narrow down the Analytics
  - *Very targeted, specific compound detection*
  - *No Screening possible*
- Consider a Simulation Study
  - *Justify a Simulation Study by proving the difficulties in the regular Leachable Study Approach*

Thank you!

Experimental Design Considerations for Extractables Simulation Studies

Dennis Jenke, Chief Executive Scientist, Triad Scientific Solutions, LLC

The Simulation Study – Value Proposition (I)

Problem:

Occasions may arise in which it is not analytically feasible (due to challenging thresholds, for example) to successfully discover and identify all actual leachables in a drug product leachables study.

Solution:

This circumstance can be managed if the activities of discovery and identification of probable leachables can be accomplished in an extraction study, where samples and analyte concentrations are more easily manipulated to achieve the necessary analytical performance.

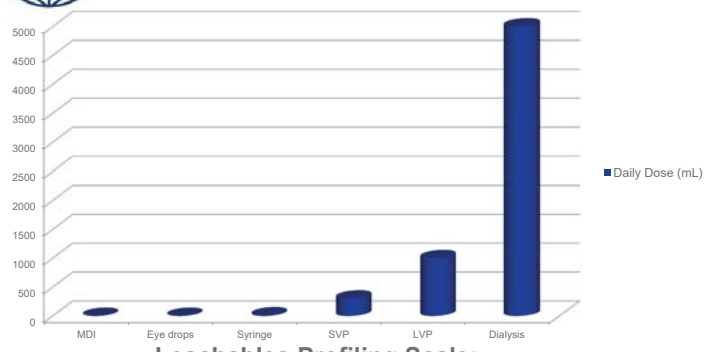
Source: *<1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems.* USP 38 – NF 33 (First Supplement), pp. 7181 – 7193. August 1, 2015.

The Simulation Study – Value Proposition (II)

Easier to do — **Leachables Profiling Scale:** — Harder to do

0 1 2 3 4 5 6 7 8 9 10

The Simulation Study – Value Proposition (IV)



Easier to do — **Leachables Profiling Scale:** — Harder to do

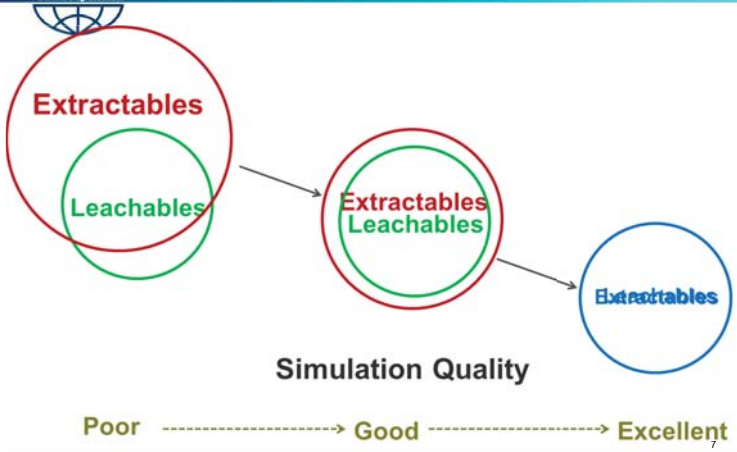
0 1 2 3 4 5 6 7 8 9 10

Simpler …

Faster …

Better!

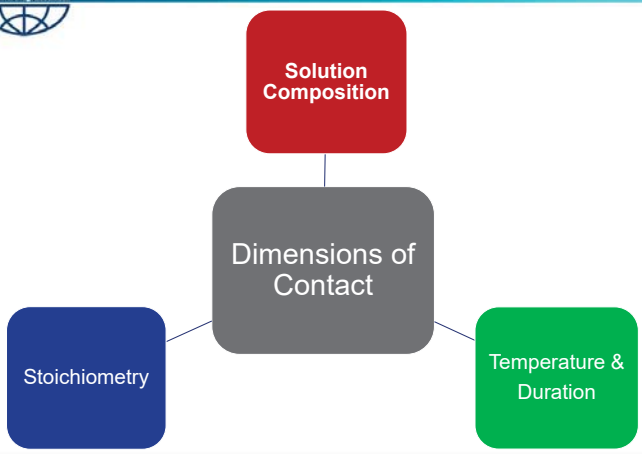
1. The drug product formulation has been replaced with one or more simulating solvents.
2. The actual use conditions of contact have been accelerated.
3. The test article may have been altered (somewhat) to provide an exaggerated and presumably worst case.



An extractables profile obtained from a properly designed and executed simulation study will almost always[1] be equal to (or greater than)[2] a leachables profile obtained for a drug product over its shelf-life.

[1]In fact, it should rarely (never) be the case that leachables >> simulated extractables.
[2]Where equal to (or greater than) means that the extractables profile includes all the members of the leachables profile with extractables levels being greater than or equal to the leachables levels.

Dimensions of Contact to be Simulated



Simulating Solution Composition

Solution Composition

1. **Polarity**
2. **pH**
3. **"Reactivity"**

Simulating Solution Composition - Polarity

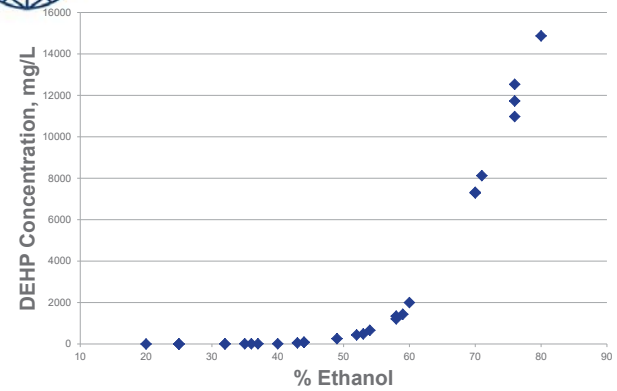
Thermodynamically,

a leachable will accumulate in a drug product to a level dictated by its solubility in the drug product.

A leachable's solubility in a drug product will depend on the "polarity" of the leachable and the drug product.

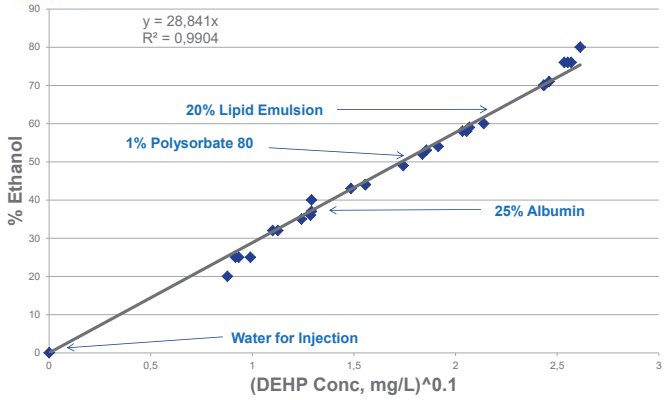
"Like dissolves like"

The Effect of "Polarity" on the "Leaching Power"



Source: Jenke, D.; Liu, N.; Hua, Y.; Swanson, S.; Bogseth, R. A means of establishing and justifying binary ethanol/water mixtures as simulating solvents in extractables studies. *PDA J Pharm Sci Technol.* **69(3):** 366-38 2(2015).

The Relative "Leaching Power" of Drug Products



Simulating Solution Composition - pH

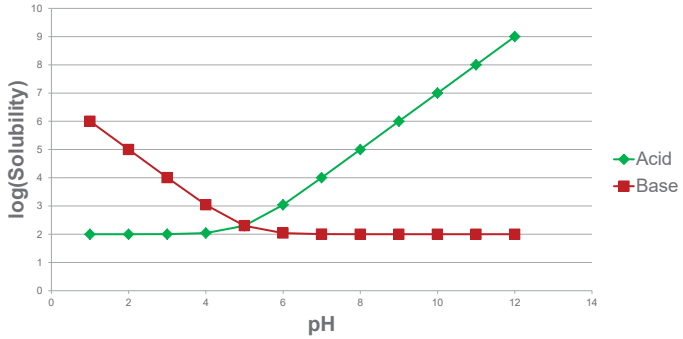
Thermodynamically,

a leachable will accumulate in a drug product to a level dictated by its solubility in the drug product.

The solubility of an acidic or basic leachable in a drug product will depend on the acid/base dissociation constant (pK_a) of the leachable and the pH of the drug product.

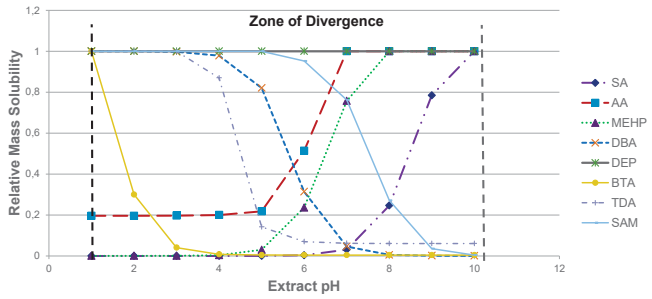
The Relative "Leaching Power" of Drug Products

The Effect of pH on the Solubility of an Acidic or Basic Extractable. The Figure considers an acidic or basic extractable with a pK_a of 5.0 and a solubility of 100 (arbitrary units). As the pH of the extracting medium increases, the solubility of the acidic extractable increases. Similarly, as the pH of the extracting medium decreases, the solubility of a basic extractable increases.



The Effect of Solution pH on the Reported Solubility of Selected Extractables

As DEP is non-ionic, its solubility is unaffected by pH. The solubility of the acidic extractables (AA, SA and MEHP) increases with increasing pH, depending on their pK_a. The solubility of the basic extractables (SAM, DBA, TDA, BTA) increases with decreasing pH, consistent with their pK_a. The Zone of Divergence spans those pH values where the weakest acid (SA) and the weakest base (BTA) achieve their maximum solubilities. A set of extraction solvents that captures essentially all possible acidic or basic extractables at their likely highest concentration must have a pH values that span the Zone of Divergence.



Source: Jenke, D. Establishing the proper pH of simulating solvents used in organic extractables assessments for packaging systems and their materials of construction used with aqueous parenteral drug products. *Pharm Outsourcing.* **15(4)**:20, 22, 24-27 (2014)

Simulating Solution Composition - Reactivity

Issue: An extractable from the container reacts with some chemical component of the drug product, altering the chemical structure of the extractable and resulting in a disconnect between the extractables and leachables profile.

- Simulation Study reveals the extractable
- Leachables Study reveals the degradation products(s)
- It is the leachable that potentially impacts a product's quality attribute.

Accelerating Clinical Contact: Temperature and Duration

Temperature
and
Duration

Accelerating Clinical Contact: Temperature and Duration

Kinetically,

a leachable will accumulate in a drug product at a rate dictated by the speed with which the leachable diffuses through the packaging.

The diffusion rate will depend on the diffusion coefficient for the leachable in the packaging material and the contact temperature.

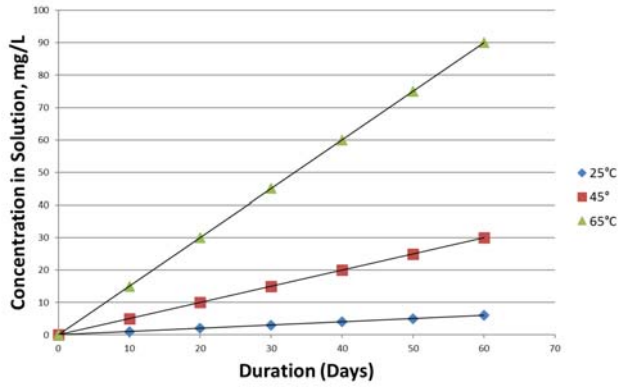
The amount of a leachable that accumulates in a drug product will depend on the diffusion coefficient, the diffusion distance and the duration of contact.

