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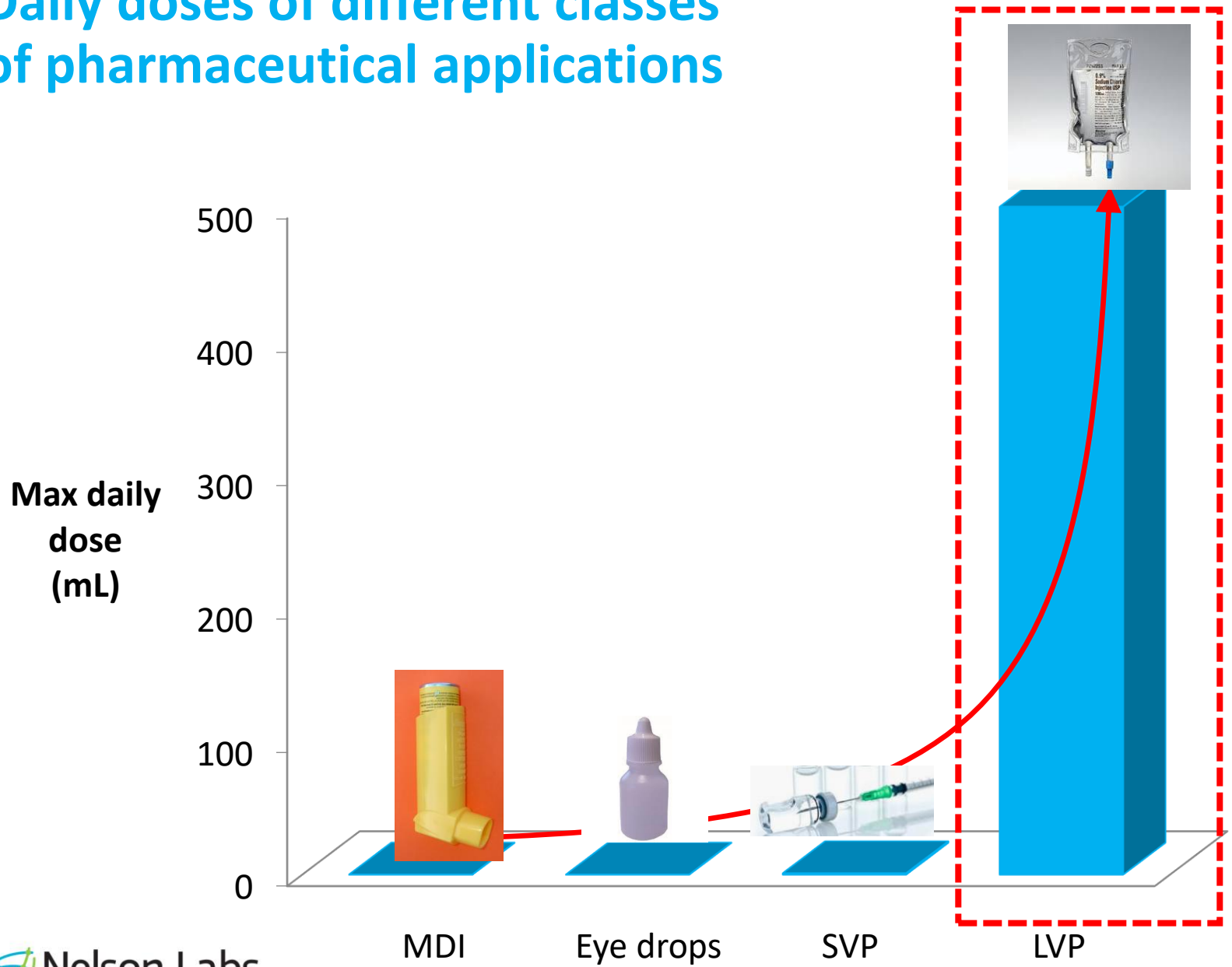
Challenges for testing of leachables migrated from a bag system into parenteral solutions

PIETER VAN WOUWE

Daily doses of different classes of pharmaceutical applications



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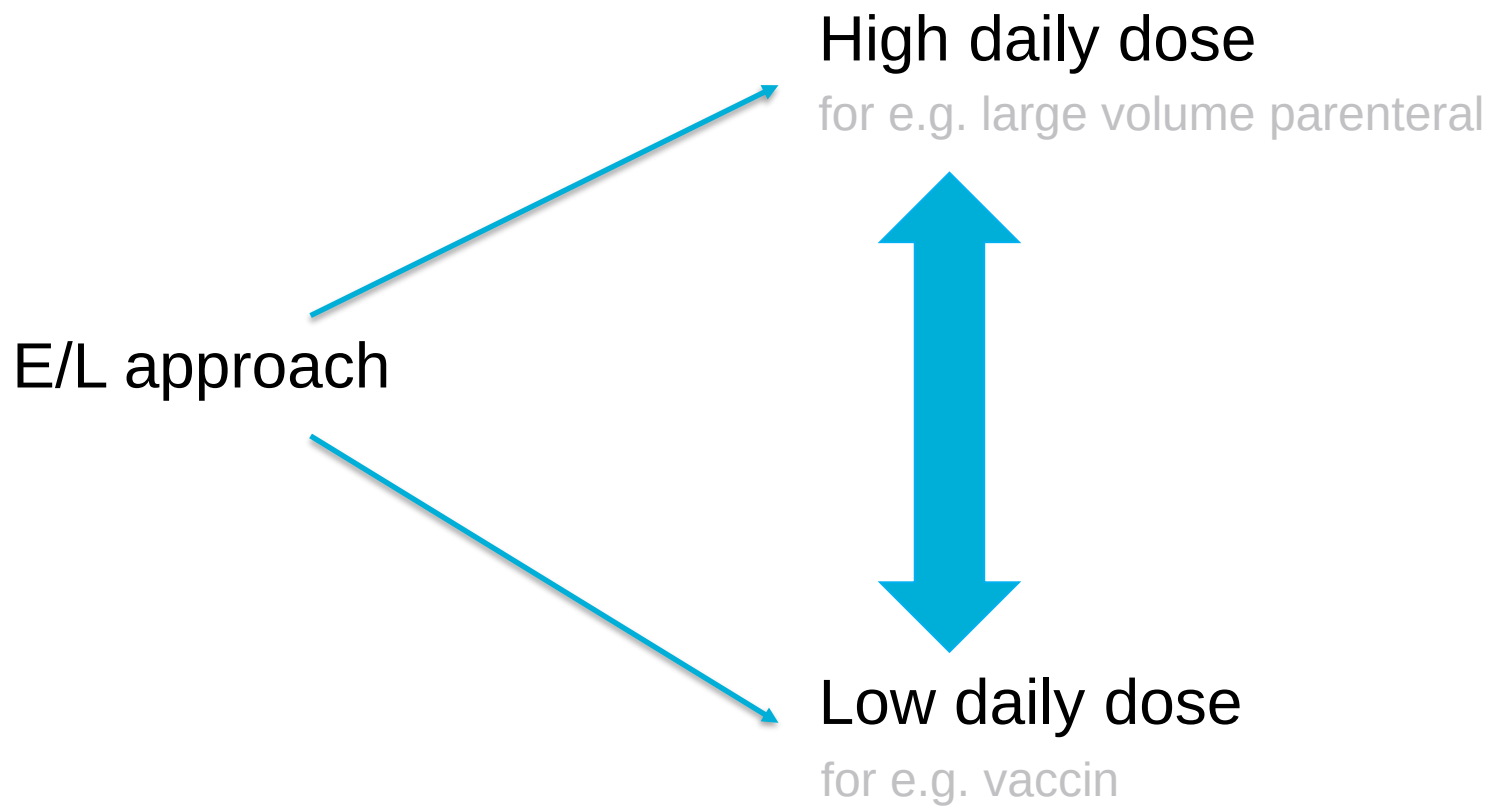
High daily dosed drug products require a different E/L approach



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Key tasks to approach LVP leachable studies

Leachable study with high daily dose

adjust “transition” from EXT to LEA study

adjust design of LEA study

anticipate additional work

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Strong interaction between analytics and toxicology is crucial in successful large volume parenteral leachable studies

