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

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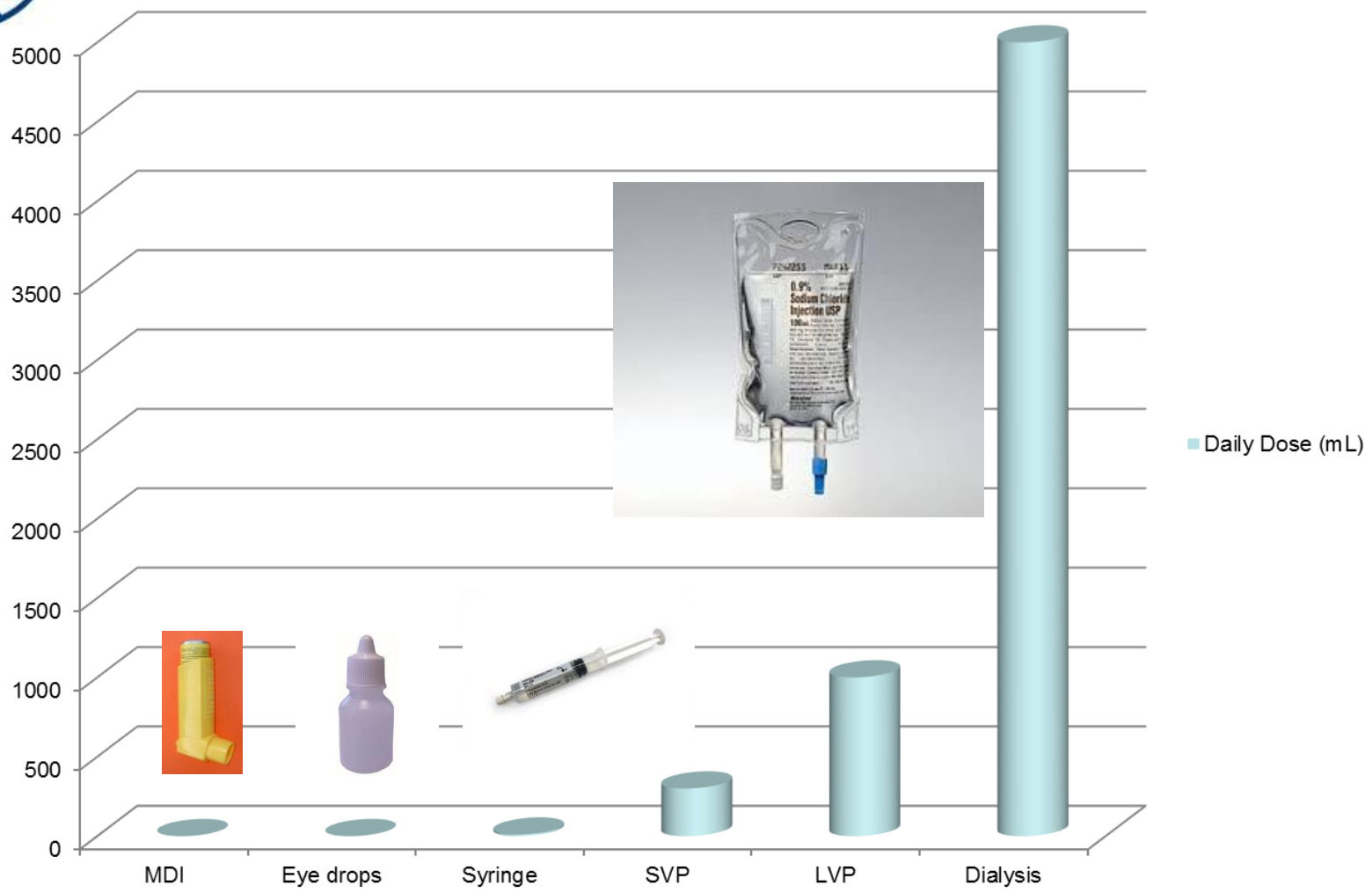
Situational Assessment

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.

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).

What is the Big Deal About Daily Dose Volume?

One of the most basic concepts in toxicological assessment is that:

“The dose makes the poison”

Paracelsus, the “Father” of modern toxicology

A substance can adversely affect health only if the amount of the substance to which an individual is exposed (dose) exceeds a tolerable threshold.

The exposure dose of a substance is the product of the concentration of the substance in the liquid medication and the volume of the liquid medication that is administered:

Dose = concentration in medication x volume of medication used

What is the Big Deal About Daily Dose Volume?

