SETTING UP EXTRACTABLE / LEACHABLE STUDIES

PDA TRAINING COURSE
EXTRACTABLES – LEACHABLES
VENICE
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Content

1. (Controlled) Extraction Studies
2. Simulation Studies
3. Leachable Studies

2. THE EXTRACTION STUDIES

STEP1

Material Characterization via Controlled Extraction Studies

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.

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**

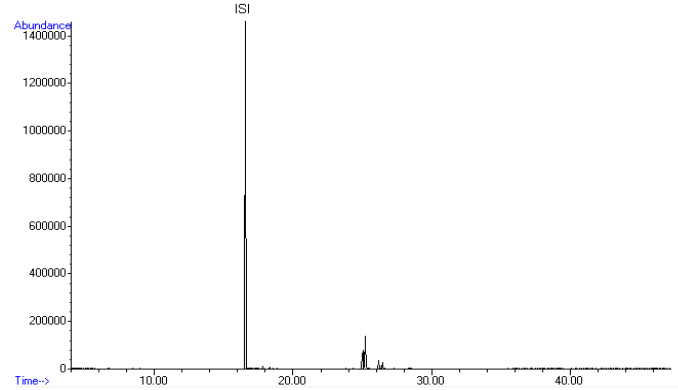
However, Justification is Needed!

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

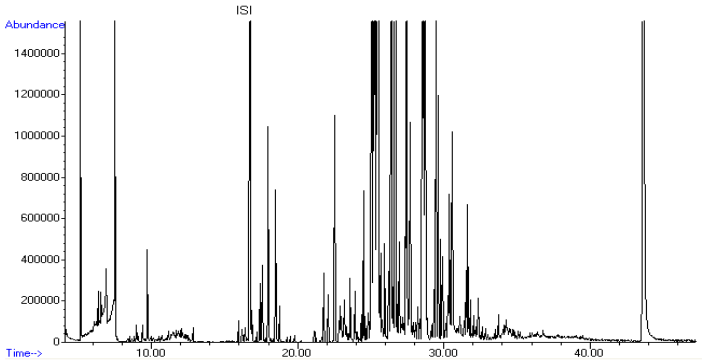
2. THE EXTRACTION STUDIES

DEPENDING UPON THE DESIGN OF E-STUDIES:

1. **LOW Nr** of extractables



2. **HIGH Nr** of extractables



HOW CAN THIS BE HARMONIZED?

2. THE EXTRACTION STUDIES

What is the PURPOSE of an Extractable 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

2. THE EXTRACTION STUDIES

What is the PURPOSE of an Extractable Study

- 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
- 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

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*

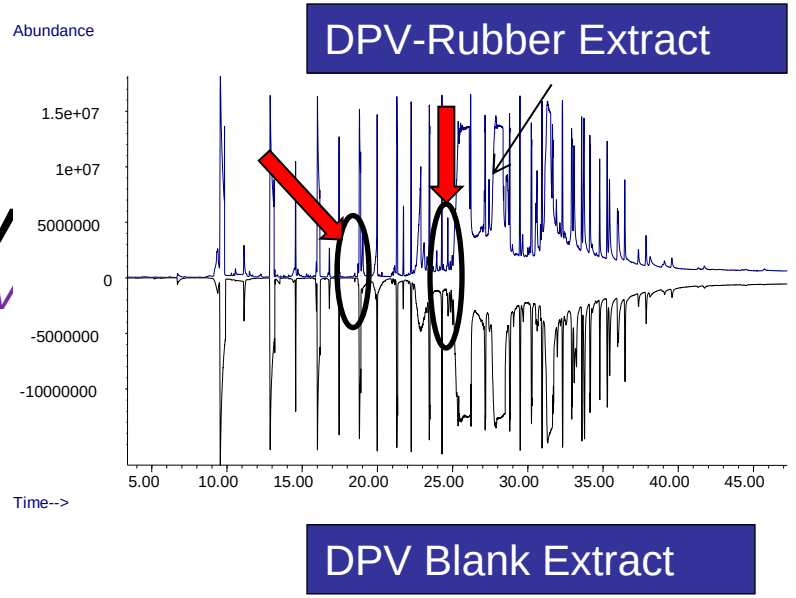
"USP <1663>: GENERATING THE EXTRACT

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

"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 <u>Simulating Solvent</u>

- *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**: **<u>NOT IDEAL</u>** TO ONLY TAKE 1 EXTRACTION SOLVENT COULD BE CONSIDERED <u>IF THE PURPOSE</u> IS TO <u>PERFROM A **SIMULATION STUDY**</u>

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.

