Use of Auxiliary Information to Support the Development and Qualification of Flexible LVP Packaging

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Presentation Outline

- Auxiliary Information
- Auxiliary Information and LVP Packaging Development
  - Material Selection
- Managing the AET Gap
  - Analytically
  - Via a Simulating Extraction Study
  - Via Preponderance of Evidence (Auxiliary Information)
- Keys to Successfully Managing the AET Gap

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What is Auxiliary Information?

Auxiliary information is information, other than extractables profiling, that speaks to the safe use of medical packaging and its materials of construction.

Types of Auxiliary Information:

- Results of tests conducted in accordance with the relevant Pharmacopeia (e.g. USP <661>, Pharm Eur 3.1, 3.2)
- Results of biocompatibility tests (e.g., USP <87>, <88>, ISO 10993)
- Conformity to relevant food contact regulations (e.g., EU 10/2011, 21 CFR 177)
- Compliance with compositional regulations and standards (e.g., REACH, Prop 65, CONEG)
- Formulation

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Use of Auxiliary Information in Developing LVP Packaging – Material Selection

The most effective way of insuring that LVP packaging will be safe for use is to use materials of construction that are safe to use.

How does one establish that a material of construction is safe to use?

- Clinical testing
- Extractables profiling followed by toxicological risk assessment
  - Case-by-case relevance
  - Expense
  - Effects of processing
- Preponderance of relevant evidence

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Use of Auxiliary Information in Developing LVP Packaging – Material Selection

The Logic of Preponderance of Relevant Evidence

A packaging system's materials of construction should be rationally and intentionally selected based on the likelihood that are safe to use in their intended application. So doing:

- Increases the likelihood that the packaging system will be safe for its intended use
- Is a useful aspect of the packaging system's regulatory file*

* Although establishing the safe use status of materials of construction is not a required part of a regulatory file ("we regulate finished items and not their materials of construction"), it provides useful commentary with respect to QbD practices, demonstrates due diligence and may "carry the day" when "grey areas" are encountered.

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Use of Auxiliary Information in Developing LVP Packaging – Material Selection

The Logic of Preponderance of Relevant Evidence

- A material that complies with the relevant Pharmacopeial Monographs is likely to be safe for its intended use in medical applications.
- A material that has been established to be biocompatible is likely to be safe for its intended use in medical applications.
- A material that is meets the requirements for use as food packaging is likely to safe for use in medical packaging.
- A material that meets compositional regulations and standards that limit the use of substances of concern is likely to be safe for its intended use in medical applications.
- A material's composition establishes its extractable profile as ingredients are logical extractables or sources of extractables.

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The Analytical Evaluation Threshold, AET

- The AET establishes that concentration in a medical product extractable or leachable above which it must be reported for toxicological risk assessment.
- The AET is **protective** of patient health by assuring that all compounds that are possible safety hazards are assessed for risk.
- The AET is applied to chromatographic methods that are used to **screen** drug products for unspecified organic leachables.
- The AET is established on a chromatogram by preparing an internal standard at the AET level, noting its response, and reporting only those peaks in a chromatogram whose response is larger than the internal standard response.

