PDA Training Course Extractables & Leachables

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Essential Principles of Chemical Characterization (Extractables)

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Presentation outline

1. Material Characterization, Selection and Qualification

2. Packaging Systems Characterization and Qualification (Extractables)
   - ✓Extractable Studies: General Considerations
   - ✓Extractable Studies: Generating the Extract
   - ✓Extractable Studies: Analyzing the Extract

1. Material Characterization, Selection and Qualification

Material Screening and Selection

- **Test Article:** Materials of Construction
- **Purpose:** Establish the material's composition
- **Test Strategy:** and Characterize the test article for ingredients (composition), biocompatibility general chemical properties.
- **Typical Approach:** Exhaustive/aggressive extraction. Target and screening analysis.
- **Impact Assessment:** During the development of a packaging system, potential materials of construction are characterized and screened for use based on their characteristics. Unsuited materials are rejected, suitable materials are adopted.
- **Value Proposition:** The best means of insuring packaging suitability is to use suitable materials of construction.

Before you run to the lab...

- Collect available safety information from the material's vendor:
  - ✓ Compendial Compliance
  - ✓ Biological Reactivity Testing
  - ✓ Use in Food Contact Applications
  - ✓ Conformance to Compositional Standards
  - ✓ Formulation
  - ✓ Processing
  - ✓ Extraction testing

- Oftentimes, the above information alone may be sufficient to support a selection decision.
- Furthermore, these types of information create a preponderance of evidence, which may make up for gaps in extractables or leachables testing when making and supporting a claim of safe for its intended use.

Important Note: Material information, especially when used to support material selection, is rarely required in a regulatory submission and is almost never adequate to qualify packaging.

Pillars of Evidence that a Material of Construction is Safe

The Importance of Material Characterization

Materials cannot be qualified as being inherently safe and therefore there is no regulatory value escribed to material characterization.

However

- If the materials of construction are well-characterized and an assessment of the characterization data suggests that they are suitable for their intended use,

Then

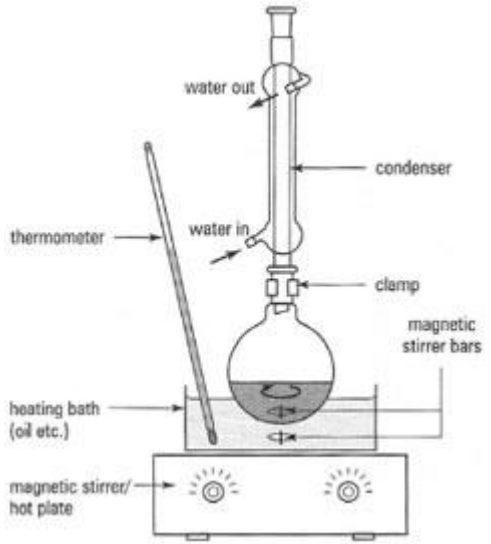
- It is likely that the packaging system assessment will be favorable (less likely that there will be unpleasant surprises during E&L and biocompatibility studies).

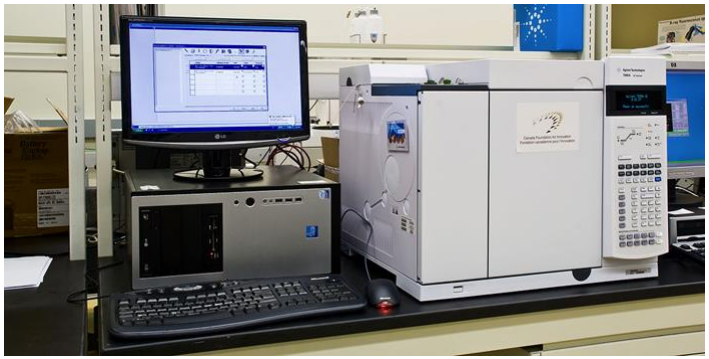
Additionally

- Material Characterization data may be the proper basis of managing change control.

2.Packaging System Characterization and Qualification - Extractables

2a. Extractable Studies: General Considerations





Acceptable Practices

- **USP <1663> Monograph**

  "Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems"

  This is an **INFORMATIONAL** monograph.

- PQRI – **Parenteral & Ophthalmic Drug Products (PDP and ODP)**

  Best Demonstrated Practice Recommendations: **Chemistry** & Toxicology

  These are **RECOMMENDATIONS.**

As was noted earlier, the official regulatory Guidance and Guidelines DO NOT reflect current regulatory requirements and thus provide little direction in terms of the proper design and execution of extractables studies. One learns what the current regulatory requirements are by experiance secured in regulatory deficiency letters and the like.

Acceptable Practices

- These two documents are either **INFORMATIONAL** 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.

What is the PURPOSE of an Extraction Study?

- Material characterization of the packaging components (as noted previously)
- "Impurities profiling" of the materials
  - ✓ Identify as many compounds as possible
  - ✓ Identify "bad actors" in the materials
  - ✓ Establishes the worst case that "it all comes out"
- Forecast leachables profile; extractables as probable leachables
- Establish leachables – extractable correlations
- Extablish target compounds to be monitored as leachables in leachables studies
  - ✓ Toxicity
  - ✓ Concentration in the materials
  - ✓ Risk for migration
- In certain cases (more applicable to OINDP): Facilitates extractable specifications for incoming raw materials.

