



SETTING UP EXTRACTABLE / LEACHABLE STUDIES

PDA TRAINING COURSE
EXTRACTABLES – LEACHABLES
Sevilla
29 – 30 November 2018

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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 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



Product Quality Research Institute

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



Product Quality Research Institute

Parenteral and Ophthalmic Drug Products Leachables and Extractables Working Group

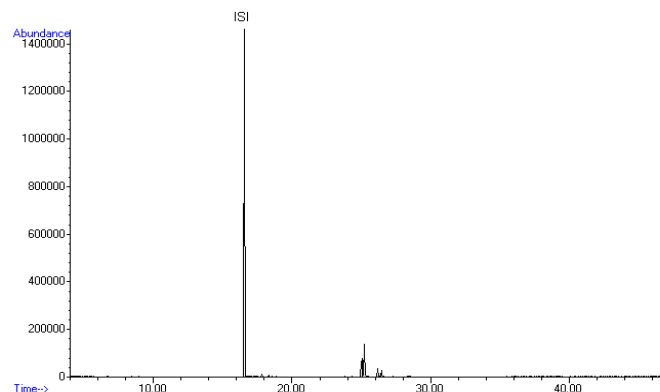
Issued and Effective
September, 2011

Study Protocol – Stage 1
Amendment #1

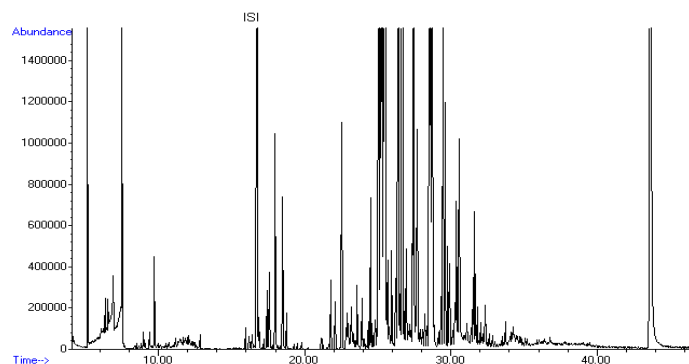
Experimental Protocol for Qualitative Controlled Extraction Studies on Material Test Articles Representative of Prefilled Syringe (PFS) and Small Volume Parenteral (SVP) Container Closure Systems

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

- **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^o, 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!!

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”

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

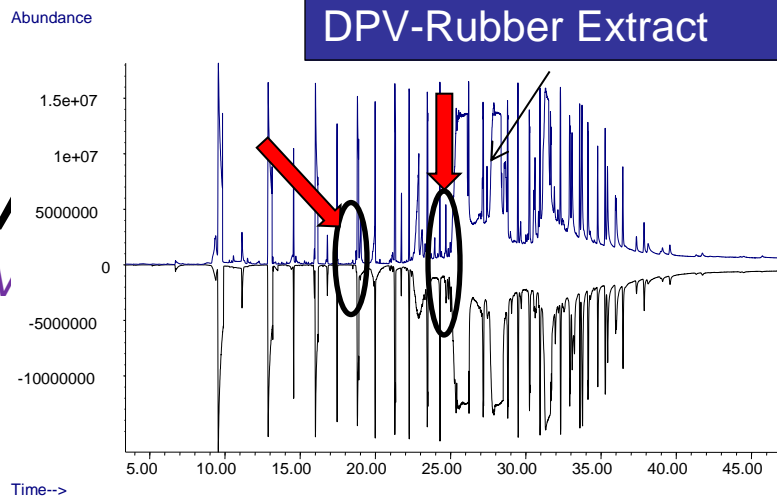
- Look for Similar or Greater Extraction Propensity
- That gives Similar Qualitative and Quantitative EXT-profile

- **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)



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 PERFORM A SIMULATION STUDY

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

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

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”

PODP Best Demonstrated Practice Recommendations

UPW	UPW	UPW/IPA	IPA	HEXANE
pH 2,5	pH 9,5	(50/50)		