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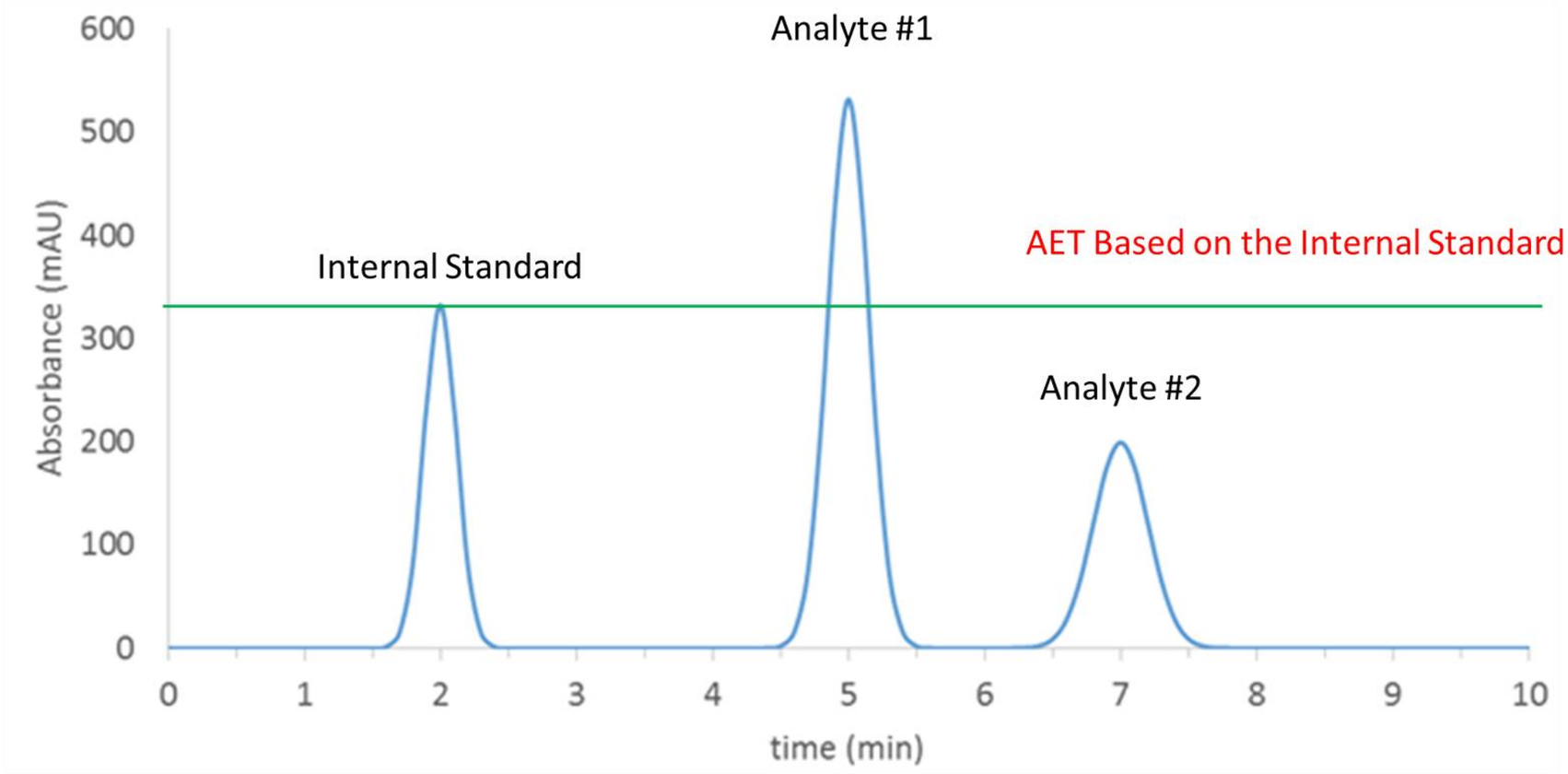
The Analytical Evaluation Threshold, AET



- The peak for Analyte #1 is above the AET line. Thus, Analyte #1 is reported for toxicological risk assessment.
- The peak for Analyte #2 is below the AET line. Thus, Analyte #2 is not reported for toxicological risk assessment.