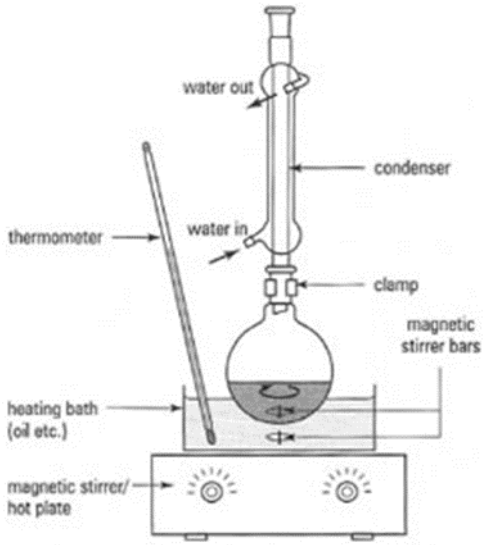
The purpose of an extraction study dictates it design.

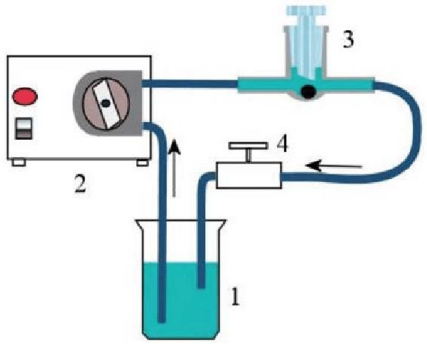
Design Space for an Extractables Study

- **Factors** that impact the 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 C/C's **materials on construction**
    - ➢ e.g., rubber versus polyolefin for BFS
  - ✓ The **knowledge of 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?

2b. Extractable Studies: Generating the Extract





Design of an Extractables Study: Extraction

Extraction Solvents

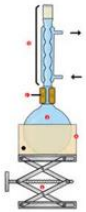
Polarity,...

pH

Extraction conditions

Time & Temperature

Autoclave



Reflux

Incubation (shaking)

Extraction ratio

Surface area to solution volume

Extraction Solvents

UPW	UPW	UPW/IPA	IPA	Hexane
pH 2.5	pH 9.5	(50/50)		
Acidic, polar extractables	Basic, polar extractables	Intermediate polarity	→	Non-polar

SIMULATION

MATERIAL CHARACTERIZATION & SIMULATION (NON AQUEUOUS DP)

Recommendations:

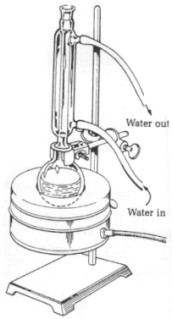
- It is not mandatory to always include these 5 solvents
- The solvents should be adjusted to the physico-chemical properties of the DP
- Justifications!!

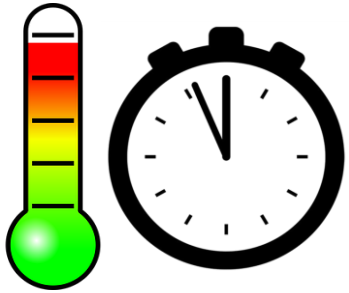
Extraction Time and Temperature

- 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





Extraction Time and Temperature

- **Possible temperature / time combinations:**
  - ✓ 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 which is for medical devices and NOT packaging)
    - ➢ 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

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...)

Extraction Stoichiometry

- Try to stay as close as possible to the ratio's of the actual use of the container

  Example

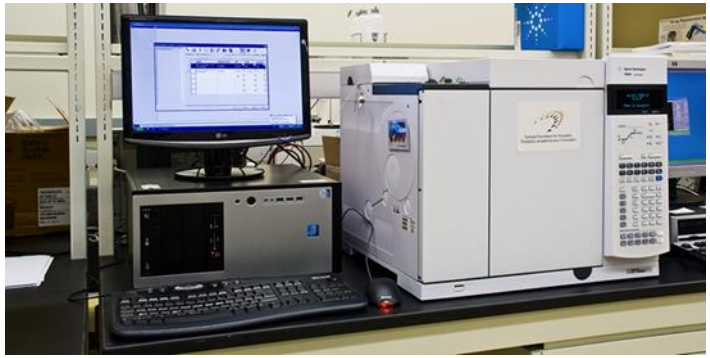
  A rubber plunger for a 10 mL PFS could be extracted at a ratio of 1 plunger per 10 mL of solvent

- For raw materials, a reasonable ratio is 1g/10mL
- For certain container closure systems (e.g., larger fill volume SVP), the final AET that may need to be considered as it might impact the extraction ratio

  Example

  For a 100 mL bag (bag weighs 10g), the unadjusted AET for a chronically administered DP is 15 µg/L. This AET may not be analytically achievable unless the extracted surface area to solution volume ratio is changed (for example, underfilling the bag).

2c. Extractable Studies: Analyzing the Extract



Analyses of the Extracts

- What has come out of the material?

