Challenges Associated with the Safety Assessment of Extractables/Leachables in Large Volume Parenterals (LVPs) and Potential Chemistry Approaches

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Situational Assessment

Among the numerous characteristics that differentiate Large Volume Parenterals (LVPs) from other dosage forms, their large dose volume is particularly noteworthy because of the practical implications of dose volume to the safety assessment of packaging system leachables.

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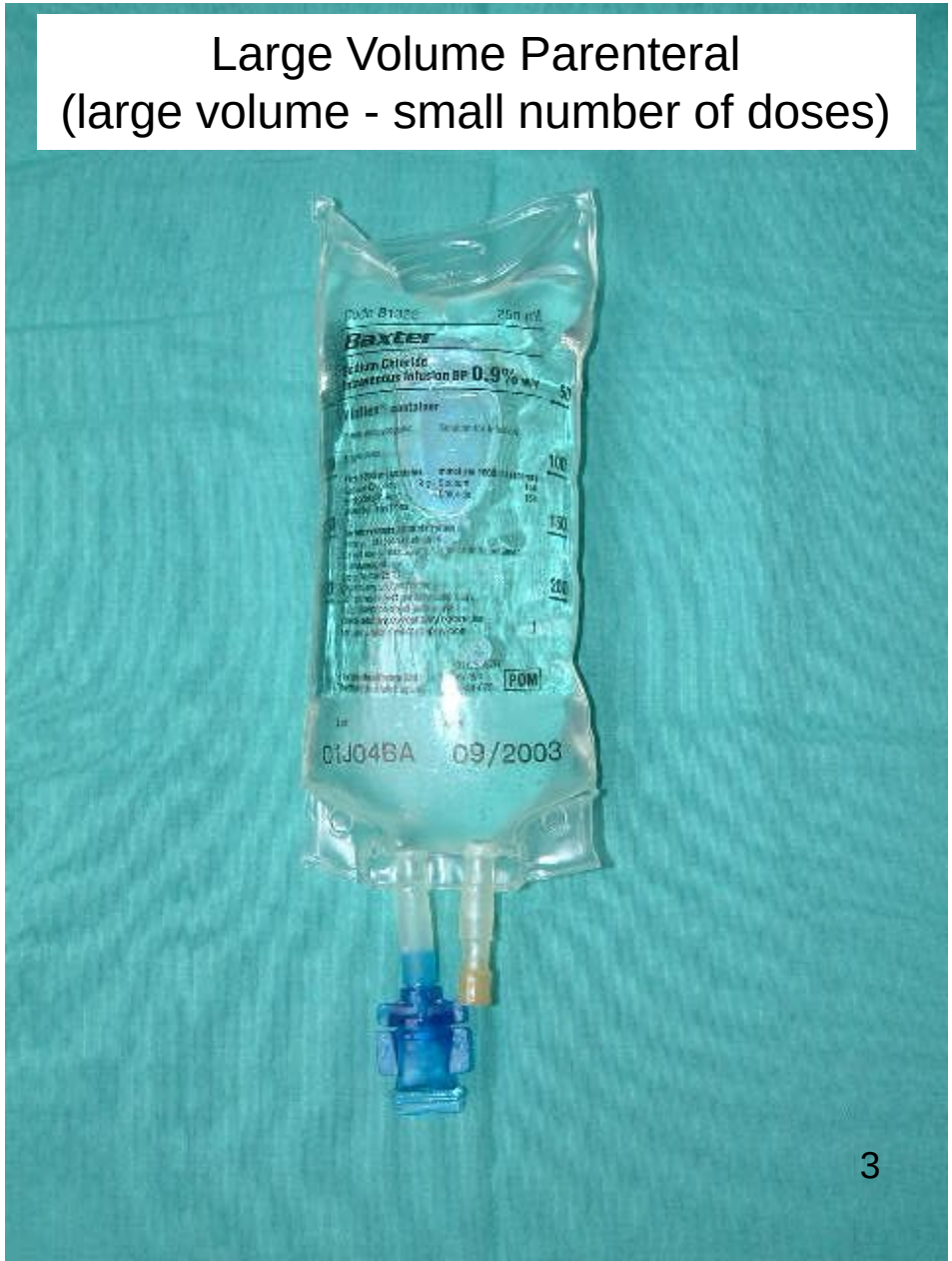
“The Situation” –Relative Dose Volumes

Metered Dose Inhaler
(small volume - large number of doses)

Large Volume Parenteral
(large volume - small number of doses)