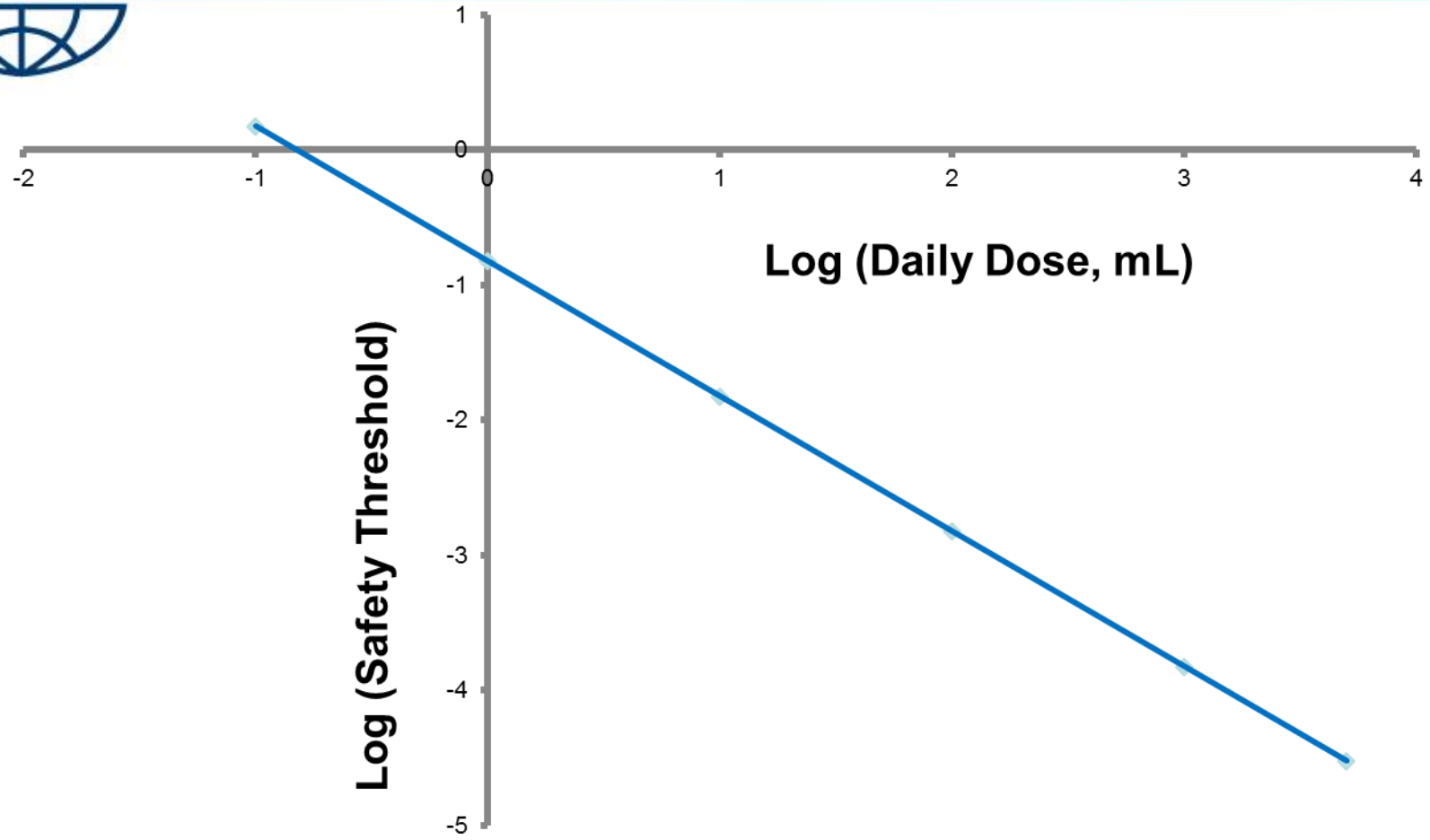
To establish the safety of a medication one must establish that it contains no substances that exceed the permissible daily dose (PDD). PDD is typically expressed in units of amount per day (for example, mg/day).

For this reason, medications are tested for their levels of substances that could be potentially unsafe. These test results are expressed as a concentration of the substance in the medication in units of amount per volume (for example, mg/L).

To establish whether the level of the substances exceeds the PDD, the PDD is "converted" to concentration units by dividing the PDD by the daily dose volume V:

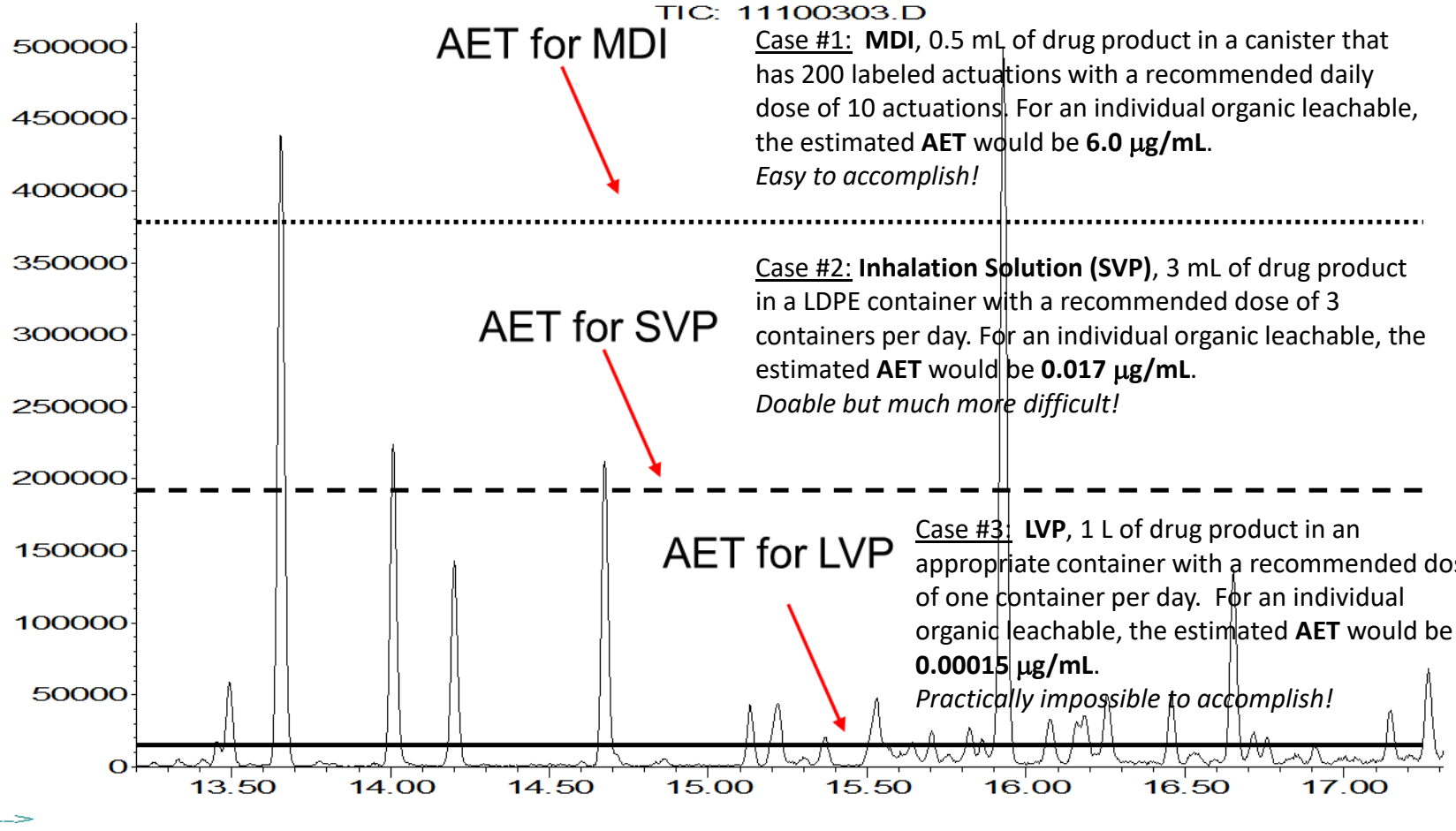
$$\text{Safety Threshold}_{\text{concentration}} = \text{PDD}_{\text{amount}}/V$$

Effect of Daily Dose Volume on the Safety Threshold



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

Effect of Daily Dose Volume on the AET



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**.
Easy to accomplish!

Case #2: **Inhalation Solution (SVP)**, 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**.
Doable but much more difficult!

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**.
Practically impossible to accomplish!

Practical Implication: More peaks to identify at lower concentrations

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 by numerical means and thus their potential safety impact cannot be established by such numerical means.