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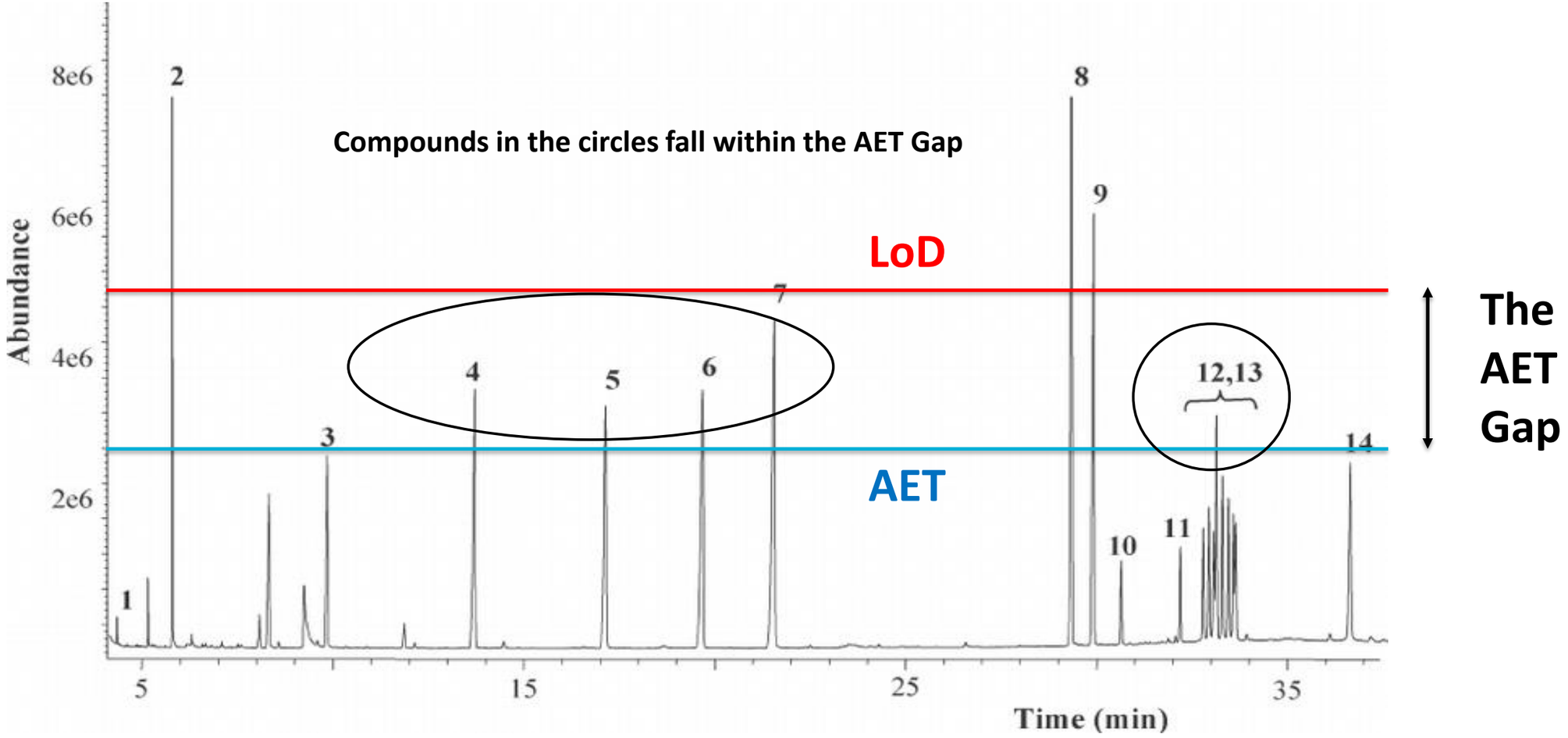
The AET Gap for LVPs

An **AET Gap** is created when the sensitivity of the chromatographic screening method (reflected here in the method's Limit of Detection, LoD) is insufficient to achieve the AET.



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The AET Gap for LVPs

The **AET Gap** is more commonly encountered in LVPs versus other pharmaceutical dosage forms because:

- The AETs are low for LVPs due to their large maximum daily dose volumes (MDDV)
- The LoDs are high for certain LVPs due to their complex chemical formulations.