Accelerating Clinical Contact: Temperature and Duration

Kinetically,

The higher the temperature, the longer the contact time and the larger the diffusion coefficient …

1. The larger will be the leachable's concentration in the drug product.
2. The more likely an equilibrium leachable concentration will be achieved.



Two Approaches for Calculating and Justifying Accelerating Conditions

1. **ASTM F1980-07 (Reapproved 2016)**: Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices.

Accelerated Aging Time at T2 = Actual Aging Time at T1 ÷ C

$$C = Q_{10}^{[(T2 - T1)/10]}$$

where Q_{10} = 10°C Reaction Rate Constant
T2 = accelerating temperature (°C)
T1 = actual temperature of contact (°C)

Note: This standard does not purport to address all of the safety concerns, if any, associated with its use.

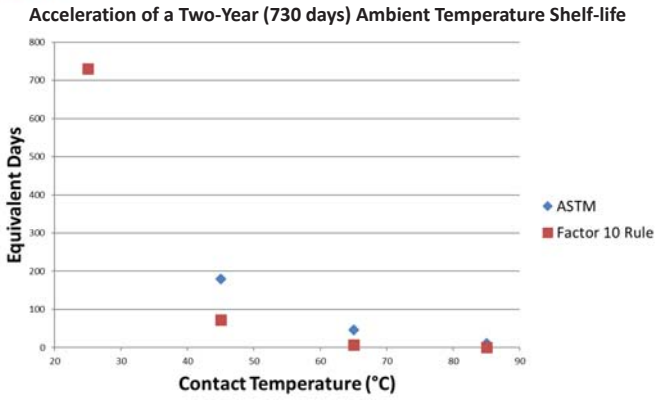
Two Approaches for Calculating and Justifying Accelerating Conditions

2. **"Factor 10 Rule"** [1] This factor 10 rule is based on the observation that activation energies for migrating substances in polymers relevant to packaging are typically in the range of 80 to 100 kJ/mole. In such a circumstance, the diffusion coefficient increases by roughly an order of magnitude for every 20°C increase in contact temperature. Thus for example, the migration rate at 40°C is ten times faster than the migration rate at 20°C

Accelerated Aging Time at T2 = Actual Aging Time at T1 ÷ C

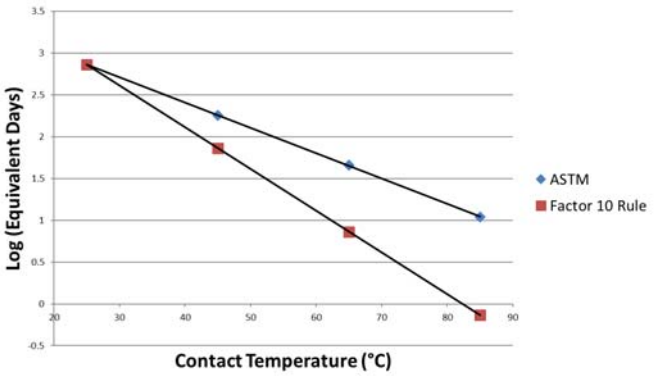
$$C = 10^{[(T2 - T1)/20]}$$

[1]R. Franz, A. Stormer. Migration of Plastic Constituents. In Plastic Packaging: Interactions with Foods and Pharmaceuticals. Wiley-VCH; Second Edition, 2008, pp. 368.



Accelerating Clinical Contact: Temperature and Duration

Acceleration of a Two-Year (730 days) Ambient Temperature Shelf-life



The Effect of Stoiciometry

Stoichiometry

1. Surface area/Solution volume
2. Material weight/Solution volume

Stoiciometry Fallicies

1. **Its all about surface area**.
2. **As the surface area to solution volume ratio increases, the concentration of leachables will increase in the same linear and 1 to 1 manner for all leachables.**

Stoiciometry Fallicies Debunked!

1. **Its all about surface area**. In fact, the way most experiments are designed, when one increases the surface area/solution volume ratio they are also increasing the material weight to solution volume ratio. More likely, then **it is all about material weight**.

2. As the surface area to solution volume ratio increases, the concentration of leachables will increase in the same linear way for all leachables.

$$C_{l,e} = m_{l,e}/V_l = m_{p,o}/[V_l + (k_{p/l} \times SA_p \times t_p)]$$

Where C is the extractable's concentration,

- m is the mass of the extractable in either phase,
- SA is the surface area of the sample being extracted,
- t is the thickness of the sample being extracted,
- $K_{p/l}$ is the extractable's plastic/solution partition coefficient,
- V is the volume of either phase, and
- the subscripts p, l, e and o refer to the plastic phase, the liquid phase, equilibrium and original respectively

R. Franz, A. Stormer. Migration of Plastic Constituents. In Plastic Packaging: Interactions with Foods and Pharmaceuticals. Wiley-VCH; Second Edition, 2008, pp. 370.

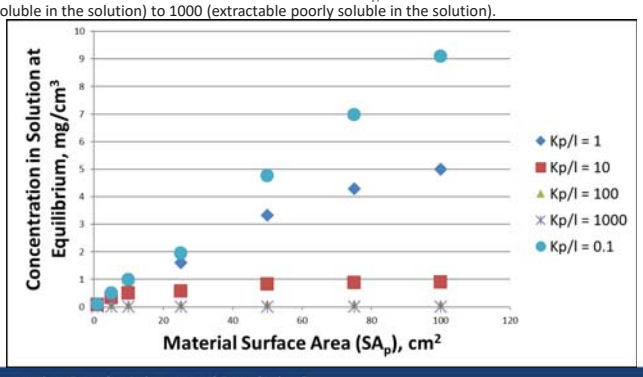
2. As the surface area to solution volume ratio increases, the concentration of leachables will increase in the same linear way for all leachables.

- **For a substance that is highly soluble in the solution, an increase in material surface area produces nearly a proportional increase in the concentration of the substance in the solution.** For example, when the surface area is increased by a factor of 100 for a substance with a $k_{p/l}$ of 0.1, the increase in the substance's concentration in solution is also nearly a factor of 100.
- **For a substance that is poorly soluble in the solution ($k_{p/l}$ = 100) a 100-fold increase in surface area produces barely a doubling of the substance's concentration in solution.**

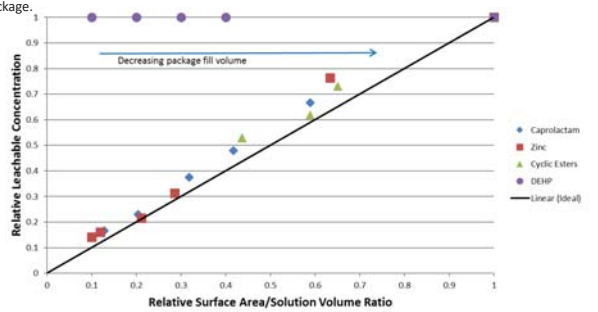
To examine the nature of this effect, the following situation is considered:

$m_{p,o}$ = 10 mg/cm^2,
V_l = 100 mL = 100 cm^3,
t_p = 1 cm, and
$k_{p/l}$ takes values ranging from 0.1 (substance highly soluble in the solution) to 1000 (substance poorly soluble in the solution).

Theoretical Relationship between the Material Surface Area and the Concentration of an Extractable in an Extracting Solution at a Constant Extracting Solution Volume. The relationship is shown for extractables with polymer/liquid partition coefficients ($k_{p/l}$) ranging from 0.1 (extractable is highly soluble in the solution) to 1000 (extractable poorly soluble in the solution).



Normalized Plot Showing the Experimental Effect of a Package's Surface Area to Solution Volume Ratio (SV/A) on the Equilibrium Concentration of Leachables in the Contained Solution. As the package's size (fill volume) decreases, its surface area to solution volume increases, resulting in an increased extractable concentration in the contained solution. Concentrations and SA/V ratios have been normalized to the corresponding values for the smallest package.



Source: Jenke, D; Rabinow, B. Proper accounting for surface area to solution volume ratios in exaggerated extractions. *PDA J Pharm Sci Technol.* **71(3)**: 225-233 (2017)

In Review:

- A properly designed and implemented extractables simulation study produces an extractables profile that is equal to or slightly exaggerated from the leachables profile for a packaged drug product.
- Critical design parameters for a simulation study include:
  - Solution Composition
  - Temperature and Duration
  - Stoichiometry
- In considering Solution Composition, the aspects of "polarity", pH and "reactivity" should be considered. Of these three, "polarity" and pH are relatively straightforward, while "reactivity" needs further consideration.
- In considering Temperature and Duration, certain mathematical conventions can be quite useful in terms of accelerating leaching.
- In considering Stoichiometry, it is noted that in many cases the surface area to solution volume ratio is just another way of saying material weight to solution volume. More importantly, the assumption of a linear relationship between stoichiometry and leachables accumulation is just that, an assumption, which may or may not be true.

References:

1. <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems. USP 38 – NF 33 (First Supplement), pp. 7181 – 7193. August 1, 2015.
2. Jenke, D.; Liu, N.; Hua, Y.; Swanson, S.; Bogseth, R. A means of establishing and justifying binary ethanol/water mixtures as simulating solvents in extractables studies. *PDA J Pharm Sci Technol.* 69(3): 366-38 2(2015).
3. Jenke, D. Establishing the proper pH of simulating solvents used in organic extractables assessments for packaging systems and their materials of construction used with aqueous parenteral drug products. *Pharm Outsourcing.* 15(4):20, 22, 24-27 (2014).
4. ASTM F1980-07 (Reapproved 2016): Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices.
5. R. Franz, A. Stormer. Migration of Plastic Constituents. In Plastic Packaging: Interactions with Foods and Pharmaceuticals. Wiley-VCH; Second Edition, 2008, pp. 368.
6. R. Franz, A. Stormer. Migration of Plastic Constituents. In Plastic Packaging: Interactions with Foods and Pharmaceuticals. Wiley-VCH; Second Edition, 2008, pp. 370.
7. Jenke, D; Rabinow, B. Proper accounting for surface area to solution volume ratios in exaggerated extractions. *PDA J Pharm Sci Technol.* 71(3): 225-233 (2017).

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Thank you!

ANALYTICAL TECHNIQUES, USED IN EXTRACTABLES TESTING

PDA TRAINING COURSE
EXTRACTABLES – LEACHABLES
Berlin
28 – 29 September, 2017

Dr. Piet Christiaens

CHALLENGES IN E/L TESTING

Challenges in E/L-Testing

Diversity of not-API Related Compounds in E/L research is Tremendous!!

Broad spectrum of:

- Types of Containers
- Types of Materials used in the Manufacture of Containers
- Number of Suppliers per Material
- Number of Grades (per supplier) for each type of Material
- Type of Sterilization (impact on material impurity profile)

Challenges in E/L-Testing

(Non Limitative) List of types of Pharmaceutical Containers

INHALATION
- *Metered Dose Inhaler Components e.g.:*
  - Gaskets
  - Stem
  - Body
  - Metering Chamber
  - Protection Ring
  - Actuator
  - Cannister
- *Dry Powder Inhaler Components*
- *Nasal Spray Systems*
- *Nasal Dropper Systems*
- ...

PARENTERAL
- *Bottles*
- *Vials*
- *(Pre-Filled) Syringes*
- *Cartridges*
- *(Rubber) Stoppers*
- *Rubber Plungers*
- *Needle Shields*
- *Tip Caps*
- *I.V. Bags*
- *Administration Sets*
- ...

OPHTHALMIC
- *Eye Dropper Systems*
- *Tubes*
- ...

DERMAL/TOPICAL
- *Spray Systems*
- *Tube systems*
- ...

SINGLE USE SYSTEMS
- *(Multilayer) Bags*
- *Tubings*
- *Connectors*
- *Ports*
- *Filters (+ Housing)*
- *Chromatographic Columns*
- *Lyo trays*
- ...

SECONDARY PACKAGING
- *Labels*
- *Adhesive/Glue (e.g. on labels)*
- *Ink*
- *Overwrap foils*
- *Blisters*
- *Cardboard packaging*
- ...