Potential Analytical Approaches to Address the LVP Situation

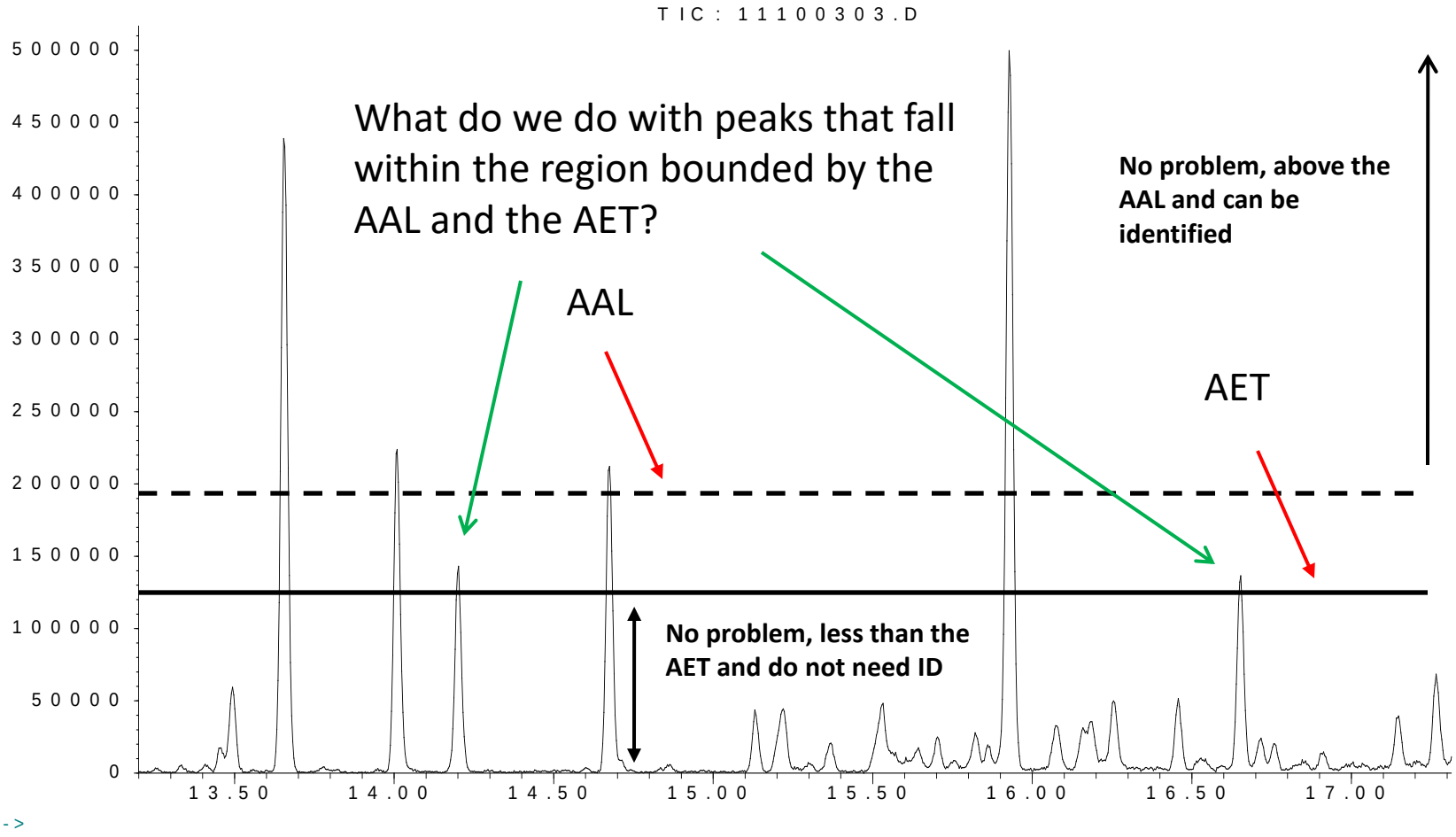
1. The Analytical Action Limit.
2. Use of the “Right” Analytical Threshold
3. The Safety Assessment Triad.
   - Controlled Extraction Study (material characterization and screening).
   - Simulation study (Extractables as worst case leachables, initial safety assessment, target ID).
   - Migration study (target leachables assessment).

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.

The Issue with the Analytical Action Limit



The Concept of the "Right" Threshold

1. Analytical thresholds for leachables are based on certain toxicological characteristics of the leachables (i.e., are they carcinogens?), certain generalizations about product usage (i.e., duration of clinical exposure) and no allowance for "benefit versus risk" analysis.

2. The values for analytical thresholds differ with respect to the aspects noted in point (1) above.

3. Matching the analytical threshold to the specific scenario being addressed insures that the analytical processes are being held to the proper performance expectations.

Using the "Right" Threshold; Is the Leachable Carcinogenic? (I)

The exact and formal definitions of the analytical thresholds such as the AET, SCT and QT bear close scrutiny:

AET = concentration 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 = amount threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic/noncarcinogenic toxic effects.

QT = amount 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.

The important points are:

1. The value of the QT will be significantly higher than the SCT.
2. The AET can be based on either the SCT or the QT if the carcinogenicity of the leachable can be established.