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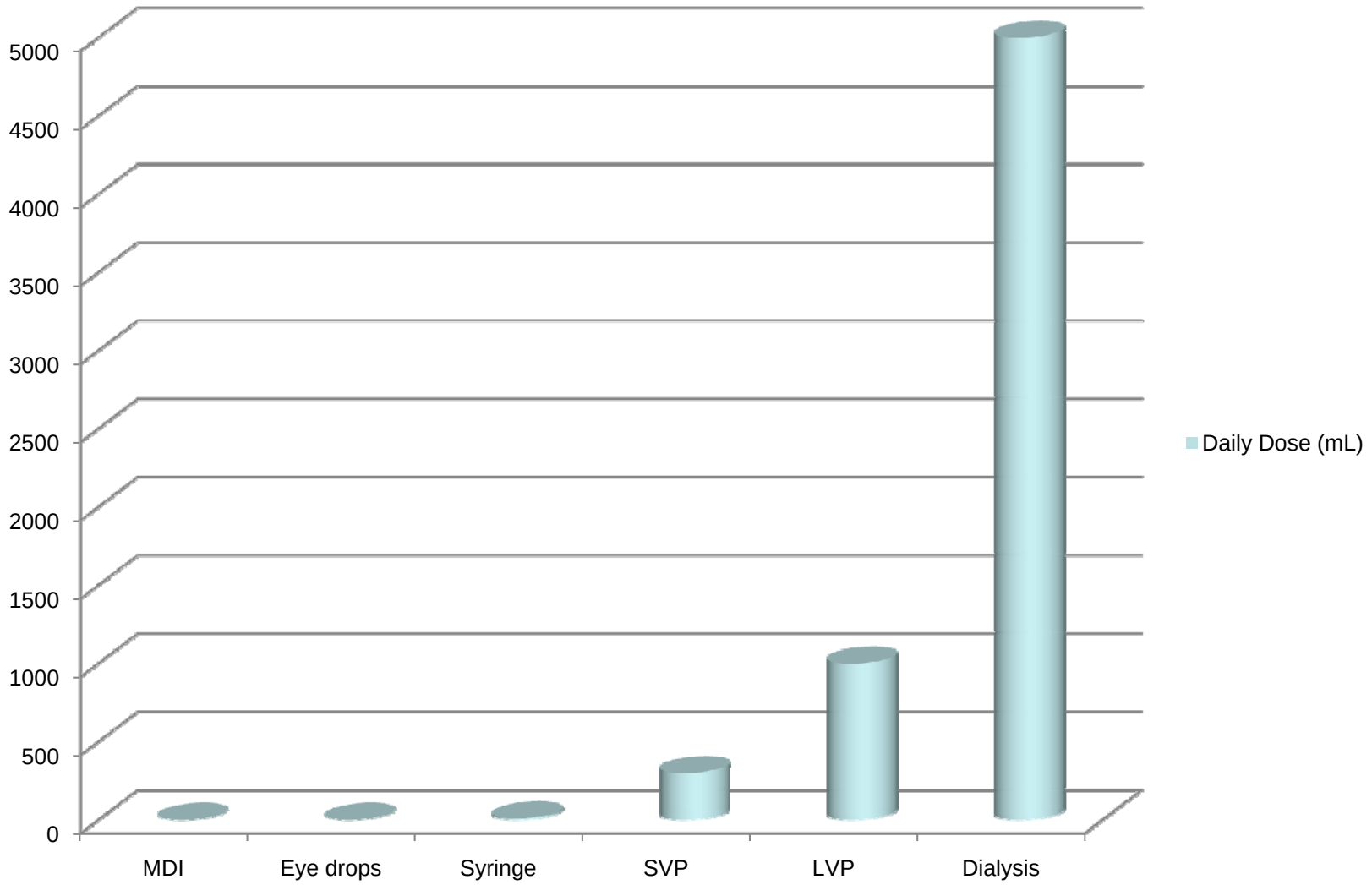
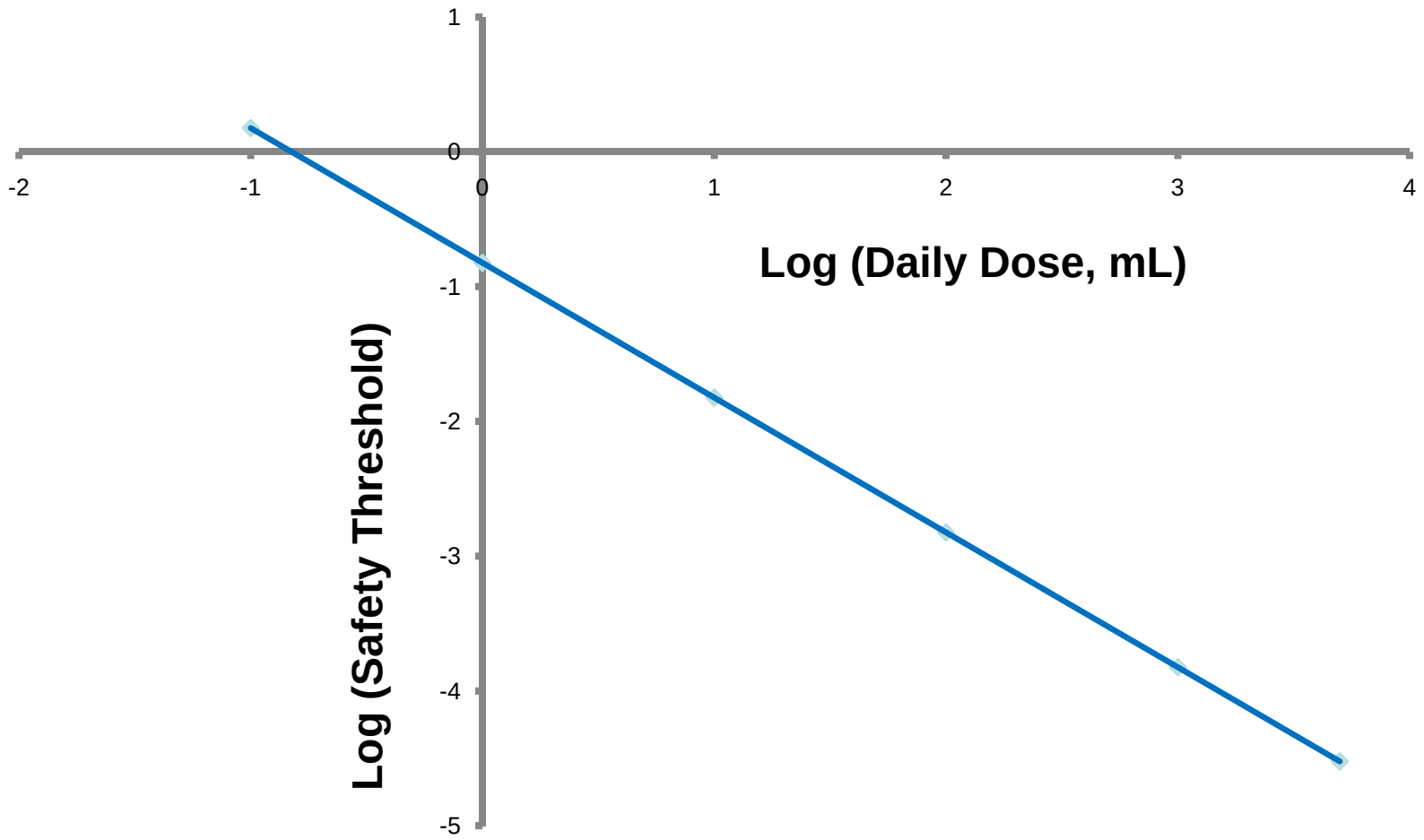
Daily Dose Volumes for General Classes of Pharmaceutical Products