Challenges in E/L-Testing

Pharmaceutical Containers can be made of different Materials

- Low Density Polyethylene
- High Density Polyethylene
- Polypropylene
- Rubbers
- Butyl Rubbers
- Chlorobutyl Rubbers
- Bromobutyl Rubbers
- EPDM Rubbers
- Isoprene Rubbers
- Nitrile Rubbers
- Latex Rubbers
- Other Rubbers
- Multi-layer Films and Foils
- Polyurethane (PU)
- Ethylvinyl Acetate (EVA)
- Ethylvinyl Alcohol (EVOH)
- Polyamide (Nylon-6, Nylon-66)
- Cyclic Olefin Copolymers (COC)
- Cyclic Olefin Polymers (COP)
- Polyethylene Terephthalate (PET, PETG)
- Polybutylene Terephthalate (PBT)
- Polyacetal (POM)
- Polymethylmethacrylate (PMMA)
- Acrylonitrile Butadiene Styrene (ABS)
- Silicone
- C-Flex
- Polycarbonate
- Teflon
- PEEK
- Glass
- Metals
- …

Challenges in E/L-Testing

Each Material has different Suppliers

EXAMPLES

Polyethylene - produced by:
- *Borealis*
- *LyondellBasell*
- *SABIC*
- *Dupont*
- *Enichem*
- *INEOS*
- *TOTAL*
- ...

Pharmaceutical Rubbers - main Global Suppliers:
- *Datwyler*
- *West Pharmaceutical*
- *Stelmi*

Each Supplier has different Different Grades!

Challenges in E/L-Testing

Each Supplier has different Different Grades

EXAMPLES

PolyEthylene - produced by:
- *Borealis: over 30 different Medical Grades*
- *LyondellBasell: over 30 different Medical Grades*
- *SABIC: over 30 different Medical Grades*
- *Dupont: different grades*
- *Enichem: different grades*
- *INEOS: different grades*
- *TOTAL: different grades*
- ...

Pharmaceutical Rubbers - main Global Suppliers:
- *Datwyler: over 100 different commercial rubber formulations*
- *West Pharmaceutical: over 100 different commercial rubber formulations*
- *Stelmi: also, a broad range of commercial rubber formulations*

Challenges in E/L-Testing

Per Material, Supplier and Grade:
what makes up the Impurities Profile?

- Solvent residues (e.g. of Polymerization)
- Polymer residues (e.g. Monomers, Oligomers)
- Catalysts
- Polymer/Rubber Additives
  - Antioxidants
  - Photostabilizers
  - Plasticizers
  - Lubricants
  - Acid Scavangers
  - Pigments/Colorants
  - Carifying/Nucleating Agents
  - Cross Linking Agents (Rubbers)
  - Initiators (Rubbers)
  - Accelerators (Rubbers)
- Polymer Additive Degradation Products
- Polymer Degradation Compounds
- Adhesives
- ...

Challenges in E/L-Testing

Conclusion:

1. The broad diversity of pharma containers, materials, suppliers and grades, leads to a extremely long list of potential impurities (leachables), introduced into the drug product

2. The compounds cannot be investigated with 1 analytical technique. Typically, at least 3 to 5 analytical techniques will need to be combined.

3. Compound Identification is of high importance, therefore the detection needs to be compound specific (e.g. MS-detection)
   - *Headspace GC/MS – Volatile Organic Compounds*
   - *GC/MS – Semi-Volatile Organic Compounds*
   - *LC/MS – Non-Volatile Organic Compounds*
   - *ICP – Metals*
   - *IC – Anions*

Challenges in E/L-Testing

Conclusion:

4. For Companies / Labs, only performing E/L-testing, every E/L-project could turn out into a high level research project (with the need for high level analytical techniques) because of the lack of materials knowledge

5. For Labs, performing E/L-studies on a routine basis, excessive analytical costs (associated with high-end analytical procedures) should be avoided in FIRST PASS testing.
   Toxikon: **TOX-RAY** development

Connecting People, Science and Regulation®

ANALYTICAL TECHNIQUES USED FOR EXTRACTABLES TESTING

Connecting People, Science and Regulation®

SAMPLE PREPARATION:

THE
MOST IMPORTANT &
THE MOST UNDERESTIMATED
ACTIVITY IN THE LAB!!!

Connecting People, Science and Regulation®

SAMPLE PREPARATION – CHALLENGES IN TRACE ANALYSIS

- Have **very experienced people** in Sample Preparation
- Very **Intensive Training** for new staff in Sample Prep
- **QC on solvents** used – select batches of clean solvents with suppliers
- **QC on extraction equipment**
- **Separate glassware**
- Precleaning of glassware – **validation of Cleaning** Procedures
- **Sampling of test articles** – how to handle Test Articles?
- **WFI sample prep** should be **separated** from solvent sample prep
- Correction for **absorbed solvents**?
- How to **concentrate extracts** – while avoiding cross contaminations
- **Storage of extracts** under controlled conditions
- **Holding times** of extracts
- Selection of **type of containers for storage** of extracts
- How to keep **DEHP** out of the Lab!

SAMPLE PREPARATION

- How to deal with **human source contaminants** (limonene, squalene, parabens, palmitic/stearic acid...)
- Headspace GC/MS: WFI should be completely SEPARATED
  - Sample prep
  - Storage of sample/extract
  - Filling into storage containers
  - Instruments
  - Holding times for HS-GC/MS are shorter!!
  - Avoid cross contamination from other solvents, regularly used in the lab (DCM, Hexane, IPA, Toluene, Chloroform...)
- Internal standards
  - Holding times of Internal Standards
  - Syringes: should be calibrated at least yearly
  - Have a cleaning procedure for syringes
  - Compatibility of Internal Standards with solvents

EXTRACTABLE STUDIES

IDENTIFICATION
IDENTIFICATION
IDENTIFICATION
IDENTIFICATION

- INCREASE THE **KNOWLEDGE** ABOUT THE COMPOSITION OF THE POLYMER
- FOCUS: IDENTIFICATION OF EXTRACTABLES
- ADDS TO INFORMATION PROVIDED BY RAW MATERIAL SUPPLIERS OR C/C MANUFACTURERS
- EXTRACTABLES LIST: FOCUS FOR LEACHABLE STUDY
- IN SOME CASES: QUANTITATIVE EXTRACTABLES STUDIES (e.g. inhalation)

EXTRACTABLE STUDIES

A **Broad Identification** in "First Pass" Extractable Studies Requires:

1. A Compound Specific Detector: **Mass Spectrometry**
2. A **Database** to allow Identification based upon Mass Spectra
   - Commercial Databases for GC/MS: NIST, WILEY
   - Self-Developed Databases (e.g. **TOX-RAY**)
   - **PROBLEM for LC/MS**: no Commercial Databases Available!

Gass Chromatography / Mass Spectrometry (GC/MS)

Headspace GC/MS (neat and after sample prep)	Direct Injection GC/MS (after sample prep)
for Volatile Compounds	for Semi-Volatile Compounds

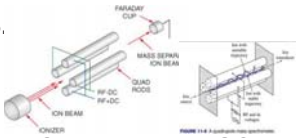
However, the GC/MS part of the Instrumentation is the same for the two techniques!!

"Standard" GC/MS: Quadrupole M.S.

Gas Chromatography: Separation of Organic Molecules based on:

- Polarity – Interaction/Affinity with the Stationary Phase
- Boiling Point – GC-Oven temperature
- Film Thickness of the Chromatographic Capillary Column
  - *Volatile Compounds: high film thickness (>1 µm)*
  - *Semi-Volatile Compounds: low film thickness (≤0.25 µm)*
- Length of the Chromatographic Capillary Column
  - *Volatile Compounds: 30 m to 60 m*
  - *Semi-Volatile Compounds: 30 m*
- Polar Organic Compounds may need more specific conditions
  - *Acids, Amines, Alcohols....*

"Standard" GC/MS: Quadrupole M.S.



General Sequence of Things in a Mass Spectrometer (GC):

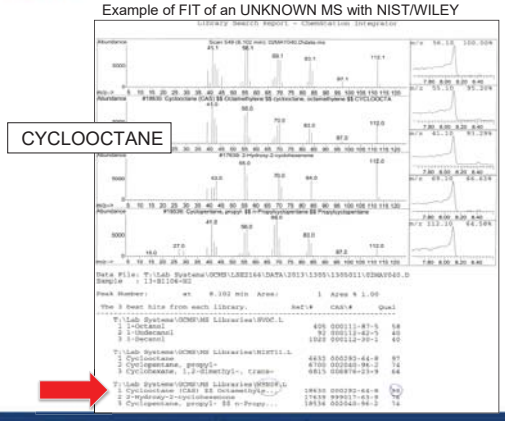
- High Vacuum
- Convert Molecules to Ions (Tungsten Filament)
- A Moving Ion (= charge) in a Magnetic Field gets deflected
- Only the right "m/z" can reach the detector and give a (charge) signal
- The charge signal is "strengthened" by a photomultiplier
- The Mass Filter (e.g. Quadrupole) scans a predefined mass range in milliseconds!
- This way, a complete mass spectrum can be obtained in a few milliseconds!

Standard GC/MS: Quadrupole M.S.

- A GC/MS "Mass Spectrometer" is ***Standardized***:
  1. Quadrupole (or Ion Trap)
  2. Ionisation: Electron Impact Ionisation of 70 eV
  3. Gives Reproducible Mass Fragmentation:
     Reproducible Mass Spectrum
  4. Mass Spectrum can be compared to commercially available Databases, such as NIST or WILEY – or self-developed MS-Databases (eg **TOX-RAY**)
  5. Can lead to Identification of Compound

Standard GC/MS: Quadrupole M.S.

Example of FIT of an UNKNOWN MS with NIST/WILEY

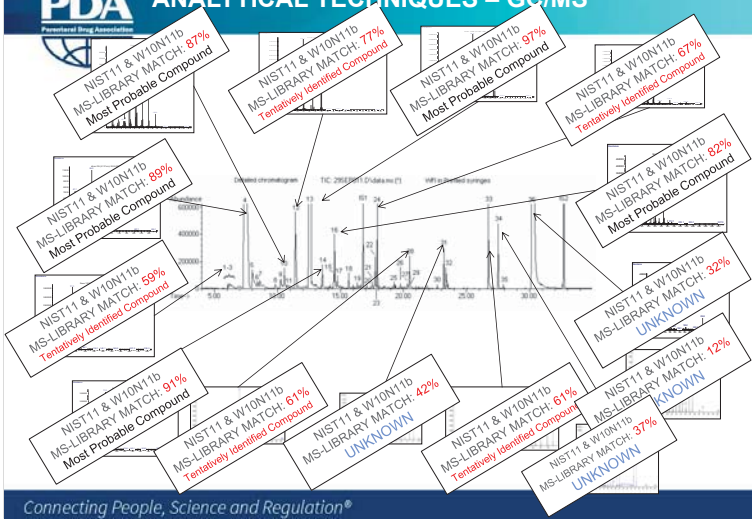


"Standard" GC/MS: Quadrupole M.S.

WHAT IS "SCREENING"?

- Trying to identify every single peak in a chromatogram
- Above a certain threshold
  - either Analytical (reporting threshold)
  - or Toxicological (e.g. AET)

Example: see next slide

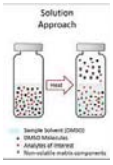


VOC

HS-GC/MS **Screening**

Volatile Organic Compounds (typically MW < 200)

- **Monomer Residues**
- **Solvent Residues from Production steps**
- **Residues from polymer treatments (e.g. Washing)**
- **Small Polymer Breakdown products**



VOC

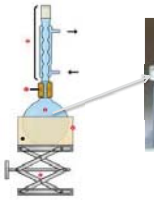
HS-GC/MS **Screening**

SVOC

GC/MS **Screening**

Semi-Volatile Organic Compounds (MW < 650)

- **Lubricants**
- **Plasticizers**
- **Antioxidants**
- **Polymer degradation products**
- **Solvents with an elevated boiling point**

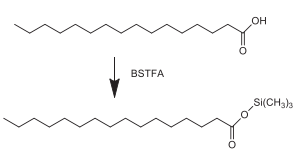


Derivatisation GC/MS

- A combined Headspace-GC/MS, GC/MS and LC/MS approach is suited for a broad list of organic compounds.
- However, compounds containing functional groups such as: ***Organic acids, Amines, alcohols, polyols, aldehydes, ketones...*** may not always be very sensitive in regular GC/MS analysis!!
- A Derivatisation Method is using BSTFA as derivatisation agent *(conversion to more volatile, less polar trimethylsilyl esters)*.

