THE ANALYTICAL EVALUATION THRESHOLD:

PDA TRAINING COURSE
EXTRACTABLES – LEACHABLES
VIENNA
23 – 24 OCT 2025

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OVERVIEW

1. **E&L testing - basic principles**

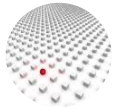
2. The analytical evaluation threshold
   - 2.1 Definition and concepts
   - 2.2 The safety concern threshold (AET)
   - 2.3 The maximum daily dose (MDD)
   - 2.4 The uncertainty factor (UF)
   - 2.5 Examples

3. Summary

1. E&L testing – basic principles

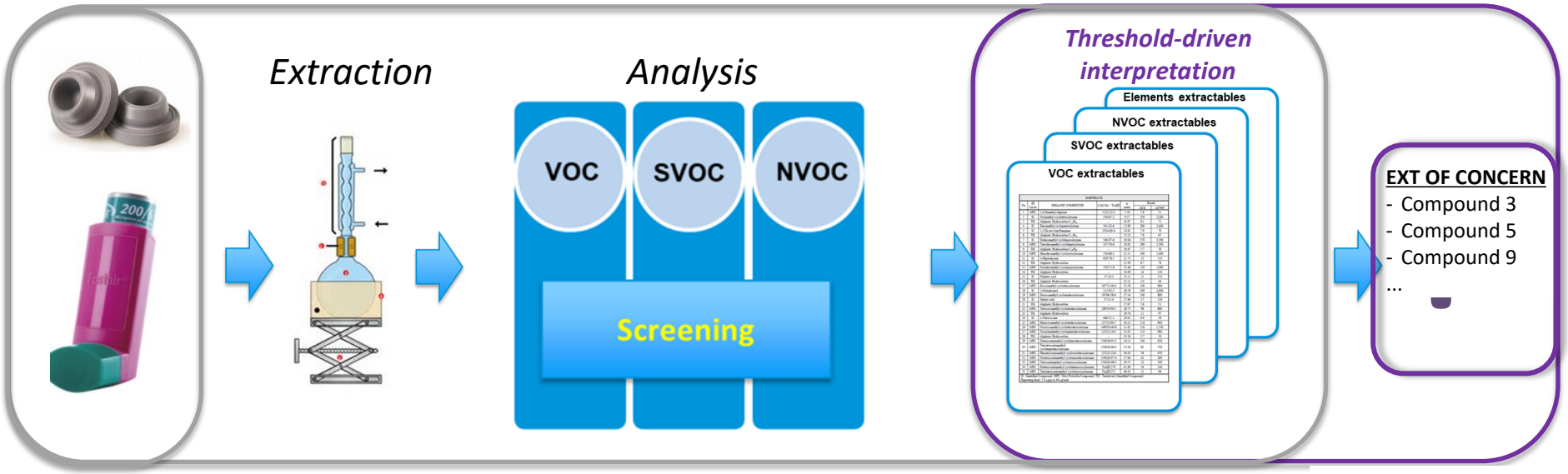
Analytics | **Safety Threshold driven approach** | **Toxicology**

Extractables study		Leachables Study	
	PHARMACEUTICAL CONTAINER	DRUG PRODUCT	
	What **CAN** come out	What **DOES** come out	
	**FOCUS: Identification**	Bridging → **FOCUS: Quantification**	
	Worst case conditions	Normal conditions	

	Screening	Bridging → Targeted & Screening	

1. E&L testing – basic principles

TYPICAL EXTRACTABLES STUDY



Packaging (test material)

Comprehensive EXT data set

Target compounds for LEA study

Applying threshold approach filters out "Extractables of Concern"

- Safety evaluation on results of an extractables study
- Critical information for leachables study