Acid
Extractables

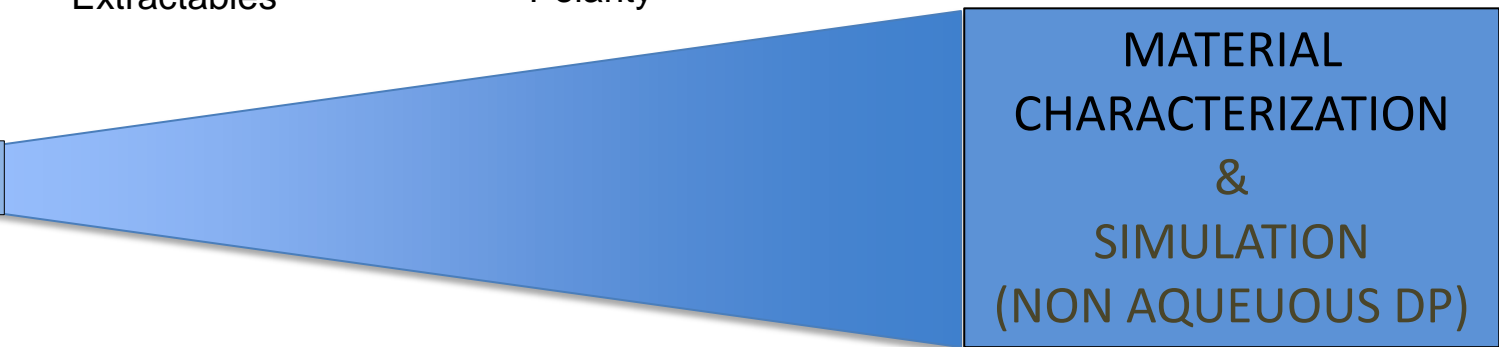
Base
Extractables

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

Example:

Extraction of a rubber component

GC/MS Semi-Volatile Organic Compound "Profile"

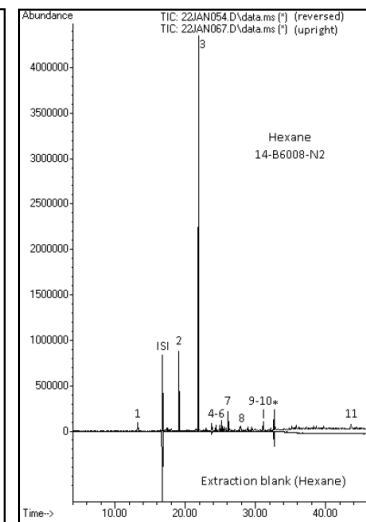
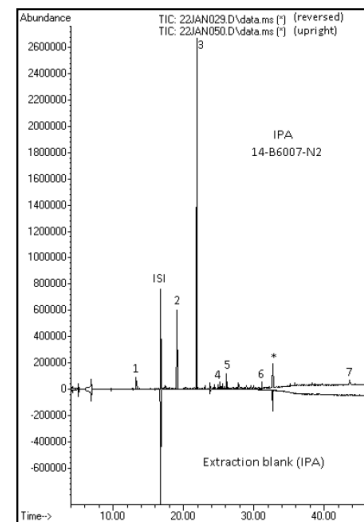
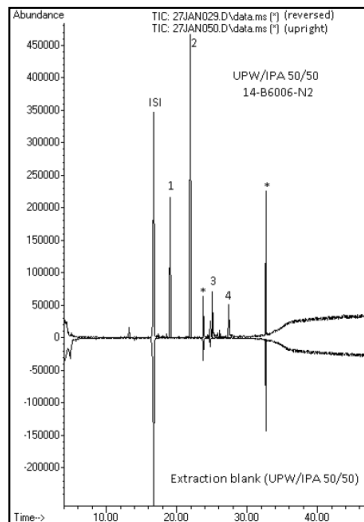
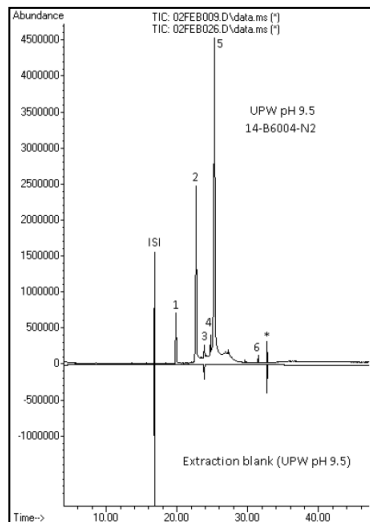
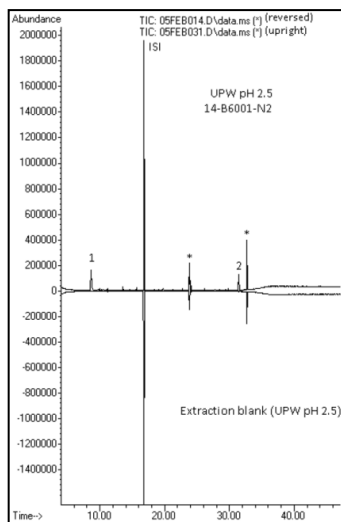
pH 2,5