Packaging Material

Extraction Solvents

Extraction conditions

Extraction ratio

Analyses of the extracts

Screening (Non-Target) Analysis

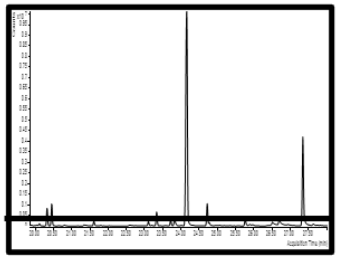
CHROMATOGRAPHIC SCREENING FOR ORGANIC EXTRACTABLES

DISCOVER ALL COMPOUNDS

ABOVE A TOX THRESHOLD (AET)

IDENTIFY ALL COMPOUNDS

(SEMI-)QUANTIFY ALL COMPOUNDS



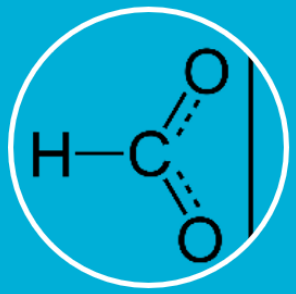
Screening for Organic Extractables

CHROMATOGRAPHIC SCREENING FOR ORGANIC EXTRACTABLES

DISCOVER
ALL COMPOUNDS

Analyses of the Extracts

Discover all extractable compounds: Orthogonal and complementary methodes

VOC	SVOC	NVOC		
				
HS-GC/MS	GC/MS	UPLC/MS	ICP/OES	IC
		(LC/UV, LC/CAD etc.)	ICP/MS	
Screening Volatiles	**Screening Semi-Volatiles**	**Screening Non-Volatiles**	GF/AAS **Extracted Elements**	**Extracted anions**

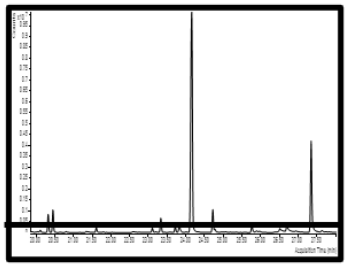
Extractables Profile : Potentially Leaching Compounds of Concern

Screening for Organic Extractables

CHROMATOGRAPHIC SCREENING FOR ORGANIC EXTRACTABLES

DISCOVER
ALL COMPOUNDS

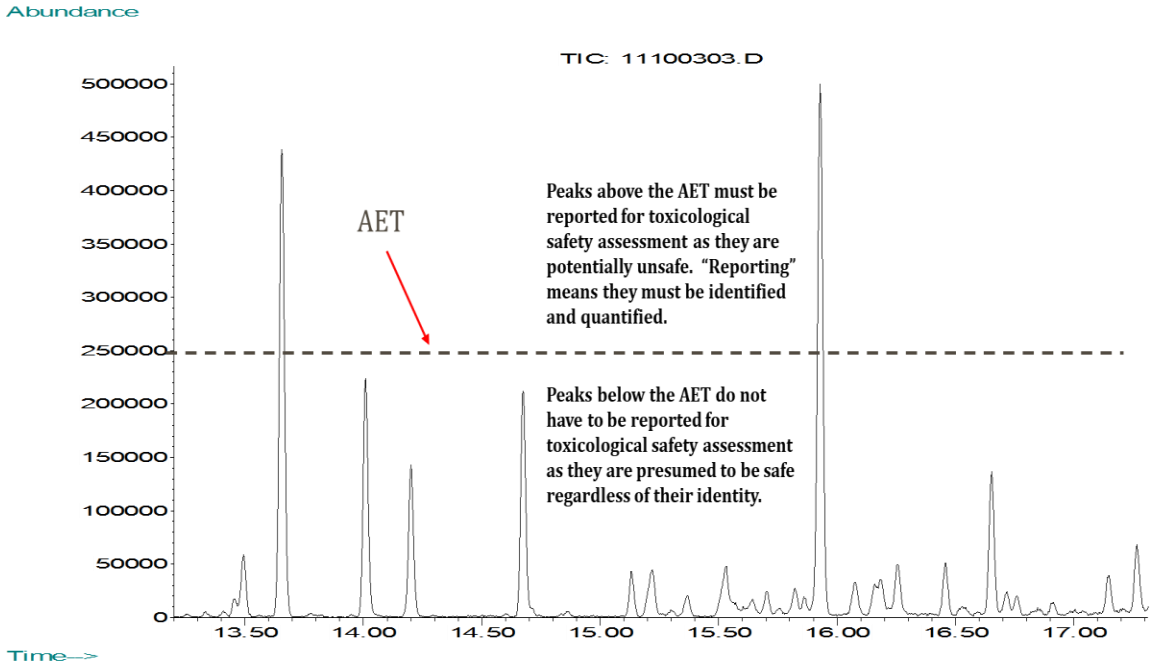
ABOVE A TOX
THRESHOLD (AET)



Analyses of the Extracts

Discover all extractable compounds: Above a Relevant Threshold

The AET Concept



The Analytical Evaluation Threshold (AET): that concentration of an extractable or leachable below which the compound does not have to be reported for safety assessment as its adverse effect on safety is negligible.

Analyses of the Extracts

Discover all extractable compounds: Above a Relevant Threshold

The AET Concept

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
PQRI for **PDP's**: SCT = see next slide

Exceptions: MBT, Nitrosamines, PNA's and "coherts of concern": as low as possible!