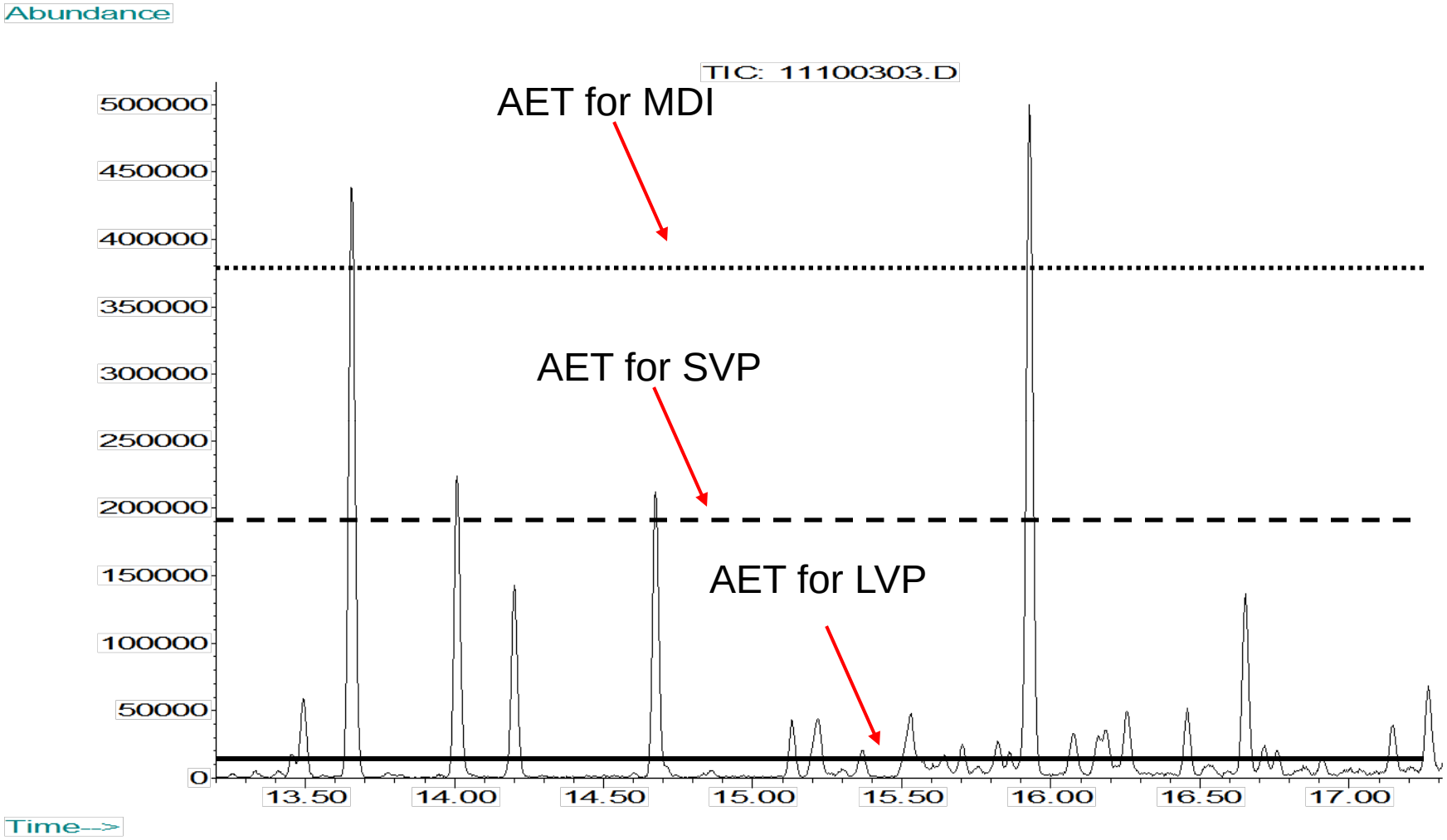
While certain dosage forms have relatively small Daily Doses Volumes (MDI, eye drops), other dosage forms have relatively large Daily Dose Volumes (LVP, dialysis).

Effect of Daily Dose Volume on an Analytical Threshold



The value of the Analytical Threshold decreases in direct proportion to the increase in Daily Dose Volume.