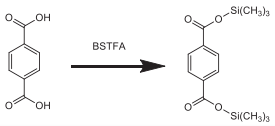
DERIVATISATION GC/MS: EXAMPLES

Peak 1: Palmitic acid



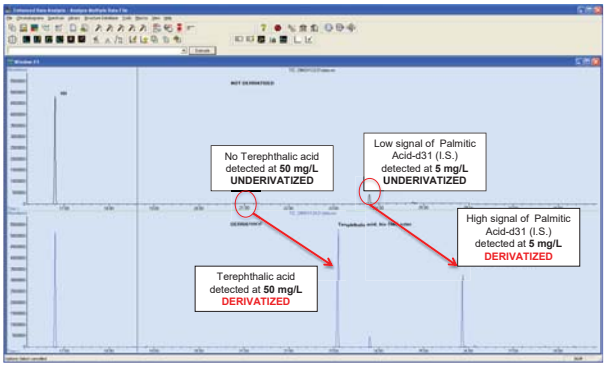
Trimethylsilyl ester of Palmitic Acid

Peak 2: Terephthalic acid



Trimethylsilyl ester of Terephthalic Acid

DERIVATISATION GC/MS: RESULTS



Other GC/MS Techniques *(High-End GC/MS)*

GC-MS (C.I.): Chemical Ionisation GC/MS

- "Soft Ionization" Compared to Electron Impact (E.I. 70eV)
- The molecule is less Fragmented
- Detection of Molecular Ion
- Allows to determine the Molecular Mass (i.e. With GC-ToF)
- Can be used for "Second Pass" Identifications

GC-QQQ or GC-"Triple Quad" Mass Spectrometer

- **Targeted** analysis in complex matrices
- Very low Detection Limits in complex matrices due to elimination of matrix interferences

Other GC/MS Techniques

GC-(Q)-ToF or GC-"Time-of-Flight" Mass Spectrometer

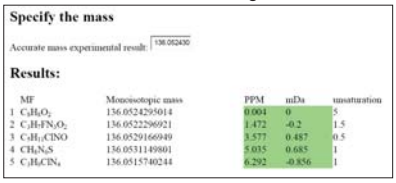
- **Accurate Mass Measurements**: what does it bring?

- Principle: Every Atom has a specific Atomic Weight
  - C= 12,00000
  - H = 1,00794
  - O = 15,9994
  - N = 14,0067
  - ...
- Look for the best combination of Atoms which will fit the Accurate Mass the best, Measured with GC-ToF.

GC-TOF Accurate Mass Measurements

Example: a Compound - Accurate Molecular Mass of 136.05243 - was detected.

What could be the Elemental Formula? Using a CALCULATOR



Specify the mass

Accurate mass experimental result: 136.05243

Results:

	MF	Monoisotopic mass	PPM	mDa	unsaturation
1	$C_8H_8O_2$	136.0524295014	0.001	0	5
2	$C_7H_7FN_2O$	136.0522296921	1.472	-0.2	1.5
3	$C_{11}H_{13}ClNO$	136.0529166949	3.577	0.487	0.5
4	CH_9N_5S	136.0531149801	5.035	0.685	1
5	$C_7H_4ClN_4$	136.0515740244	6.292	-0.856	1

Most Probably, the Elemental Formula of this molecule is $C_8H_8O_2$

Cross Examining results of other Analytical results, revealed that this compound is **4-methylbenzoic acid**

However, this conclusion cannot be drawn, based solely on accurate mass!

ANALYTICAL TECHNIQUES – D.I.-GC/MS

Other GC/MS Techniques

- **GC-ToF** or GC-"Time-of-Flight" Mass Spectrometer

➢ For extracts with a lot of "Unknown" compounds, the extracts are analyzed with GC-ToF (in E.I. and C.I. Mode) in order to determine the

1. **Molecular Ion and hence the Elemental Composition (CI and/or EI)**
2. **Fragment information (EI)**
3. In combination with existing data, determine more about the **Structure and Source** of the compound
4. In some cases, in combination with **Derivatization Procedure**
5. In some cases, a **full identification** of the compound

ANALYTICAL TECHNIQUES – LC/MS (UPLC-HRAM)

However: Overlap with compounds from GC/MS *(Volatile & Semi-Volatile Compounds)*

The principle of HPLC

- High Pressure
- Separation, mostly reverse phase chromatography
- Optimizing separations by
  - Selection of Chromatographic Column (Polarity, Length...)
  - Selection of the Elution Solution (WFI, MeOH, ACN...)
- Detection of the Compounds (UV: DAD; Mass Detection)

5. ANALYTICAL TECHNIQUES TO PERFORM E/L STUDIES

VOC	SVOC	NVOC
HS-GC/MS **Screening**	GC/MS **Screening**	UPLC/MS **Screening**

Non-Volatile Organic Compounds

- **Fillers**
- **Plasticizers**
- **Antioxidants**
- **Anti-slip agents**
- **...**

ANALYTICAL TECHNIQUES – LC/MS (UPLC-HRAM)

HPLC - UV

Advantages

- Standard Equipment in a Lab
- Cost
- UV-Detector can be a *nice addition* to other Detectors, e.g. MS

Disadvantages

- Not a Universal Detector (Target Molecules need Chromophores)
- Non specific
- Not very Sensitive
- Information about the Detected Molecule is limited
  - E.g. Is the molecule linked to the API?

LC-MS

Advantages

- Specificity
- Sensitivity
- More can be said about the Identity of the Compound
- Quality of Information HRAM > Low Resolution
- Allows to build Databases for Identification

Disadvantages

- Cost
- Not a Universal Detector (Target Molecules need to Ionize)
- However, different Ionisation Modes allow a broader detection of Compounds (APCI+/-; ESI+/-)

LC-MS

Older systems:
LOW Resolution Mass spectrometer
Ion Trap/Single Quad

Accuracy of Mass Detection is poor: 1 Dalton

m/z 220 can be distinguished from 221

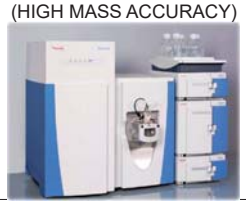
HIGH Resolution LC-MS (LC-HRAM)
Orbitrap/Time-of-Flight (ToF)
Accuracy of Mass Detection - Orbitrap:

Mass error : sub ppm
m/z 220,2456 can be distinguished from m/z 220,2457

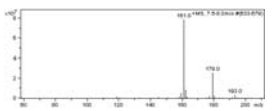
MAJOR ADVANTAGES!
- » Robust: accurate mass is independent of the system
- » High Accuracy in mass detection allows elemental composition analysis of an unknown analyte
- » Extremely powerfull if coupled to a UPLC
- » Building specificity into your databases based on mass accuracy and retention time!

LC-ION TRAP
(LOW MASS ACCURACY)

LC-ORBITRAP
(HIGH MASS ACCURACY)

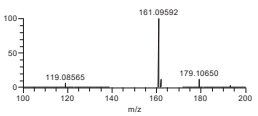


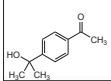
LOW RESOLUTION MASS



No information

HIGH RESOLUTION ACCURATE MASS
$C_{11}H_{14}O_2$ exact monoisotopic mass: 179.10666
Mass error:
1 ppm





Peroxide curative related compound from EPDM rubber

VOC	SVOC	NVOC	ELEMENTS
HS-GC/MS Screening	GC/MS Screening	UPLC/MS Screening	ICP/OES

- Elements
- Heavy metals
- Quantitative

ICP-OES

ICP-OES or ICP-MS:

- Metals from Glass
- Metals from Rubbers
- Catalysts, used on the polymerization
- Fillers, added to Polymers
- Acid Scavengers
- Activator systems for Rubbers
- ...

ICP-MS

ICP-OES

VOC	SVOC	NVOC		
HS-GC/MS **Screening**	GC/MS **Screening**	UPLC/MS **Screening**	ICP/OES	IC

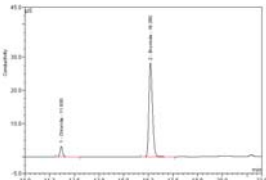
OTHER TECHNIQUES

Ion Chromatography:

- PolyOlefins (e.g. After Irradiation/Ageing): Acetate & Formate
- Halobutyl Rubbers: Bromide, Chloride, Fluoride
- Other trace impurities: Nitrite, Nitrate, Phosphate, Sulphate

• Example: Halobutyl rubbers may contain traces of bromide or chloride ions, either from side-products generated during the halogenation step, or rubber degradation products, or impurities. Additionally, fluoride may be released from fluoropolymer coatings

Sample: reflux extract with WFI (water for injection) of a halobutyl rubber



OTHER SPECIFIC METHODS

- ✓ **GF-AAS** For Silicone Oil Detection
- ✓ **ESI**-UPLC-HRAM (**Electron Spray**: BPOG Method)
- ✓ **HPLC-UV** for TMPTMA (glue residue)
- ✓ HPLC-UV for S_8 (Cross Linker)
- ✓ **pH** (release of acidic/alkalinic agents in UPW)
- ✓ **Conductivity** (release of salts in UPW)
- ✓ **Non-Volatile Residue** (gravimetric residue)
- ✓ **FTIR** – characterization of NVR
- ✓ **Total Organic Carbon**: *reconsiliation with concentration of organic compounds from chromatographic techniques*
- ✓ ...

ANALYTICAL TECHNIQUES USED FOR LEACHABLES TESTING

LEACHABLES STUDIES

TECHNIQUES USED IN LEACHABLE STUDIES

- ✓ Headspace GC/MS: Volatile Compounds
- ✓ Direct Injection GC/MS: Semi-Volatile Compounds
- ✓ D.I. GC-QQQ: Semi-Volatile Compounds
- ✓ LC-QQQ: Non-Volatile Compounds
- ✓ Ion Chormatography: (An)Ions
- ✓ ICP-OES or ICP-MS: Metals

Specific Analysis/Techniques for specific target analyses...

(See further presentation *"Leachable Studies"*)

ANY QUESTIONS?

EXTRACTABLES & LEACHABLES FOR SVP-INJECTABLES

PDA Post-Conference E/L-Workshop
Berlin
28 - 29 September, 2017

Dr. Piet Christiaens
Toxikon Europe NV

PDA Content

1. Regulatory Considerations for SVPs
   - US
   - EU
2. Typical Materials of Construct (MoC's) for SVP C/C
   - Rubbers 101
   - Glass & Glass related issues for E/L
   - COP/COC
3. Container Closure Systems for SVP's
   - Vials
   - Prefilled Syringes
   - Cartridges
   - Delivery Devices with Short Term Contact
4. Conclusion

PDA Content

1.Regulatory Considerations -SVP

REGULATORY: US

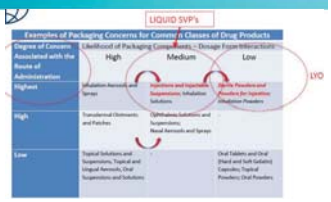
LIQUID SVP's

Examples of Packaging Concerns for Common Classes of Drug Products

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

LYO

Revision of "Table 1" in USP <1664>,
Originally Included into the FDA Guidance for Industry (1999):
"Container/Closure systems for Packaging Human Drugs and Biologics"



Remark:

1. the "Medium" *Likelihood of Packaging - DP Interaction* for Liquid SVP's is mainly based upon the observation that most Parenteral DP are Aqueous Based. For Non-aqueous based drug products: more caution is needed!