pH 9,5

UPW/IPA 50/50

IPA

HEXANE



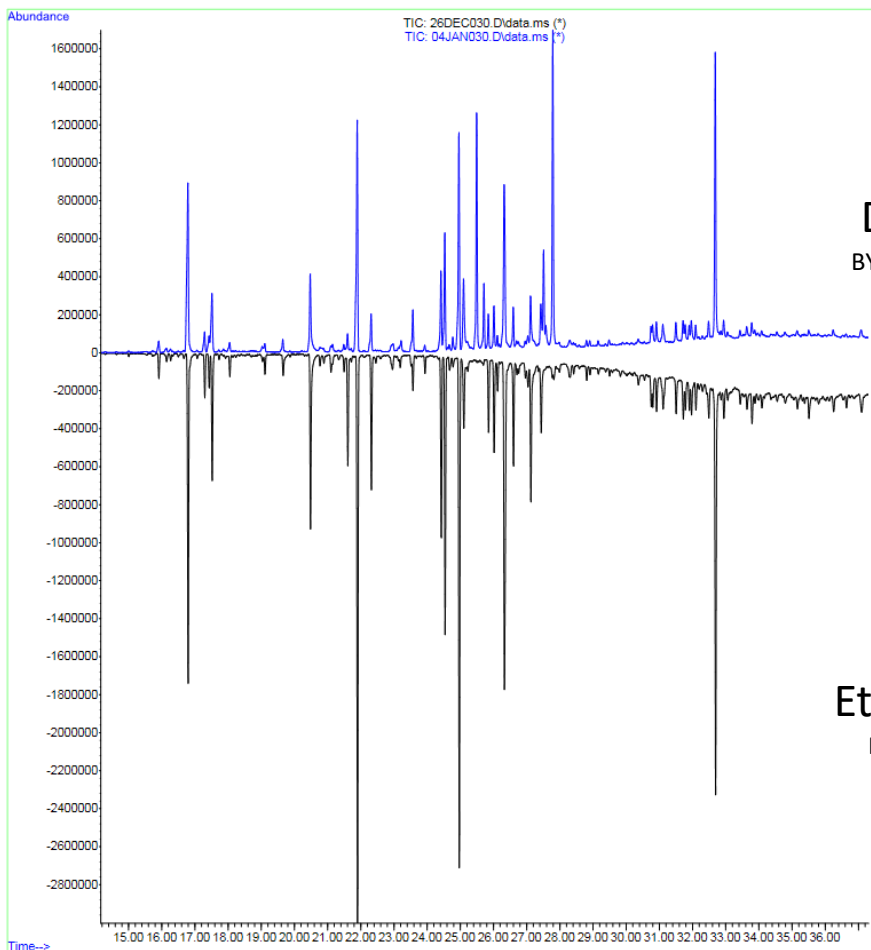
IS: Internal Standard for GC/MS

*: 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

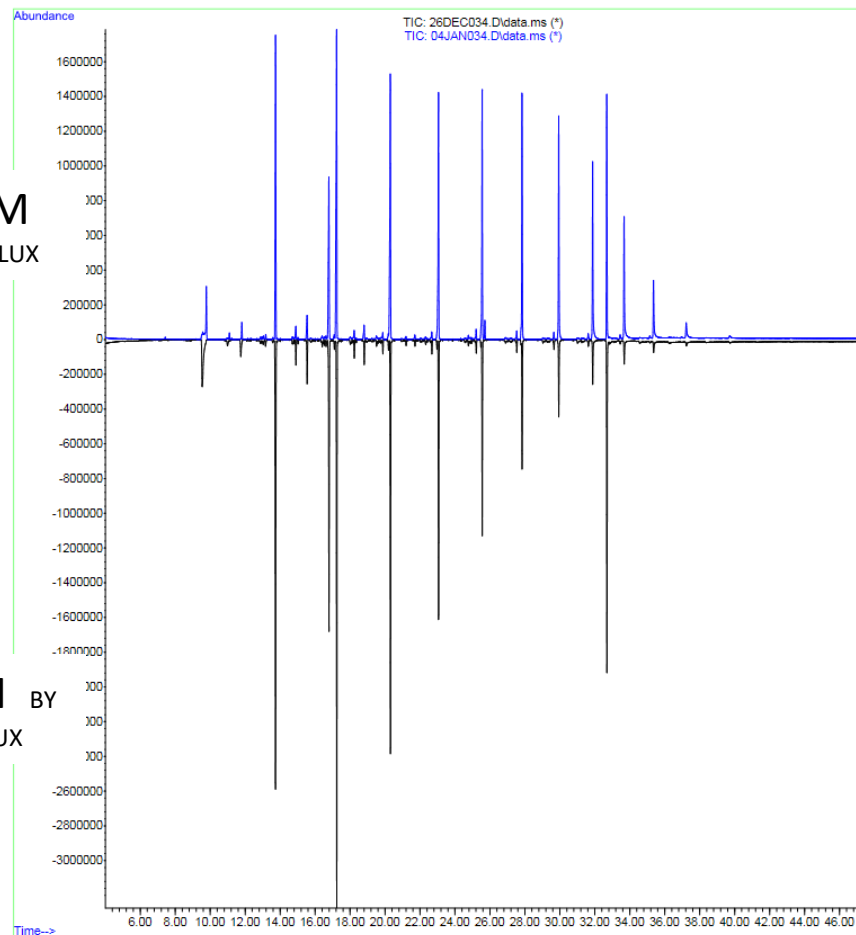
Rubber



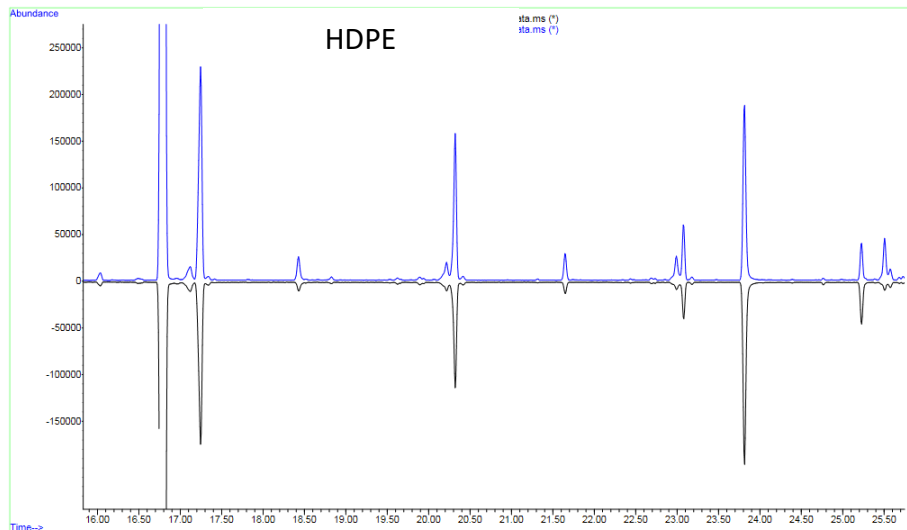
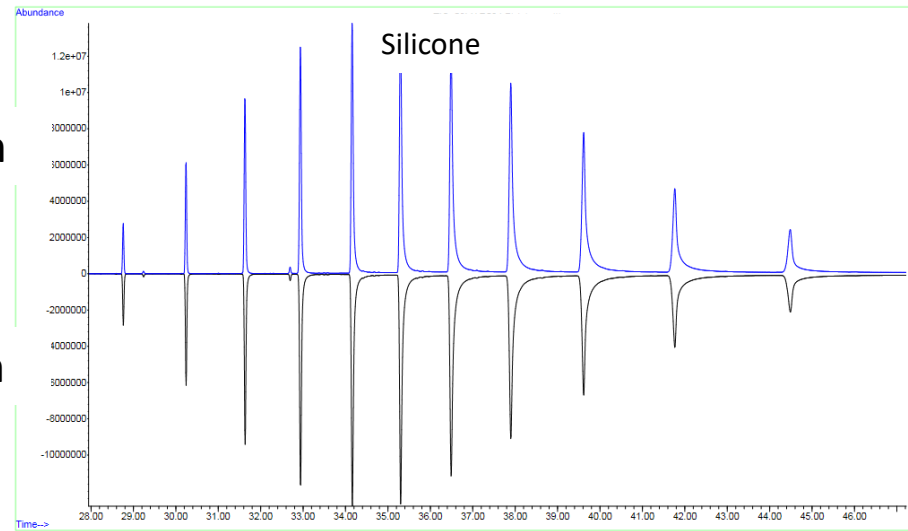
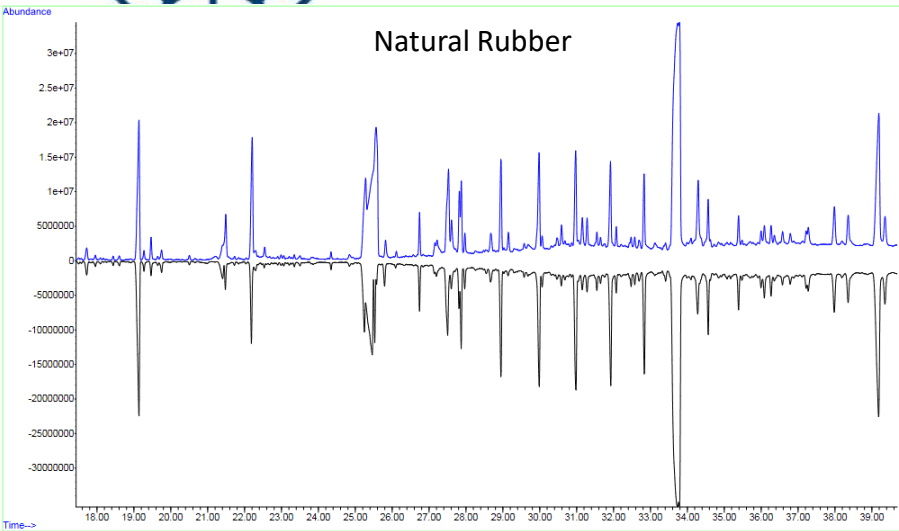
DCM
BY REFLUX

EtOH BY
REFLUX

HDPE



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

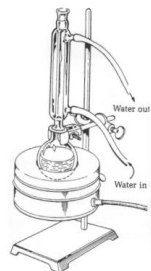
(This is different for simulation studies: see next presentation)

USP <1663> “Generating the Extract”

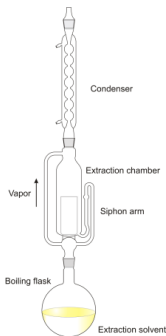
Mechanism of Extraction – Extraction Technique

Reflux or Soxhlet Extractions

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



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 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

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	Cross Linking	HPLC-UV
Silicone Oil	Lubrification	GF-AAS

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
 - ...

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 Alkaline 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.*