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** 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 *(not a worst case EXT profile)*

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

Extraction Solvents

What do you want to learn from an Extraction Study?

"Impurities Profile" of a material- MATERIAL CHARACTERIZATION

Exhaustive Extraction Solvents

PQRI PDP &(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

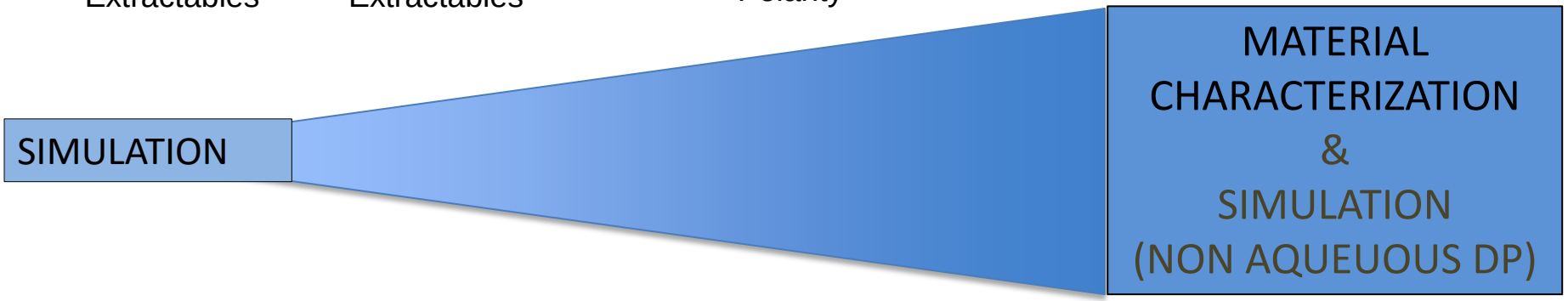
BPOG: 0.5N NaOH
0.1M Phosphoric Acid
WFI (neutral)
5 M NaCl
EtOH/WFI 50/50
1% Tween

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



REMARK: REMEMBER: THE PQRI-PODP DOCUMENT IS A RECOMMENDATION:

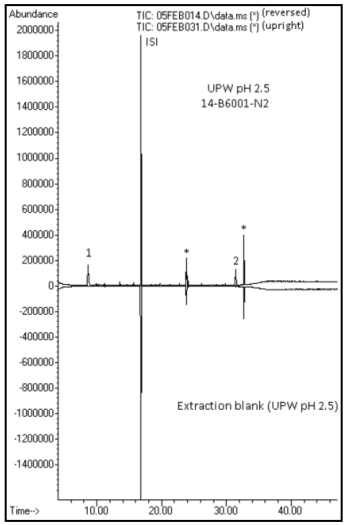
- *It is not Mandatory to ALWAYS include these 5 Extraction Solvents into the EXT Design*
- *Even the selection of solvents, or their PCHEM Properties may be Changed According to Actual Drug Product PCHEM Properties*
- *However, a Justification is always Necessary!!*

2. THE EXTRACTION STUDIES

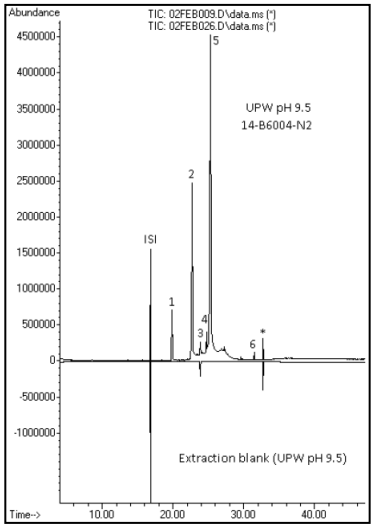
Example: *Extraction of a rubber component*

GC/MS Semi-Volatile Organic Compound "Profile"