Using the "Right" Threshold; Is the Leachable Carcinogenic? (II)

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

QT — **≈50 μg/day**

SAR Assessment

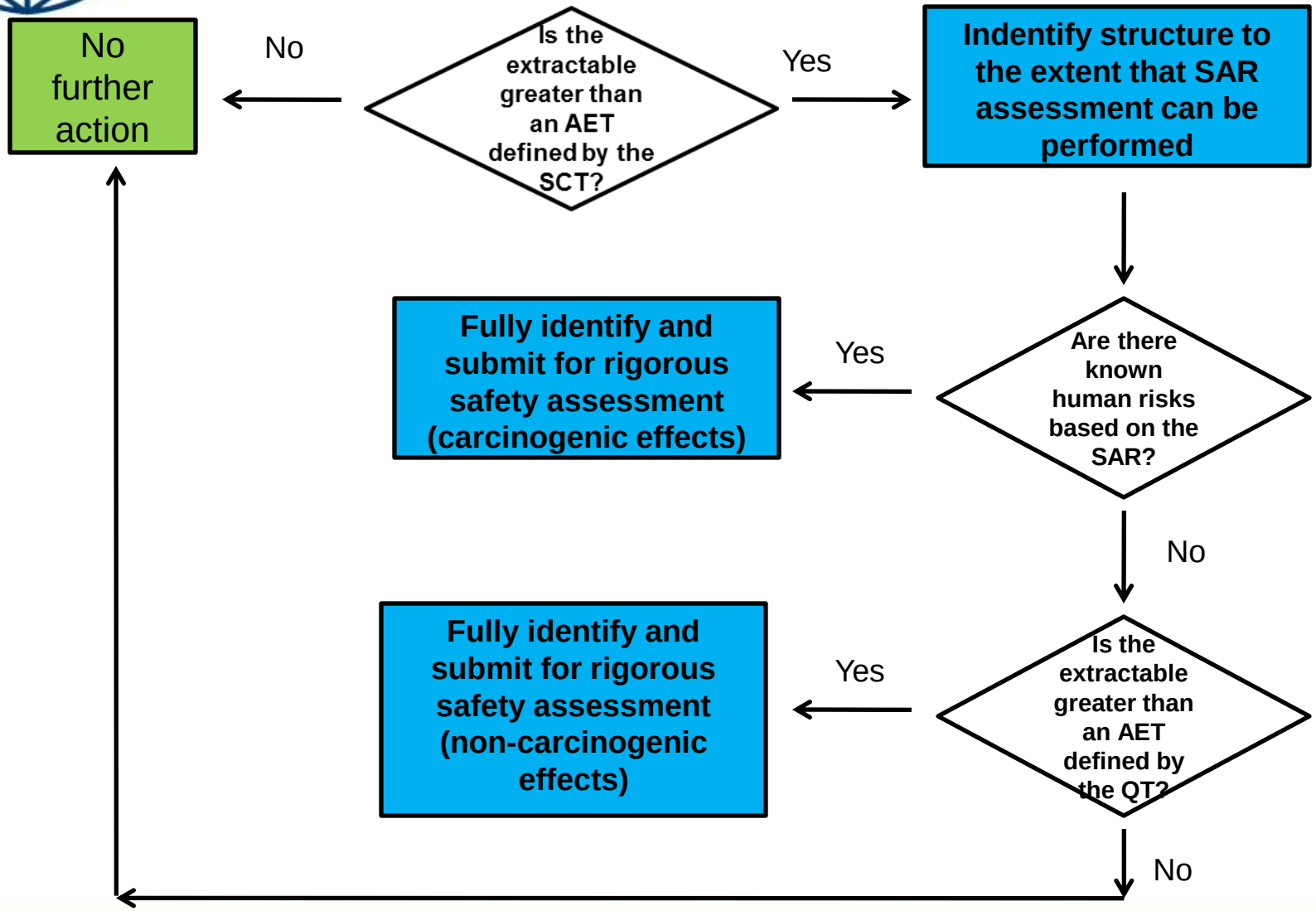
Compound presents an acceptable safety risk in terms of potential non-carcinogenic toxic effects but not in terms of potential carcinogenic toxic effects