Discover all Extractable Compounds: Above a Relevant Threshold

The AET Concept

SCT: **For Parenteral Drug Products (PDP's)**

Tox Endpoint	Others	Sensitizer & Irritant	Carcinogen
Class	Class I	Class II	Class III
Threshold Level (µg/day)	50	5	1.5

SCT for **Non-Chronic** Treatments

SCT for **Chronic** Treatments

Discover all Extractable Compounds: Above a Relevant Threshold

The AET Concept

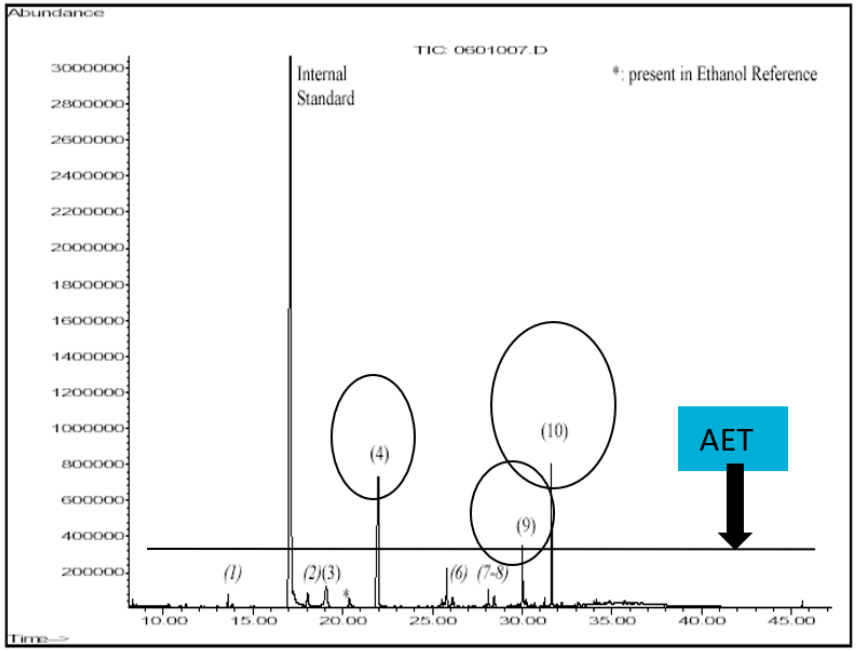
AET: Analytical Evaluation Threshold

Translate SCT

↓

into Analytical Threshold
for Extractable Studies

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



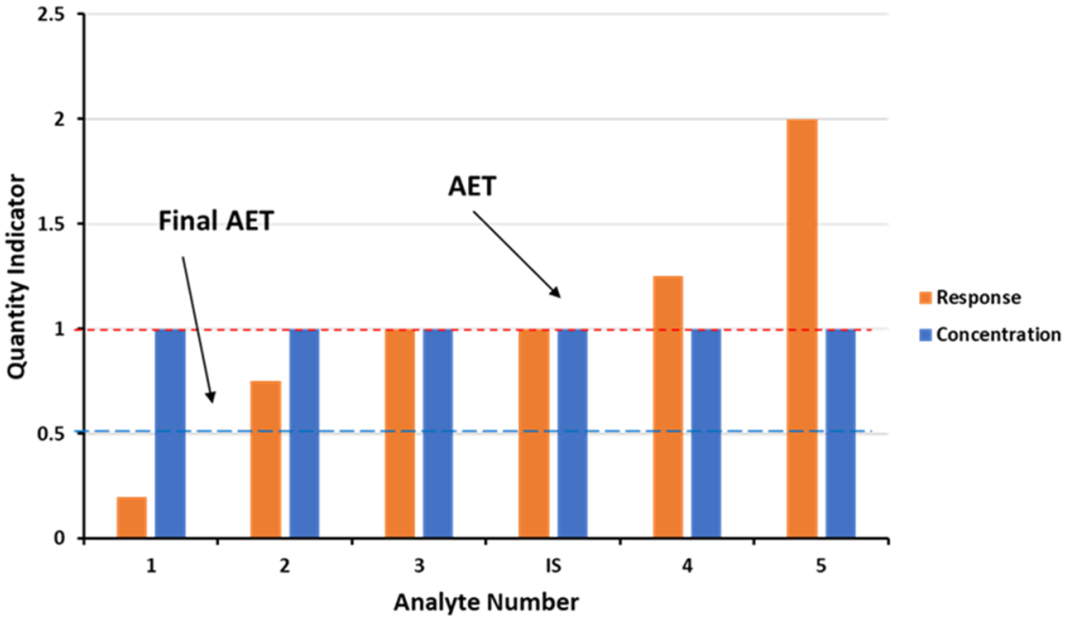
AET = ACTION LIMIT
ACTION = IDENTIFY and (SEMI-) QUANTIFY all compounds above the AET

Adjusting the AET

Using the AET as has been described presumes that all extractables/leachables have the same response factor. In practice, this is not the case and response factors can vary significantly from compound to compound.

Thus, the AET is adjusted downwards to account for response factor variation. Doing so means that poor responding compounds are properly accounted for.

Compounds 1 and 2 are poorly responding compounds and their response makes their concentrations appear to be lower than they really are. Thus, poorly responding compounds can be judged to be below the AET based on response when in fact they are at or above the AET based on their concentrations (false negative).



Compounds 4 and 5 are strongly responding compounds and their response makes their concentrations appear to be higher than they really are. Thus, strongly responding compounds can be judged to be at or above the AET based on response when in fact they are below the AET based on their concentrations (false positive).

Adjusting the AET

The AET is adjusted downward via the use of an Uncertainty Factor, UF:

Final AET = AET/UF

The Uncertainty Factor, UF, is calculated based on the distribution of response factors in a database populated by injecting reference standards at known concentration, noting their responses, and calculating their response factors.