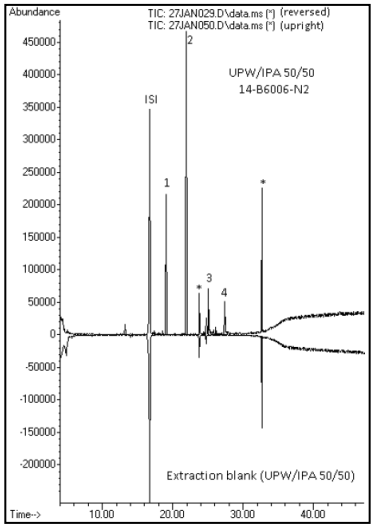
pH 2,5



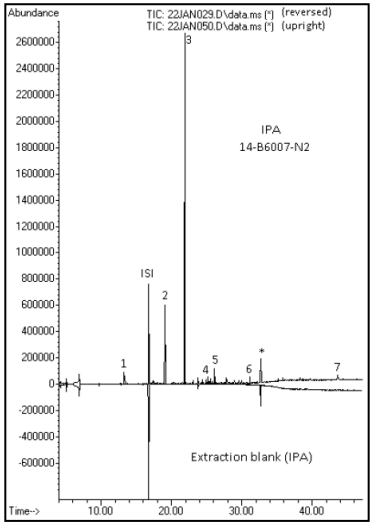
pH 9,5



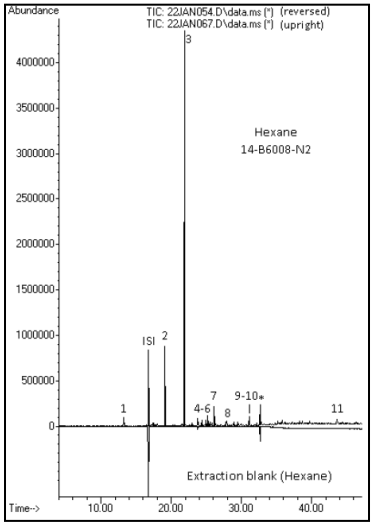
UPW/IPA 50/50



IPA



HEXANE



IS: Internal Standard for GC/MS

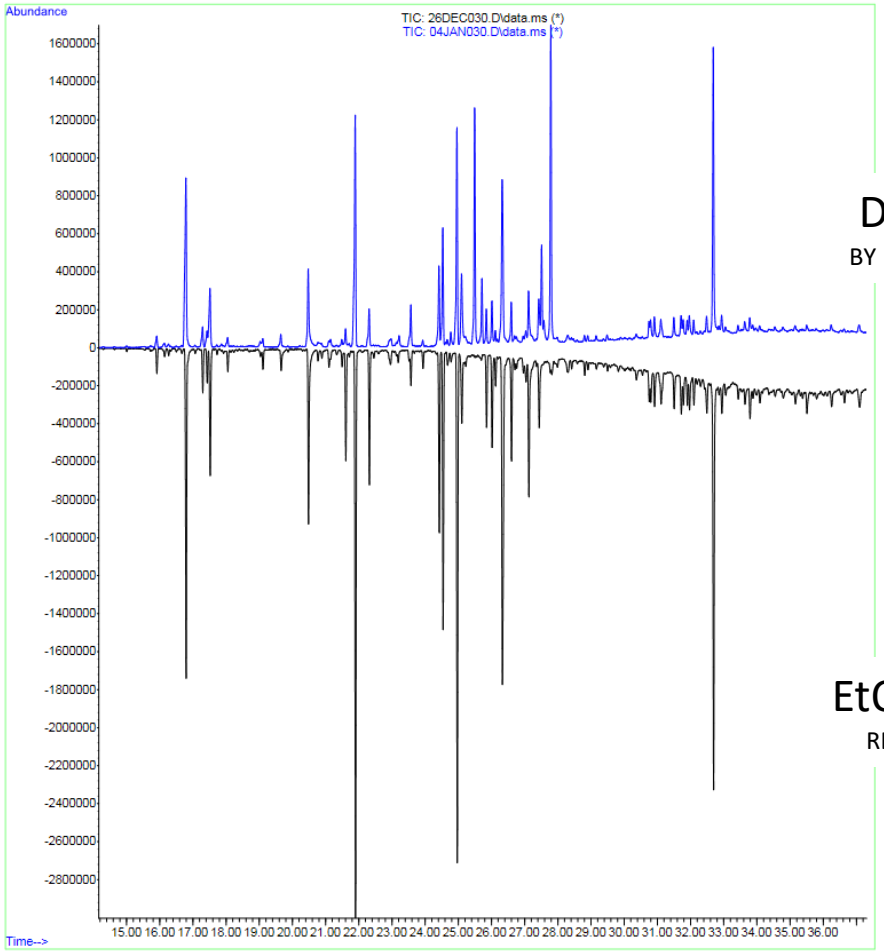
*: Internal Standard for LC/MS (not used in this GC/MS evaluation)

