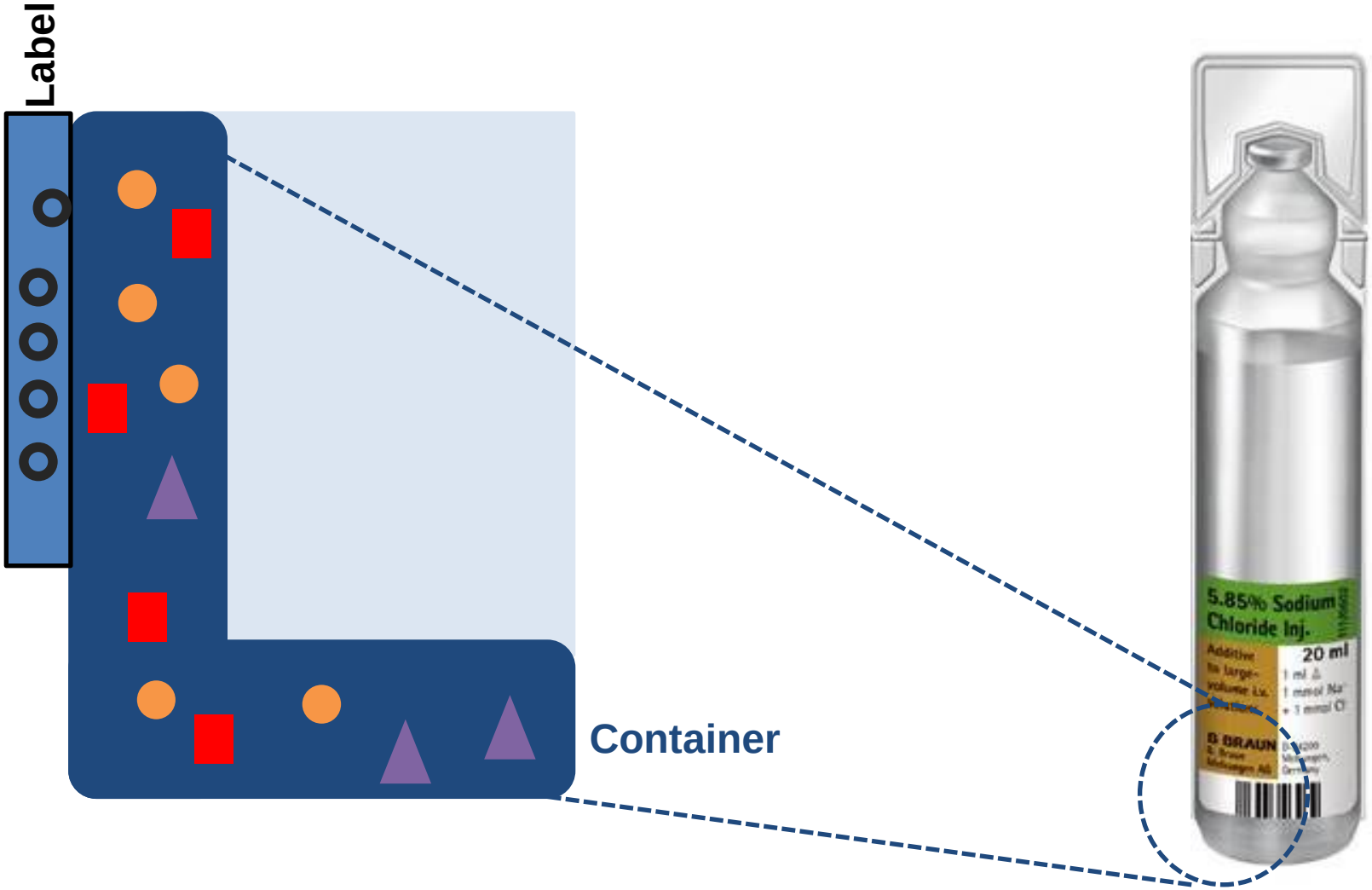
PDA Training Course Extractables & Leachables