UF= 1/(1-RSD)

where RSD is the relative standard deviations of the response factors in a database.

UF Values Employed by Nelson Labs	
Analytical Method	**UF**
HS-GC/MS	10
GC/MS	2
LC/MS (APCI or ESI)	5

Discover all Extractable Compounds: Above a Relevant Thrshold

The AET Concept: EXTRACTABLE STUDIES

Non-Chronic Treatment

Example :
1 Dose per day, administered to the Patient
Vial containing **1 Dose**
1 vial = 1 stopper (ext study on stopper)
Uncertainty factor UF (here; 2 as an example in Pharma)

Extractables AET

For SVP: try to extract the components with a solvent volume = volume of the DP in contact with the C/C-system

1 stopper extracted in 10 mL of solvent
Assessment of Extractables of the Rubber Stopper

$$\text{AET} = \frac{\textbf{5 µg/day } (\boldsymbol{SCT})}{\text{1 Dose/day}} \cdot \frac{\text{1 Dose}}{\boldsymbol{stopper\ (ext)}} \cdot \frac{\boldsymbol{stopper\ (ext)}}{10mL\ extract} \frac{1}{\text{2 (=UF)}} = \text{250 µg/L}$$

It is "suggested good practice" to screen** (as close to, or) **at the AET in an Extraction Study

Discover all Extractable Compounds: Above a Relevant Threshold

The AET Concept: LEACHABLE STUDIES

Non-Chronic Treatment

Example :
1 Dose per day, administered to the Patient
Vial containing **1 Dose**
1 vial = 1 stopper (ext study on stopper)
Uncertainty factor UF (here; 2 as an example in Pharma)

Leachables AET

Per vial, 10 mL of Drug Product is stored
Assessment of the Leachables in Drug Product

$$\text{AET} = \frac{\textbf{5 µg/day } (\boldsymbol{SCT})}{\text{1 Dose/day}} \cdot \frac{\text{1 Dose}}{\text{vial (lea)}} \cdot \frac{\textit{vial (lea)}}{10mL\ of\ DP\ in\ Vial} \frac{1}{\text{2 (=UF)}} = \text{250 µg/L}$$

*Per FDA, it is **mandatory** to identify and quantify all leachables above the AET (= 250 µg/L)*

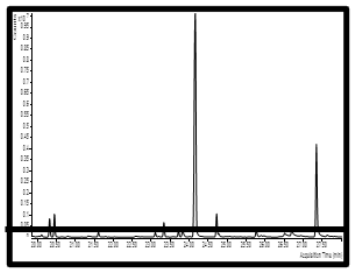
Screening for Organic Extractables

CHROMATOGRAPHIC SCREENING FOR ORGANIC EXTRACTABLES

DISCOVER
ALL COMPOUNDS

ABOVE A TOX
THRESHOLD (AET)