Effect of Daily Dose Volume on the AET



Practical Implication: More peaks to identify at lower concentrations

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A Numerical Illustration

Case #1: **MDI**, 0.5 mL of drug product in a canister that has 200 labeled actuations with a recommended daily dose of 10 actuations. For an individual organic leachable, the estimated **AET** would be **6.0 μg/mL**.

Case #2: **Inhalation Solution**, 3 mL of drug product in a LDPE container with a recommended dose of 3 containers per day. For an individual organic leachable, the estimated **AET** would be **0.017 μg/mL**.

Case #3: **LVP**, 1 L of drug product in an appropriate container with a recommended dose of one container per day. For an individual organic leachable, the estimated **AET** would be **0.00015 μg/mL**.

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Problem Statement, Safety Assessment of Leachables in LVPs

AETs for LVPs may be so low that even state of the art, best demonstrated practice analytical methods may not be able to accomplish the functions of discovery and identification for all necessary leachables.

If leachables cannot be detected and identified then obviously they cannot be toxicologically assessed and thus their potential safety impact cannot be established.

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Potential Analytical Approaches to Address the LVP Situation

1. The Analytical Action Limit.
2. Impurity Limits for Materials Used in LVP Packaging.
3. The Safety Assessment Triad.
    1. Controlled Extraction Study (material characterization and screening).
    2. Simulation study (Extractables as worst case leachables, initial safety assessment, target ID).
    3. Migration study (target leachables assessment).

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The Concept of the Analytical Action Limit

The Analytical Action Limit (AAL) is that concentration of an analyte below which the activities of discovery and identification cannot be reliably performed.

If the AAL can be established for a particular analytical method, the AAL can be compared to the AET and the safety risk associated with the difference between the AET and AAL can be established.

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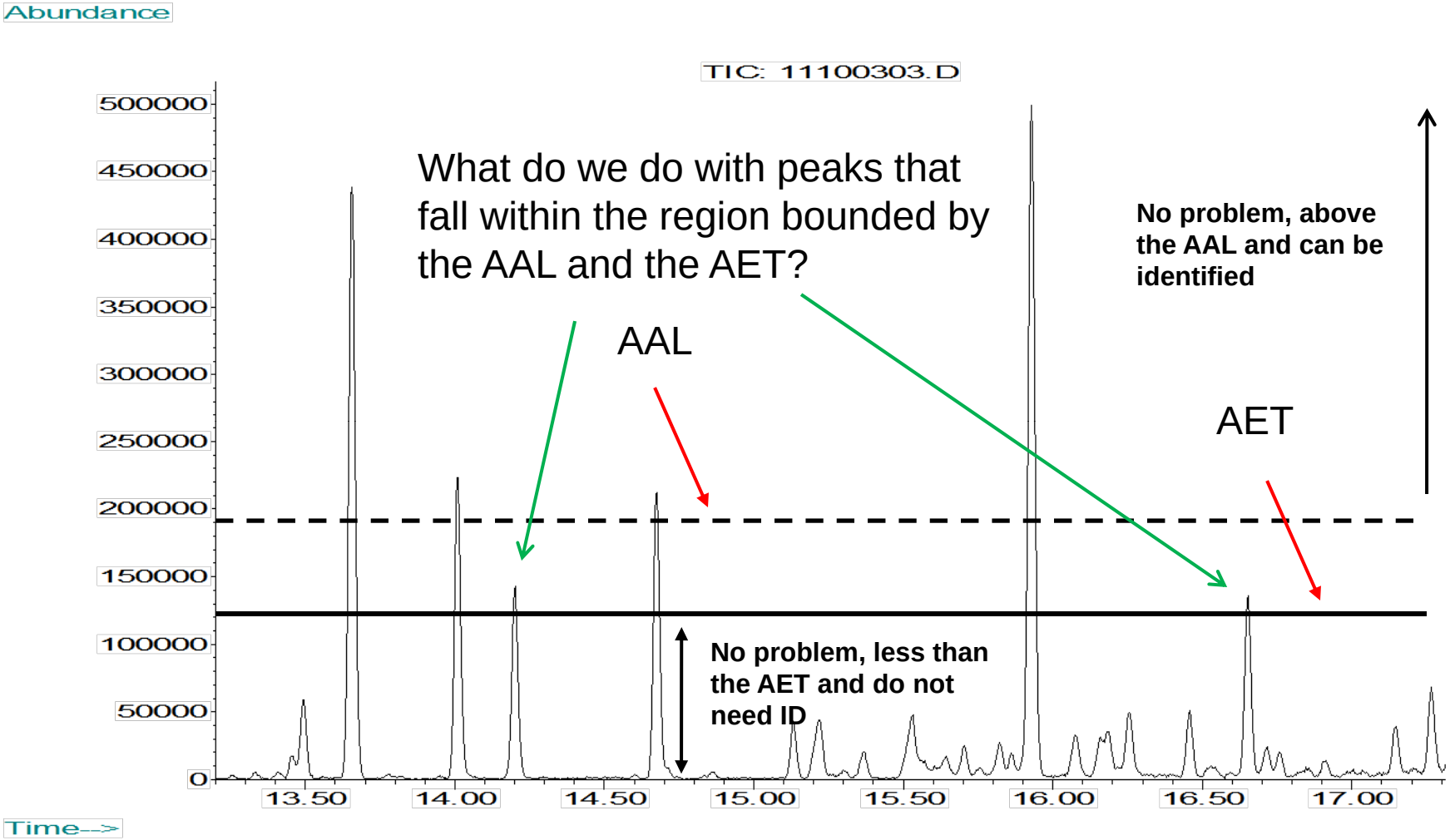
The Issue with the Analytical Action Limit



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The Concept of Impurity Limits for Materials used in LVP Packaging

1. A pharmaceutical product consists of the drug-containing solution and the packaging.

2. The packaging for a pharmaceutical product is thus a component of that pharmaceutical product, in the same way that the active ingredient and exicpients are components of the drug-containing solution.