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Outline

Transition from extractable to leachable study

Design of the leachable study

Further steps based on leachable data

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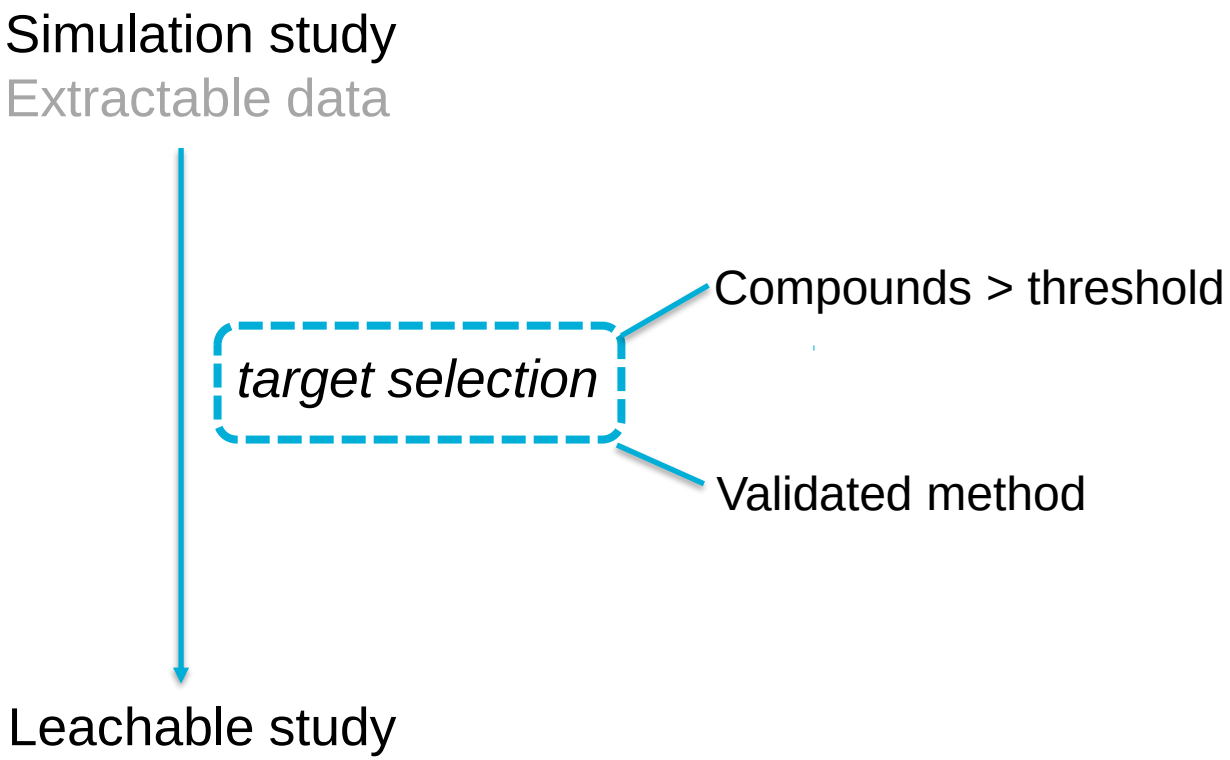
“Critical” target compounds should be selected from extractable data, and should be monitored in the leachable study



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Safety concern threshold for parenteral drug products (PDP, PQRI)

Specific to route of administration

Threshold below which a leachable would have a dose so low as to present negligible safety concerns from mutagenic and non mutagenic toxic effects

PQRI thresholds

Tox endpoint	General tox.	Sensitizer & irritant	Carcinogen
Class	Class I	Class II	Class III
Threshold level (µg/day)	5	5	1.5 (PDP-SCT)

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The analytical evaluation threshold for screening methodology

$$\text{Final AET} \quad (\mu g/L) = \frac{1.5\ \mu g/day\ (SCT)}{\text{Max daily dose (L/day)} \times \text{uncertainty factor}}$$

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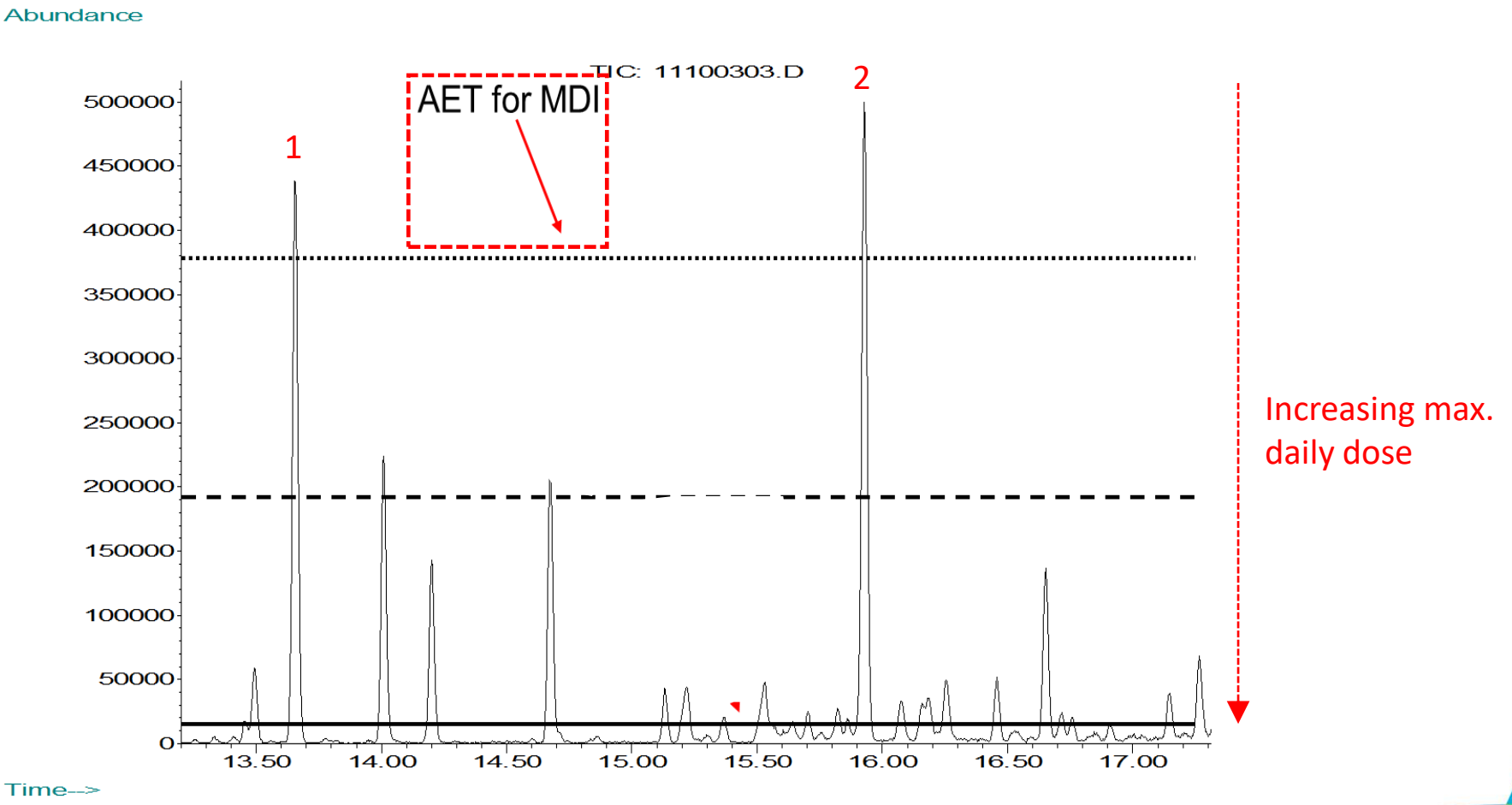
Lower AETs in extractable study result in more target compounds for leachable study



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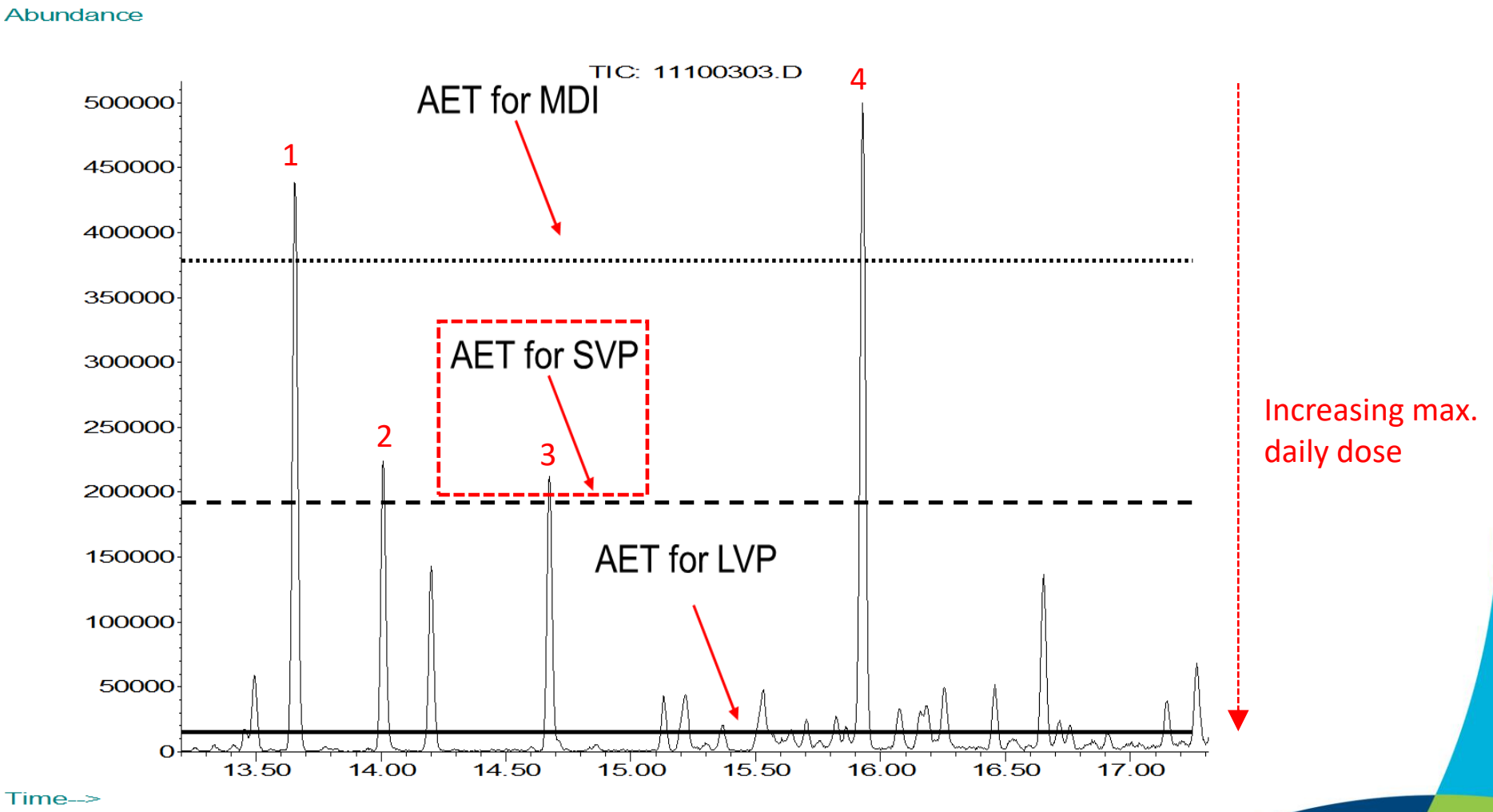