IDENTIFY
ALL COMPOUNDS

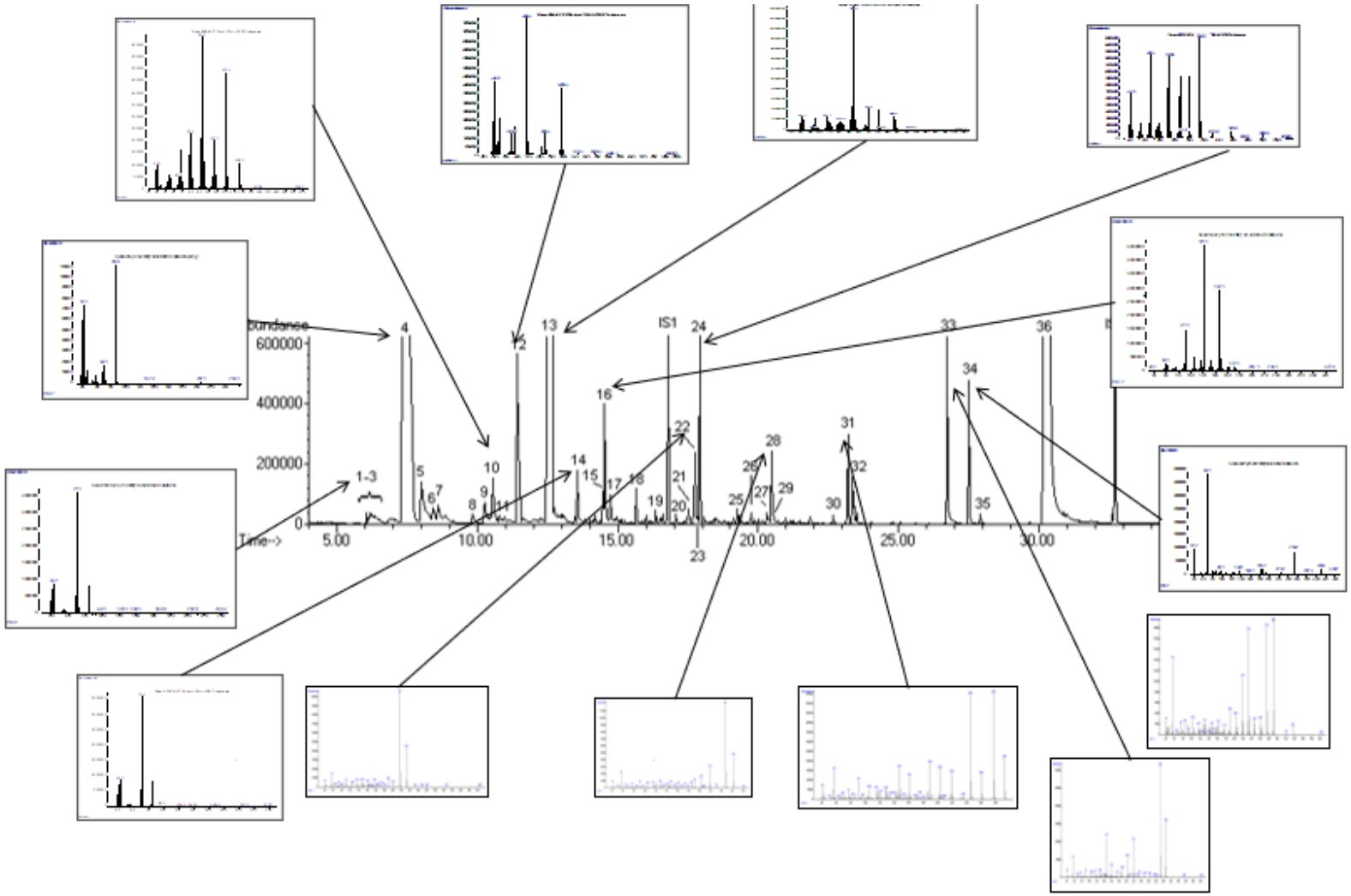


Discover all Extractable Compounds: Identification

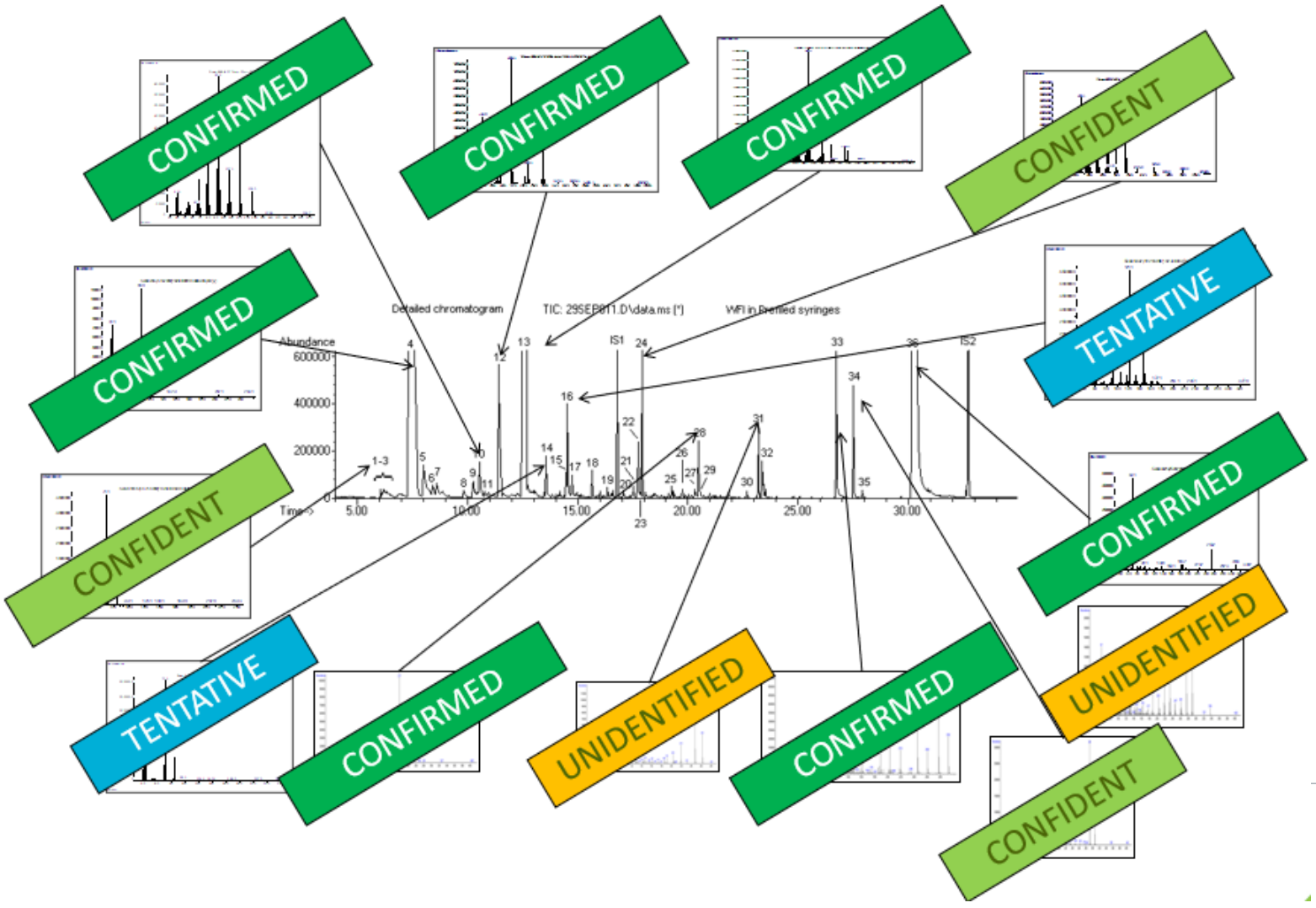
Why is Identification so important?

