SETTING UP EXTRACTABLE / LEACHABLE STUDIES

PDA TRAINING COURSE
EXTRACTABLES – LEACHABLES
ROME
01 – 02 March, 2018

Dr. Piet Christiaens
Content

1. The Chemical Assessment Triad
2. (Controlled) Extraction Studies
3. Simulation Studies
4. Leachable Studies
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
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

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

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

**Finished Product Assessment**

Discover, identify, and quantitate leachables that have migrated from the contact material or system and into the finished pharmaceutical product
1. THE CHEMICAL ASSESSMENT TRIAD

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

**Material Screening and Selection**
Characterize candidates and assess their worthiness for application; focus on composition

**Finished Product Assessment**
Discover, identify, and quantitate leachables that have migrated from the contact material or system and into the finished pharmaceutical product

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**
Find + Identify all leachables

Material Screening and Selection
Characterize candidates and assess their worthiness for application; ingredients as probable extractables and tentative leachables

Simulation Study
Worst-case simulation; extractables as probable leachables

Product Assessment
Actual case; measurement of confirmed 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
BUT no standard approach, e.g. packaging ↔ manufacturing

Packaging:
- Controlled extraction study:
Characterize composition candidates

Manufacturing:
- Standard tests:
Potential to adversely affect safety

**1. THE CHEMICAL ASSESSMENT TRIAD**

**Material Screening and Selection**

*Controlled extraction study; screening and selection, ingredients as probable extractables and tentative leachables*

**Simulation Study**

*Simulated extraction study; worst-case safety assessment, extractables as probable leachables*

**Product Assessment**

*Actual case safety assessment; measurement of targeted, confirmed leachables*

**Material Screening and Selection**

*Subject candidates to standard methods (e.g., USP <661>) and use results to select viable options*

**Simulation Study**

*Worst-case simulation; extractables as probable leachables*

*Migration study, measure targeted leachables*

**Product Assessment**

*Actual case; measurement of confirmed leachables*
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

1. THE CHEMICAL ASSESSMENT TRIAD

**Material Screening and Selection**
Material characterization; perform controlled extraction study to establish composition, eliminate potential “bad actor” materials

**Simulation Study**
Identification of target leachables; extractables as probable leachables

**Product Assessment**
Actual case; measurement of confirmed leachables

**Material Screening and Selection**
Material characterization; perform controlled extraction study to establish composition, eliminate potential “bad actor” materials

**Simulation Study**
Worst-case simulation; extractables as probable leachables

**Product Assessment**
Actual case; measurement of confirmed leachables
1. THE CHEMICAL ASSESSMENT TRIAD

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

Material Screening and Selection
Characterize candidates and assess their worthiness for use, ingredients as probable extractables and tentative leachables

Material Characterization
Controlled extraction study

Risk Estimation
General tests to estimate risk

Simulation Study
Worst case simulation; extractables as probable leachables

Migration study, measure target leachables
Screening study, discover, ID, and measure leachables

Product Assessment
Actual case; measurement of confirmed leachables
1. THE CHEMICAL ASSESSMENT TRIAD

**Material Characterization:** Ingredients as Probable Extractables and Tentative Leachables

Filter out bad materials
No safety assessment

**Simulation Study:** Extractables as Probable Leachables

Greatest possible concentration
Worst case safety impact

**Product Assessment:** Extractables as Confirmed Leachables

Real case safety impact
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. Material Characterization
1. THE CHEMICAL ASSESSMENT TRIAD

- Ingredients
- Bulk Plastic

Characterize, Ingredients → Screen → Acceptable

Reject or Revise

1. Material Characterization
2. Simulation study

AET = TTC/SCT

Derek?
2. Simulation study
3. Migration study
3. Migration study
Key for success: collaboration of Product developers, Analytical scientists, and toxicological experts.
2. THE EXTRACTION STUDIES

STEP 1
Material Characterization via Controlled Extraction Studies
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.
These Two Documents are 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.