01 June 2022

Setting Up Extractable Studies: Do’s and Don’ts

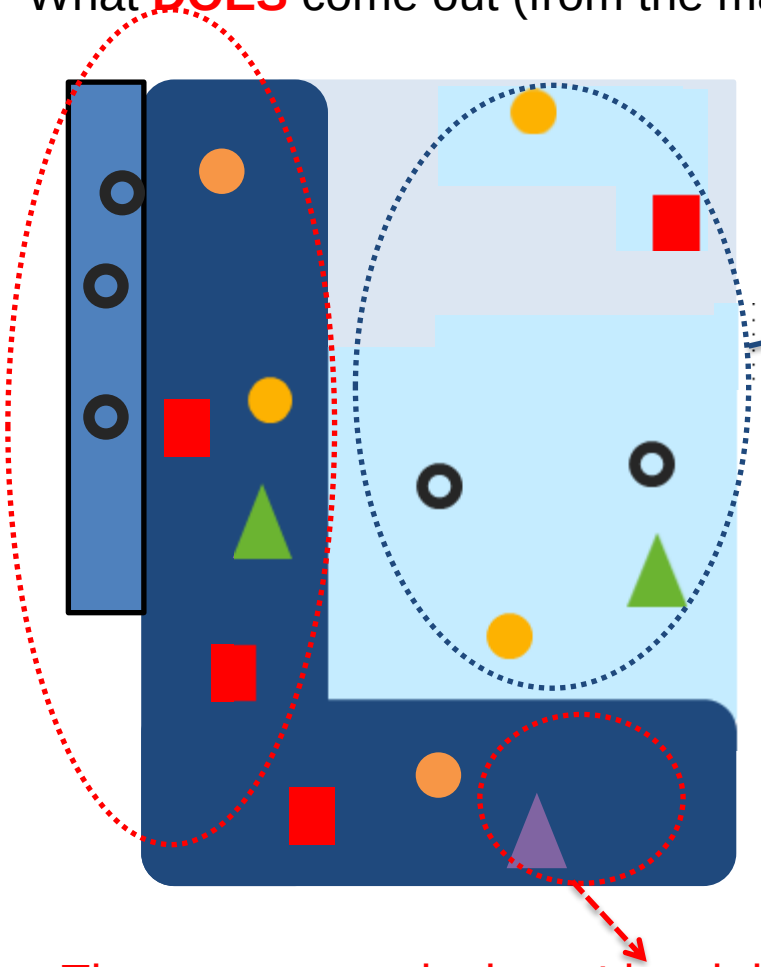
Dries Cardoen

Extractables & Leachables



Extractables & Leachables

What **DOES** come out (from the material) in the drug product?

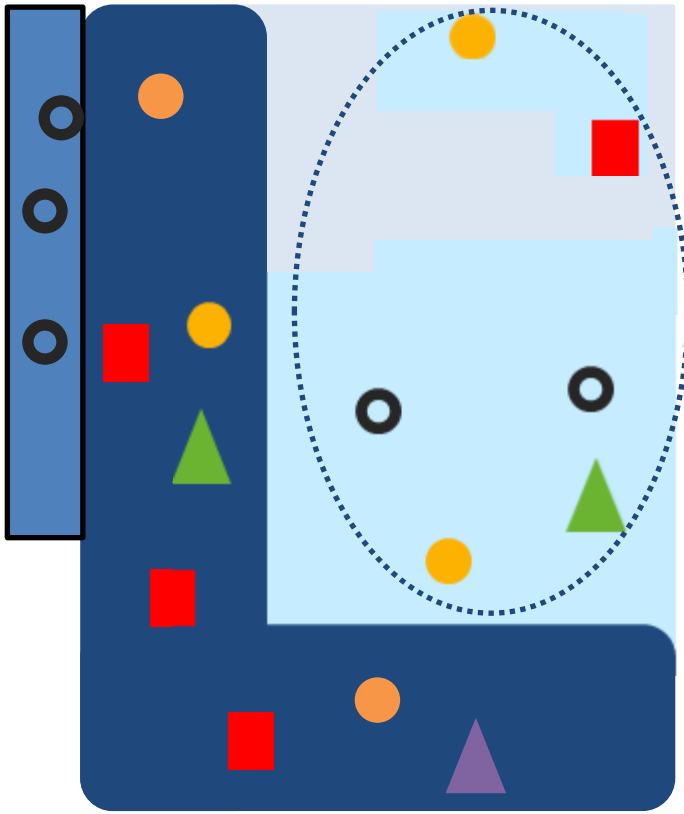


Leachables!

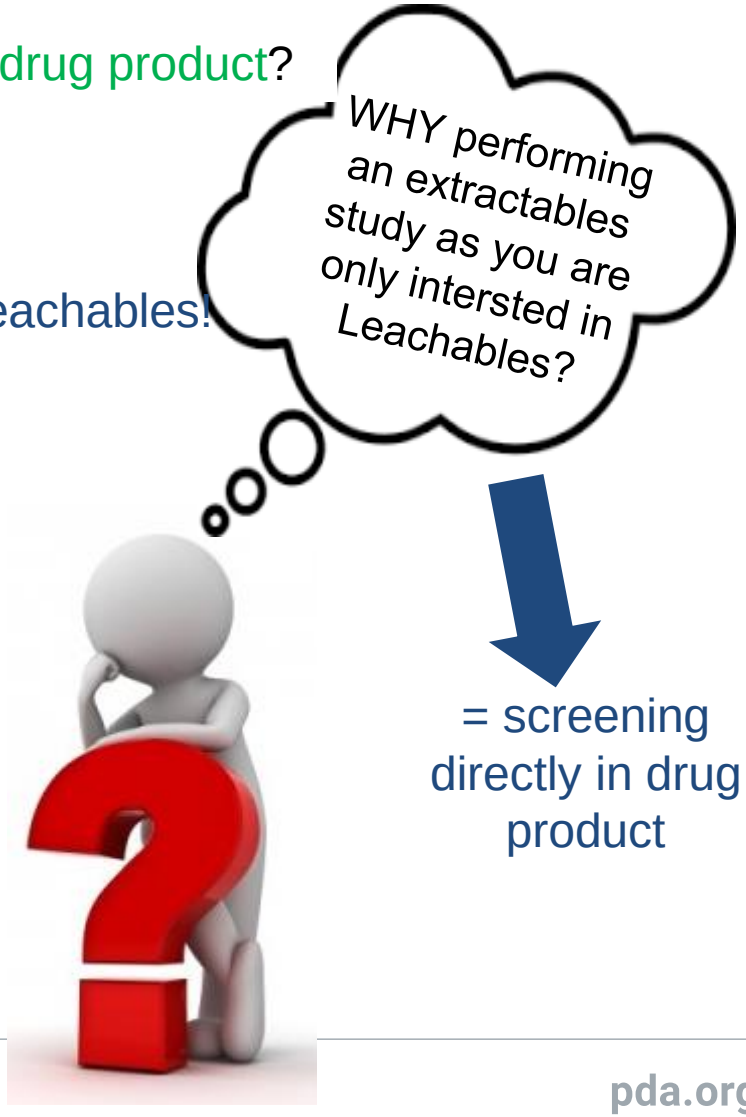
These compounds do **not** leach in the drug product

Extractables & Leachables

What **DOES** come out (from the material) in the drug product?



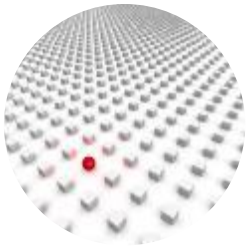
Leachables!