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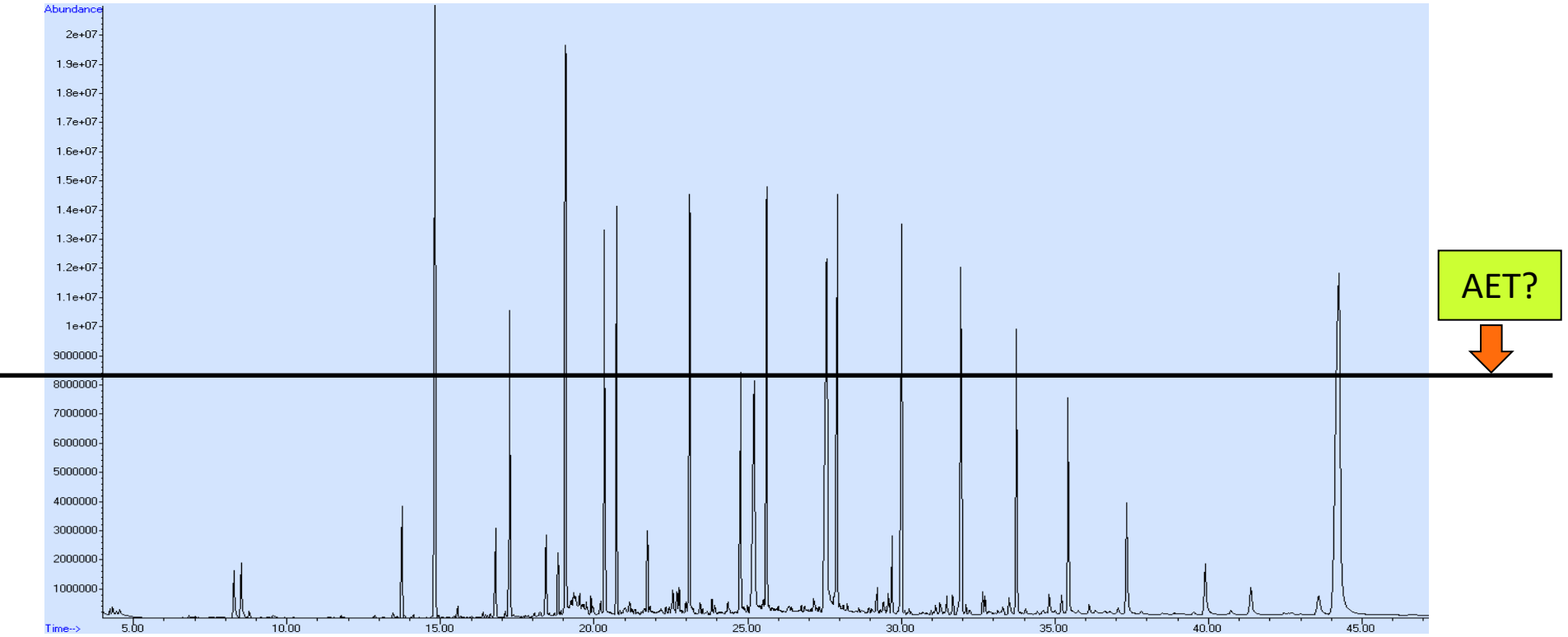
2.1 The AET– definition and concepts

AET = is defined as the threshold at or above which a chemist should identify and quantify (semi-quantification) a particular leachable and/or extractable and report it for potential toxicological assessment.



2.1 The AET– definition and concepts

Which information do we need to calculate the (final)AET?

$$\text{(final) AET} = \frac{\text{SCT}}{\text{MDD x UF}}$$

1. (generic) **toxicological threshold** (~in µg/day)

2. A **maximum daily dose/exposure to the patient**
(~in L/day for a leachables study)
(~in units/day for an extractables study)

3. An analytical **uncertainty factor**

= translation of toxicological threshold (µg/day) to a an analytical concentration (µg/L or µg/unit)

2.2 The AET– safety concern threshold (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"*

$$\text{(final) AET} = \frac{\text{SCT}}{\text{MDD x UF}}$$

PQRI (Product Quality Research Institute)

- SCT dependent on the **administration route** of the final product:
  - **0.15 µg/day** for OINDPs (Orally Inhaled and Nasal Drug Products)
  - **1.5 µg/day** (cf. TTC of ICH M7) for PDPs (Parenteral Drug Products)

  - ODPs: Ophthalmic Drug Products (concentration based thresholds)
  - Oral and Topical/Transdermal products (no thresholds defined)

2.3 The AET – maximum daily dose

For a **leachables** study (~results in **µg/L**)

Maximum daily dose volume (in L/day)

-> For e.g. ***1 mL/day*** *for a vaccin ,* ***0.5 L/day*** *for a LVP drug product*

$$\text{(final) AET} = \frac{\text{SCT}}{\text{MDD x UF}}$$

For an **extractables** study (~results in **µg/test item** or **µg/g**)

Maximum test items/g of test item exposed per day

-> For e.g. a rubber stopper of a vial, and 2 vials are administered per day, ***2 rubber stoppers/day*** *are exposed to the patient*

2.4 The AET– the uncertainty factor

ANALYTICAL UNCERTAINTY FACTOR

To account for the analytical uncertainy of the screening method (response factor variation)

Previously: UF of 2 was typically accepted (PQRI (OINDP))

$$\text{(final) AET} = \frac{\text{SCT}}{\text{MDD x UF}}$$

Current state of the art:

- Based on In-house database:

$$UF = \frac{1}{(1 - RSD)^*}$$

*RSD = relative standard deviation of response factors

ISO 10993-18

USP1664

ICHQ3E

Table 1: Overview of the statistical evaluation of the RRF values for GC/MS and LC/MS (APCI and ESI)

Technique/ Method	Nelson Labs SOP	N° of RRF Entries	Average RRF	Standard Deviation	RSD	Uncertainty Factor (UF)
GC/MS	SOP0487 SOP0245	2194	0.61	0.30	0.49	2
LC/MS (APCI)	SOP0264	652	0.84	0.67	0.80	5
LC/MS (ESI)	SOP0268	201	1.04	0.79	0.76	(4) =>5

2.5 The AET– Examples

Leachable study (~in µg/L drug product)

Polio Vaccine
Safety concern threshold = 1.5 µg/day
Max daily dose volume: 0.001 L/day

mAB for treatment of arthritis
Safety concern threshold = 1.5 µg/day
Max daily dose volume: 0.020 L/day

$$\text{(final) AET} = \frac{\text{SCT}}{\text{MDD} \times \text{UF}}$$

$$\text{(final) AET} = \frac{1.5\ \mu g/day}{0.001\ L/day \times UF} = \frac{1500\ \mu g/L}{UF}$$

$$\text{(final) AET} = \frac{1.5\ \mu g/day}{0.020\ L/day \times UF} = \frac{75\ \mu g/L}{UF}$$

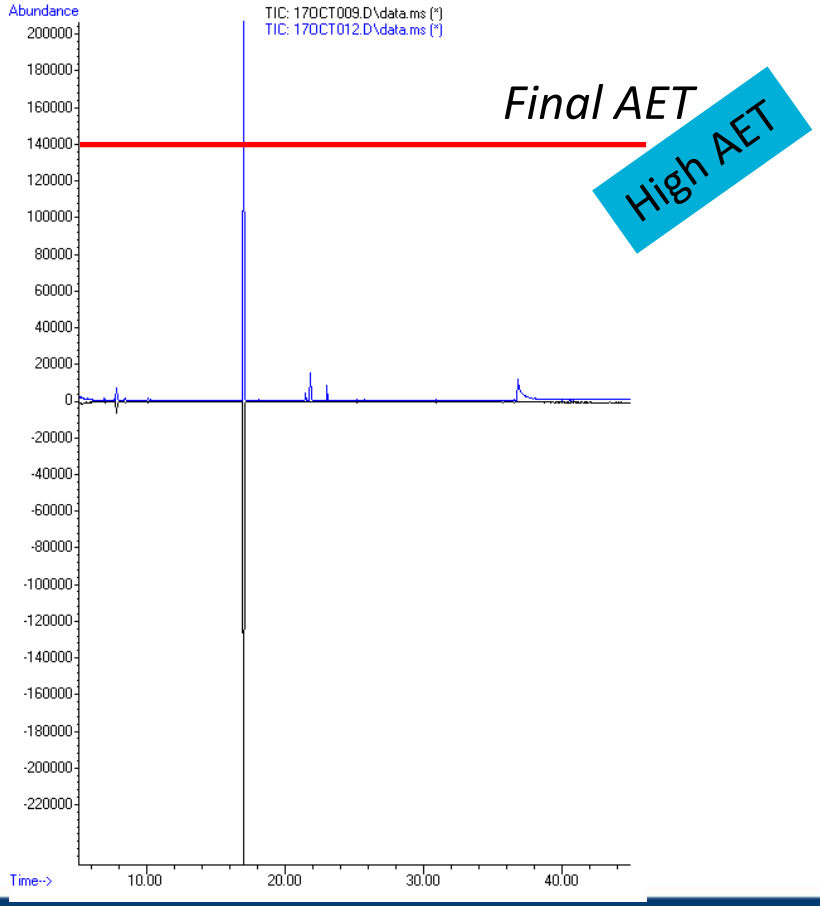
UF = 2 for (HS-)GC/MS and 5 for HRAM-UPLC/MS