**Parenteral and Ophthalmic Drug Products (PODP) Leachables and Extractables Working Group**

**Issued and Effective**

September, 2011

- Study Protocol – Stage 2
  - Experimental Protocol for Simulation Study of Blow-Fill-Seal (BFS) PODP Container Closure Systems

- Study Protocol – Stage 1
  - Amendment #1
  - Experimental Protocol for Qualitative Controlled Extraction Studies on Material Test Articles Representative of Prefilled Syringe (PFS) and Small Volume Parenteral (SVP) Container Closure Systems
DEPENDING UPON THE DESIGN OF E-STUDIES:

1. **LOW Nr** of extractables

2. **HIGH Nr** of extractables

HOW CAN THIS BE HARMONIZED?
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
What is the **PURPOSE** of an Extraction Study?

- Facilitates "**Timely Development**" of safe 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 the 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 Alternative
  - REMARK: Extraction at High T with DP/DPV lead to degradation (eg Polysorbate)
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
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 too mild
- Difficult to select the right set of extraction conditions (e.g. Extraction time, temperature!)
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
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

...
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.

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?

<table>
<thead>
<tr>
<th>“Impurities Profile” of a material-MATERIAL CHARACTERIZATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exhaustive Extraction Solvents</strong></td>
</tr>
<tr>
<td>PQRI OINDP: Isopropanol, Hexane, Dichloromethane</td>
</tr>
<tr>
<td>BPSA: EtOH</td>
</tr>
</tbody>
</table>

- Allows to determine the “TOTAL POOL” of Material Impurities

<table>
<thead>
<tr>
<th>Risk Assessment of Total Conc. of Material Impurities</th>
</tr>
</thead>
<tbody>
<tr>
<td>• More Complete</td>
</tr>
<tr>
<td>• More Challenging</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Incorporate a level of “Simulation” already in the Extraction Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exaggerated Extraction Solvents</strong></td>
</tr>
<tr>
<td>PQRI PODP: WFI pH 2.5, WFI pH 9.5, IPA/UPW 50/50</td>
</tr>
<tr>
<td>BPSA: UPW</td>
</tr>
<tr>
<td>BPOG: 0.5N NaOH, 0.1M Phosphoric Acid, WFI (neutral), 5 M NaCl, EtOH/WFI 50/50, 1% Tween</td>
</tr>
</tbody>
</table>

- Risk Assessment is |
- • More Realistic wrt final Use |
- • Does not really assess “Total Pool”
2. THE EXTRACTION STUDIES

<table>
<thead>
<tr>
<th></th>
<th>UPW</th>
<th>UPW</th>
<th>UPW/IPA (50/50)</th>
<th>IPA</th>
<th>HEXANE</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>2.5</td>
<td>9.5</td>
<td>(50/50)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Acid Extractables**

**Base Extractables**

**Intermediate Polarity**

**Non-Polar**

**MATERIAL CHARACTERIZATION & SIMULATION (NON AQUEOUS 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!!
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”**

<table>
<thead>
<tr>
<th>pH 2.5</th>
<th>pH 9.5</th>
<th>UPW/IPA 50/50</th>
<th>IPA</th>
<th>HEXANE</th>
</tr>
</thead>
</table>

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

Rubber

HDPE

DCM BY REFLUX

EtOH BY REFLUX
2. THE EXTRACTION STUDIES

- **Natural Rubber**
  - 24h
  - 72h

- **Silicone**
  - 24h
  - 72h

- **HDPE**
  - 24h
  - 72h
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)
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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 reflux 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
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
“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,
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 1 h

- 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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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...)