If one cannot detect down to the AET then potentially unsafe leachables are not reported for assessment and the risk of unsafe leachables is not adequately addressed.

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Potential “Solutions” to the AET Gap

Analytical

Conceptual

Logical

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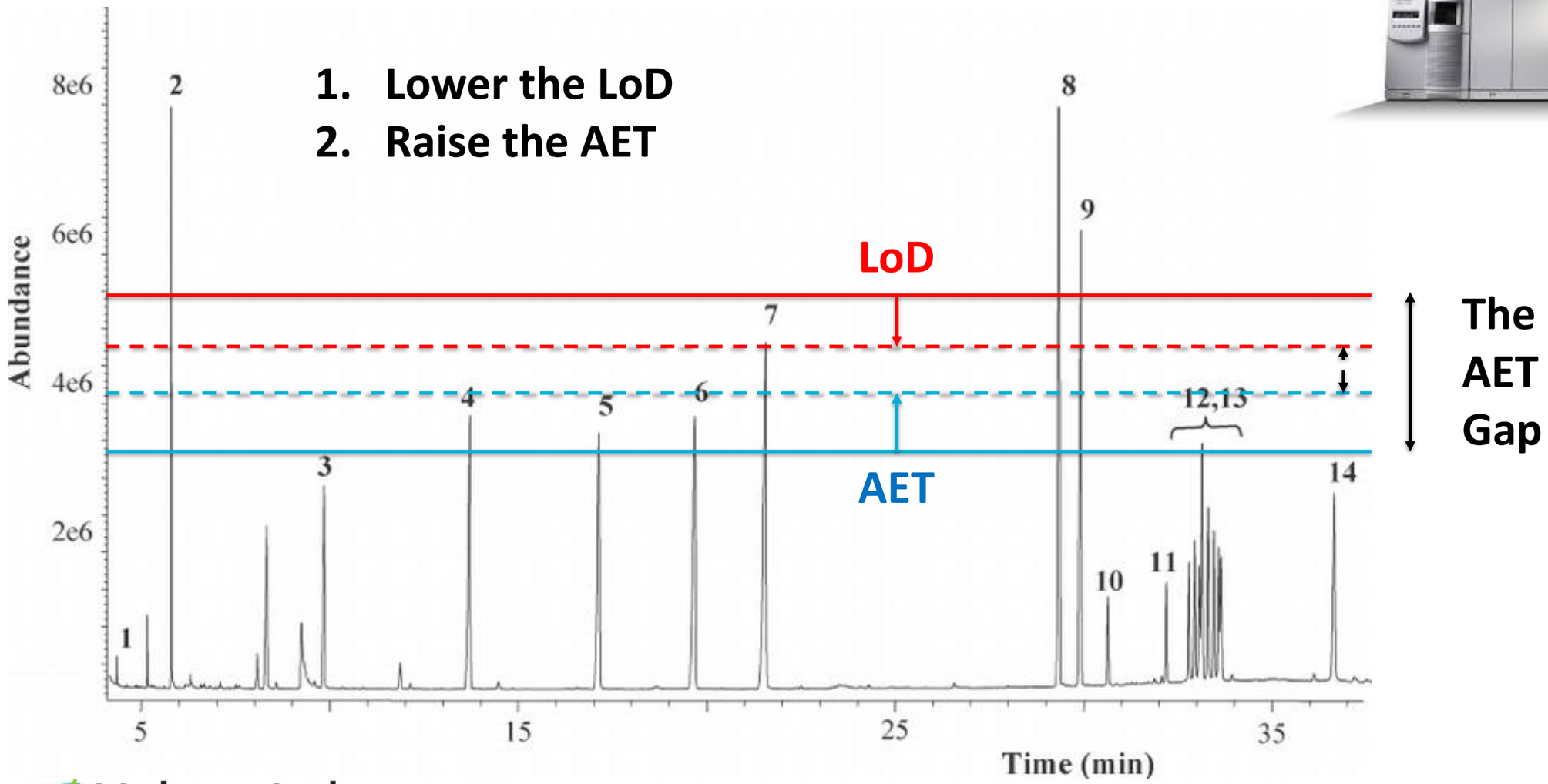
Analytically Closing the AET Gap