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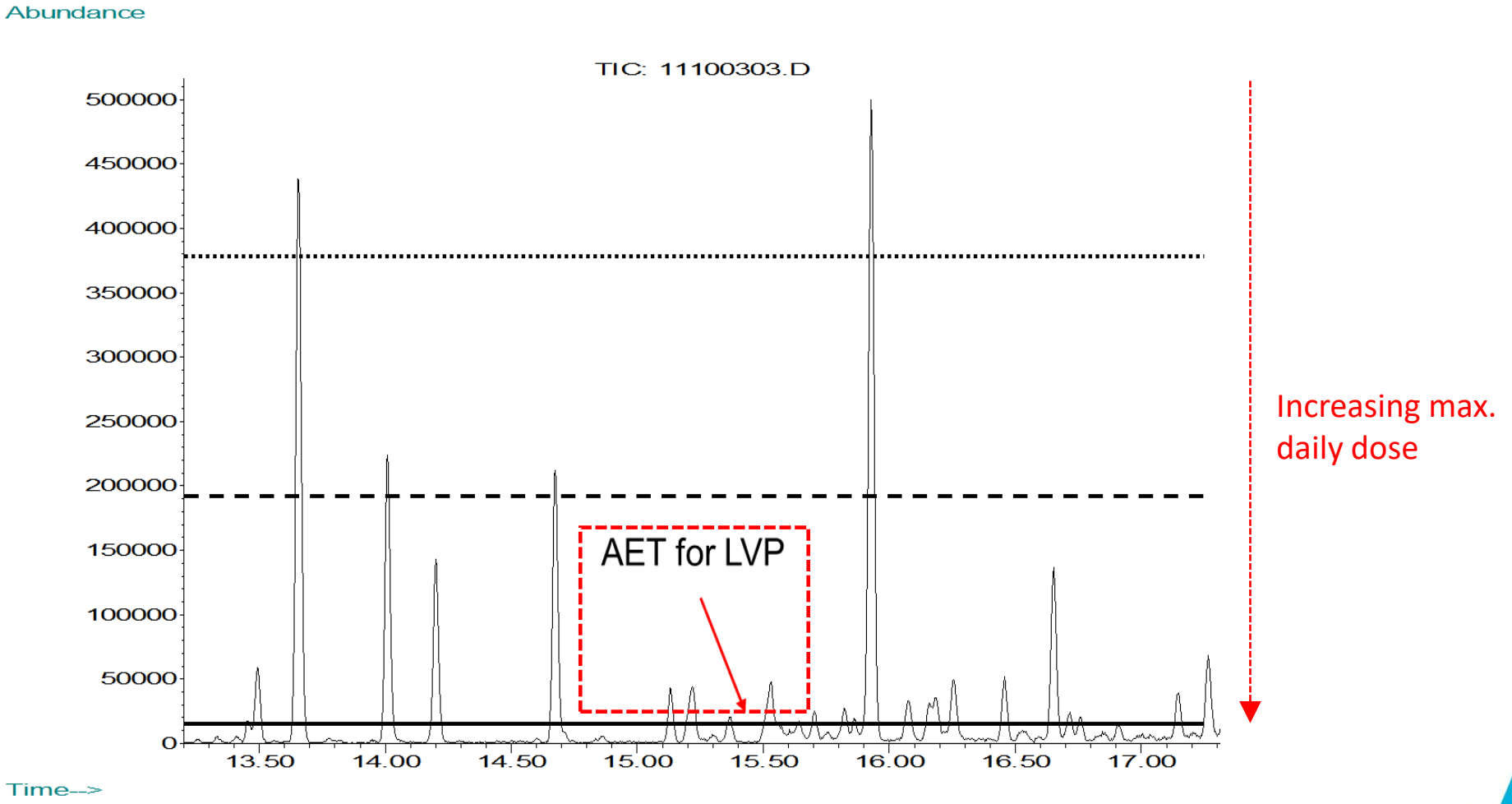
Lower AETs in extractable study result in more target compounds for leachable study



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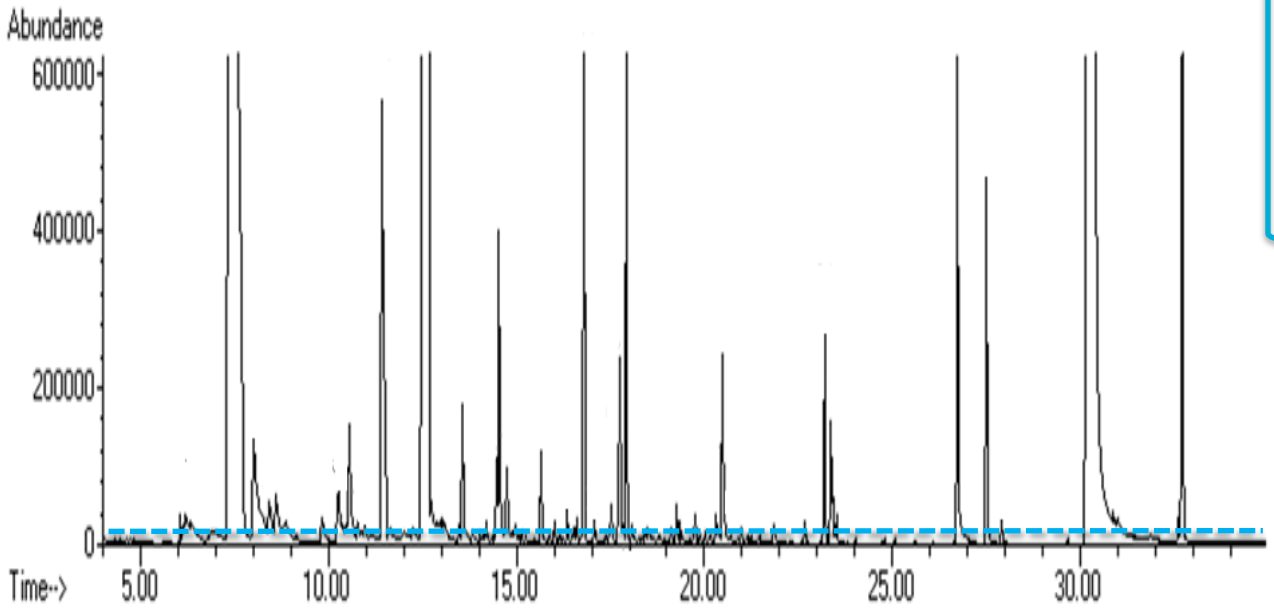
High number of compounds above the (final) AET in the simulation study

!! 60 differential compounds > final AET !!

	µg/l
COMPOUND 1	8
COMPOUND 2	8.2
COMPOUND 3	5.9
COMPOUND 4	5.6
COMPOUND 5	6.2
COMPOUND 58	6.2
COMPOUND 59	170
COMPOUND 60	110



SCT ~ Final AET (1.5 µg/day) ~ 3 µg/l

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Toxicological data should support further refining of target selection

Simulation study

Extractable data

target selection

toxicologist

Leachable study

Permitted Daily Exposure values as valuable alternative for PQRI limits

Permitted Daily Exposure (PDE):

-compound specific
-proposed by toxicologist based on data
-typically orders of magnitude higher than PQRI threshold

PQRI thresholds:

-generic thresholds
-conservative

Tox endpoint	General tox.	Sensitizer & irritant	Carcinogen
Class	Class I	Class II	Class III
Threshold level (µg/day)	5	5	1.5 (PDP-SCT)

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Evaluation of extractable data against compound specific final AET (PDE based)

	PDE (µg/day)	Final "cmp" specific AET (µg/l)		Result (µg/l)
COMPOUND 1	38800	11800	>	8
COMPOUND 2	600	182	>	8.2
COMPOUND 3	5000	1510	>	5.9
COMPOUND 4	3000	908	>	5.6
COMPOUND 5	50	15	>	6.2
COMPOUND 6	153	46	<	62
…				
COMPOUND 17	5	1.5	<	3.2
…				
COMPOUND 23	5	1.5	<	1.6
…				
COMPOUND 26	5	1.5	<	3.2
…				
COMPOUND 58	50	15	>	6.2
COMPOUND 59	100000	30300	>	170
COMPOUND 60	800	242	>	110