2. THE EXTRACTION STUDIES

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

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

AET: ANALYTICAL EVALUATION THRESHOLD

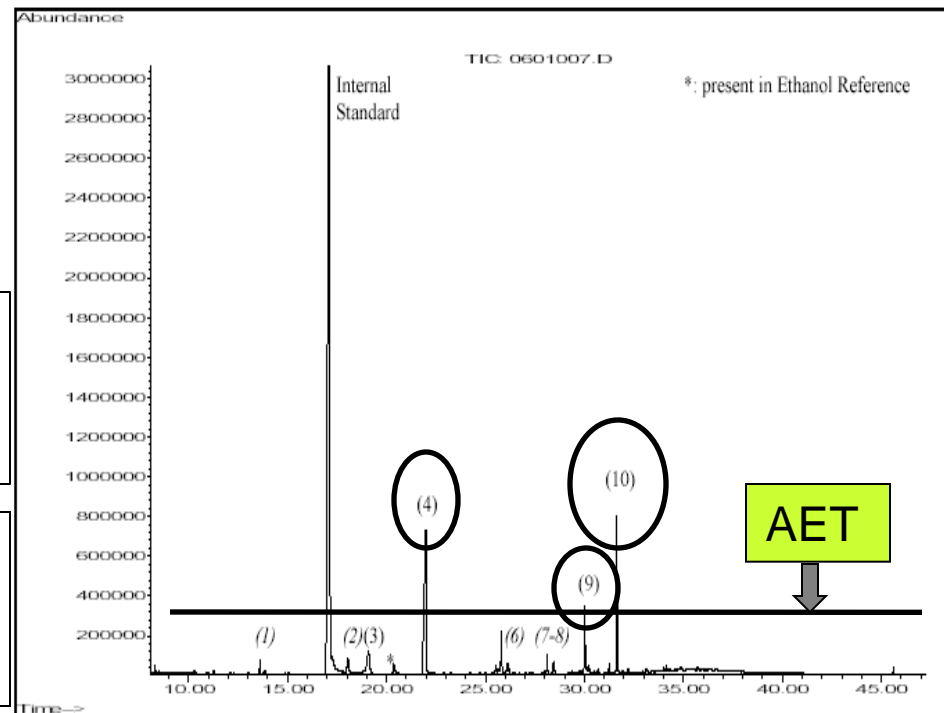
Translate SCT



into Analytical Thresholds
for Extractable Studies

Taking into account:

- Total N^o of doses / packaging
- Max. N^o of doses administered / day



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**

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
 - ...

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):

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

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

Final AET = 25 $\mu\text{g} / \text{Barrel}$ **50% uncertainty for screening methods**

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

	Threshold ($\mu\text{g}/\text{day}$)	Final AET ($\mu\text{g}/\text{barrel}$)	Final AET (mg/Kg)	Final AET (mg/L)
Class I	50	25	12	5
Class II	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

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

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	Class 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

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

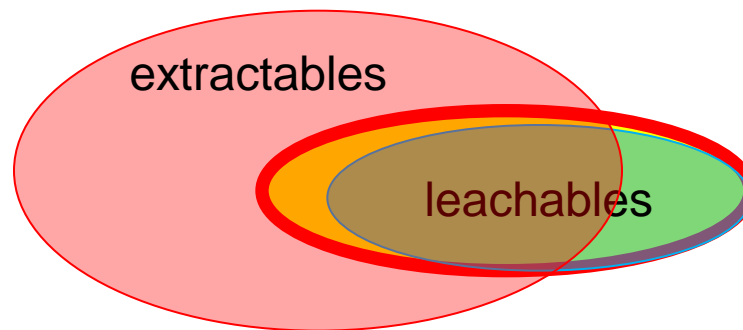
STEP 2

SIMULATION STUDY

» 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”

PDA® 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



Only for visualization - rubber plunger surface area to solution >> 10

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

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

STEP 3

MIGRATION / LEACHABLE STUDY

- **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

- **TIMING:** 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 the DP and the C/C system

USP <1664>: The Design of Leachable Studies

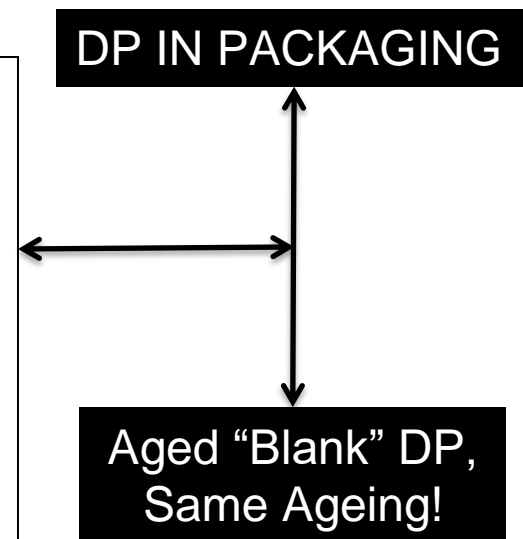
- Will **depend upon the purpose and goals** of a Leachable Study
- However, they require **similar types of information**
 - Chemical Composition of Packaging
 - Details of Mfg. Process
 - Extractables Assessment
 - ALL potential sources should be assessed
 - Primary Packaging
 - Secondary Packaging (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 and end up in the Final DP: **Should be treated as Leachables!!**