1. Lower the LoD
2. Raise the AET



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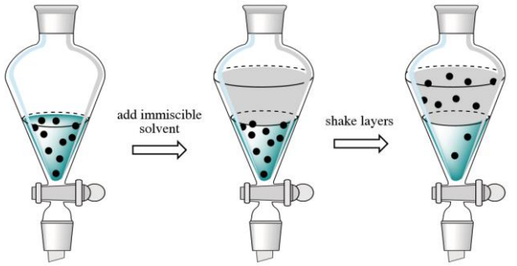
Analytical “Solutions” to the AET Gap

1. Lower the LoD

    - Adopt instrumentation with inherently greater sensitivity
    - Optimize analytical method for sensitivity
    - Adopt multiple methods
    - Use Sample preparation techniques
        - Matrix (interference) elimination
        - Sample concentration



2. Raise the AET by managing AET adjustment (reduce the uncertainty factor, UF)
    - Use detection method with highly reproducible response factors
    - Adopt multi-method approach

Adjusted AET = Initial AET ÷ UF

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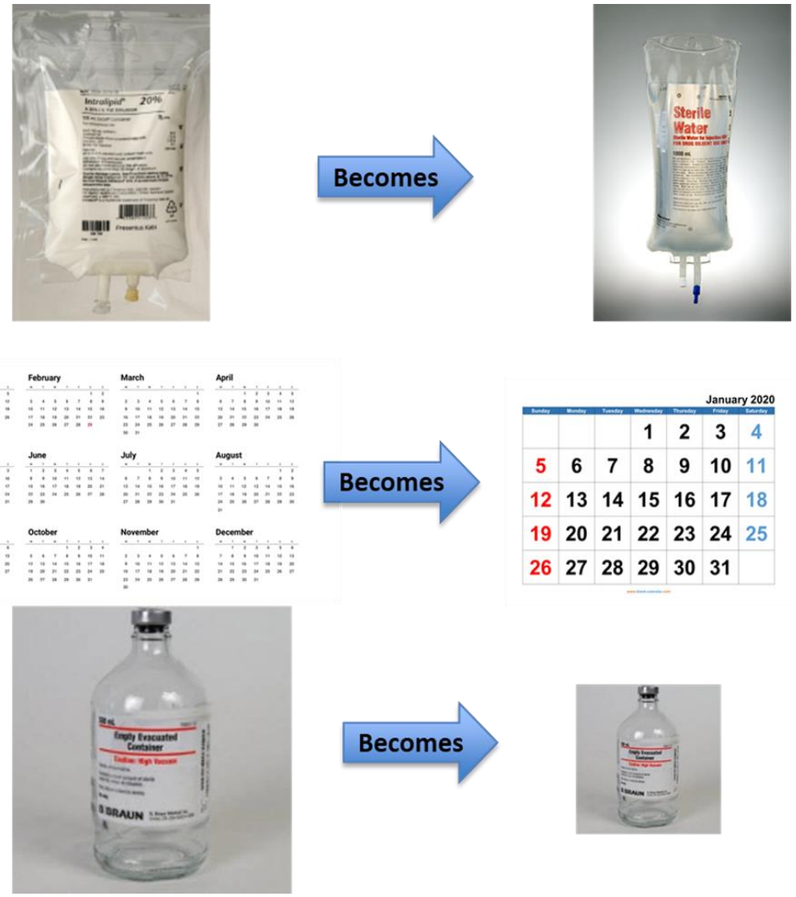
Conceptual “Solution” to the AET Gap: The Simulation (Extraction) Study

Use a properly designed extraction study to mitigate the analytical challenges of testing the drug product!