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

2. THE EXTRACTION STUDIES

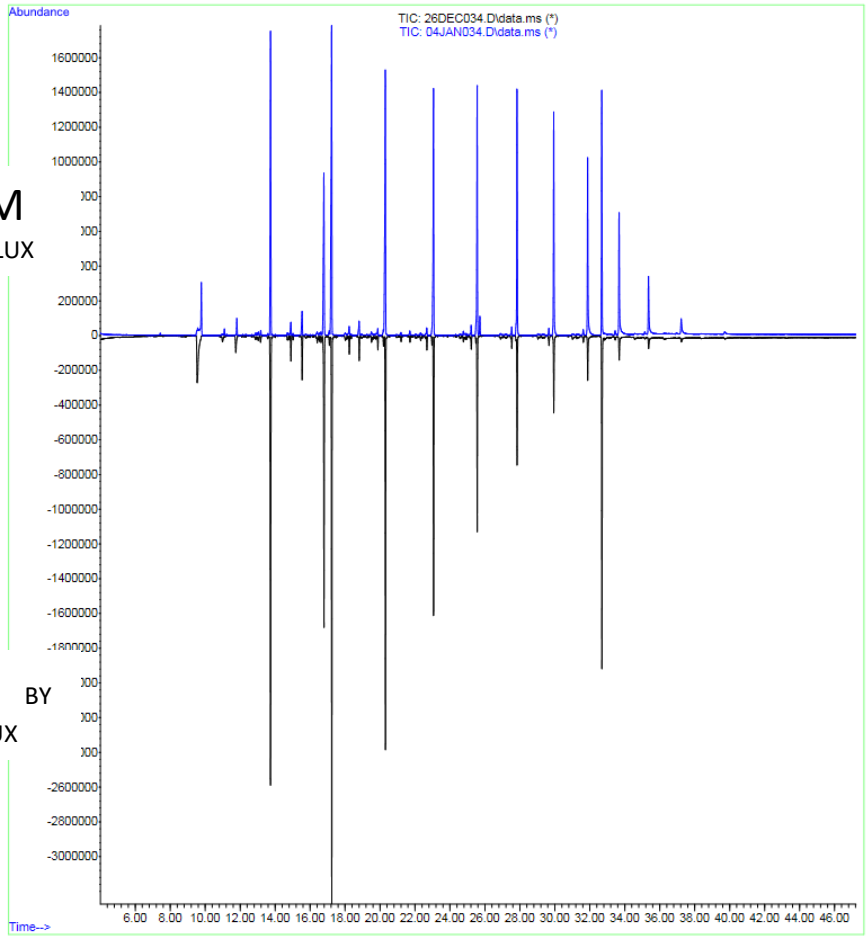
Rubber

HDPE

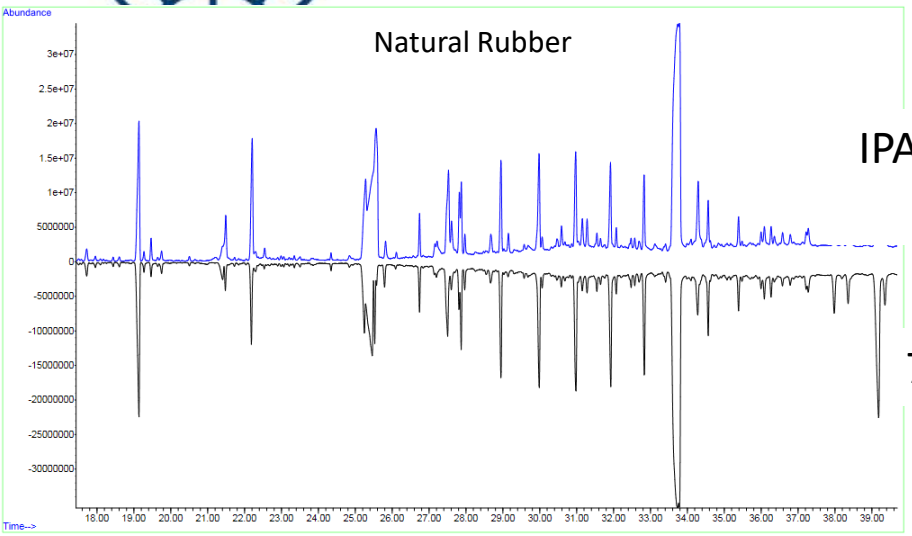


DCM
BY REFLUX

EtOH BY
REFLUX