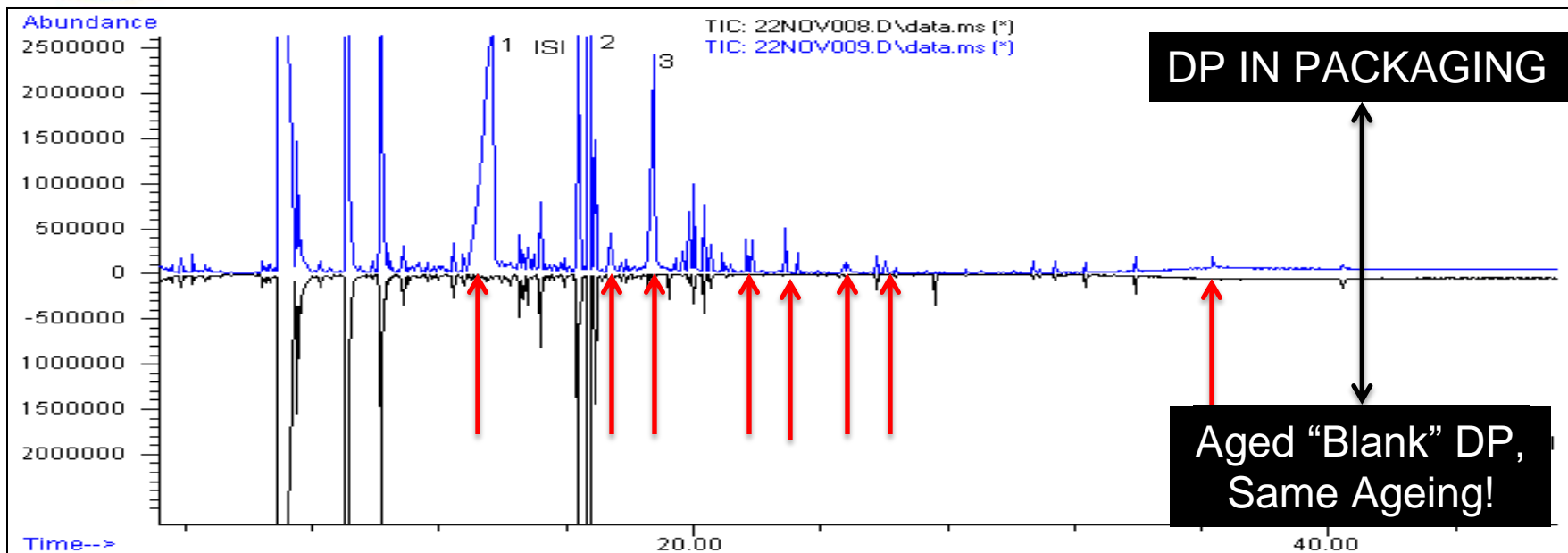
Typically, a **Leachable Study** is looking at all **DIFFERENTIAL** peaks in a **Comparative Assessment** between:

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

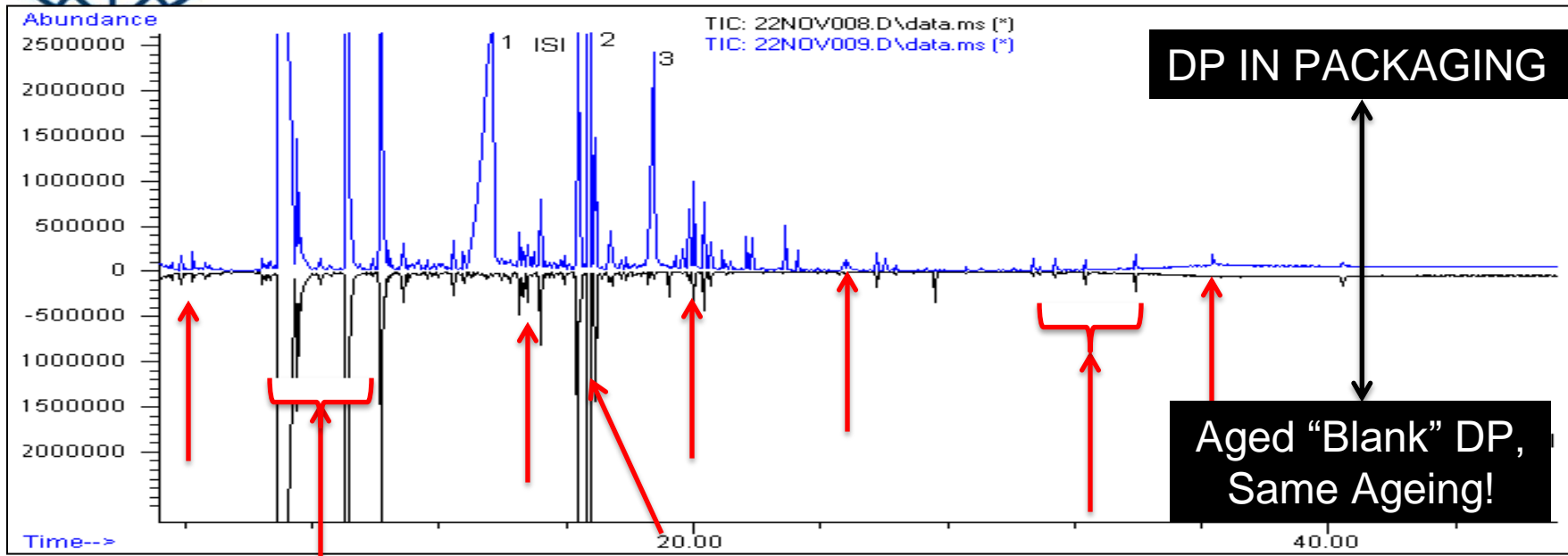
Every Compound that is present in the DP, aged in the Packaging System But NOT in the DP, aged in inert container

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)...

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. 0.9% 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...”



LEACHABLE STUDIES ≡ STABILITY STUDIES

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 100 ± 25%
- Accuracy in low, mid and high range < 25%
- Precision in low, mid and high range

Other: Intermediate Precision, Robustness...

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



LEACHABLE STUDIES ≡ STABILITY STUDIES

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

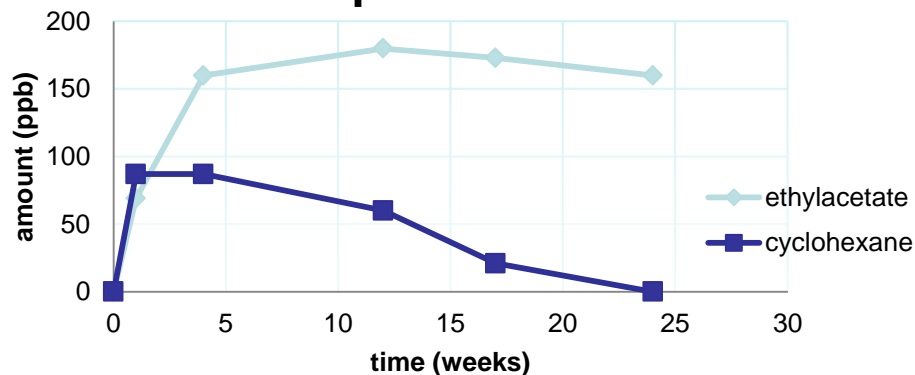
VOC (Volatile Organic Compounds)

monitoring Ethylacetate and Cyclohexane

Conclusion: Ethylacetate: asymptotic behaviour

**Cyclohexane: disappears: 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 $5 \pm 3^{\circ} \text{C}$	×	×	×	×	×
Pharmaceutical Matrix in Inert Containers (Blank) at $5 \pm 3^{\circ} \text{C}$	×	×	×	×	×
Pharmaceutical Matrix in Pre-filled Syringes (Test Item) at $25 \pm 3^{\circ} \text{C}$	-	×	×	-	-
Pharmaceutical Matrix in Inert Containers (Blank) at $25 \pm 3^{\circ} \text{C}$	-	×	×	-	-
× = sampling time point					

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 GC/MS
Semi-Volatile Organic Compounds (SVOC) SCREENING	
VALIDATED METHOD	LC/QQQ UPLC/HRAM
Non-Volatile Organic Compounds (NVOC) SCREENING	
Element Analysis	ICP
Anions: fluoride, chloride, and bromide	IC
Sulfur (S ₈)	LC/UV

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!