SCT — **1.5 μg/day**

PQRI PODP Recommendation

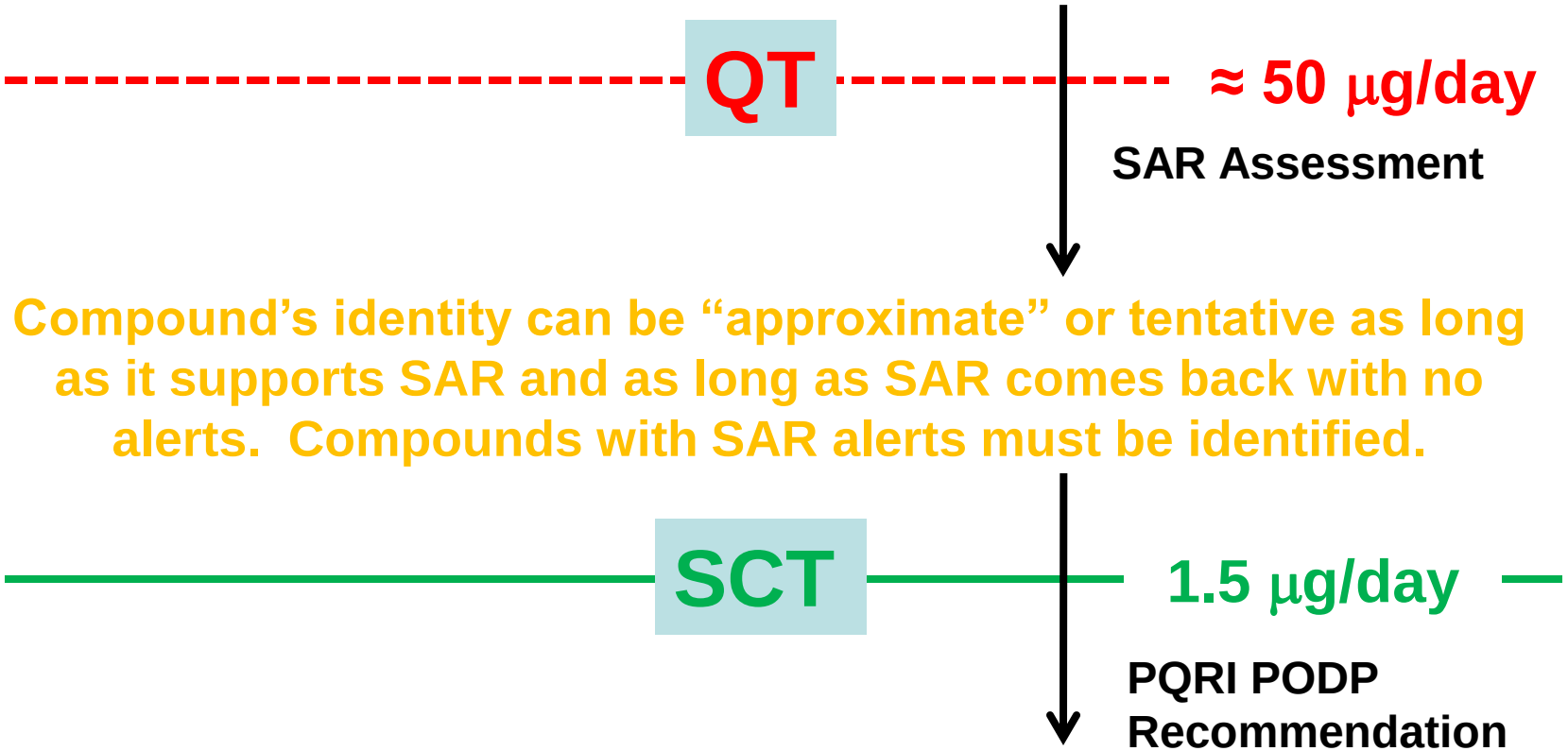
Compound presents an acceptable safety risk in terms of both carcinogenic and non-carcinogenic toxic effects (no toxic effects)

Using the "Right" Threshold; Is the Leachable Carcinogenic? (III)



Using the "Right" Threshold; Is the Leachable Carcinogenic? (IV)

Compound identity must be confirmed is all cases



Compound's identity can be "approximate" or tentative as long as it supports SAR and as long as SAR comes back with no alerts. Compounds with SAR alerts must be identified.

Compound does not need to be identified in any case.

Using the "Right" Threshold; Is the Leachable Carcinogenic? (V)

Lesson:

It is very important that one remembers the "SAR endpoint" as a viable identification objective. However, even if the SAR endpoint is applicable, one may still be inclined to pursue full identification. If an identification is "easy", then by all means get the confirmed ID. However if the ID is "hard", then maybe one can stop once a "tentative" or "estimated" ID has been secured to support the 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.

Using the "Right" Threshold; What is the duration of clinical exposure?

The magnitude of the threshold depends on the duration of clinical exposure, with higher thresholds being appropriate for shorter durations.

M7 Acceptable Thresholds for Genotoxic and Carcinogenic Impurities						
	Duration of Clinical Exposure					
	< 14 days	14 days – 1 month	1 – 3 months	3 to 6 months	6 to 12 months	> 12 months
Genotoxic and carcinogenic impurity threshold (µg/day)	120	60	20	10	5	1.5