2. THE EXTRACTION STUDIES
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
2. THE EXTRACTION STUDIES

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 Tailored Analyses for specific “known” Compounds, present in specific materials
  - Derivatisation GC/MS
  - S8 for (certain) rubbers
  - TMPTMA (HPLC) for adhesives
  - Acrylic Acid
  - Formaldehyde
  - ...
## 2. THE EXTRACTION STUDIES

<table>
<thead>
<tr>
<th>Categories</th>
<th>Examples</th>
<th>Techniques Used</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anions</strong></td>
<td>Fluoride, Acetate, Formate, Chloride, Nitrite, Bromide, Nitrate, Sulphate, Phosphate</td>
<td>Ion Chromatography</td>
</tr>
<tr>
<td><strong>Metals/Cations</strong></td>
<td>Ag, Al, Ba, Ca, Cd, Co, Cr, Cu, Fe, In, K, Mg, Mn, Na, Ni, Pb, Si, Sr, Ti, Zn...</td>
<td>ICP-OES or ICP-MS</td>
</tr>
<tr>
<td><strong>Volatile Organic Compounds (VOCs)</strong></td>
<td>Monomers, solvents, polymer treatment residues, smaller polymer breakdown products</td>
<td>Headspace GC/MS SCREENING (semi-quantitative)</td>
</tr>
<tr>
<td><strong>Semi-Volatile Organic Compounds (SVOCs)</strong></td>
<td>Lubricants, Plasticizers, anti-oxidants, polymer degradation products</td>
<td>GC/MS SCREENING (semi-quantitative)</td>
</tr>
<tr>
<td><strong>Non-Volatile Organic Compounds (NVOCs)</strong></td>
<td>Polymer additives: anti-oxidants, nucleating agents, UV-stabilizers, fatty acids, waxes, Polymer Degradation Products</td>
<td>LC-UV UPLC-HRAM SCREENING</td>
</tr>
<tr>
<td><strong>Sulfur</strong></td>
<td>Cross Linking, Lubrification</td>
<td>HPLC-UV GF-AAS</td>
</tr>
</tbody>
</table>
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 Alkalineic compounds in Aqueous Extracts

**Conductivity**: Release of Salts in Aqueous Extracts

... 

- These Techniques and Methods only allow a limited identification (FTIR) or no Identification at all.
- TOC reconciliation with Chromatographic Methods may be considered, but is always a Challenge.
Safety Evaluation of Extractable Results: Learning from the PQRI PODP Threshold Approach
"Threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and non-carcinogenic toxic effects"
Translate SCT into Analytical Thresholds for Extractable Studies

Taking into account:
- Total \( N \)° of doses / packaging
- Max. \( N \)° of doses administered / day
PQRI: SUGGESTED THRESHOLDS FOR PARENTERAL & OPHTHALMIC APPLICATIONS – current status

<table>
<thead>
<tr>
<th></th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold Level (µg/day)</td>
<td>50 (to be confirmed)</td>
<td>5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

**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.
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
- ...

Connecting People, Science and Regulation®
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
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
AET: **ANALYTICAL EVALUATION THRESHOLD**

Formula used (see PQRI recommendations):

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

Class I: 

\[
\text{Est. AET} = \frac{50 \, \mu g \, / \, day}{1 \, \text{dose} \, / \, day} \cdot \frac{1 \, \text{dose}}{1 \, \text{Barrel}} = 50 \, \mu g \, / \, \text{barrel}
\]

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

50% uncertainty for screening methods
Further Calculations will give the following AET levels for the respective Classes:

<table>
<thead>
<tr>
<th>Class</th>
<th>Threshold (µg/day)</th>
<th>Final AET (µg/barrel)</th>
<th>Final AET (mg/Kg)</th>
<th>Final AET (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>50</td>
<td>25</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Class II</td>
<td>5</td>
<td>2,5</td>
<td>1,2</td>
<td>0,5</td>
</tr>
<tr>
<td>Class III</td>
<td>1,5</td>
<td>0,75</td>
<td>0,37</td>
<td>0,15</td>
</tr>
</tbody>
</table>