= screening directly in drug product

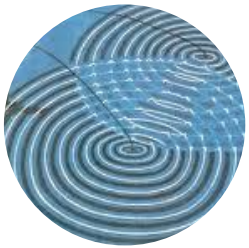
Extractables & Leachables

Drug product

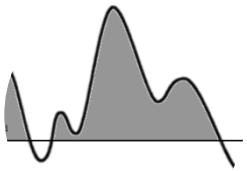


Screening

Compatible with drug product?



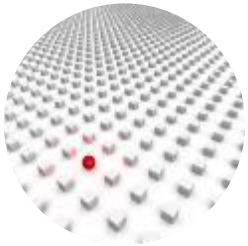
Interference?



Threshold?

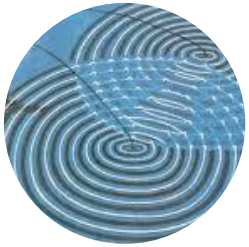
Extractables & Leachables

Drug product

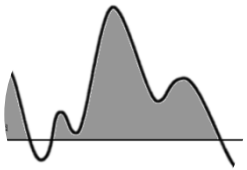


Screening

Compatible with drug product?



Interference?



Threshold?

THE ANSWER: YOU NEED EXTRACTABLES DATA

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

Purpose of an Extraction Study

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.

Purpose of an Extraction Study

These two documents ar either **INFORMAL** or **RECOMMENDATIONS**

Allow flexibility in design

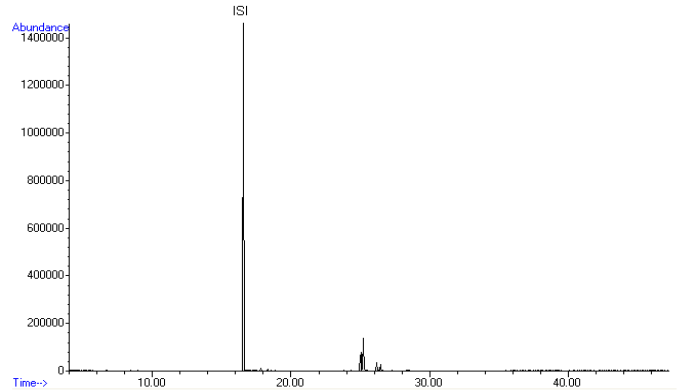
What is the *intent*? => **Strategy** of testing
How to design the study for the envisioned intent? => **Tactics**

However, justification is needed!

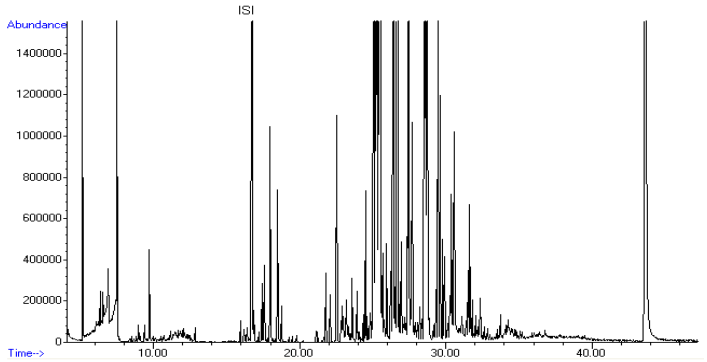
Both **identifying the necessity** for an extraction study, as well as **justifying the design**, is the responsibility of the holder of the NDA.

Purpose of an Extraction Study

1. **LOW Nr** of extractables



2. **HIGH Nr** of extractables



HOW CAN THIS BE HARMONIZED?

Useful documentation prior to testing

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/PLASTIC

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!!

Design Space of an Extraction Study

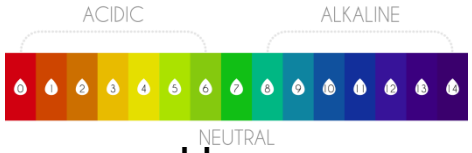
VARIABLES that may/will have an impact on the study design of an extractables study

- 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?
- Packaging versus Manufacturing Equipment
  - **Dedicated session**

DESIGN OF AN EXTRACTABLES STUDY: EXTRACTION

Extraction Solvents

Polarity,...

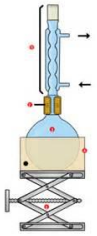


pH

Extraction conditions

Time & Temperature

autoclave



Reflux

Incubation (shaking)

Extraction ratio

Guidelines

PQRI ISO

Filling volume

SELECT WORST CASE CONDITIONS REPRESENTATIVE FOR FINAL APPLICATION

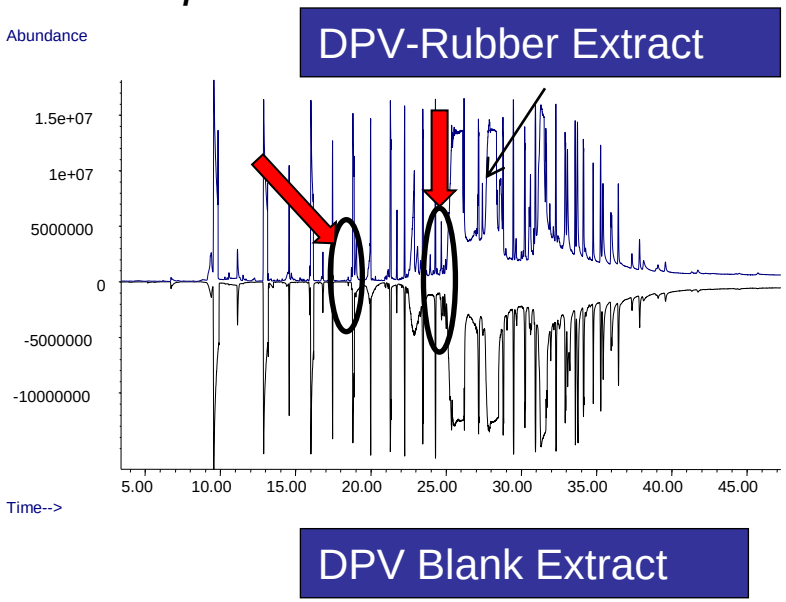
USP <1663> “Generating the Extract”