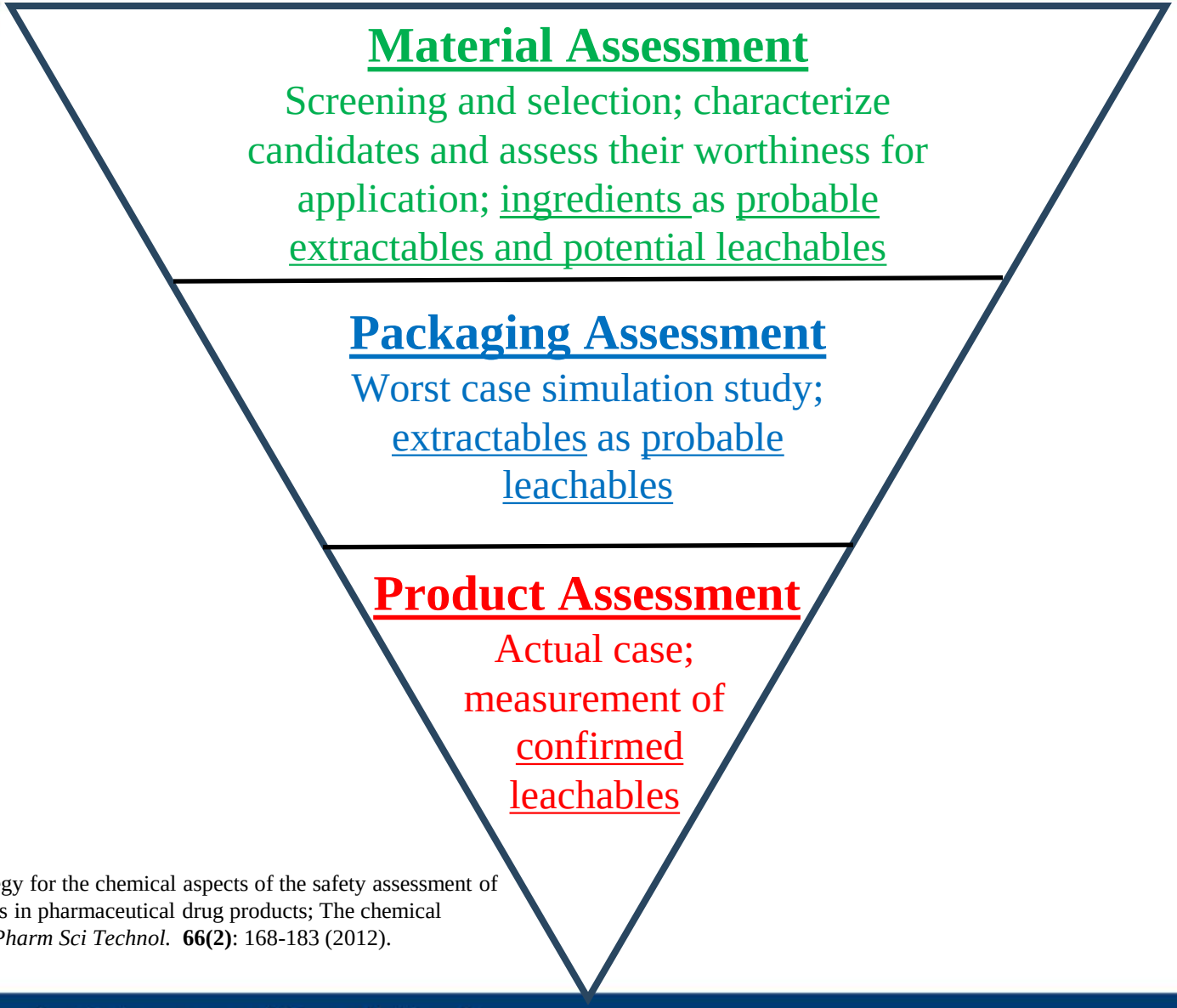
Guidance for Industry. M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). May, 2015.

Using the "Right" Threshold; 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

A Process Answer to the LVP Challenge; The Safety Assessment Triad



D. Jenke. A general strategy for the chemical aspects of the safety assessment of extractables and leachables in pharmaceutical drug products; The chemical assessment triad. *PDA J Pharm Sci Technol.* **66(2)**: 168-183 (2012).

The Safety Assessment Triad:
Material Assessment

"The best way to ensure that a packaging system does not materially affect the safety or quality of a packaged pharmaceutical product is to construct the packaging systems from raw materials that are well-characterized and appropriately inert."

Purpose:

Chemically characterize candidate materials to establish their composition.