2. The "Low" *Likelihood of Packaging - DP Interaction* for LYO SVP's is mainly based upon the observation that:
   1. the *interaction* between a solid (Lyo cake) a material (eg rubber) *is limited*
   2. AND, there is *limited direct contact* between Lyo cake and Rubber closure

   However the Mechanism of interaction for a LYO Cake and its MoC may not need always a direct contact.
   BE CAREFUL when "rationalizing" a LYO application as being Non Critical!!!

Additional Concern for **BioPharmaceuticals**

Leachables, Leading
to **Immunogenic Responses**
Directly or Indirectly
(via e.g. Protein interactions)

Guidance for Industry

Immunogenicity Assessment for Therapeutic Protein Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

Consequences for EFFICACY – some of the concerns:

Development of "***Neutralizing Antibodies***" *(e.g. through chemically modified therapeutic protein product)* can **block the efficacy** of therapeutic protein products

May also change the Pharmacokinetics
- Enhancing Clearance
- Or Prolonging Product Activity

Leached materials from the container closure system may be a source of materials that enhance immunogenicity, either by chemically modifying the therapeutic protein product or by having direct immune adjuvant activity

FDA Guidance for Industry, 2014

Guidance for Industry

Immunogenicity Assessment for Therapeutic Protein Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

Consequences for SAFETY – some of the concerns: *(e.g. "...through chemically modified therapeutic protein product...")*

- Anaphylaxis (serious, accute allergenic reaction)
- Cytokine Release Syndrome
- "Infusion Reactions"
- Non-Acute Reactions
- Cross-reactivity to Endogeneous Proteins

Leached materials from the container closure system may be a source of materials that enhance immunogenicity, either by chemically modifying the therapeutic protein product or by having direct immune adjuvant activity

FDA Guidance for Industry, 2014

REGULATORY: US

Guidance fo
Immunogenicity
Therapeutic Protein Products

Interactions between therapeutic protein products and the container closure may negatively affect product quality and immunogenicity. These interactions are more likely with prefilled syringes of therapeutic protein products. These syringes are composed of multiple surfaces and materials that interact with the therapeutic protein product over a prolonged time period and thus have the potential to alter product quality and immunogenicity. The following are other container closure considerations pertinent to immunogenicity:

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2014
Clinical/Medical

"... Interactions are more likely with prefilled syringes of therapeutic protein products..."

"... Materials that interact with the therapeutic protein product over a prolonged time and thus have the potential to alter product quality and immunogenicity..."

FDA Guidance for Industry, 2014

REGULATORY: US

- Glass and air interfaces can denature proteins and cause aggregation in glass syringes and vials.
- Glass vials have been known to delaminate at higher pH and with citrate formulations, potentially creating protein-coated glass particles, which may enhance immunogenicity of the therapeutic protein product (Fradkin et al. 2011). ➡ Delamination
- Silicone oil-coated syringe components provide a chemical and structural environment on which proteins can denature and aggregate. ➡ Silicone Oil
- Appropriate in-use stability studies should be performed to confirm that conditions needed to maintain product quality and prevent degradation are adequately defined. ➡ In Use Stability Studies
- Leached materials from the container closure system may be a source of materials that enhance immunogenicity, either by chemically modifying the therapeutic protein product or by having direct immune adjuvant activity, including the following: ➡ Directly – Indirectly leading to enhanced immunogenicity
  - Organic compounds with immunomodulatory activity may be eluted from container closure materials by polysorbate-containing formulations: a leachable organic compound involved in vulcanization was found in a polysorbate formulated product when the stopper surfaces were not Teflon coated (Boven et al. 2005). ➡ Eprex - Case
  - Metals that oxidize and aggregate therapeutic protein products or activate metalloproteinases have been found in various products contained in prefilled syringes or in vials. For example, tungsten oxide that leached from the syringe barrel was reported to cause protein aggregation (Bee et al. 2009); and leached metals from vial stoppers caused increased proteolysis of a therapeutic protein because of activation of a metalloproteinase that co-purified with the product. ➡ Tungsten Oxide Leading to Protein aggregation

REGULATORY: US

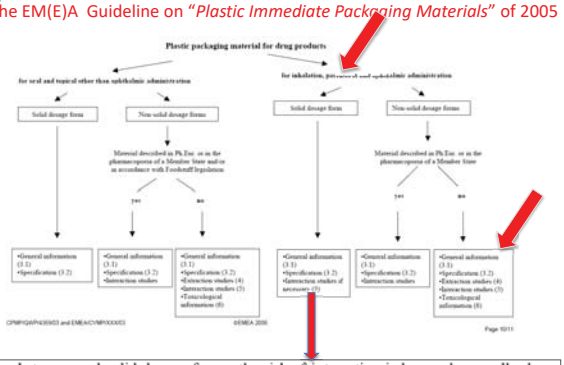
Sponsors should conduct a comprehensive extractables and leachables laboratory assessment using multiple analytical techniques to assess the attributes of the container-closure system that could interact with and degrade protein therapeutic products.

Because the United States Pharmacopeia *elastomeric closures for injections* tests do not adequately characterize the impact of leachables in storage containers on therapeutic protein products under real-time storage conditions, leachables must be evaluated for each therapeutic protein product in the context of its storage container under real-time storage conditions[8].

Testing for leachables should be performed on the product under stress conditions,[9] as well as under real-time storage conditions, because in some cases the amount of leachables increases dramatically over time and at elevated temperatures. Product compatibility testing should be performed to assess the effects of container closure system materials and all leachables on product quality.

REGULATORY: EU

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

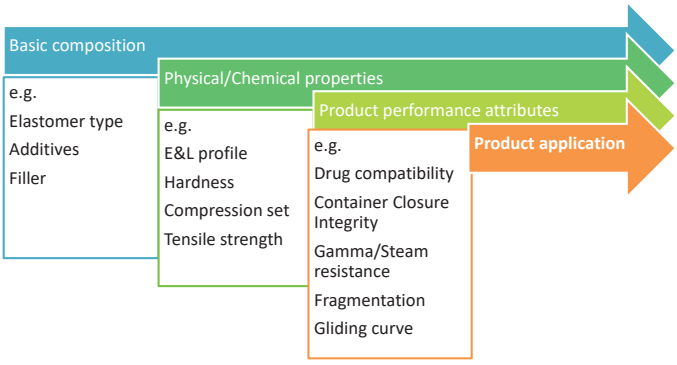


For solid active substances and solid dosage forms: the risk of interaction is low and generally does not require a content/container interaction study. Solid dosage forms intended for inhalation or parenteral use, e.g. lyophilised products, may need interaction studies between the packaging material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

2. Typical Materials of Construction for SVP Container/Closure Systems

elastomeric closures

Supported by Datwyler



What is rubber?

•An **elastic** material
•A **compounded** material
•Long Term Contact vs. Short Term Contact

•Basis of a rubber → polymer →**elastomer**
•**Elasticity via crosslinking** (curing, vulcanising) the elastomer
•Additional ingredients to „**tune" the rubber**

Compounded material of:

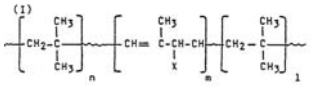
1. Elastomer
2. Filler
3. Cure system
4. Pigment
5. Other ingredients



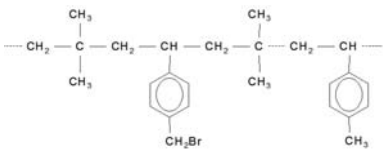
1. Elastomers

Halobutyl (BromoButyl, ChloroButyl)

Cleanest curing system
Lowest permeability
High resistance to ageing



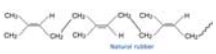
Regular **butyl** still on the market, and also newer types like **BIMS** (Brominated isobutylene para-methylstyrene)



1. Elastomers

Natural rubber / Polyisoprene

Natural rubber : latex allergy discussions
Historically the oldest elastomer type
Need complex curing systems
Good elastic properties
Polyisoprene (synthetic) replaces Natural rubber



SBR (styrene-butadiene rubber)

Intermediate permeability
Typically used for pre-assembled EtO sterilized components (e.g. Needle Shields)

MoC's FOR SVP-INJECTABLES - RUBBERS

1. Elastomers

Nitrile rubber

Typically used for mineral oil based drugs

Silicone rubber

High permeability

Typically not used for parenteral applications

EPDM rubber

For niche applications

MoC's FOR SVP-INJECTABLES - RUBBERS

2. Fillers

- Fillers give **mechanical strength** (stiffness) to a rubber
- Attributes **physical properties** to a rubber compound
  - **More filler = Harder compound**
  - →Better for **gliding** profile plungers
  - →Better **against stickiness** in bulk
  - →**Worse for stopper piercing** (coring!)
- Inorganic fillers ('white compounds')
  - –Aluminum silicate (clay)
  - –Magnesium silicate (talc)
  - –Silicate
  - –[Calcium carbonate]
- Carbon black ('black compounds')
  - –Undesired for cleanliness reasons
  - –May be associated with PNA's

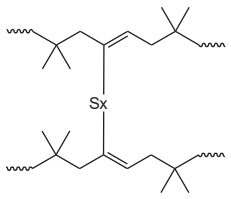
MoC's FOR SVP-INJECTABLES - RUBBERS

3. Cure systems

- **Cure system:**
  - –Crosslinking agent
  - –Activator : gives the onset of vulcanization
  - –Accelerator : speeds up the vulcanization
    - Easily extractable organic molecules such as thiurams, sulfonamides, thiazoles, ...
- **Modern cure systems**
  - –Aim at giving little extractables
- **Historic cure systems**
  - –Use easily extractable organic accelerators

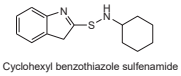
MoC's FOR SVP-INJECTABLES - RUBBERS

Rubber Curing / Vulcanization:

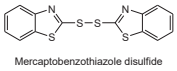


Rubber crosslinking requires S-Donors, activators, accelerators
Activator: ZnO / Stearic acid

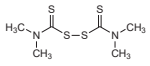
Rubber Curing - Accelerators:



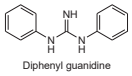
Cyclohexyl benzothiazole sulfenamide



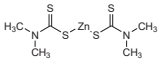
Mercaptobenzothiazole disulfide



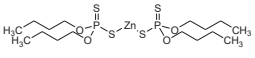
Tetramethylthiuram disulfide(TMTD)



Diphenyl guanidine

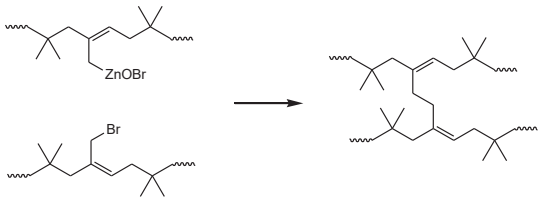


Zinc dimethyldithiocarbamate



Zinc dibutylphosphorodithiate

ZnO as Cross-Linking Compound in Halobutyl-Rubbers:



4. Pigments

- **Inorganic pigments**
  - –Titanium dioxide
  - –Traces of carbon black
  - –Oxides of iron
- **Organic pigments**
  - –Avoided in modern compounds

5. Other ingredients

- **Halobutyl polymer stabilizers**
  (to prevent dehydrohalogenation during processing)
  - –Calcium stearate
  - –Epoxydized soybean oil
- **Anti-oxidants**
  - –Already present in halobutyl elastomer
  - –Hindered phenol type anti-oxydants
  - –Additionally added to improve environmental stability (ageing)
- **Plasticizer, Waxes, Oil**
  (introduce softness, anti-"coring")
  - –High polymeric weight plasticizers, Paraffinic oil
  - –To tune a formulation (e.g. reduce coring)
- **Processing aids**

MoC's FOR SVP-INJECTABLES - RUBBERS

Smart selection of ingredients can tune a rubber compound

E.g. recipe based on hydrophobic ingredients will show better E-profile with aqueous drugs.