Extraction Solvents

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 may lead to degradation (eg Polysorbate)*



Purpose of an Extraction Study

Extraction Solvents

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

Purpose of an Extraction Study

Extraction Solvents

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

DISADVANTAGE: **Risk of missing** the presence of compounds

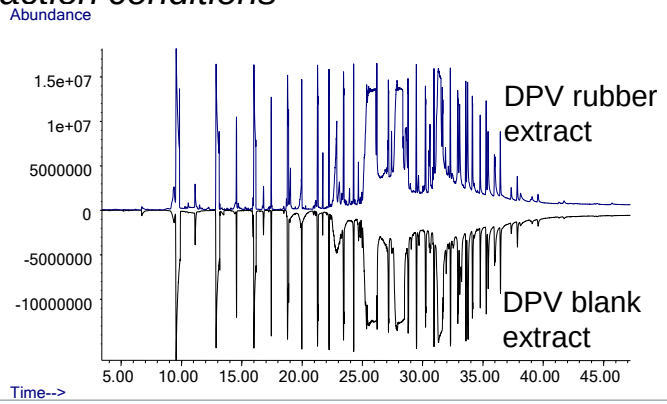
- *Matrix interference of DP(V) (see previous slide)*

Risk of **misinterpretation of analytical data**

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

Risk of underestimating the concentration of compounds

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



USP <1663>: Generating the Extract

Extraction Solvents

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

Extraction Solvents

- ***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>

USP <1663>: Generating the Extract

Extraction Solvents

- ***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.*

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*

USP <1663>: Generating the Extract

Extraction Solvents

If: PURPOSE: <u>Material Characterization</u> *<u>(not a worst case EXT profile)</u>*

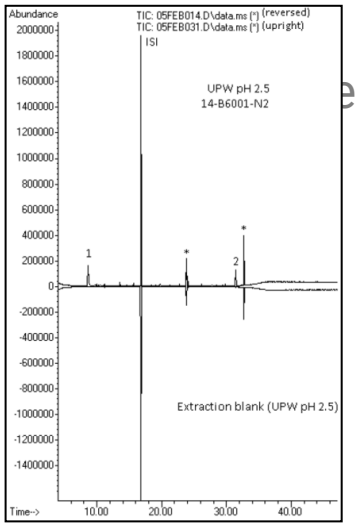
- ***Use POWERFUL extraction Solvents***
  - *GOAL: to have an Efficient Quantitative & Qualitative Extraction*
  - *Powerful Extraction Solvents*
    - *Softening*
    - *Swelling*
    - *Dissolving*

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

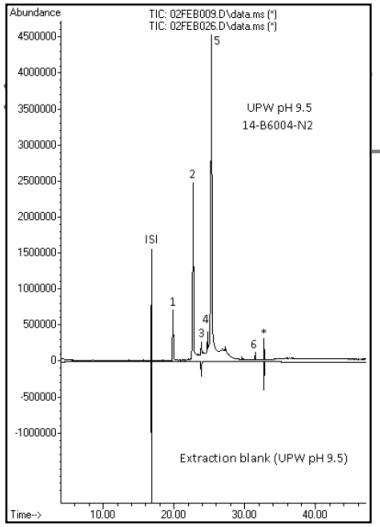
USP <1663>: Generating the Extract

Extraction Solvents

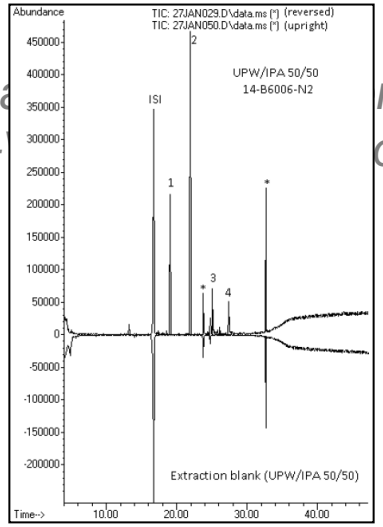
pH 2,5



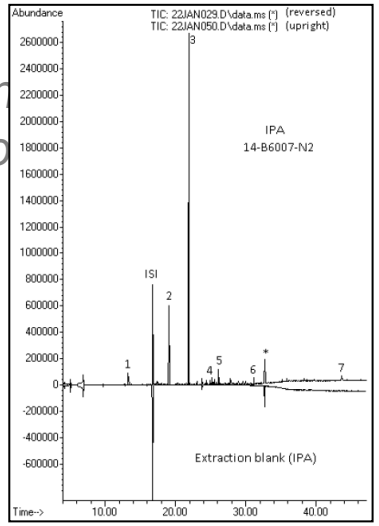
pH 9,5



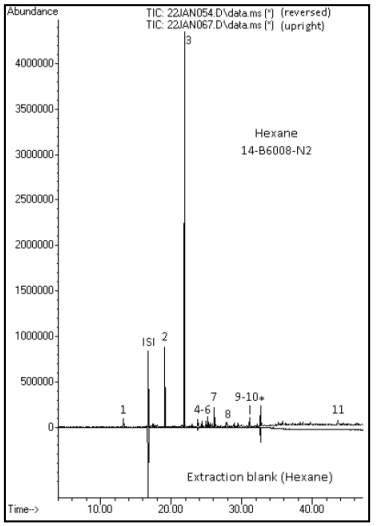
UPW/IPA 50/50



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!