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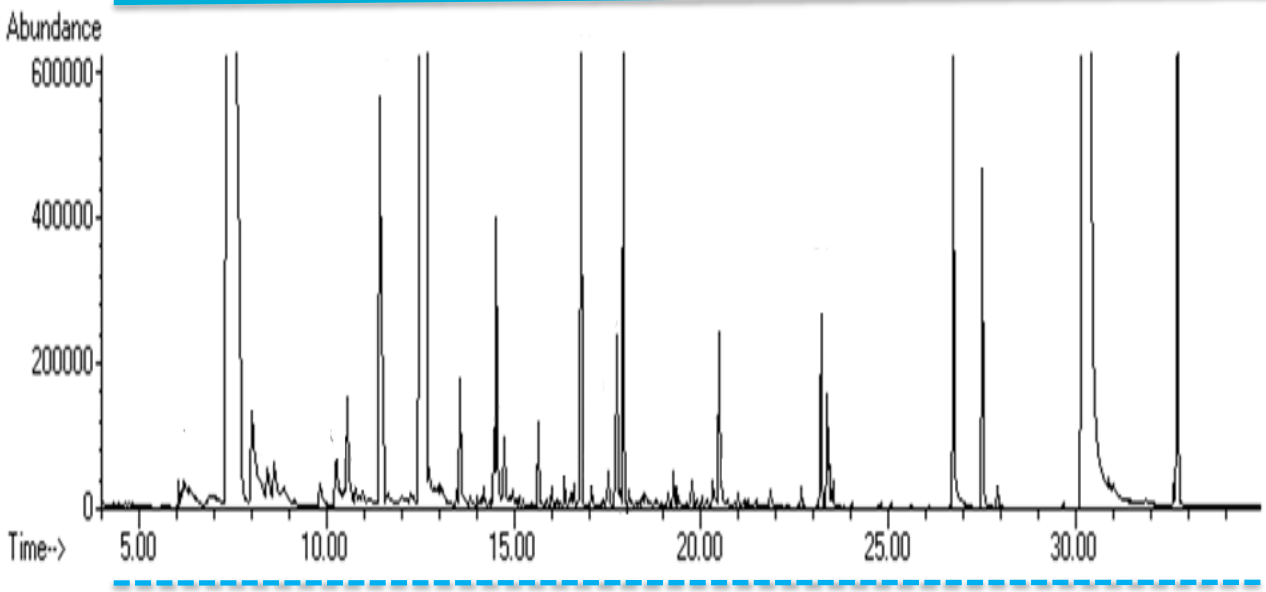
Only limited amounts of target compounds to be monitored in leachable study

Only 4 compounds > compound specific (PDE based) final AET

!! 60 compounds > final AET !!



COMPOUND 1
COMPOUND 2
COMPOUND 3
COMPOUND 4
COMPOUND 5
COMPOUND 6
...
COMPOUND 17
...
COMPOUND 23
...
COMPOUND 26
...
COMPOUND 58
COMPOUND 59
COMPOUND 60

Final AET
(5 µg/day) ~ 3 µg/m²

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Outline

Transition from extractable to leachable study

Design of the leachable study

Further steps based on leachable data

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Leachable study consists of targeted methods and screening

Targeted
(typically validated method)

(Expected) target compounds

screening

Unexpected compounds

All compounds above 1.5 or 5 µg/day should be identified!

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Target compounds preferably addressed by validated methods

GC-QQQ, LC-QQQ,…

Further optimized in function of target compound(s)

Specificity, LOD, LOQ, accuracy, precision, calibration range (ICH Q2D)

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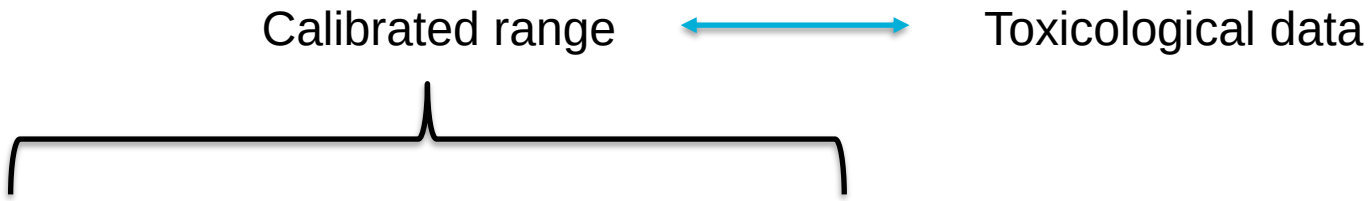
Calibration range and LOQ are based on toxicological data (PDE)



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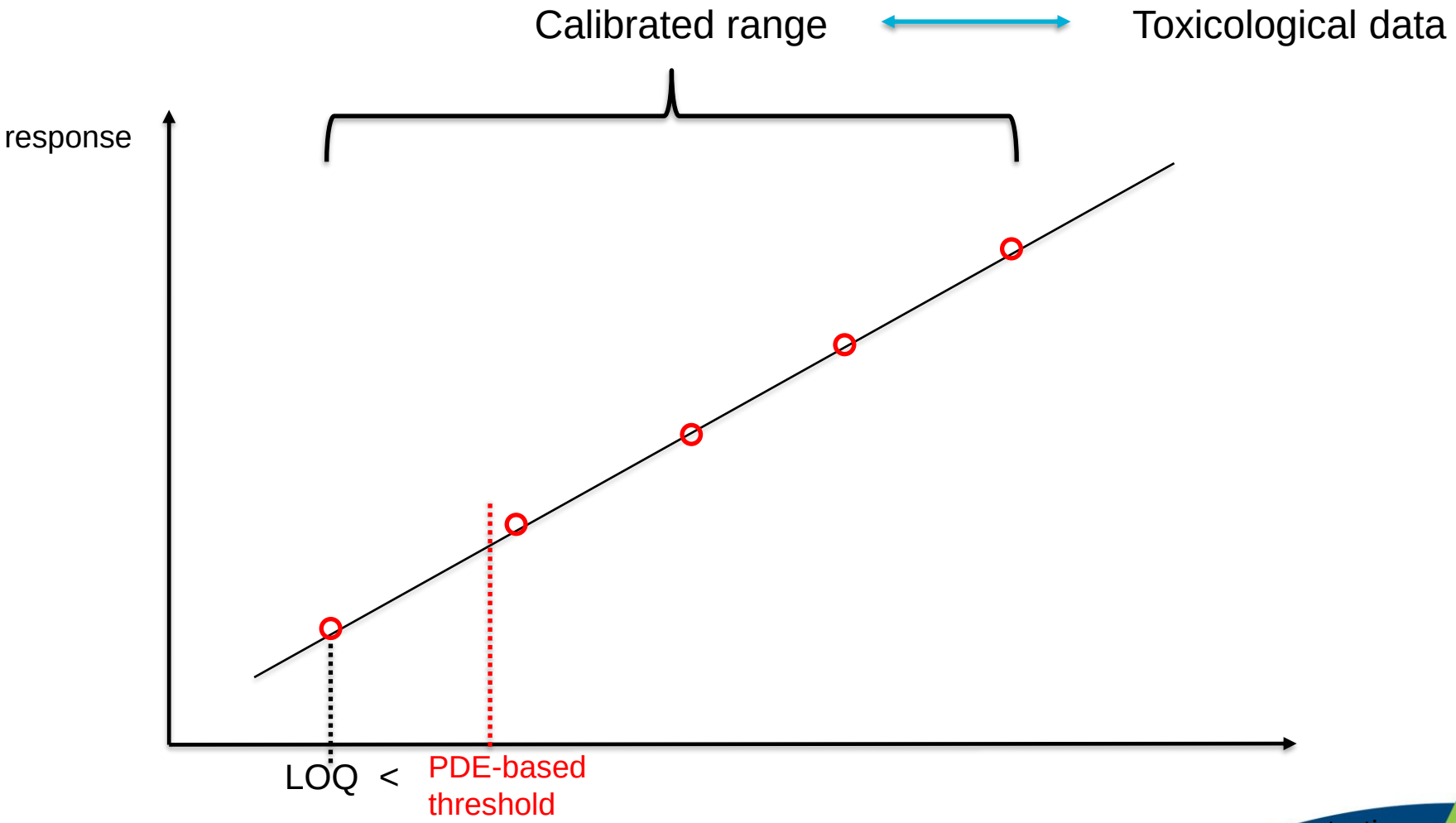

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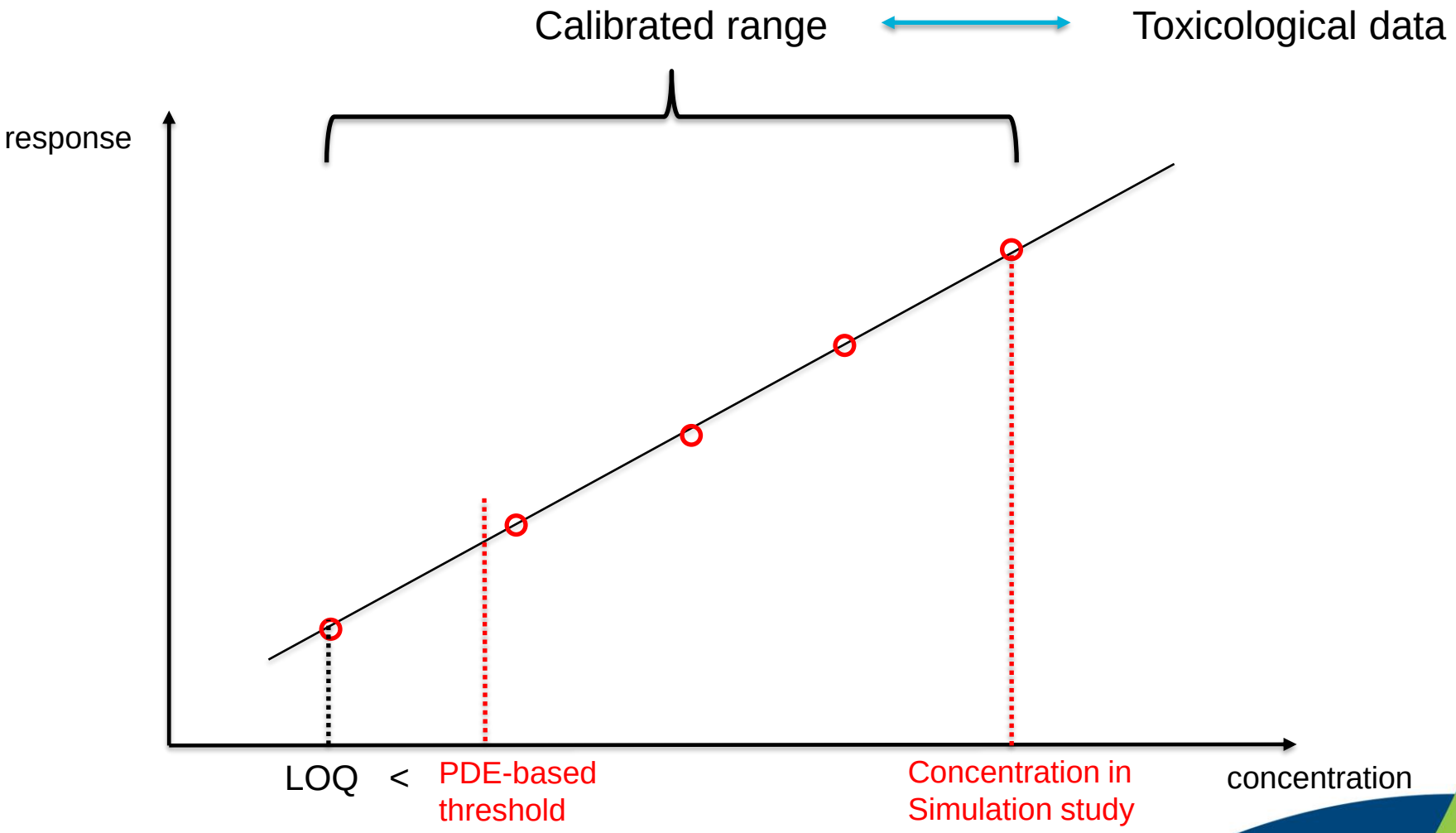