E.g. blend of halobutyl and SBR can *tune* the permeability

E.g. MgO replaces ZnO to avoid Zn-ion extraction

E.g. low water absorption compounds for lyo applications

MoC's FOR SVP-INJECTABLES - RUBBERS

But in general too many ingredients should be avoided : negative impact on E-profile

→ *"what you don't put in, can't come out"*

MoC's FOR SVP-INJECTABLES - RUBBERS

Number of Leachables from rubbers in PFS is determined by:

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

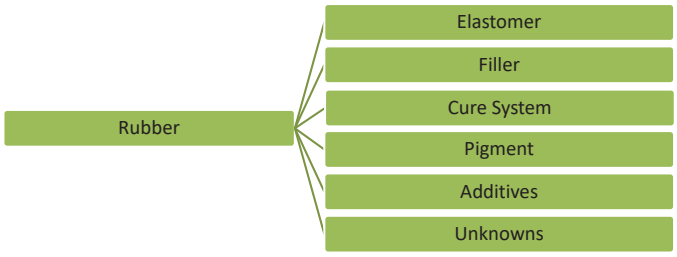
MoC's FOR SVP-INJECTABLES - RUBBERS

THE COMPOSITION OF RUBBERS CAN BE VERY COMPLEX!!

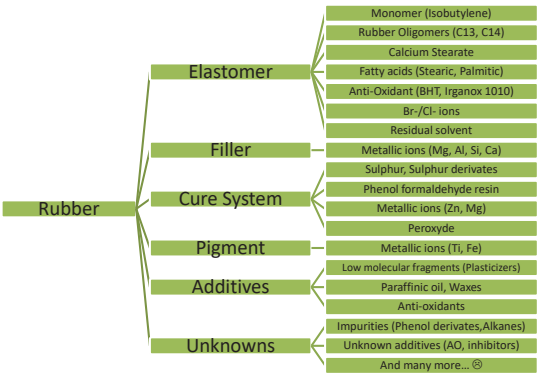
RUBBER EXTRACTABLES: SUM OF

1. **INITIAL INGREDIENTS** OF THE RUBBER FORMULATION
2. **IMPURITIES** OF THESE INGREDIENTS
   *(e.g. Residual Solvents, **Oligomers in Elastomer**, Halides in Halobutyl Rubber…)*
3. **REACTION/DEGRADATION PRODUCTS** DURING RUBBER PRODUCTION

MoC's FOR SVP-INJECTABLES - RUBBERS

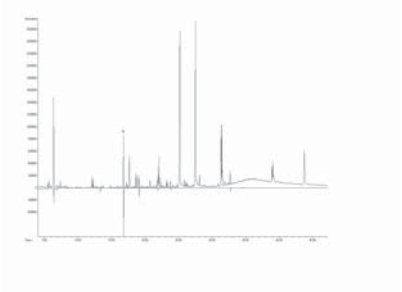


MoC's FOR SVP-INJECTABLES - RUBBERS



MoC's FOR SVP-INJECTABLES - RUBBERS

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

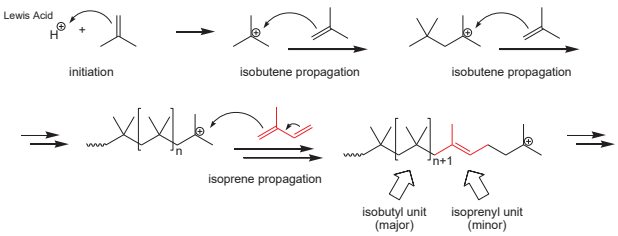


"OLD" RUBBER

"NEW" RUBBER

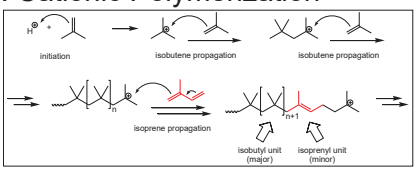
MoC's FOR SVP-INJECTABLES - RUBBERS

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



- Note: the Polymerization Starts with a Isobutene Unit (present in high excess!!)
  - *98 – 99 mol% is isobutylene*
  - *1 – 2 mol% is isoprene*

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

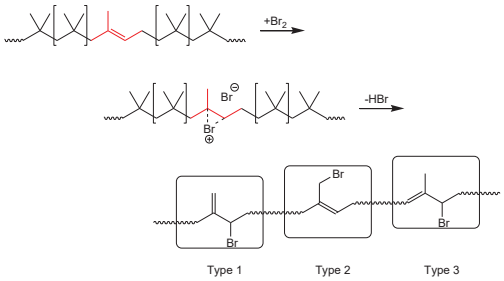


- *98 – 99 mol% is isobutylene*
- *1 – 2 mol% is isoprene*

*Means for **Butyl Elast(IIR)**(that approx. **per 100 C-C bonds** in the back bone, **1 is a double** (C=C) bond (if 2%)*
*Compared with **Polyisoprene**: **Per 100 C-C bonds** in the backbone, approx. **33 will be double** (C=C) bonds*

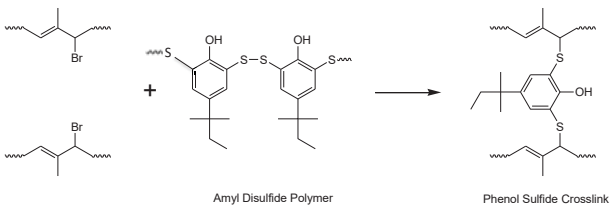
Less double bonds in IIR means:
*Butyl Elastomer (IIR) is **less prone to Oxidation***
*Butyl Elastomer (IIR) needs an **more efficient cross linking reaction** compared to Polyisoprene*
Bromination of the backbone helps to address this (Br is a good leaving group)

Bromination of a Butyl Elastomer (BIIR)



Bromination of the Backbone makes Elastomer
(with a relatively Low N° of double bonds in backbone)
more reactive in vulcanization/cross linking

Vultac Curing of (Halobutyl) Elastomers



Amyl Disulfide Polymer — Phenol Sulfide Crosslink

Bromide: good leaving group!

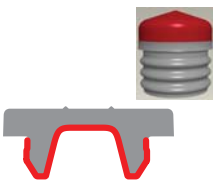
Bond Energy C-H 413 J/mol ⇔ C-Br 209 J/mol

Explains Br⁻ release from bromobutyl rubbers

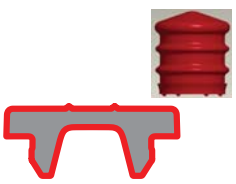
COATED RUBBERS

Significant step improvement in E&L terms are the coated closures.
Key attribute : barrier effect from the fluoropolymer !
Simplified extractables profile
Improved compatibility with drugs/excipients

Film coating technology

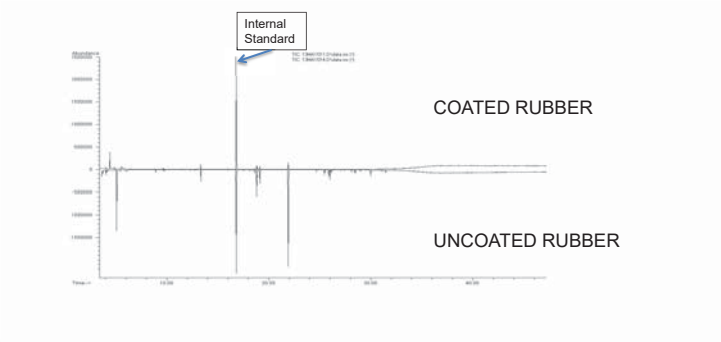


Spray coating technology



MoC's FOR SVP-INJECTABLES - RUBBERS

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



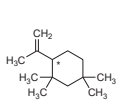
MoC's FOR SVP-INJECTABLES - RUBBERS

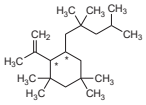
RUBBER OLIGOMERS:
MAY NEED MORE ATTENTION

MoC's FOR SVP-INJECTABLES - RUBBERS

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

- Considered as
  - Cyclic aliphatic hydrobarbon compounds
  - One double bond
- No experimental data / Literature data is known about toxicity of these compounds
- Structure Activity Relationship Assessment (SAR): compound of low tox. risk.


C13 oligomer


C21 oligomer

MoC's FOR SVP-INJECTABLES - RUBBERS

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

- Considered as
  - **HALOGENATED** Cyclic Aliphatic Hydrobarbon compounds (Allyl Halide)
  - **Alkylating Agents**
  - One double bond
- Structure Activity Relationship (SAR) Assessment:

CARCINOGENICITY IN HUMANS IS PLAUSIBLE

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

MoC's FOR SVP-INJECTABLES - RUBBERS

For potential Mutagenic/Carcinogenic compounds:

SCT: 0.15 µg/day (PQRI OINDP)

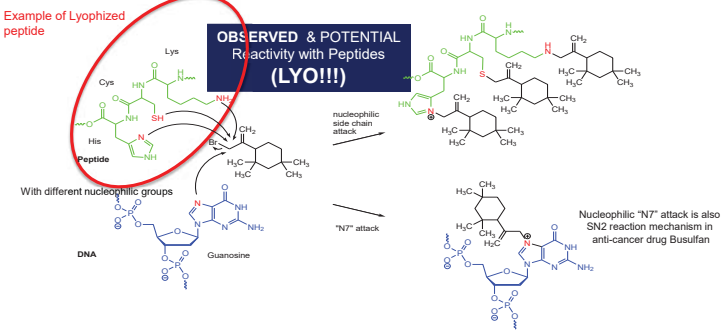
SCT: 1.5 µg/day (PQRI-PODP; ICH guideline on Genotoxic Impurities)

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

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

MoC's FOR SVP-INJECTABLES - RUBBERS

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



MoC's FOR SVP-INJECTABLES - RUBBERS

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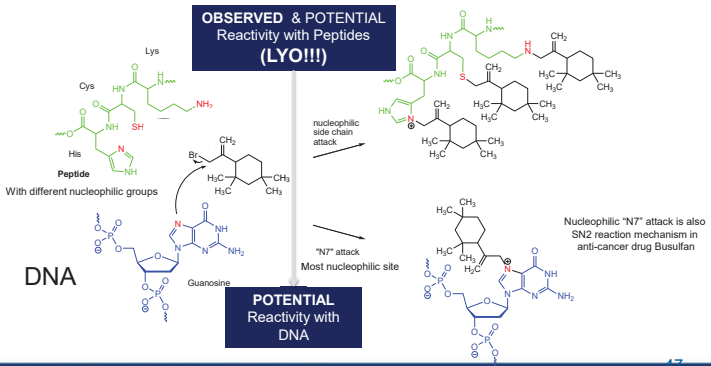


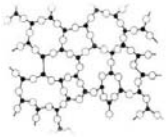
Glass

&

Glass Related Issues

Vials, Prefilled Syringes, Cartridges

Glass as Vial/Barrel Material



- SiO_2 is the backbone structure
- CaO increases the hardness and chemical resistance
- Al_2O_3 increases the chemical resistance
- Na_2O, B_2O_3 lowers the melting point
- COLOURED Glass:
  - *Fe_2O_3, TiO_2: amber glass*
  - *CuO: Blue Glass*
  - *Mn^{3+}: Violet*

PDA MoC's FOR SVP-INJECTABLES - GLASS

Glass as Vial/Barrel Material

MAJOR EXTRACTABLES FROM GLASS:

- *Alkali release (e.g. Na_2O) impacted by contact time, temperature, sterilization*
- *Silica release (Si_2O) impacted by contact time, pH (alkaline!) temperature, sterilization*

MINOR EXTRACTABLES FROM GLASS:

- *K (K_2O), B (B_2O_3), Ca (CaO), Al (Al_2O_3) more in Alkaline environment!*

Connecting People, Science and Regulation®

PDA MoC's FOR SVP-INJECTABLES - GLASS

Glass as Barrel Material

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

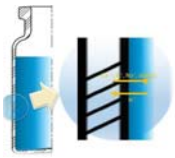
Exchange of Na^+ with H^+ :