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Extraction Solvents

PQRI Product Quality Research Institute - PODP best demonstrated practice **recommendations**

UPW	UPW	UPW/IPA	IPA	Hexane
pH 2.5	pH 9.5	(50/50)		
Acid extractables	Alcalinic extractables	Intermediate polarity	→	Non-polar

SIMULATION

MATERIAL CHARACTERIZATION & SIMULATION (NON AQUEUOUS DP)

Recommendations:

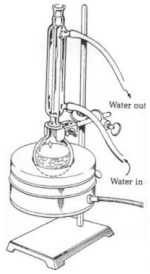
- It is not mandatory to always include these 5 solvents
- The solvents should be adjusted to the physico chemical properties of the DP
- Justifications!!

USP <1663>: Generating the Extract

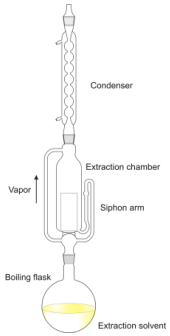
Extraction Techniques

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

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Extraction Techniques

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

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Extraction Techniques

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 smulation, less exhaustive

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Extraction Conditions

Consideration for “In-Situ” Extractions:

- Static Extraction: Pharmaceutical Packaging
- Dynamic Conditions, often considered for Production Items
    - *Tubings*
    - *Filters*
    - *Pump systems (also for IV administrations)*
- Dynamic extraction is a better simulation if the contact between the components and the DP/DS is also dynamic,

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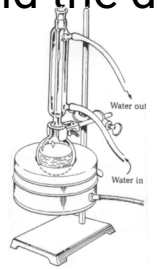
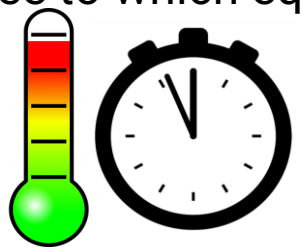
Extraction Time and Temperature

USP<1663> "Generating the extract" section "Extraction time and temperature"

The combination of extraction time and temperature establishes the magnitude of

the driving force and the degree to which equilibrium is achieved





Time and temperature are closely linked to the extraction technique that is used

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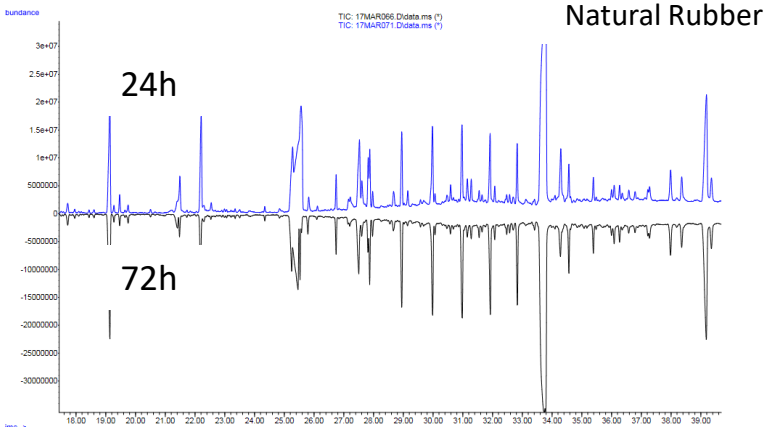
Extraction Time and Temperature

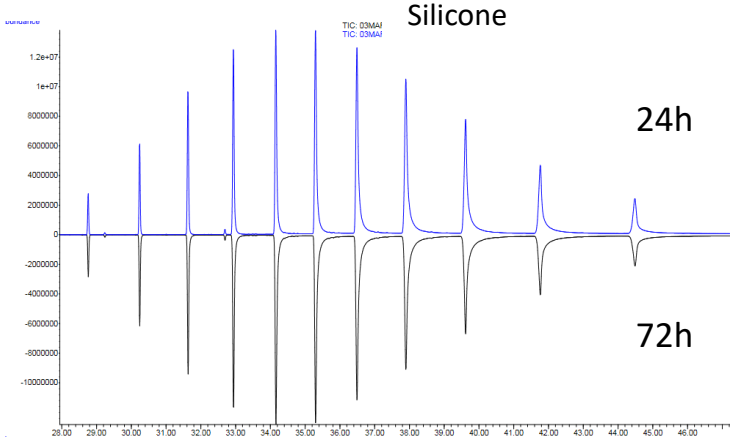
Typical temperature / time settings:

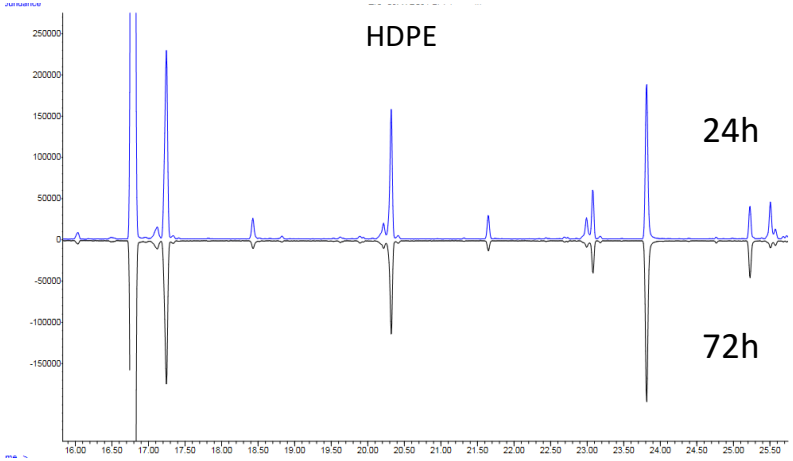
- **Reflux** with organic solvents:
  - Boiling temperature, 8 h
- **Soxhlet** with organic solvents:
  - Boiling temperature, 24 h
- **Sonication:**
  - Room temperature, ½ to 1h
- **Sealed vessel** and **"*in situ*" extraction**:
  - 50°C, 72 h (ISO 10993-12)
  - 24h below boiling point of extraction solvent = equivalent to 8h reflux
- **Headspace enrichment**:
  - 40 minutes, temperature is selected based on the type of material (from 70°C for LDPE up to 150° for rubbers / elastomeric material)
- **Dynamic Extractions**:
  - Extraction Conditions are determined based upon the conditions of use