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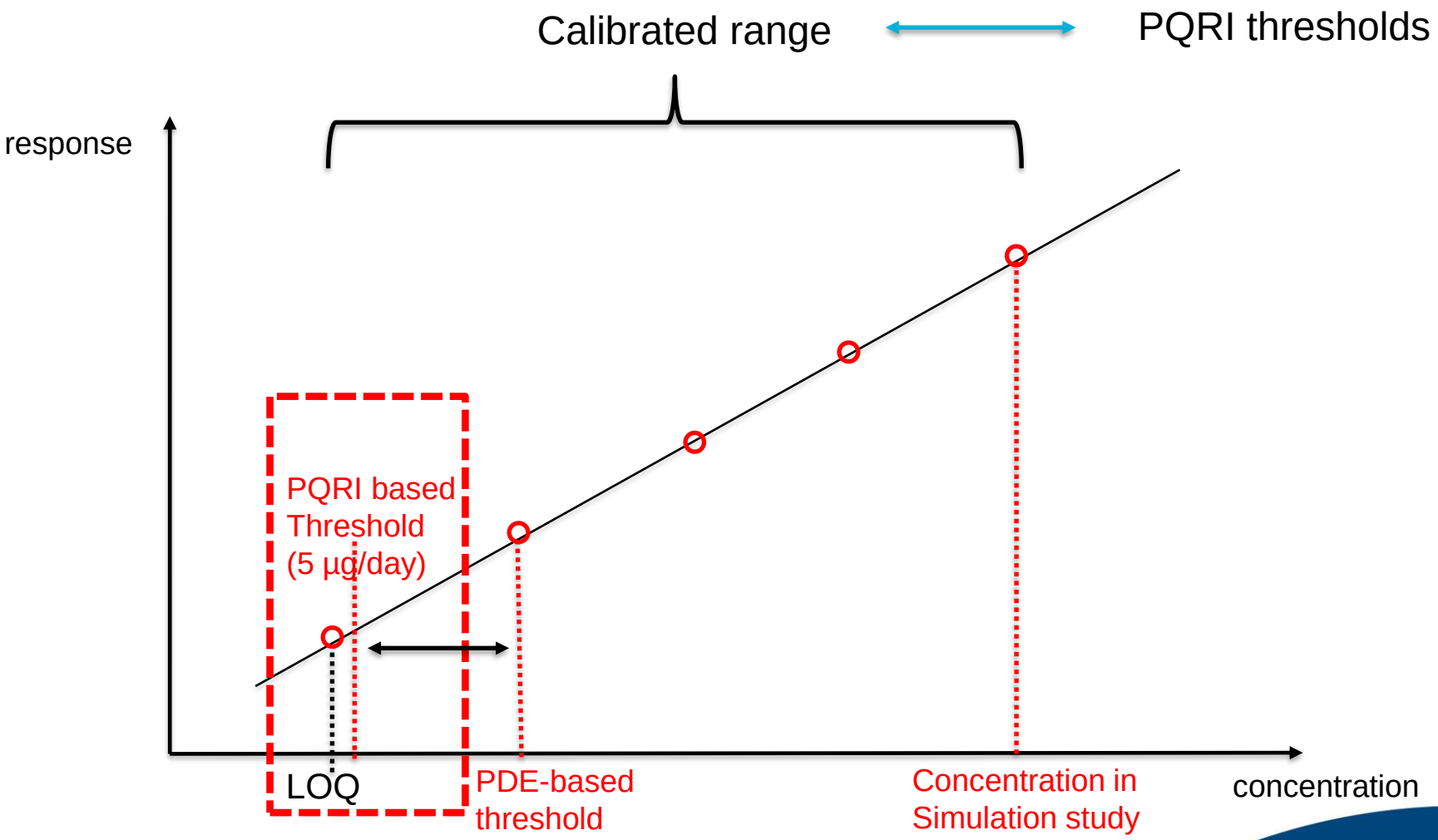
Calibration range and LOQ are based on PQRI thresholds



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Leachable study should consist of targeted methods and screening

Targeted
(typically validated method)

(Expected) target compounds

screening

Unexpected compounds

All compounds above 1.5 or 5 µg/day should be identified!

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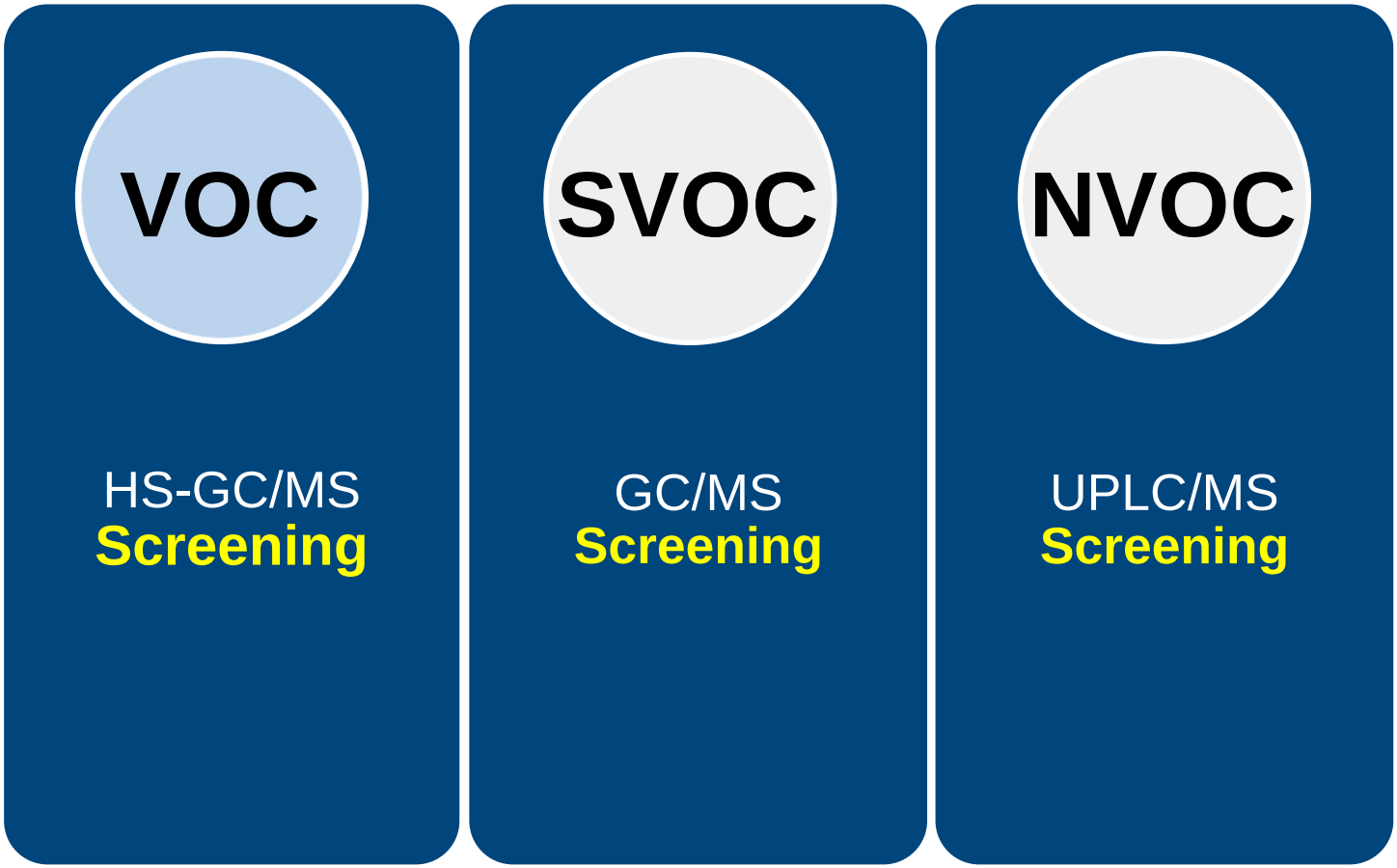
Screening with Nelson Labs state-of-the-art methodology