Injected before annealing

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

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

Removed by rinsing



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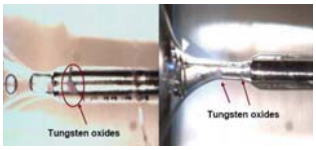
PDA MoC's FOR SVP-INJECTABLES - GLASS

Glass as Barrel Material

TUNGSTEN RESIDUES

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



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Glass as Barrel Material

GLUE RESIDUES

- *Glue is used to glue in the staked needle into the PFS-system*
- *Prolonged contact with a drug product may release glue components*
- *Target compounds may depend upon the glue used.*
  (e.g. Loctite 3345, Loctite 3081, or other grades)

Glass as Barrel Material – Related Compound

1. PRODUCT AND COMPANY IDENTIFICATION

Product name: Loctite 3345
Product type: Ultraviolet adhesive

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

IDH number: 256930
Item number: 33417
Region: United States
Contact information:
Telephone: 860.571.5100
MEDICAL EMERGENCY Phone: Poison Control Center
1-877-671-4608 (toll free) or 1-303-592-1711
TRANSPORT EMERGENCY Phone: CHEMTREC
1-800-424-9300 (toll free) or 1-703-527-3887
Internet: www.henkelna.com

3. COMPOSITION / INFORMATION ON INGREDIENTS

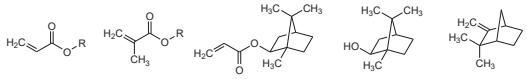
Hazardous components	CAS NUMBER	%
Polyurethane Methacrylate Resin	Proprietary	30 - 60
Tetrahydrofurfuryl methacrylate	2455-24-5	10 - 30
Hydroxyalkyl methacrylate	27813-02-1	10 - 30
Acrylic acid	79-10-7	5 - 10
High boiling methacrylate	7534-94-3	5 - 10
Propylidynetrimethyl trimethacrylate	3290-92-4	1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

Glass as Barrel Material – Related Compounds

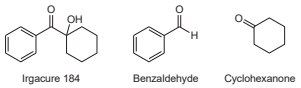
EXTRACTABLES RELATED TO GLASS BARRELS:

GLUE RESIDUES

Base Polymer



UV curing / activation

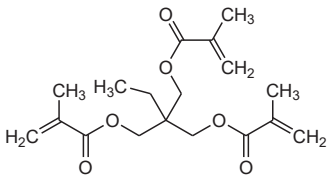


Glass as Barrel Material – Related Compounds

EXTRACTABLES RELATED TO GLASS BARRELS:

GLUE RESIDUES

The key indicator compound TMPTMA



MoC's FOR SVP-INJECTABLES - GLASS

Glass as Barrel Material – Related Compounds

SILICONE OIL RESIDUES

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

Barrel Materials

Polypropylene (PP)

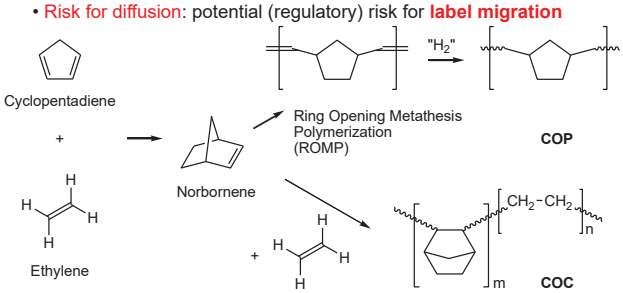
Cyclic Olefin (Co-)Polymer COC/COP

Glass

MoC's FOR SVP-INJECTABLES – COP/COC

COP: Cyclic Olefin Polymers
COC: Cyclic Olefin Copolymers

- Relatively Clean Materials
- High Tg, rigid materials
- However, low gas barrier (O_2) properties
- Risk for diffusion: potential (regulatory) risk for **label migration**



CRITICAL PARTS OF A POLYMER SYRINGE WRT E/L

PRIMARY PACKAGING (Direct Contact between DP and Material):

- The Barrel: COC, COP, PP
- The Piston: Rubber
- The Tip Cap: Rubber
- The Needle

} Same Concern as for Glass PFS

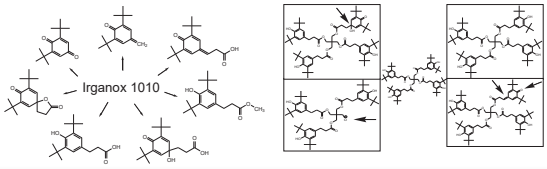
SECONDARY PACKAGING (No Direct Contact between DP and Material):

- *The Needle Shield (should it be considered as primary or secondary?)*: Rubber
- **The Label:** Adhesive, Ink, other Label Components
- In some Cases: The Lacker
- In some Cases: The Packaging of the Syringe (Overwrap, Tubs,...)

} Specific for Polymer PFS!

TYPICAL COMPOSITION OF **COMMERCIAL POLYMERS,**
e.g. For Barrel Manufacture

- Additives *(BHT, Irganox 1010, Stearates, Pigments, Clarifyers...)*
- Residues *(Monomers, Solvent Residues, Processing Residues..)*
- Oligomers *(Mainly for PP)*
- Potential Degradation Compounds from Polymers
  - *Organic Acids, Aldehydes, Ketones, Alcohols, Chain Scission Fragments...*
- Degradation Compounds from Polymer Additives

Example: 

Regulatory Requirements for Secondary Packaging

➢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."

SECONDARY PACKAGING

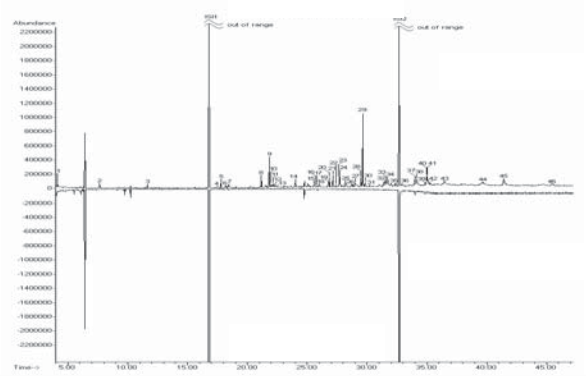
➢**Label**

- ➢ Adhesive
- ➢ paper
- ➢ Ink
- ➢ Varnish

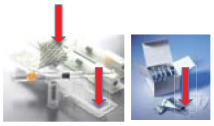
Typical extractable compounds:

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)

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



SECONDARY PACKAGING

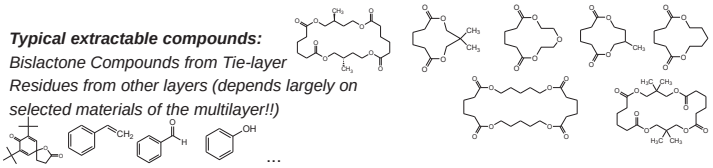


➢ **Overwrap/Overpouch/Blister**

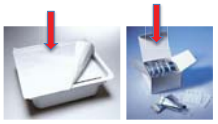
(to compensate for potential lower barrier properties of the Polymer)

- ➢ 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!!)



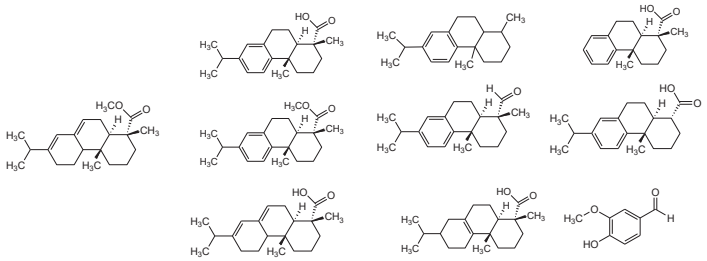
SECONDARYY PACKAGING



➢ **Tubs** for Nested Syringes (eg Tyvek)

➢ **Carton / Paper *(may also from label)***:

Example Structures of abietic acids / abietates (& Vanillin)



3. **Container/Closure Systems for SVP's:**
Information Relevant
to the Design of an E&L Study

3. Container/Closures for SVP's

1.Vials:

3. Container/Closures for SVP's

VIALS for
Liquid Drug Products or 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 **Drug Product** Solution
      - Potential Diffusion of Compounds through rubber, into solution
      - Temperature
    - ✓ VOC, SVOC and NVOC & some metals may cause a **Safety Issue**
    - ✓ VOC, SVOC, NVOC, Silicone Oil and some Metals may also be **Reactive** e.g. with reconstituted DP: also potential Performance & **Quality Issue**!
    - ✓ Also, Ions may need to be "checked off"...

3. Container/Closures for SVP's

LYO-CAKE VIAL

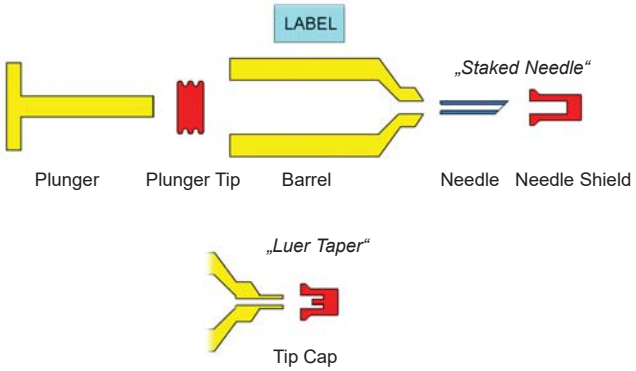
- Sources of impurities, coming from packaging
  - **Glass**: Metals (may not be necessary to be studied in EXT Study, if glass composition is available, direct assessment in LEA study)
  - **Rubber Closure:**
    - ✓ **No Direct Contact** between DP and Closure (upright)
    - ✓ **HOWEVER:** Release 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.

3. Container/Closures for SVP's

2. Pre-Filled Syringe:

3. Container/Closures for SVP's

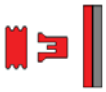
PRE-FILLED SYRINGE: COMPOSING PARTS



3. Container/Closures for SVP's

BARREL –
Glass, COC/COP, PP, Silicone Oil, ...

NEEDLE –
Metals, Tungsten (W), Needle Glue, ...



RUBBER SEALINGS (Plunger Tip, Tip Cap, Disks) -
Rubber, Silicone, ...

SECONDARY (Needle Shield, Label, Stem, ...) –
Rubber, Label Adhesive, ...

3. Container/Closures for SVP's

Pre-Filled Syringes

- **BARREL**: ***Metals*** (may not be necessary to be studied in EXT Study, if glass composition is available, direct assessment in LEA study) ***Silicone Oil*** residues may cause protein aggregation
- **Rubber Plunger** ***(very similar to rubber stopper for vial):***
  - ✓ Typically, higher migration when solution is in contact
  - ✓ Migration will be determined by:
    - Solubility of leachables in **Drug Product** Solution
    - Potential **Diffusion of Compounds through rubber**, into solution
    - **Temperature**
  - ✓ VOC, SVOC and NVOC may cause a safety issue
  - ✓ VOC, SVOC, NVOC, Silicone Oil and some Metals may also be **Reactive** with reconstituted DP: also potential Performance & Quality Issue!
  - ✓ Also, Ions may need to be "checked off"...
  - ✓ Coated versus Non-Coated plungers

3. Container/Closures for SVP's

Pre-Filled Syringes

- **GLUE for staked needle**: Glue residues may for protein denaturation
- **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.