USP <1663>: Generating the Extract

Extraction Time and Temperature







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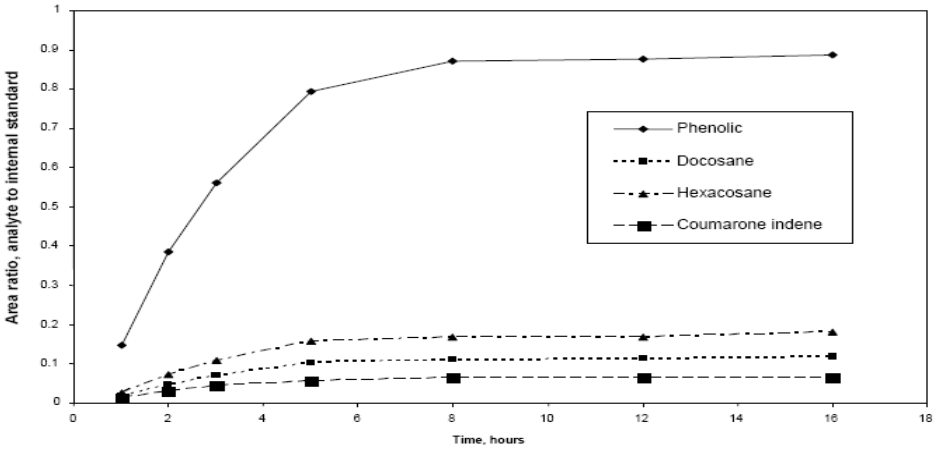
Extraction Time and Temperature

Asymptotic extraction profile - exhaustive extractions:



PQRI-Example:

- Test article: sulphur cured elastomer
- Extraction: DCM – soxhlet

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

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 concentrated 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...)

USP <1663>: Generating the Extract

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

What **CAN** come out of the **material**?

PACKAGING/MATERIAL

Extraction Solvents

Extraction conditions

Extraction ratio

ANALYSES OF THE EXTRACTS

Analyses of the extracts

A **broad identification** in “First Pass” extractable studies requires:

1. A compound specific detector: **Mass Spectrometry**

2. A **database** to allow Identification based upon Mass Spectra
   - Commercial Databases for GC/MS: NIST, WILEY
   - Customized Databases


IDENTIFICATION
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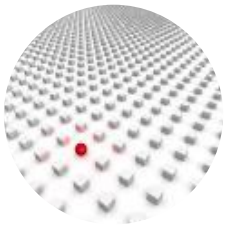
Analyses of the extracts

Extract

Identification



Screening

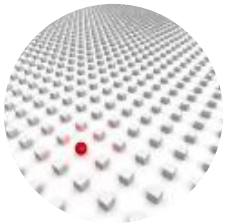
Trying to identify every single peak in a chromatogram