-Nelson Labs screener database
-commercial libraries (NIST, Wiley)

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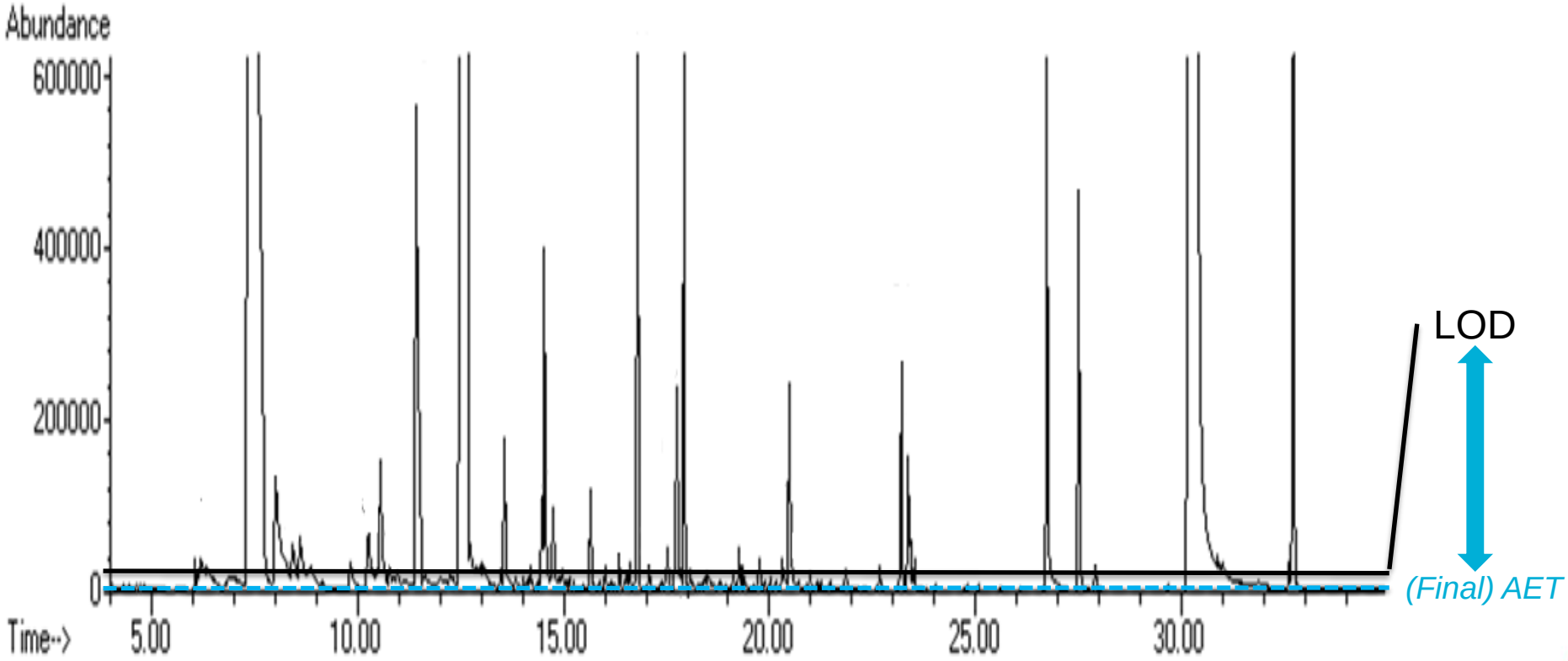
What if the final AET can not be reached



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Adjusting both the ageing/leaching set-up and sample preparation might lead in reaching the (final) AET level

Leaching/ageing Set-up

Sample preparation

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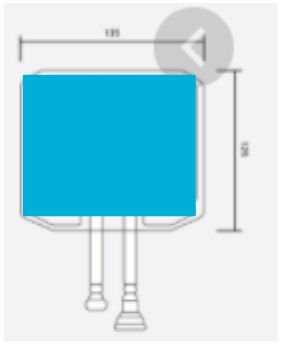
The use of small scale versions of the commercial bag system allows screening at lower AETs

Commercial bag (for e.g. 1 L):
- low surface/volume
- low leachable concentration

Small scale bag (for e.g. 250 mL)
- high surface/volume
- high leachable concentration



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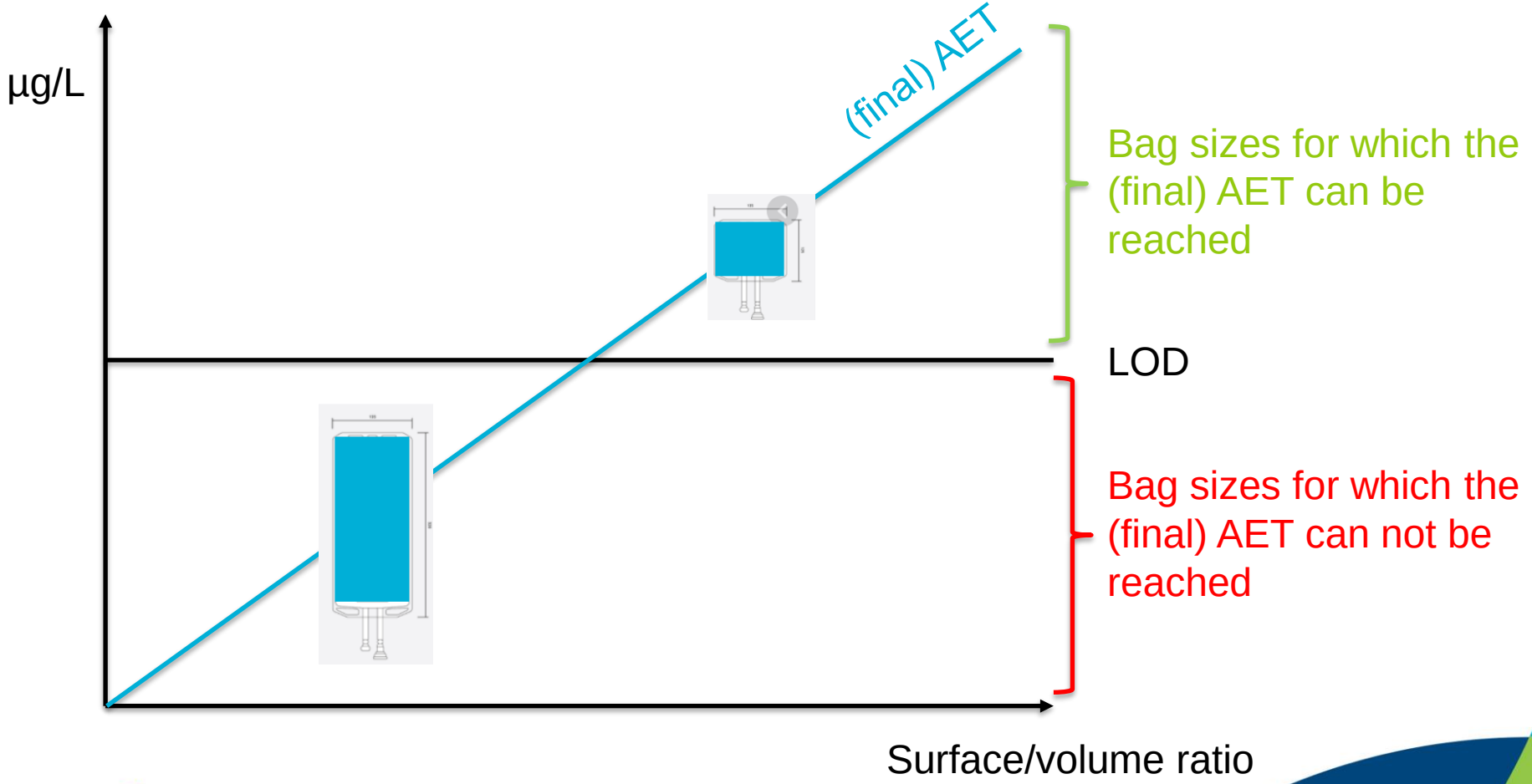
The aimed (final) AET will linearly increase with the surface to volume ratio of the bag (if concentrations < solubility limits)