- **CORRECTLY** Linking a **Compound's Identity** to its **Toxicological Information**
- Identify **Bad Actors**?
- Important for **RRF correction** in semi-quantification (see later)
- Important to make a **correlation between extractables and leachables**
- Important to **select targets** for monitoring in **leachable studies**
  - ➢ Method development & validation

Discover all Extractable Compounds: Identification



Discover all Extractable Compounds: Identification



Discover all Extractable Compounds: Identification

CONFIRMED

- Authentic Standard Analysis (with CoA) confirms Mass Spectrum and Retention Time
- **CONFIRMED Class should be optimized** as Unequivocal Identifications are extremely important
- NELSON: the NELSON LABS Discovery and Screener Database

CONFIDENT

- Analytical Standard NOT available
- Excellent Mass Spectral Matching (MSM)with MS-library
- additional Expert Review & Verification

TENTATIVE

- Analytical Standard NOT available
- Lower fit with MS-library:
- Expert Review only reveals limited structural information, eg “Class” of compounds, Elemental Formula...

UNIDENTIFIED

Screening for Organic Extractables

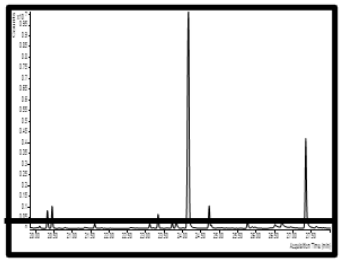
CHROMATOGRAPHIC SCREENING FOR ORGANIC EXTRACTABLES

DISCOVER ALL COMPOUNDS

ABOVE A TOX THRESHOLD (AET)

IDENTIFY ALL COMPOUNDS

(SEMI-)QUANTIFY ALL COMPOUNDS

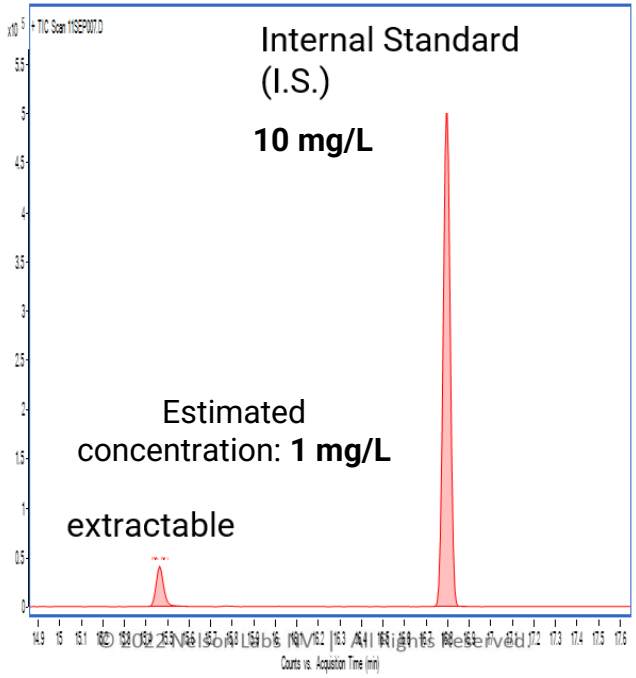


Discover all Extractable Compounds: Quantitation

Estimated Concentration

Assuming
$RF_{IS} = RF_{[EXT]}$

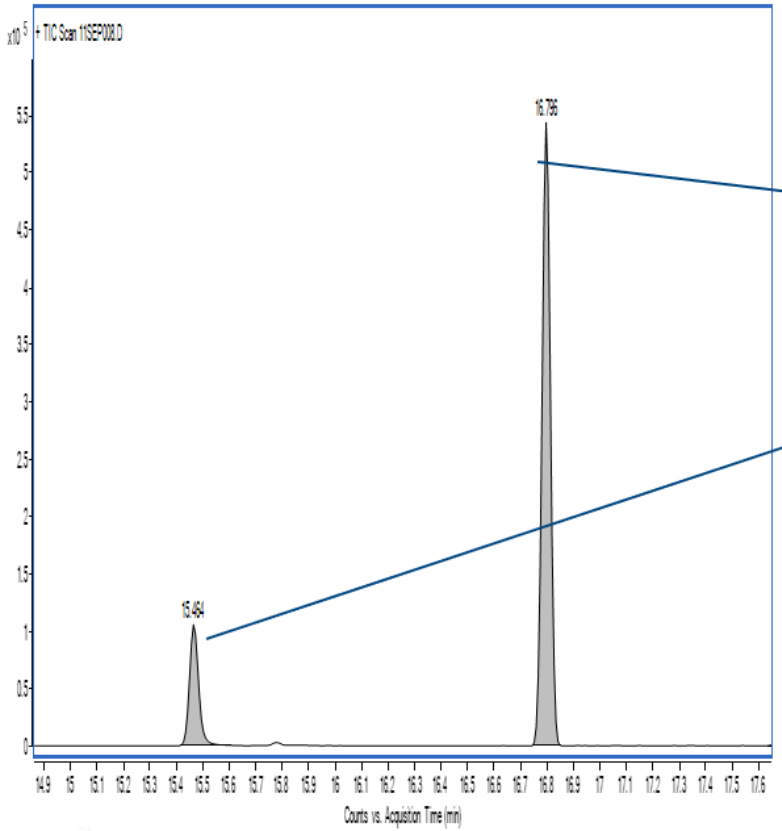
$$[Ext]_{Estimated} = \frac{Response_{Ext} \,.\, [I.S.]}{Response_{I.S.}}$$