3. Contaminants in the drug-containing solution can be derived from the active ingredient and excipients. The levels of such contaminants in the drug-containing solution can be controlled by controlling the limits of these contaminants in the active ingredient and/or the excipients.

4. Contaminants in the drug-containing solution can be derived from the packaging. The levels of such contaminants in the drug-containing solution can be controlled by controlling the limits of these contaminants that can be leached from the packaging.

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The Mathematics of Impurity Limits for Materials used in LVP Packaging

Scenario:

LVP bag weighing 20 grams that holds 1 L of drug-containing solution

Extractable Impurity Level in the packaging = 1 μg/g (1 ppm by weight, note that 1 ppm = 0.0001% impurity level)

Question:

What is the level of the packaging related impurity in the drug-containing solution?

Answer:

1 μg/g x 20 grams/1L = 20 μg/L (20 ppb by volume)

AET (one bag per day scenario):

0.15 μg/L (0.15 ppb by volume)

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Packaging Impurity Limits versus API Impurity Limits

Scenario:

LVP bag weighing 20 grams that holds 1 L of drug-containing solution; drug containing solution contains 0.1 mg/mL API. Impurity limit for packaging is 1 μg/g, impurity limit for API = 0.1% by weight.

Question:

What is the level of the impurities in the drug-containing solution?

Answer:

1 μg/g x 20 grams/1L = 20 μg/L (20 ppb by volume) for the packaging impurity

0.1 mg/mL x 1000 mL = 100 mg API
100 mg API x 0.001 mg impurity/mg API = 0.1 mg impurity (= 100 μg)
100 μg/1 L = 100 μg/L (100 ppb by volume) for the API impurity

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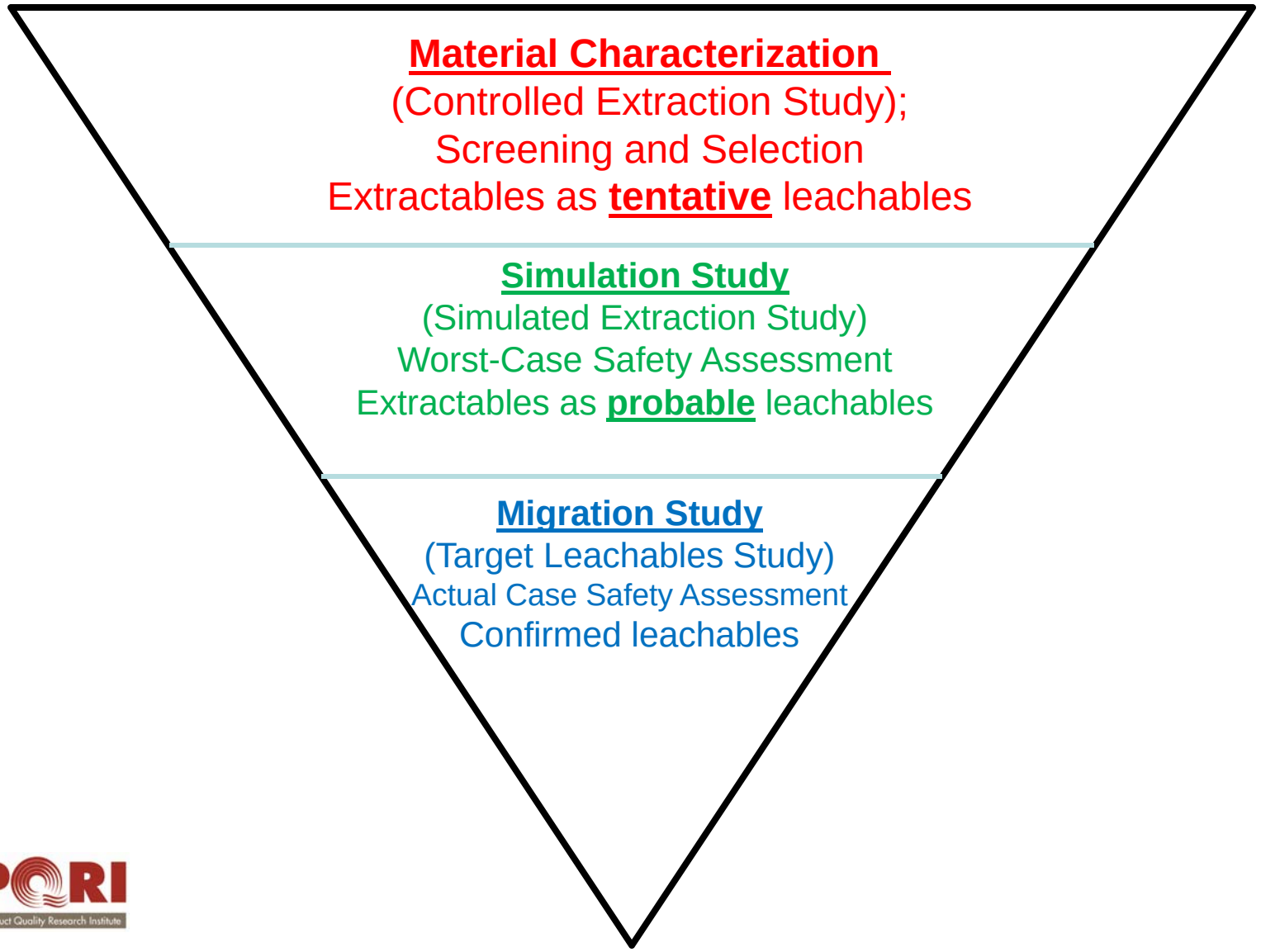
The Safety Assessment Triad



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The Safety Assessment Triad:
Material Characterization

Purpose:

Chemically characterize candidate materials to establish their composition.