2.5 The threshold approach – organic compounds

Polio Vaccine

Safety concern threshold = 1.5 µg/day

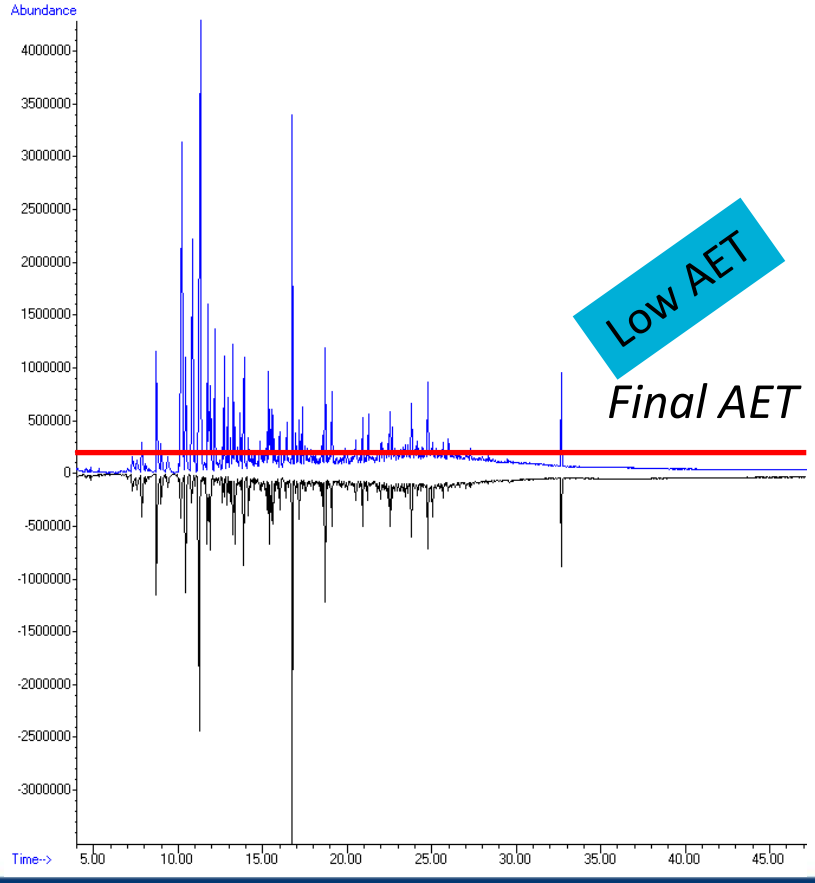
Max daily dose volume: 0.001 L/day



mAB for treatment of arthritis

Safety concern threshold = 1.5 µg/day

Max daily dose volume: 0.020 L/day



2.5 The threshold approach – organic compounds

Extractables study (~in µg/test item)

Barrel of a prefilled syringe (containing 0.8 mL of DP)
-> 1 prefilled syringe is administered maximum per day
Safety concern threshold = 1.5 µg/day
Maximum daily exposure to a patient: 1 barrel/day

$$\text{(final) AET} = \frac{1.5\ \mu g/day}{1\ barrel/day \times UF}$$

$$= \frac{1.5\ \mu g/barrel}{UF}$$

UF = 2 for (HS-)GC/MS and 5 for HRAM-UPLC/MS

2.5 The threshold approach – organic compounds

Extractables study (~in µg/test item)

Label of a LDPE bottle (90 mL fill volume, containing 60 max. daily doses of 1.5 mL)
Safety concern threshold = 1.5 µg/day
Maximum daily exposure to the patient: 1/60 label/day

$$\text{(final) AET} = \frac{1.5\ \mu g/day}{1/60\ label/day \times UF}$$

$$= \frac{90\ \mu g/label}{UF}$$

UF = 2 for (HS-)GC/MS and 5 for HRAM-UPLC/MS

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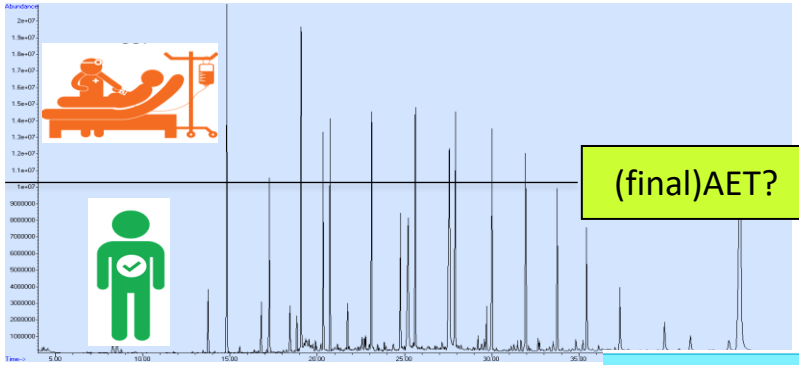

Generic tox threshold

PQRI
Product Quality Research Institute

-> 1.5 µg/day for PDP

$$\text{(final) AET} = \frac{\text{SCT}}{\text{MDD} \times \text{UF}}$$

Analytical uncertainty factor

$$UF = \frac{1}{(1 - RSD)}$$

Maximum daily dose