Barrel weight: 2g
Extr. Ratio: 1 barrel/5 mL
2. THE EXTRACTION STUDIES

Typical Results for an Exhaustive Extraction on a Polymer Barrel

<table>
<thead>
<tr>
<th>COMPOUND #</th>
<th>EXT result mg/L extract</th>
<th>EXT result mg/Kg Barrel</th>
<th>EXT result µg/Barrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPOUND #1</td>
<td>0,1</td>
<td>0,25</td>
<td>0,5</td>
</tr>
<tr>
<td>COMPOUND #2</td>
<td>0,2</td>
<td>0,5</td>
<td>1</td>
</tr>
<tr>
<td>COMPOUND #3</td>
<td>1,25</td>
<td>3,13</td>
<td>6,3</td>
</tr>
<tr>
<td>COMPOUND #4</td>
<td>2</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>COMPOUND #5</td>
<td>0,4</td>
<td>1,0</td>
<td>2,0</td>
</tr>
<tr>
<td>COMPOUND #6</td>
<td>0,25</td>
<td>0,63</td>
<td>1,3</td>
</tr>
<tr>
<td>COMPOUND #7</td>
<td>13</td>
<td>32,5</td>
<td>65</td>
</tr>
<tr>
<td>COMPOUND #8</td>
<td>0,1</td>
<td>0,25</td>
<td>0,5</td>
</tr>
<tr>
<td>COMPOUND #9</td>
<td>27</td>
<td>67,5</td>
<td>135</td>
</tr>
<tr>
<td>COMPOUND #10</td>
<td>0,4</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>COMPOUND #11</td>
<td>0,1</td>
<td>0,25</td>
<td>0,5</td>
</tr>
<tr>
<td>COMPOUND #12</td>
<td>5,5</td>
<td>13,8</td>
<td>27,5</td>
</tr>
<tr>
<td>COMPOUND #13</td>
<td>32,5</td>
<td>81,3</td>
<td>163</td>
</tr>
<tr>
<td>COMPOUND #14</td>
<td>1,2</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>COMPOUND #15</td>
<td>0,35</td>
<td>0,88</td>
<td>1,8</td>
</tr>
</tbody>
</table>
## 2. THE EXTRACTION STUDIES

<table>
<thead>
<tr>
<th>Compound #</th>
<th>EXT Result (mg/L)</th>
<th>Class</th>
<th>Threshold for Class (µg/day)</th>
<th>AET for Class (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.10</td>
<td>Class I</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>0.20</td>
<td>Class I</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>1.25</td>
<td>Class III</td>
<td>0.75</td>
<td>0.15</td>
</tr>
<tr>
<td>4</td>
<td>2.00</td>
<td>Class I</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>0.40</td>
<td>Class II</td>
<td>2.5</td>
<td>0.5</td>
</tr>
<tr>
<td>6</td>
<td>0.25</td>
<td>Class I</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>13.00</td>
<td>Class II</td>
<td>2.5</td>
<td>0.5</td>
</tr>
<tr>
<td>8</td>
<td>0.10</td>
<td>Class III</td>
<td>0.75</td>
<td>0.15</td>
</tr>
<tr>
<td>9</td>
<td>27.00</td>
<td>Class I</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>0.40</td>
<td>Class II</td>
<td>2.5</td>
<td>0.5</td>
</tr>
<tr>
<td>11</td>
<td>0.10</td>
<td>Class III</td>
<td>0.75</td>
<td>0.15</td>
</tr>
<tr>
<td>12</td>
<td>4.50</td>
<td>Class I</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>13</td>
<td>32.50</td>
<td>Class III</td>
<td>0.75</td>
<td>0.15</td>
</tr>
<tr>
<td>14</td>
<td>1.20</td>
<td>Class I</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>15</td>
<td>0.35</td>
<td>Class II</td>
<td>2.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>
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, further 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 classes 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
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!
## 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
- Regulatory 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
3. THE SIMULATION STUDIES