Extraction:

Conditions sufficiently aggressive (including choice of extraction solvents) to establish the composition, little or no consideration given to mimicking the conditions of contact when the materials used in packaging, utilization of standardized extraction and testing protocols

Safety Assessment:

High–level, generally semi-quantitative toxicological assessment looking for “compounds of potential impact”. Assessment to be used in screening of packaging candidates.

Outcome:

Approval or rejection of material as a packaging system candidate.

The Safety Assessment Triad:

Simulation Study, Primary Assessment

Purpose:

Establish the worst case (highest possible) accumulation of leachables.

Extraction:

Conditions chosen to mimic the worst case conditions of contact between the drug product and packaging; conditions may be adjusted to accelerate (but not greatly exaggerate) attainment of the worst case. Justified simulating solvents used.

Safety Assessment:

Detailed toxicological assessment of all extractables (as potential leachables) above the AET. Output is a safety risk assessment for all such extractables.

Outcome:

Some extractables will have negligible safety risk (safety assessment completed). Some extractables may have unacceptable safety risk. Either packaging is rejected or such extractables are established as target leachables in migration studies.

The Safety Assessment Triad:

Simulation Study, How low do you go?

The exact and formal definitions of the AET, SCT and QT bear close scrutiny:

AET = threshold at or above which a chemist should begin to identify a particular leachable and/or extractable and report it for potential toxicological assessment.

SCT = threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and noncarcinogenic toxic effects

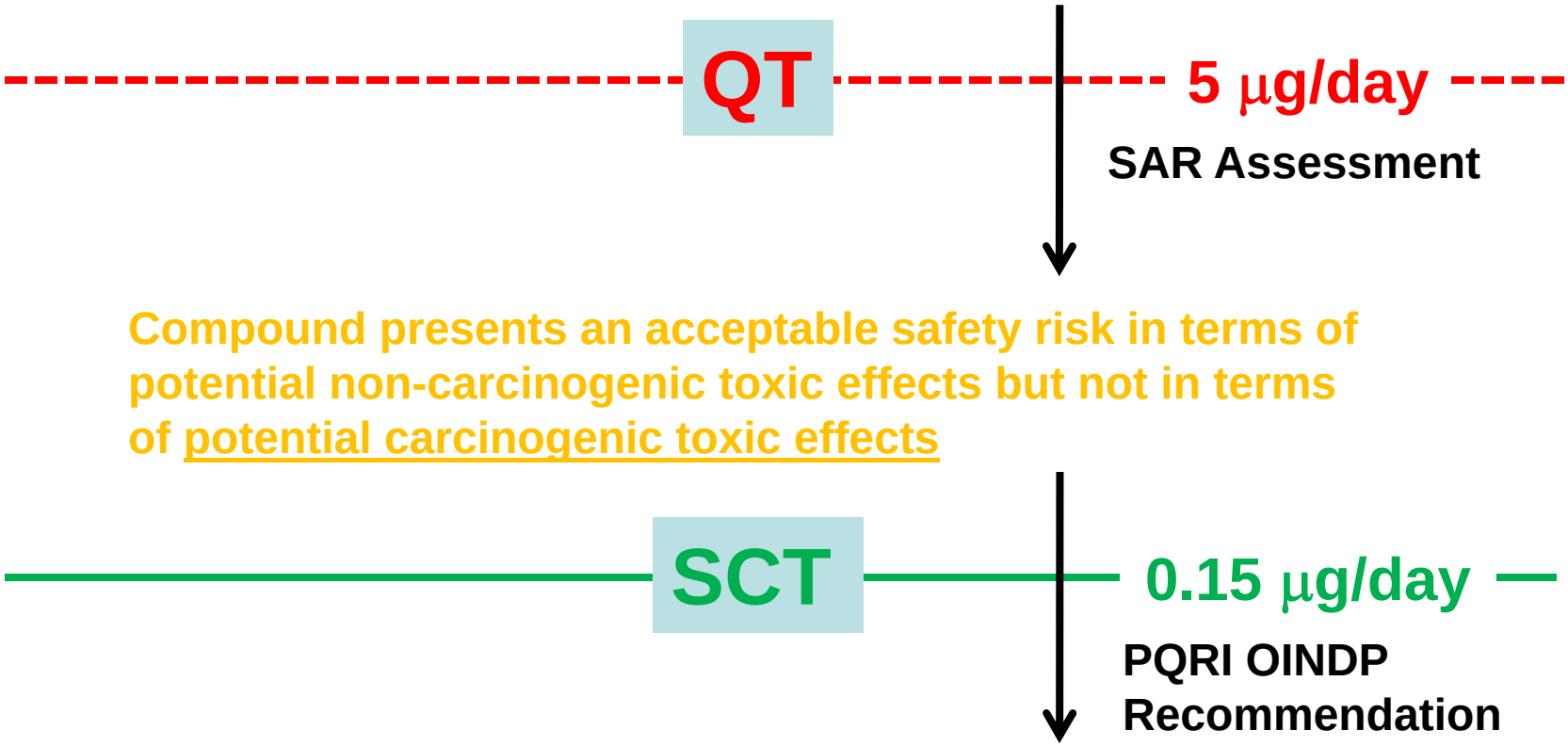
QT = threshold below which a given non-carcinogenic leachable is not considered for safety qualification (toxicological assessments) unless the leachable presents structure-activity relationship (SAR) concerns.