Targeted

Analyses of the extracts

Extract

Identification



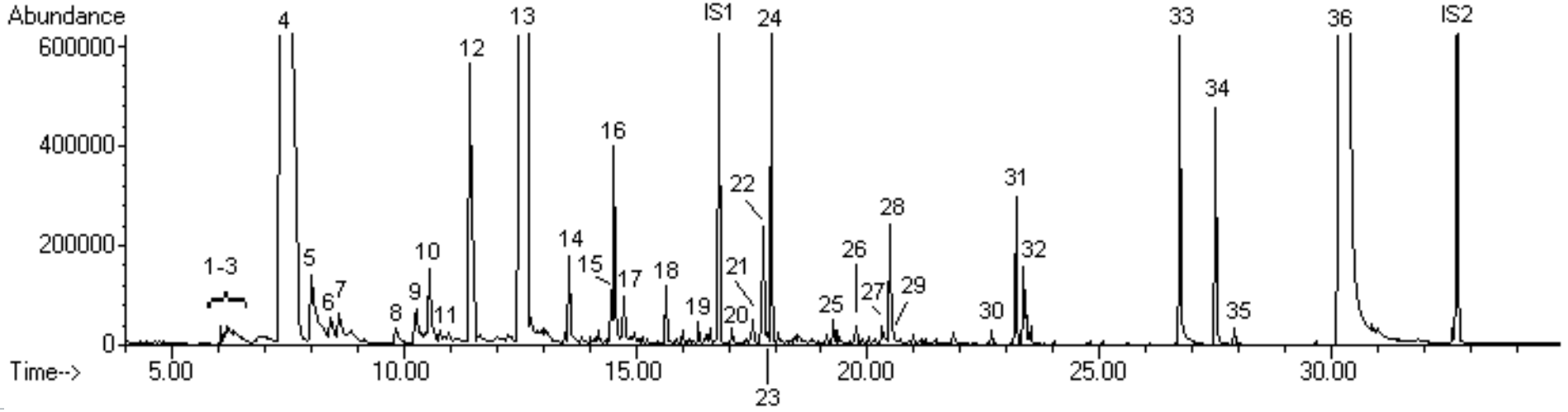
Screening

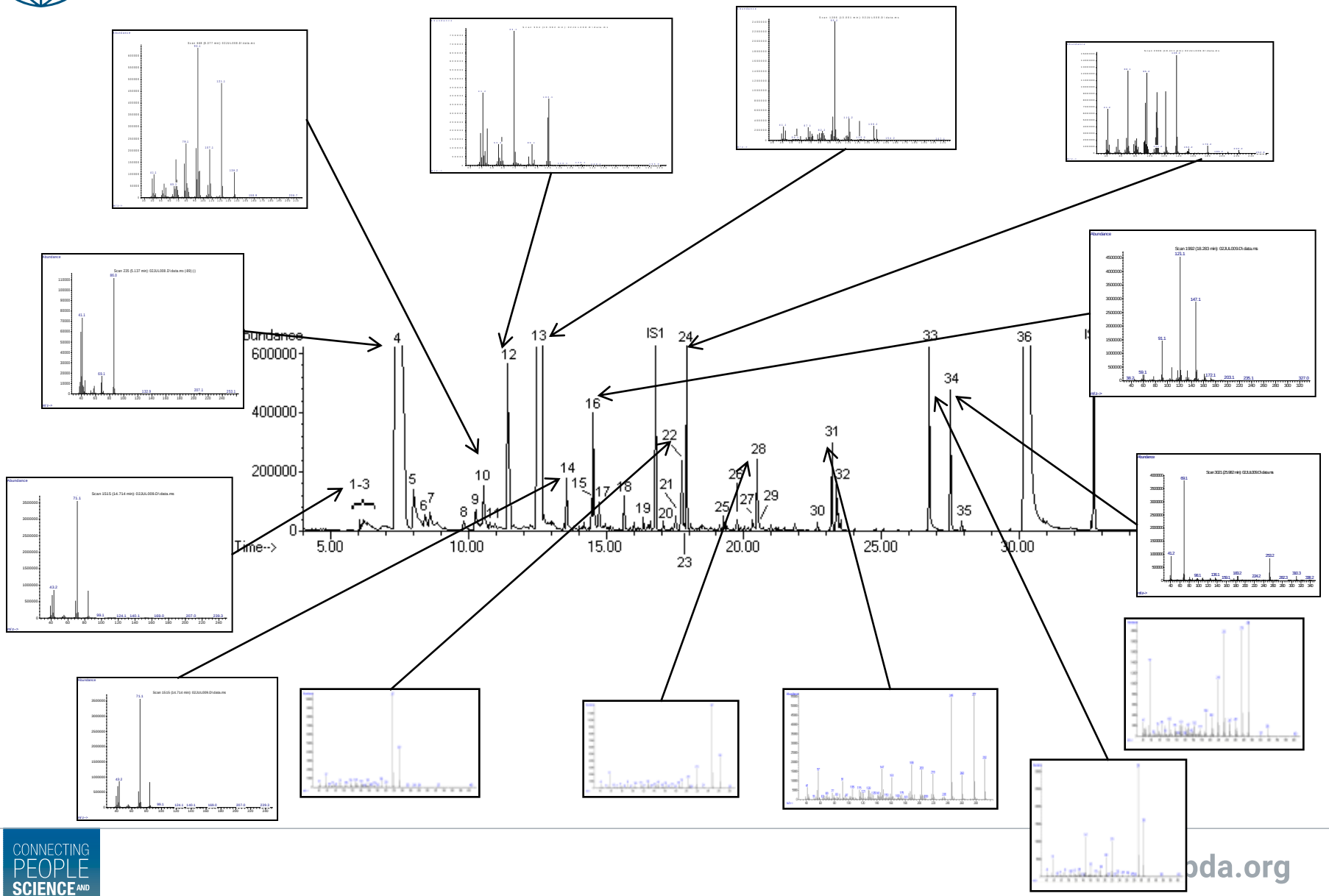
Trying to identify every single peak in a chromatogram

Analyses of the extracts

SCREENING: HOW DOES IT WORK?