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?”

\[\text{e.g. 20\% EtOH in UPW: More Documentation is needed} \]
\[\text{Simulant = DP: Yes} \]

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

\[\text{e.g. 20\% EtOH in UPW: No, needs to be studied} \]
\[\text{Simulant = DP: Yes} \]
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 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))
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**
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
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” exercise 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 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)

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)...
4. THE MIGRATION / LEACHABLE STUDIES

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...
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
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
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...”
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
- Quantification Limit
- Accuracy in low, mid and high range\[ 100 \pm 25\% \]
- 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

<table>
<thead>
<tr>
<th>General case</th>
<th>25±2° C/ 60±5%RH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30±2° C/ 65±5%RH</td>
</tr>
<tr>
<td></td>
<td>40±2° C/ 75±5%RH</td>
</tr>
<tr>
<td>DS intended for storage in refrigerator</td>
<td>5±3° C</td>
</tr>
<tr>
<td></td>
<td>25±2° C/ 60±5%RH</td>
</tr>
<tr>
<td>DS intended for storage in freezer</td>
<td>-20±5° C</td>
</tr>
<tr>
<td>DP in semi-permeable containers</td>
<td>25±2° C/ 40±5%RH</td>
</tr>
<tr>
<td></td>
<td>30±2° C/ 35±5%RH</td>
</tr>
<tr>
<td></td>
<td>30±2° C/ 65±5%RH</td>
</tr>
<tr>
<td></td>
<td>40±2° C/ 25±5%RH</td>
</tr>
<tr>
<td>Ultralow temperature for biotech products</td>
<td>-80° C</td>
</tr>
</tbody>
</table>
4. THE MIGRATION / LEACHABLE STUDIES

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!!

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

<table>
<thead>
<tr>
<th>Type of Solution</th>
<th>Storage Time (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Pharmaceutical Matrix in Pre-filled Syringes (Test Item) at 5 ± 3 °C</td>
<td>×</td>
</tr>
<tr>
<td>Pharmaceutical Matrix in Inert Containers (Blank) at 5 ± 3 °C</td>
<td>×</td>
</tr>
<tr>
<td>Pharmaceutical Matrix in Pre-filled Syringes (Test Item) at 25 ± 3 °C</td>
<td>-</td>
</tr>
<tr>
<td>Pharmaceutical Matrix in Inert Containers (Blank) at 25 ± 3 °C</td>
<td>-</td>
</tr>
</tbody>
</table>

× = sampling time point
Example Setup of the Study
Analytical Program for Leachable study of a Pre-Filled Syringe

<table>
<thead>
<tr>
<th>TARGET COMPOUNDS</th>
<th>ANALYTICAL METHOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>VALIDATED METHOD</td>
<td>Headspace GC/MS</td>
</tr>
<tr>
<td>Volatile Organic Compounds (VOC) SCREENING</td>
<td></td>
</tr>
<tr>
<td>VALIDATED METHOD</td>
<td>GC/QQQ</td>
</tr>
<tr>
<td>Semi-Volatile Organic Compounds (SVOC) SCREENING</td>
<td>GC/MS</td>
</tr>
<tr>
<td>VALIDATED METHOD</td>
<td>LC/QQQ</td>
</tr>
<tr>
<td>Non-Volatile Organic Compounds (NVOC) SCREENING</td>
<td>UPLC/HRAM</td>
</tr>
<tr>
<td>Element Analysis</td>
<td>ICP</td>
</tr>
<tr>
<td>Anions: fluoride, chloride, and bromide</td>
<td>IC</td>
</tr>
<tr>
<td>Sulfur (S₈)</td>
<td>LC/UV</td>
</tr>
</tbody>
</table>
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
Analytical Techniques used for LEACHABLE

Specific Techniques for Monitoring Leachables at low levels:

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