Note that in the Triad for LVPs, the term “leachable” is replaced by the term “extractable” as the extractable is being used to establish the worst case leachable.

The Safety Assessment Triad:

Simulation Study, How low do you go?

Compound presents an unacceptable safety risk in terms of both potential carcinogenic and non-carcinogenic toxic effects



Compound presents an acceptable safety risk in terms of both carcinogenic and non-carcinogenic toxic effects (no toxic effects)

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The Safety Assessment Triad:
Simulation Study, How low do you go?

The question of how low do you go is a question that relates to the identification of a compound not its concentration estimation.

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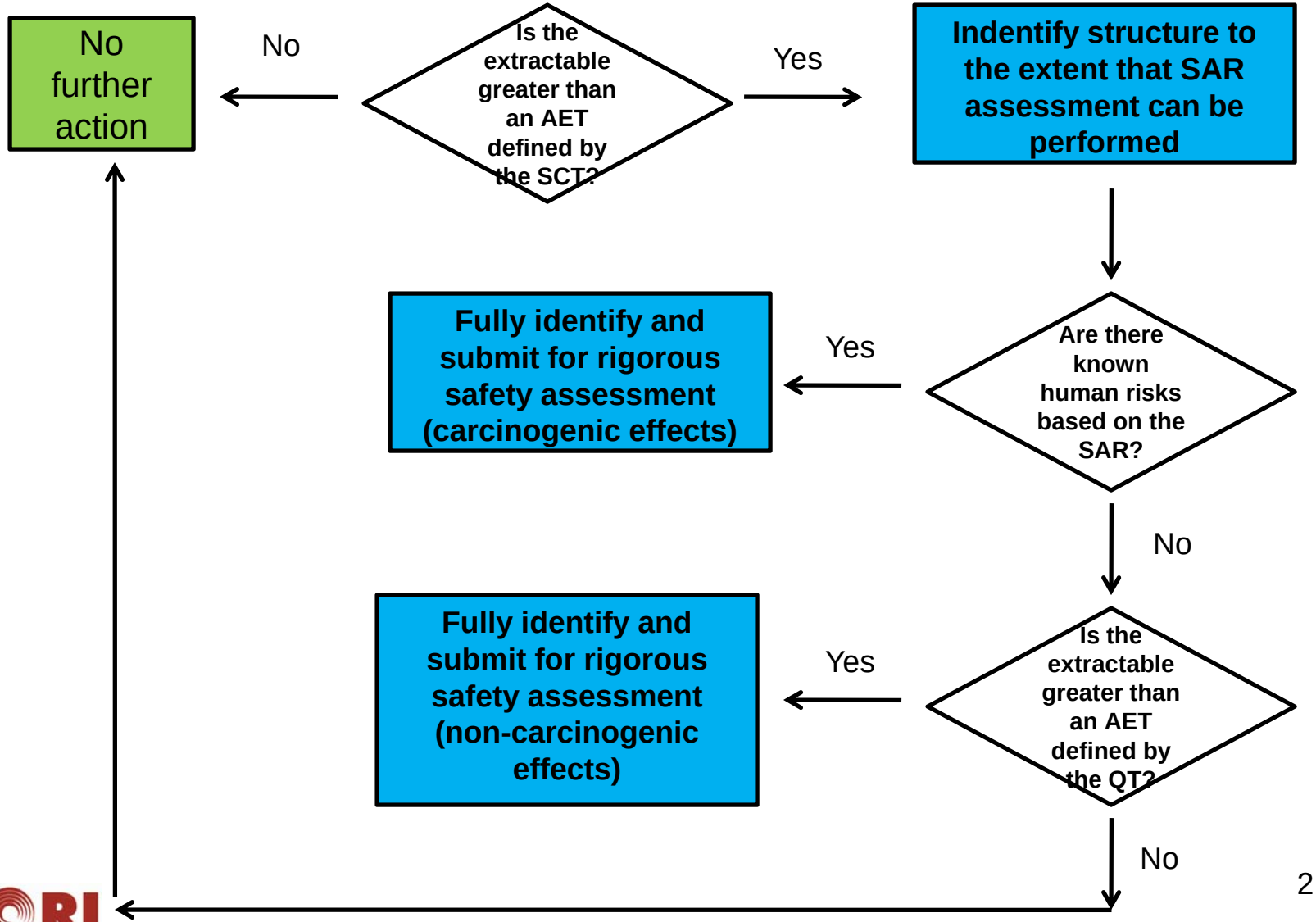
The Safety Assessment Triad:

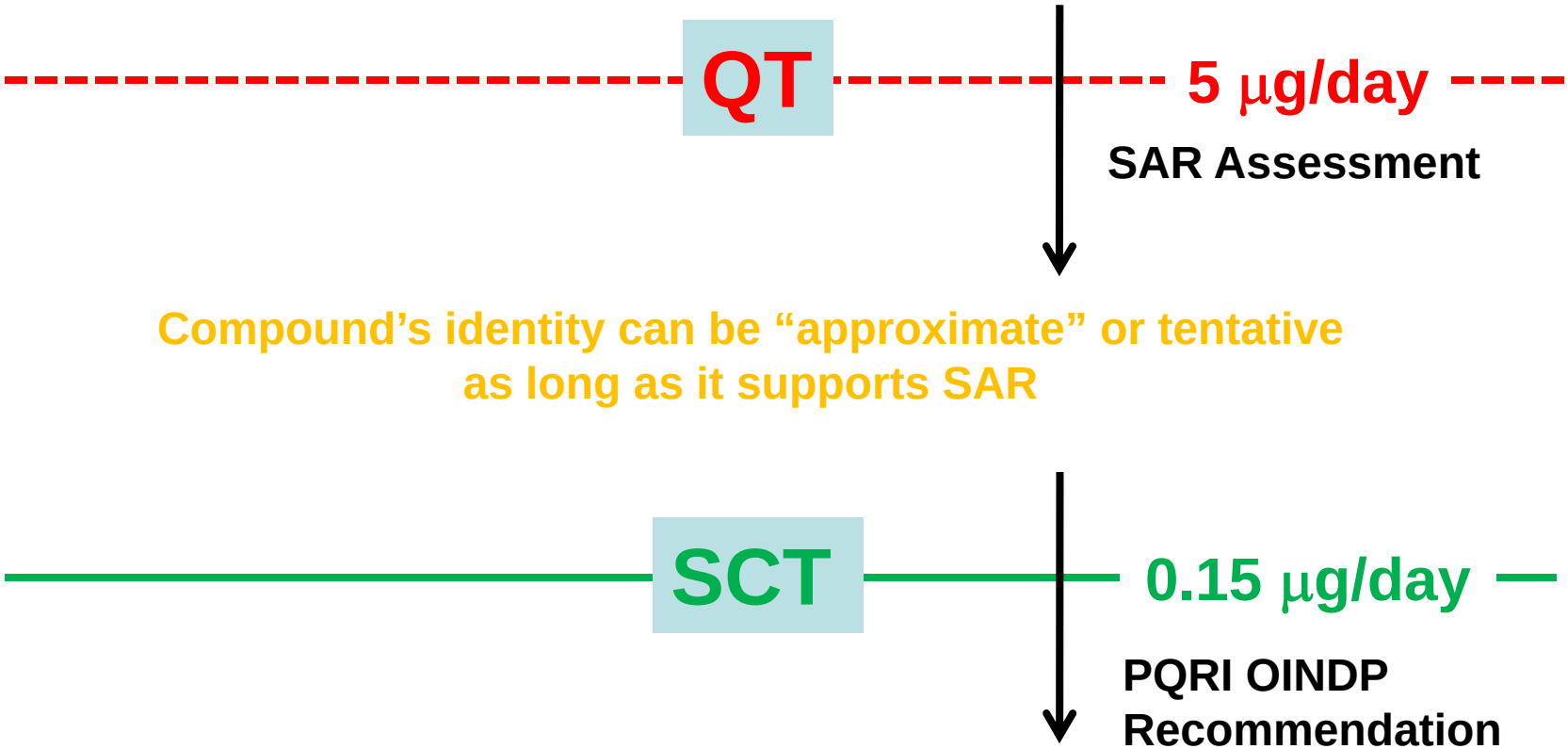
Simulation Study, How low do you go?



The Safety Assessment Triad:

Simulation Study, How low do you go?

Compound identity must be confirmed



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The Safety Assessment Triad:

Simulation Study, How low do you go?

Lesson:

It is very important that one remembers the "SAR endpoint" as a viable identification objective. If an identification is "easy", then by all means get the confirmed ID. However if the ID is "hard", then maybe you can stop once you have enough of a "tentative" or "estimated" ID to support SAR.

This is especially important for LVPs as it can be anticipated that LVPs will have lower AETs, regardless of whether the AET is based on the SCT or the QT.

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The Safety Assessment Triad:
Migration Study, Supporting Assessment

Purpose:

Establish the actual accumulation of target leachables.

Leaching:

Actual conditions of use. Drug-containing solution.

Safety Assessment:

Detailed toxicological assessment of all targeted leachables. Output is a safety risk assessment for all such leachables.

Outcome:

Some leachables will have negligible safety risk (safety assessment completed, approve packaging).
Some leachables may have unacceptable safety risk. In this case, reject packaging.

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The Safety Assessment Triad:

Migration Study, Use of the AET

- At this point in the assessment process the focus is target leachables
- Because these are target leachables, toxicological data is available and has already been assessed (e.g., a Permissible daily exposure, PDE, has been determined).
- The PDE (expressed in μg/day) can be converted to a maximum allowable concentration in the drug product (MAC, expressed in units of μg/mL). The MAC establishes the quantitation target concentration for the analytical method used to measure the target leachables.

MAC = PDE/Daily dose volume (mL)

- Analyte concentrations less than the MAC are intrinsically safe and do not need to be numerically determined and reported (for safety assessment purposes) but may be used for trending over time.
- Analyte concentrations greater than the MAC represent an unacceptable safety risk.

Thus the AET is used in the Migration study to address the possibility of "new" leachables that were not previously discovered as extractables or the possibility that a leachable has insufficient tox data to do a proper assessment.

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The Safety Assessment Process:

Focusing on both sides of the Balance

Assessment could give some weight to this consideration

Assessment could consider actual product use situations and use appropriate uncertainty adjustments

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