3. Container/Closures for SVP's

Concern for – Glass PFS - Polymer PFS	Concern for – Glass PFS	Concern for – Glass PFS	Concern for – Glass PFS	Concern for - Polymer PFS	Concern for - Polymer PFS
(COATED) RUBBER	NEEDLE GLUE	TUNGSTEN (W)	GLASS BARREL	COC/COP/PP BARREL	LABEL (ADHESIVE)
MONOMER REMAINDERS & POLYMER FRAGMENTS FILLERS: *Clay, Talc, Carbonates…* ANTIOXIDANTS: *BHT, Irganox 1010, Irgafos 128, ...* CURING AGENTS: *S,S-Donors, Phenol-Formaldehyde…* ACTIVATORS: *ZnO / Stearic Acid* ACCELERATORS: *Carbamates, Sulfenamides…* OTHERS: *Pigments, Stabilizers, Release agents…*	- POLYMER FRAGMENTS - UV CURING-ACTIVATORS	A Tungsten pin is used in the production of glass pre-filled syringes to keep the syringe hub open (cavity where the staked needle is glued in)	Major: Silica (SiO_2) Alkali (e.g. Na_2O) Minor: K (K_2O), B (B_2O_3), Ca (CaO), Al (Al_2O_3) Colored glass: Fe_2O_3,TiO_2,CuO, Mn^{3+} Sulfate (from dealkalization) Silicone oil (provides lubricity)	POLYMER FRAGMENTS SOLVENTS ANTIOXIDANTS: *BHT, Irganox 1010, ...* ACID SCAVENGERS: *Stearate,...* LUBRICANTS: *FA Esters, ...* WAXES SLIP ADDITIVES: *Erucamide, Oleamide, ...* PLASTICIZERS RELEASE AGENTS PIGMENTS Optional: Silicone Oil	Permeable Plastic Materials (e.g. PP, ...) INK and ADHESIVE constituents in a complex composition, but at low concentrations POLYMER FRAGMENTS, SOLVENTS, PHOTO-INITIATORS, STABILIZERS, TACKIFIERS, ... *e.g. Acrylates, PVA, NR, Benzophenone, Irgacure 184, Irgacure 651, Irganox 1010, Dehydroabietic Acid, DCHP, TBPP, Siloxanes, ...* ***Potential Concern: SECONDARY PACKAGING***

Piston / Needle Shield / Tip Cap

3. Container/Closures for SVP's

3. Cartridges

3. Container/Closures for SVP's

Cartridges

- **BARREL**: ***Metals*** (may not be necessary to be studied in EXT Study, if glass composition is available, direct assessment in LEA study) ***Silicone Oil*** residues may cause protein aggregation
- **Cartridge Plunger (same as for PFS!):**
  - ✓ Typically, higher migration when solution is in contact (inverted)
  - ✓ Migration will be determined by:
    - Solubility of leachables in Reconstitution Solution (typically inorganic aqueous solution (*typically low solubility for most non-polar organic compounds*)
    - Potential Diffusion of Compounds through rubber, into solution
    - Temperature
  - ✓ VOC, SVOC and NVOC may cause a safety issue
  - ✓ VOC, SVOC, NVOC, Silicone Oil and some Metals may also be **Reactive** with reconstituted DP: also potential Performance & Quality Issue!
  - ✓ Also, Ions may need to be "checked off"...

3. Co[illegible]/Closures for SVP's

Cartridges

- **Sealing Disk:**
  - ✓ Typically, a sealing disk is a **two-layered** system
  - ✓ The **inner layer** has **product contact** (primary contact), should be the focus of the investigation
  - ✓ *"One Sided" extraction* mimics the product contact, avoids contribution of the outer layer
  - ✓ Complete Extraction of the 2 layered sealing disk can be considered as "Worst Case"
  - ✓ Both approaches can be taken and have found regulatory acceptance

3. Container/Closures for SVP's

4. Administration of Reconstituted Drug Product:

Disposable Syringe

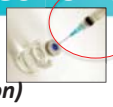
IV-Bag System (+Administration Set)

Pump System

SEE CASE STUDY LATER

3. Container/Closures for SVP's

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)).*
- ***"In Use" Stability Studies may be required***

3. Container/Closures for SVP's

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,...)

3. Container/Closures for SVP's

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

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.

Case Study

CASE STUDY:

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

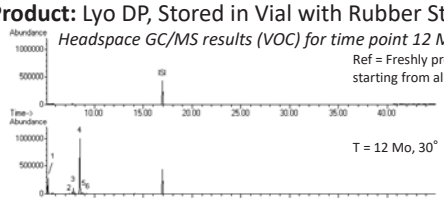
Purpose of Study:

- 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 Study

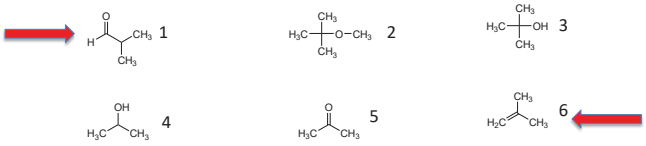
1. Drug Product: Lyo DP, Stored in Vial with Rubber Stopper

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



Ref = Freshly prepd lyo soln, starting from all ingredients

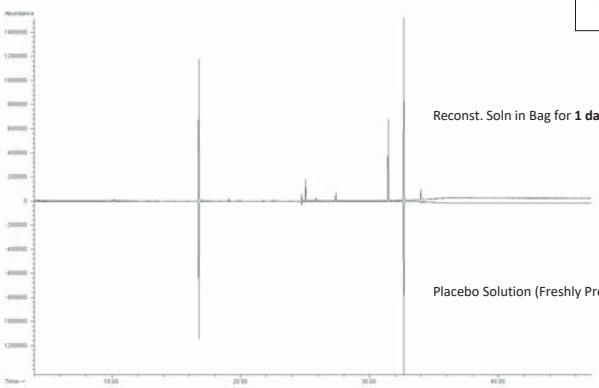
T = 12 Mo, 30° C, 75%RH



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

Case Study

2. Administration: I.V. Bag

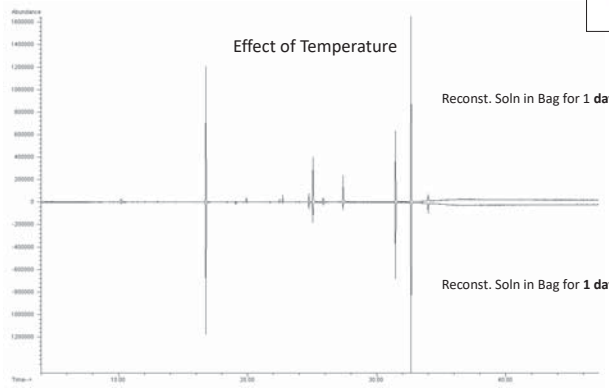


Reconst. Soln in Bag for **1 day** at **5° C**

Placebo Solution (Freshly Prepared)

PDA Case Study

2. Administration: I.V. Bag



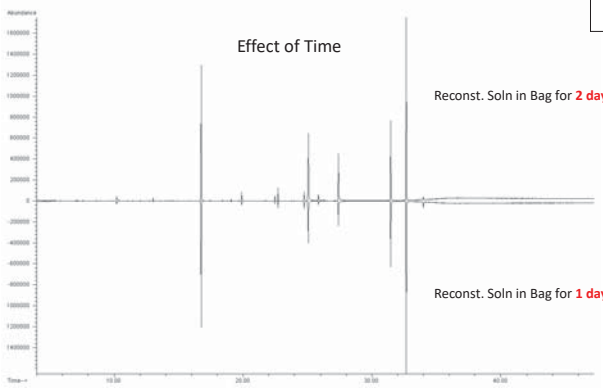
Effect of Temperature

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

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

PDA Case Study

2. Administration: I.V. Bag



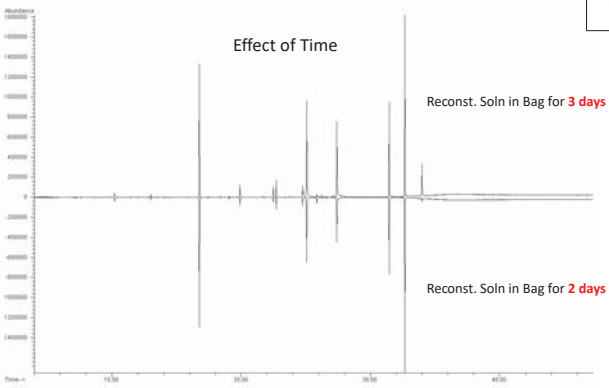
Effect of Time

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

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

PDA Case Study

2. Administration: I.V. Bag



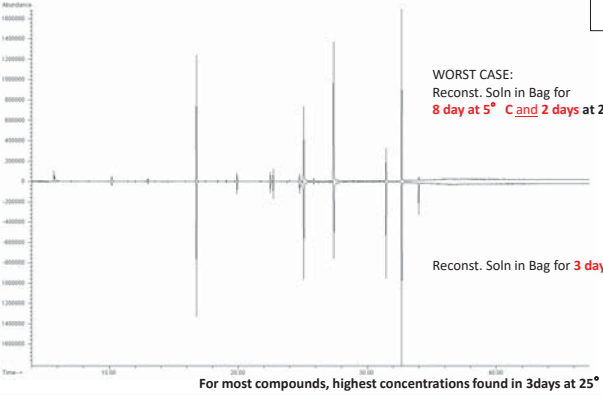
Effect of Time

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

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

PDA Case Study

2. Administration: I.V. Bag

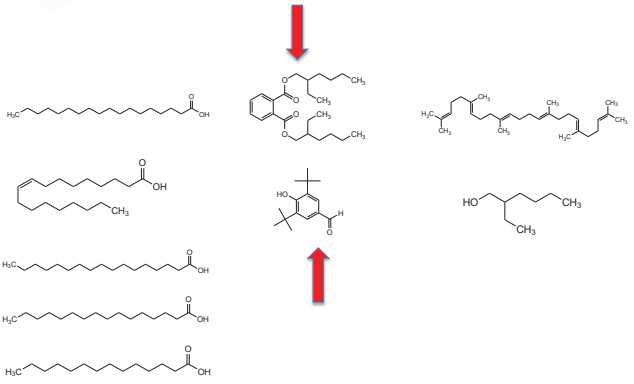


WORST CASE:
Reconst. Soln in Bag for
8 day at 5° C and **2 days at 25° C**

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

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

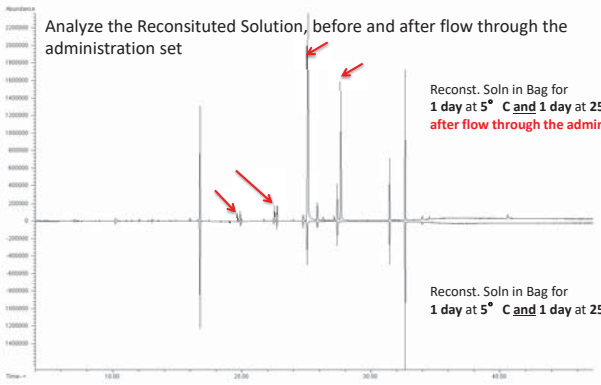
PDA Case Study



PDA Case Study

3. Administration: Contribution of Administration Set

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

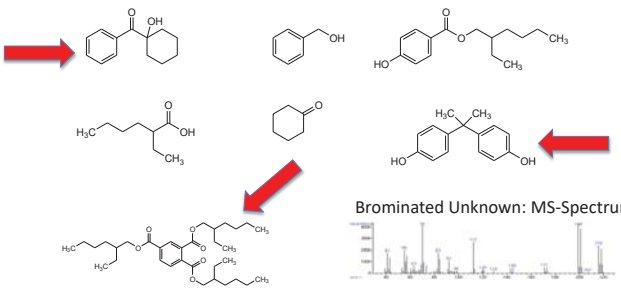


Reconst. Soln in Bag for **1 day** at **5° C** and **1 day** at **25° C** **after flow through the administration set**

Reconst. Soln in Bag for **1 day** at **5° C** and **1 day** at **25° C**

PDA Case Study

3. Administration: Contribution of Administration Set



Brominated Unknown: MS-Spectrum

PDA ANY QUESTIONS?

For further questions, please contact:
piet.christiaens@toxikon.be
http://www.toxikon.be/extractables-leachables-parenteral-injectables.html