Extraction:

Conditions sufficiently aggressive 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:

Packaging Assessment, Simulation Study

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:

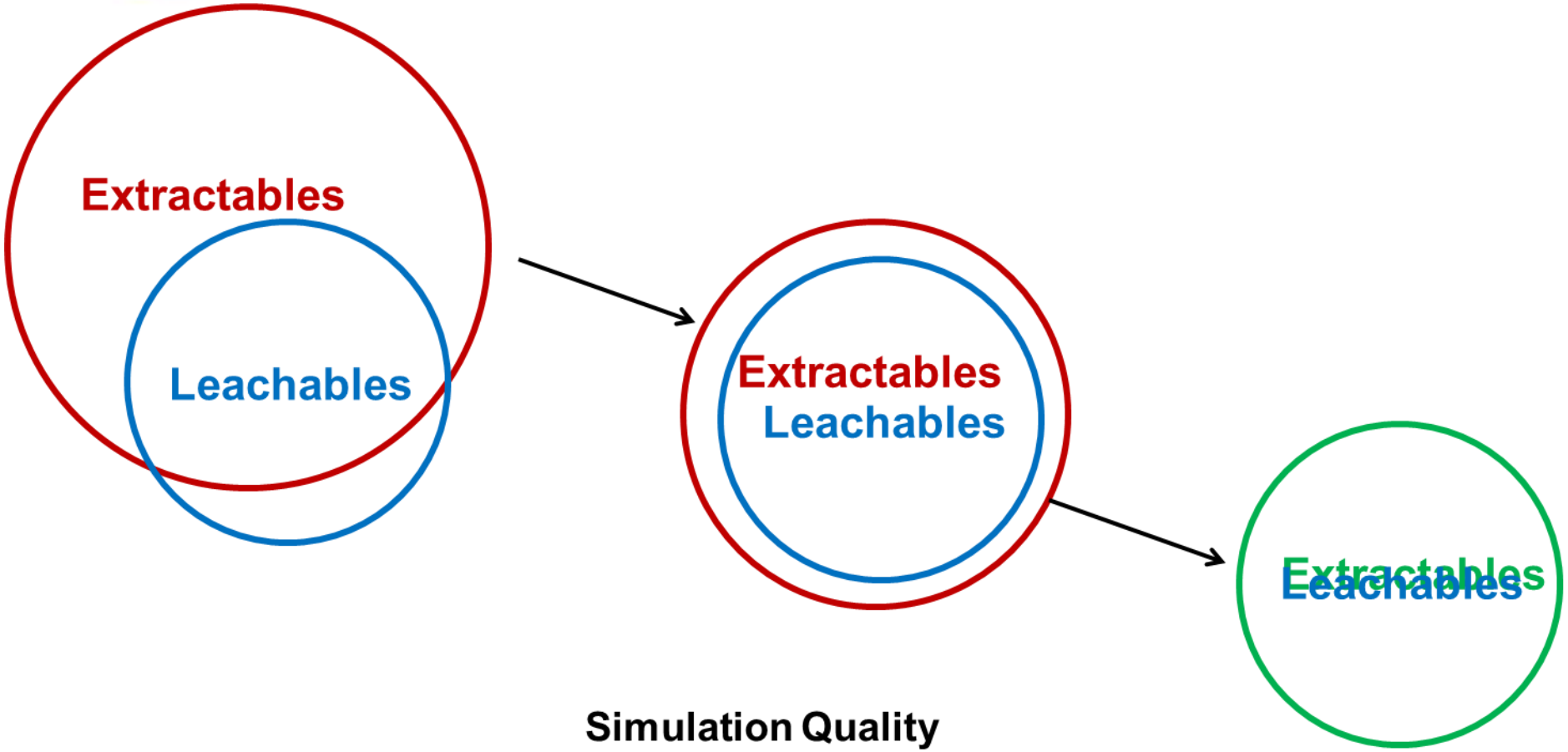
Detailed toxicological assessment of all extractables (as potential leachables) above the AET. Output is a safety risk assessment for all such extractables.

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 targeted as leachables in migration studies.

The Safety Assessment Triad:

Value Proposition for the Simulation Study



The Safety Assessment Triad:

Value Proposition for the Simulation Study

1. The simulating solvents are more analytically expedient than are drug products, therefore one can more easily achieve lower AETs.

2. Use of accelerated conditions produces a more realistic profile in less time then exaggerated or real time studies.

3. Use of a small number of simulating conditions can build a design space that is applicable to a larger number for drug products.

4. Helps to focus leachables migration studies on targeted compounds as it establishes the basis of target selection.

The Safety Assessment Triad:

Product Assessment, Targeted Migration Study

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.

The Safety Assessment Triad:

Migration Study, Use of the AET (I)

- 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)

The Safety Assessment Triad:

Migration Study, Use of the AET (II)

- 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.

References:

1. Guidance for Industry. M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). May, 2015.
2. D. Jenke. A general strategy for the chemical aspects of the safety assessment of extractables and leachables in pharmaceutical drug products; The chemical assessment triad. *PDA J Pharm Sci Technol.* 66(2): 168-183 (2012).
3. Safety Thresholds and Best Demonstrated Practices for Parenteral and Ophthalmic Drug Products. Product Quality Research Institute (PQRI). September, 2017.

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Thank you!