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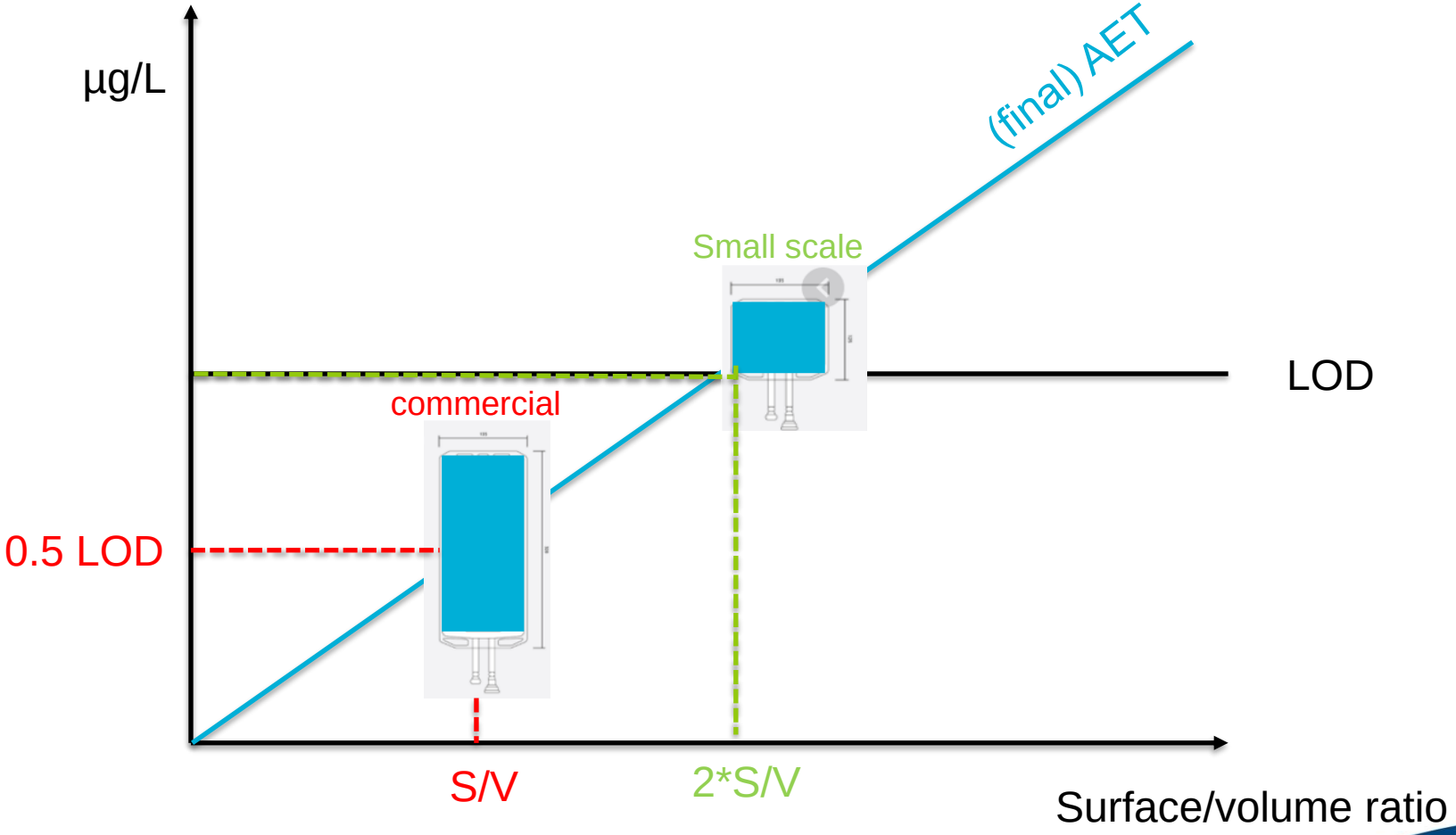
The aimed (final) AET will linearly increase with the surface to volume ratio of the bag: practical example



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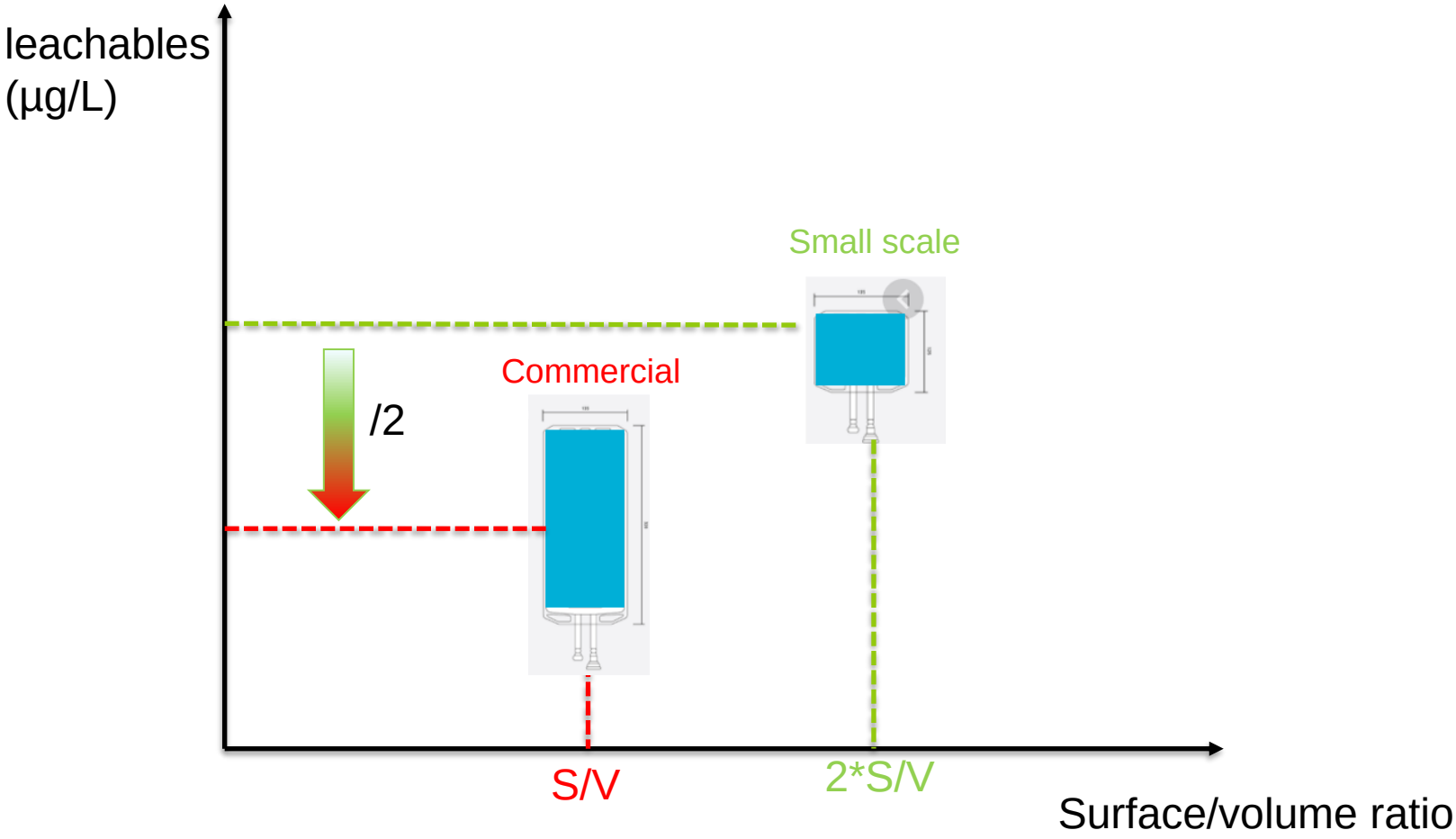
Results obtained in small scale model should be back-calculated to commercial bag system



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Adjusting both the ageing/leaching set-up and sample preparation might lead in reaching the (final) AET level

Leaching/ageing Set-up

Sample preparation

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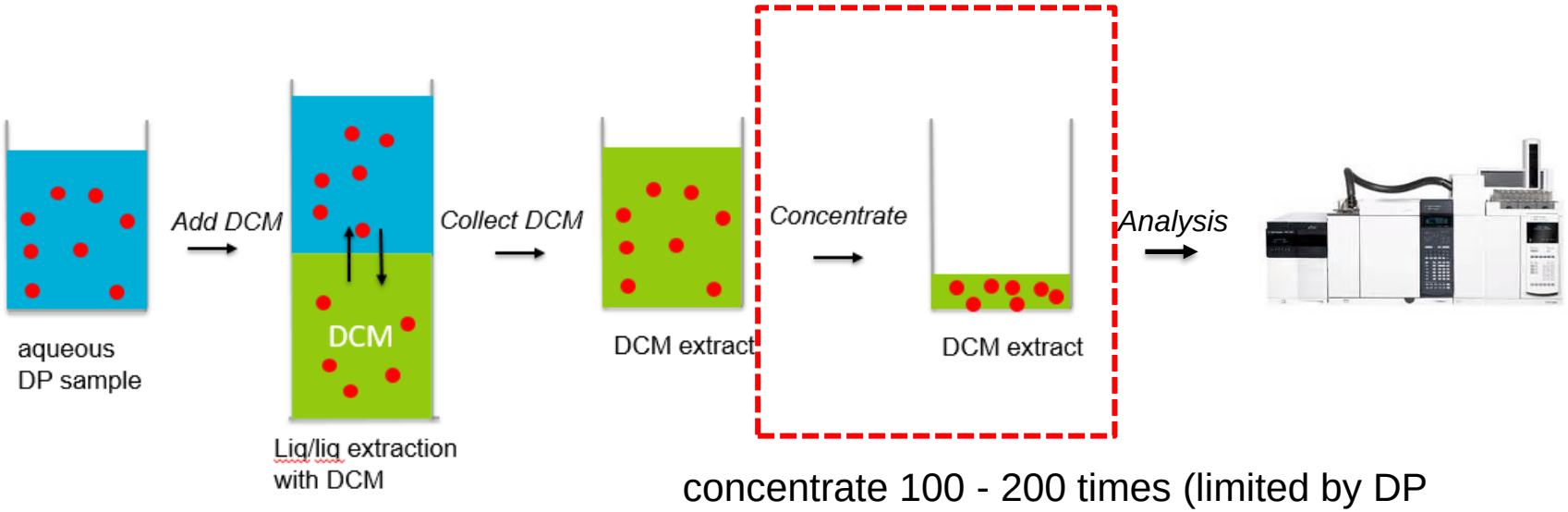
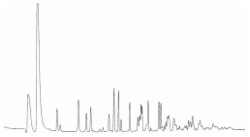
Adjust sample preparation methodology: further concentration of the (leachables) in the drug product increases the sensitivity