Discover all Extractable Compounds: Quantitation

Relative response factor (RRF) corrected quantification

Step 1: Determine the RRF Factor for the ext compound



Analysis of EXT Standard
[EXT] = 10 ppm and [I.S.] = 10 ppm

$[I.S.]_{known}$ = 10 mg/L

$Area_{[I.S.]}$ = 100

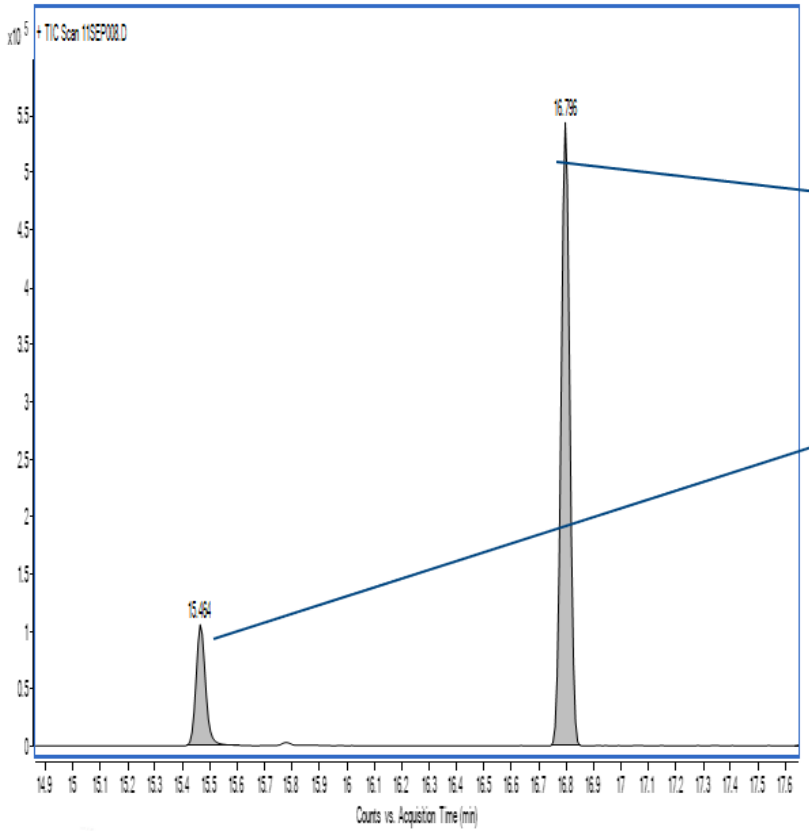
$[EXT]_{known}$ = 10 mg/L

$Area_{[EXT]}$ = 20

Discover all Extractable Compounds: Quantitation

Relative response factor (RRF) corrected quantification

Step 1: Determine the RRF Factor for the ext compound



Analysis of EXT Standard
[EXT] = 10 ppm and [I.S.] = 10 ppm

$[I.S.]_{known}$ = 10 mg/L

$Area_{[I.S.]}$ = 100

$[EXT]_{known}$ = 10 mg/L

$Area_{[EXT]}$ = 20

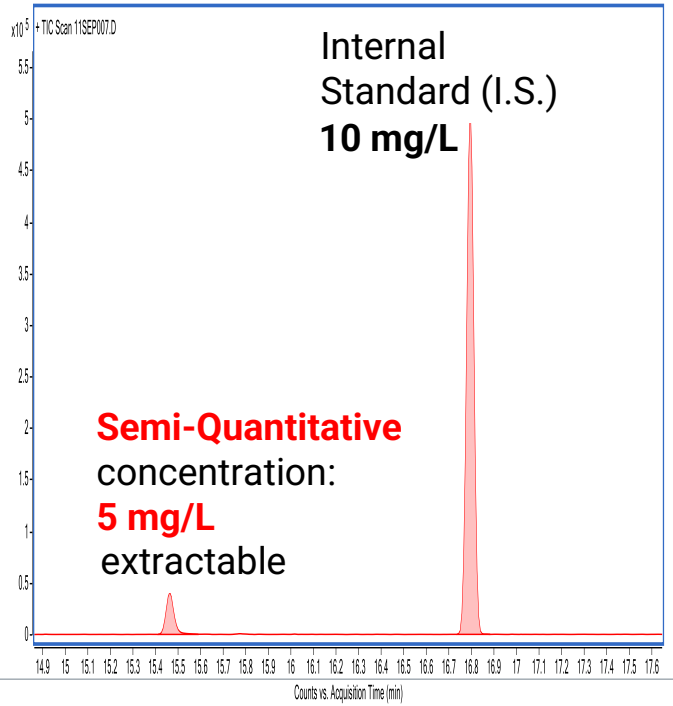
Relative Response Factor (RRF) EXT = 0,2

Chromatogram of EXT STANDARD

Discover all Extractable Compounds: Quantitation

Semi-Quantitative Concentration

Step 2: Using experimentally derived **RRF = 0.2**



$$[Ext]_{Semi-Quant} = \frac{Response_{Ext} \,.\, [I.S.]}{\boldsymbol{RRF_{ext}}\, Response_{I.S.}}$$

PDA Training Course Extractables & Leachables

Thanks