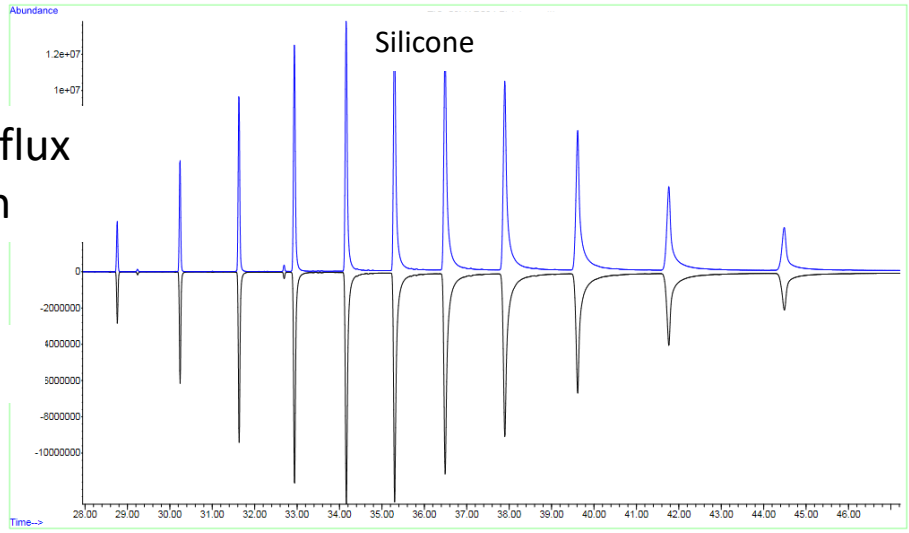


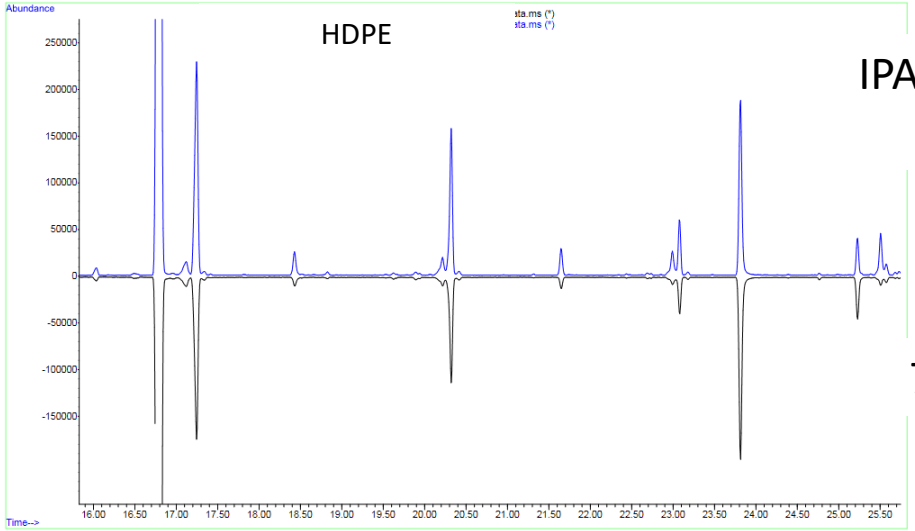
2. THE EXTRACTION STUDIES



IPA Reflux
24h

72h





IPA Reflux
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.