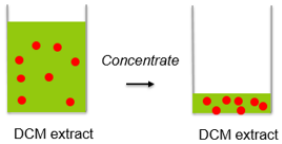


concentrate 100 - 200 times (limited by DP interference)
=>Decrease LOD in DP sample

“Clean” sample preparation of utmost importance in LVP studies



Even small contaminations further complicate the low AET evaluations



Concentration step also concentrates possible contaminations

Use of high purity solvents

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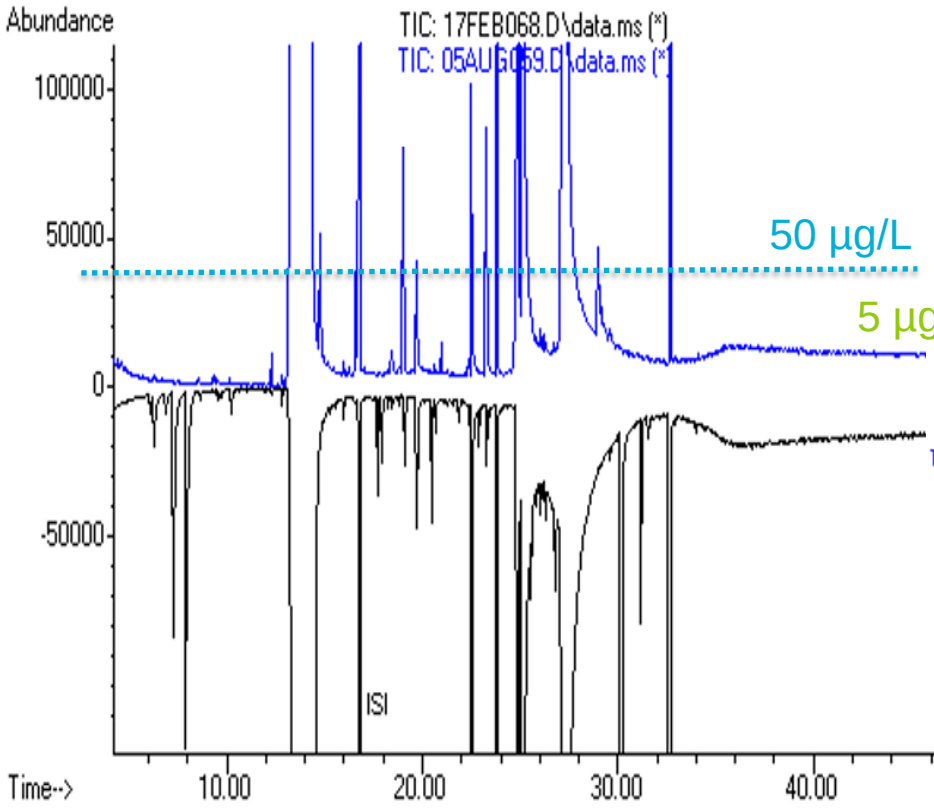
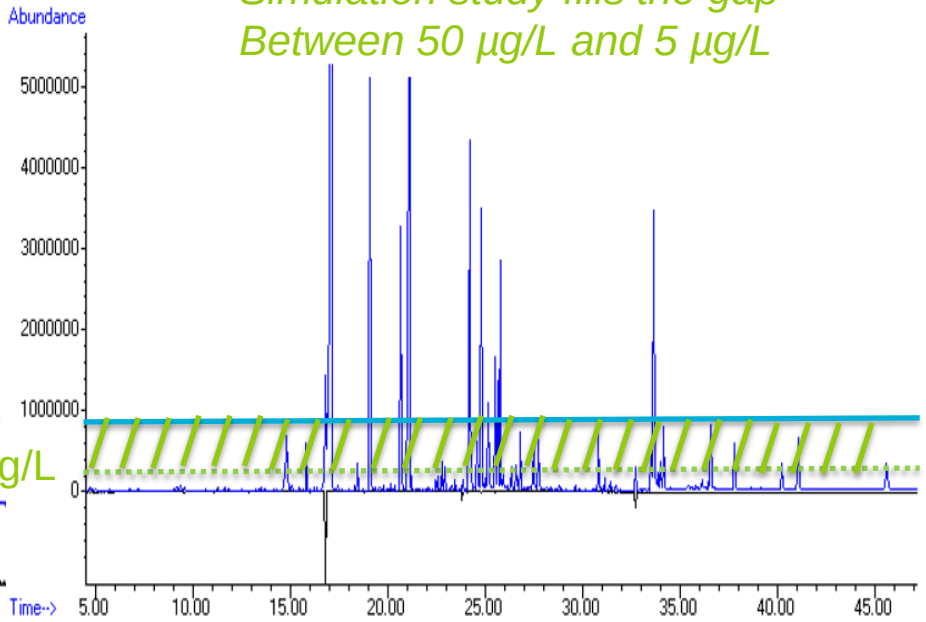
Simulation study might “fill the gaps” if final AET can not be reached in drug product

Case study: 25% human albumin
-max. daily dose = 0.5 L
-final AET (5 µg/day) = 5 µg/L

Screen as low as possible in DP



Simulation study fills the gap Between 50 µg/L and 5 µg/L



Outline

Transition from extractable to leachable study

Design of the leachable study

Further steps based on leachable data

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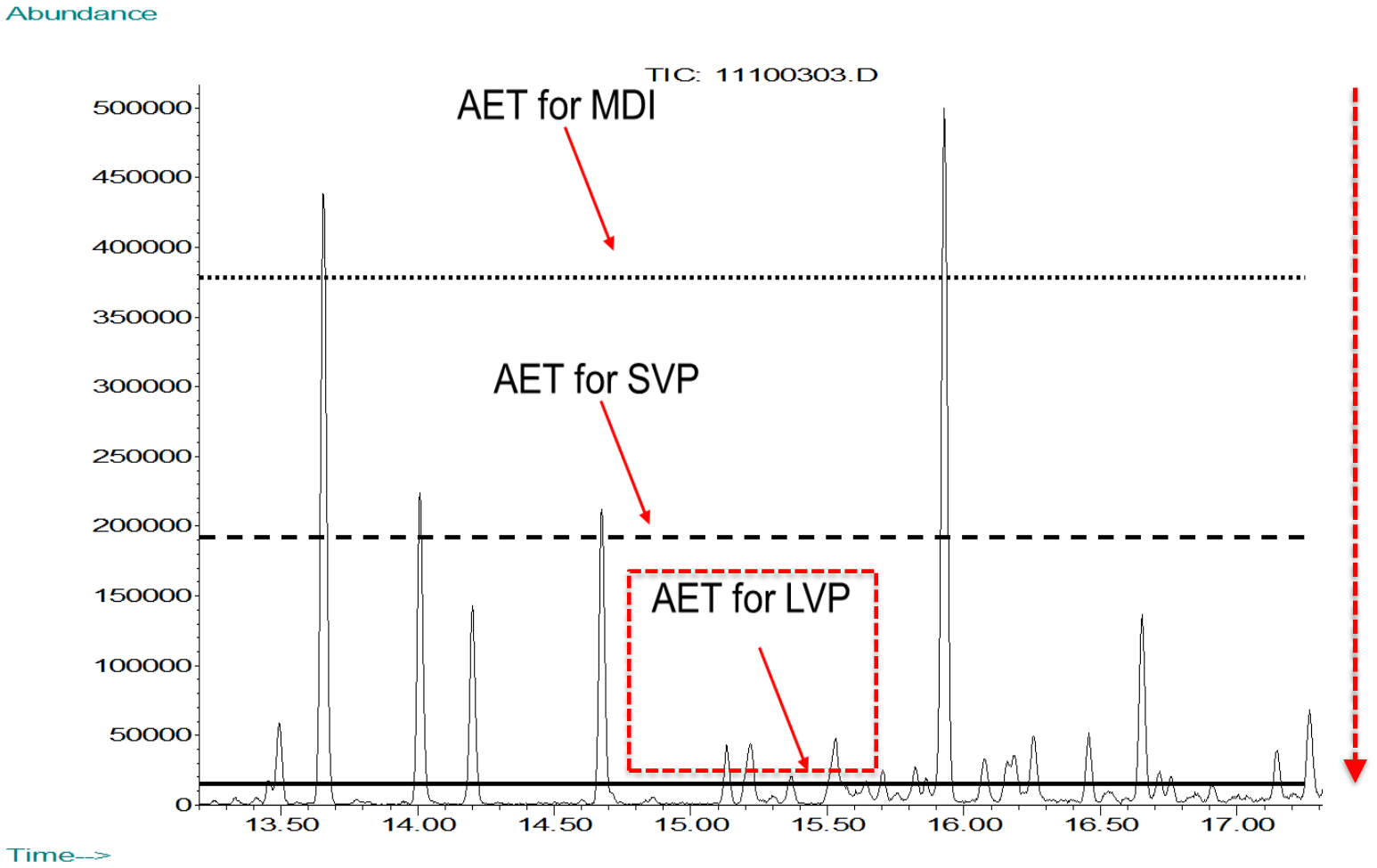
Screening leachable data will result in (non target) compounds above the final AET



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Both additional analytical & toxicological work is required for compounds detected above (final) AET

Identification of unknowns: second pass testing

Typically present at low concentrations

-Compounds which migrate at very low concentrations from plastics

-Secondary leachables

-Antioxidant degradation products

Permitted Daily Exposure values/Safety statements are required

Determined by toxicologist

Necessary for additional analytical work

Additional measurements with validated methods

PDE values necessary

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Conclusion

Transition from extractable to leachable study
Toxicological data for target selection

Design of the leachable study
Adjustments in design and sample prep

Further steps based on leachable data
Identification work, PDEs and validation

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