IDENTIFICATION




Abundance
600000
400000
200000
0
Time-->
5.00
10.00
15.00
20.00
25.00
30.00
1-3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
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21
22
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IS1
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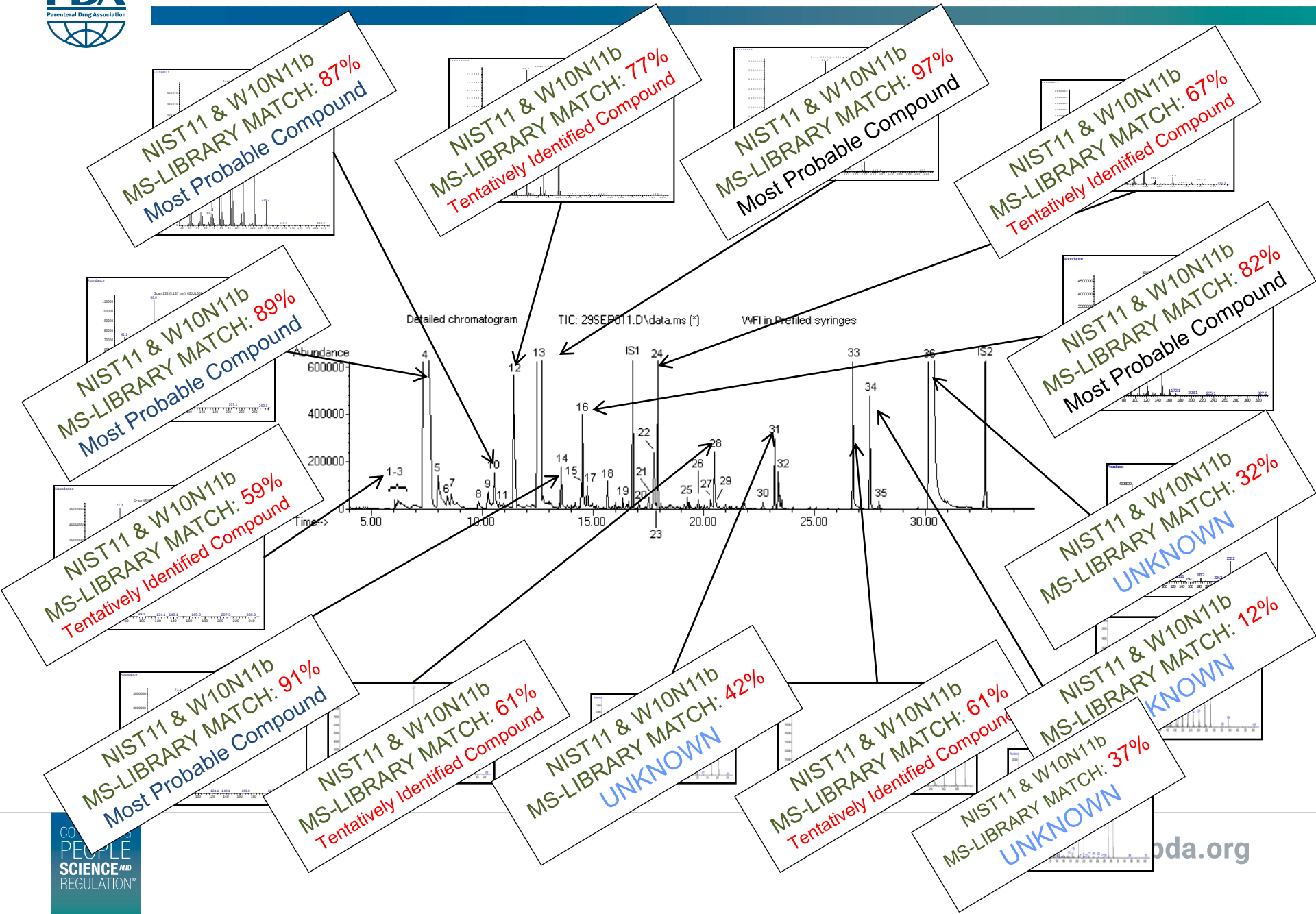
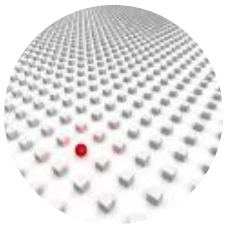
35
36


NIST11 & W10N11b
MS-LIBRARY MATCH: 87%
Most Probable Compound
NIST11 & W10N11b
MS-LIBRARY MATCH: 77%
Tentatively Identified Compound
NIST11 & W10N11b
MS-LIBRARY MATCH: 97%
Most Probable Compound
NIST11 & W10N11b
MS-LIBRARY MATCH: 67%
Tentatively Identified Compound
NIST11 & W10N11b
MS-LIBRARY MATCH: 89%
Most Probable Compound
NIST11 & W10N11b
MS-LIBRARY MATCH: 82%
Most Probable Compound
Detailed chromatogram
TIC: 29SEP011.D\data.ms (*)
WFI in Prefiled syringes
Abundance
Time-->
NIST11 & W10N11b
MS-LIBRARY MATCH: 59%
Tentatively Identified Compound
NIST11 & W10N11b
MS-LIBRARY MATCH: 32%
UNKNOWN
NIST11 & W10N11b
MS-LIBRARY MATCH: 91%
Most Probable Compound
NIST11 & W10N11b
MS-LIBRARY MATCH: 61%
Tentatively Identified Compound
NIST11 & W10N11b
MS-LIBRARY MATCH: 42%
UNKNOWN
NIST11 & W10N11b
MS-LIBRARY MATCH: 61%
Tentatively Identified Compound
NIST11 & W10N11b
MS-LIBRARY MATCH: 12%
UNKNOWN
NIST11 & W10N11b
MS-LIBRARY MATCH: 37%
UNKNOWN

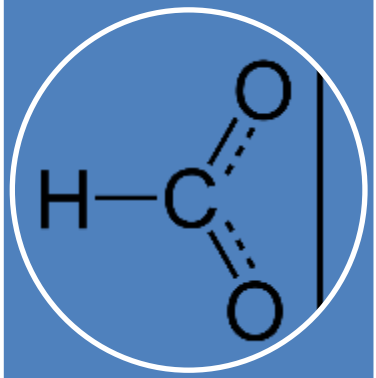
Extract

Identification



Screening

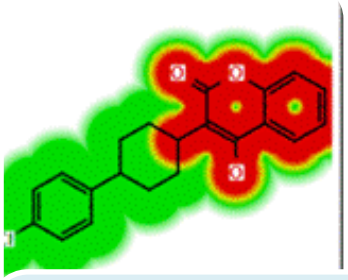
Orthogonal techniques

VOC	SVOC	NVOC		
HS-GC/MS **Screening**	GC/MS **Screening**	UPLC/MS **Screening**	ICP/OES ICP/MS	IC GF-AAS LC/UV ...

EXTRACTABLES PROFILE:Potentially Leaching Compounds of Concern

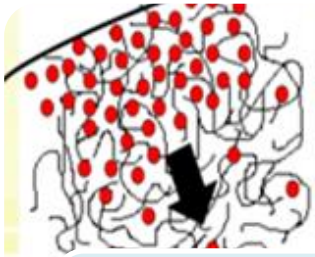
Identification

- Knowledge of material
- What **CAN** come out



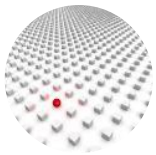
Initial Toxicological Evaluation

Example:
Cramer + Derek Nexus
Toxicologist/ consultant
Select Targets



LEACHABLES

- What **DOES** come out in the drug product



Screening

Target

TIME FOR QUESTIONS