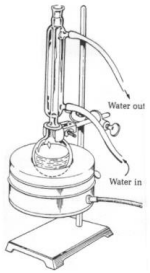
In Extraction Studies, both the Temperature and Time of the Extraction are – in large part determined by the Extraction Technique that is selected

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

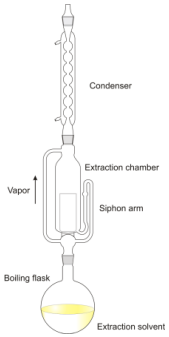
"USP <1663>: GENERATING THE EXTRACT

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

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,

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

"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

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STEP 2

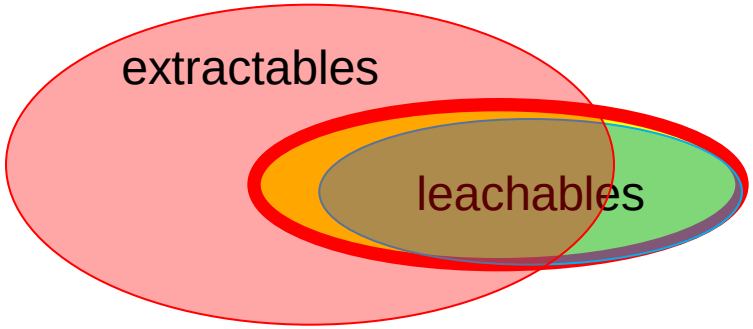
SIMULATION STUDY

Purpose of a 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"**

Conditions for 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

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

3. THE SIMULATION STUDIES

Regulatory Acceptance of SIMULATION Study

Think as a Reviewer!

"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

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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

"USP <1664>: Leachable Studies

- **TIMING:** LEA studies are especially relevant
  - During **Late Stage product development (Phase III)**
  - 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

4. THE MIGRATION / LEACHABLE STUDIES

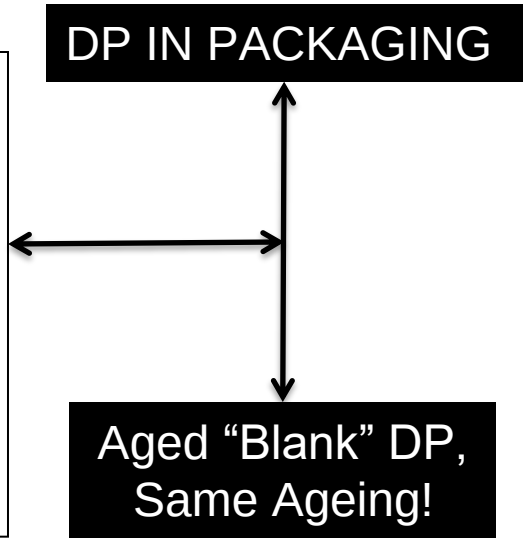
"USP <1664>: The Design of Leachable Studies

- 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!!**

4. THE MIGRATION / LEACHABLE STUDIES

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)*

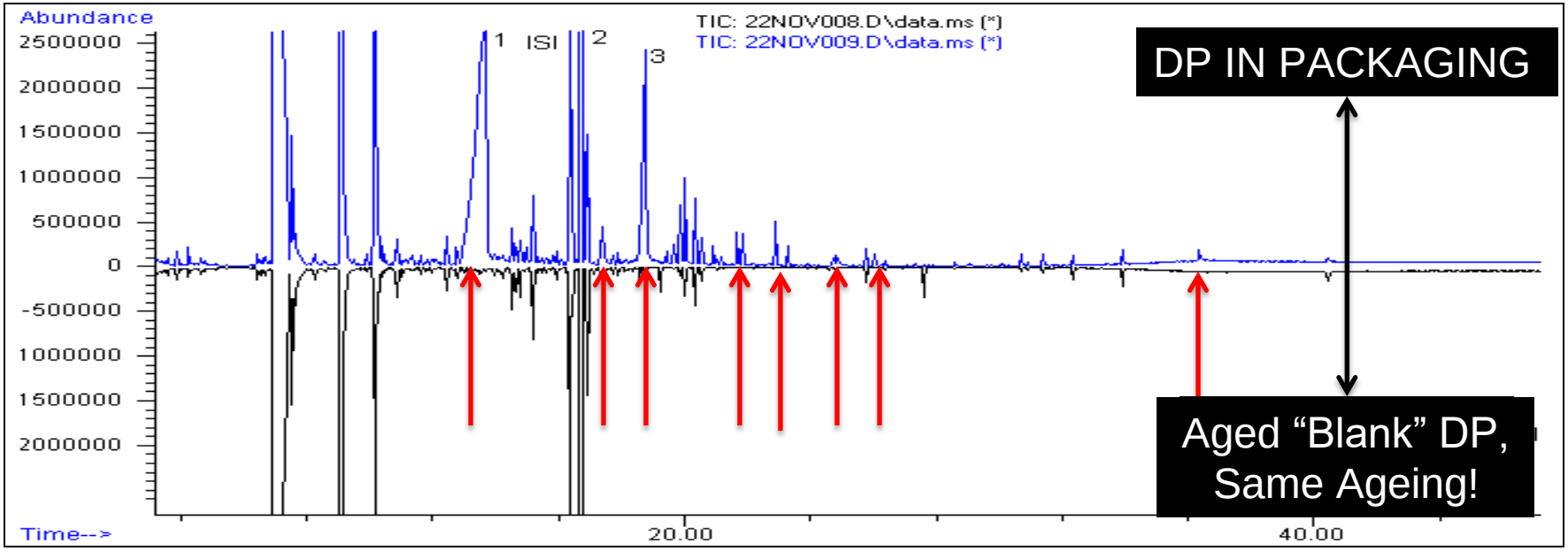


Every Compound that is present in the DP, aged in the Packaging System But NOT in the DP, aged in inert container

CONSIDERED AS LEACHABLE

This avoids that DP Degradation would be assessed as "Leachables"!!

4. THE MIGRATION / LEACHABLE STUDIES



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

"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

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

4. THE MIGRATION / LEACHABLE STUDIES

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

4. THE MIGRATION / LEACHABLE STUDIES

"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

4. THE MIGRATION / LEACHABLE STUDIES

"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

4. THE MIGRATION / LEACHABLE STUDIES

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!!

4. THE MIGRATION / LEACHABLE STUDIES

STABILITY CONDITIONS –CLIMATIC ZONES

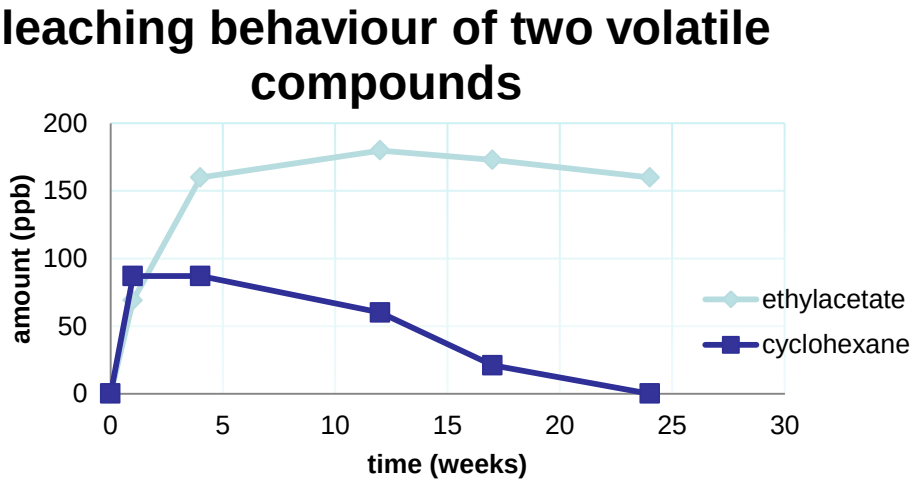
General case	**25±2° C/ 60±5%RH**
	30±2° C/ 65±5%RH
	40±2° C/ 75±5%RH
DS intended for storage in refrigerator	5±3° C
	25±2° C/ 60±5%RH
DS intended for storage in freezer	-20±5° C
DP in semi-permeable containers	25±2° C/ 40±5%RH
	30±2° C/ 35±5%RH
	30±2° C/ 65±5%RH
	40±2° C/ 25±5%RH
Ultralow temperature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

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

4. THE MIGRATION / LEACHABLE STUDIES

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

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

4. THE MIGRATION / LEACHABLE STUDIES

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*

4. THE MIGRATION / LEACHABLE STUDIES

FDA Requirement

(see Dr. Dan Mellon – youtube)

"Identify ALL leachables above a QT of 5 µg/day"

- This means that TARGET methods are NOT sufficient
  - *If you use target quantitative methods, the identification of the compound was established upfront.*

- Conclusion: ALWAYS add a SCREENING step in your leachables assessment

Thank you!