1. The drug product formulation has been replaced with one or more simulating solvents that are easier to test.

2. The actual use conditions of contact have been accelerated.

3. The test article may have been altered (somewhat) to provide an exaggerated and presumably worst case.



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“Logical” Solution to the AET Gap: The Preponderance of Evidence Approach

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The “Logic” of the Preponderance of Evidence Approach

Leachables in the “Gap” are likely to be safe if the packaging system is inherently safe.

A packaging system is as safe as its individual materials of construction are safe.

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Pillars of Evidence that a Packaging System and/or its Materials of Construction are Safe

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Justification of the “Preponderance of Evidence” Approach; Regulatory Precedence

Guidance for Industry

Container Closure Systems for Packaging Human Drugs and Biologics

Safety:

Case 1s: Typically provided are USP Biological Reactivity Test data, extraction/toxicological evaluation, limits on extractables, and batch-to-batch monitoring of extractables.
Case 2s: Typically provided are USP Biological Reactivity Test data and possibly extraction/toxicological evaluation.
Case 3s: Typically, an appropriate reference to the indirect food additive regulations is sufficient for drug products with aqueous based solvents. Drug products with non-aqueous based solvent systems or aqueous based systems containing co-solvents generally require additional suitability information **Case 4s**: Typically, an appropriate reference to the indirect food additive regulations is sufficient.
Case 5s: Typically, an appropriate reference to the indirect food additive regulations for all components except the mouthpiece for which USP Biological Reactivity Test data is provided.

EMEA/CVMP/205/04: GUIDELINE ON PLASTIC IMMEDIATE PACKAGING MATERIALS

- … if the plastic packaging material is used for non-solid medicinal products intended for oral or topical (except ophthalmic) administration, or for non-solid active substances … the supplier can certify compliance with the foodstuff legislation.
- If the plastic material or additives used are described in the European Pharmacopoeia, the pharmacopoeia of a Member state or have been approved for use in food packaging, toxicological data may not be required.

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Justification of the “Preponderance of Evidence” Approach

Three of the four pillars of evidence are based on extraction studies and extractables assessment.

- All three of these pillars of evidence start with an extraction of the test article.
- All three pillars of evidence end with the testing of the extract.

The pillars differ from a “typical” chemical extraction study in the testing of the extract:

- In Biocompatibility testing, the extract is directly tested for biological effects via biological systems (whereas in chemical extractables testing, biological effect is inferred from analytically determined identity and concentration)
- In Compendial testing, the extracts are tested for general chemical properties and to establish composition (whereas in chemical extractables testing, extracts are tested to establish individual analytes (e.g., extractables)
- Analytical testing for Food approval is generally targeted while chemical extractables testing is typically screening.

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Justification of the “Preponderance of Evidence” Approach

“Clean” Composition

“A compound cannot be a leachable in a drug product if it is not present in the packaging system (or material of construction) in the first place.”

Types of Compositional Evidence:

- Formulation of Item
- Compliance to Compositional Standards (e.g., REACH, SVHC)
- Vendor extraction studies

There is a significant difference between “not intentionally added” and “confirmed to be absent.”

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Keys to Successfully Managing the AET Gap

1. Acknowledge (openly) that the Gap Exists
2. Quantify the size of the Gap.
3. Minimize the Gap.
    - Optimize analytical methods (including sample preparation) for sensitivity
    - Establish the necessary and appropriate AET and lessen any required AET adjustment
4. Communicate the due diligence efforts applied to minimizing the gap.
5. Consider performing a simulation extraction study. Be aware of the regulatory perspectives on the design and use of simulations studies.
6. Collect the available “preponderance of evidence” and create your “safe use defense”.
7. Effectively and completely “tell your story” with respect to the AET gaps and how you have managed it.

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Thank you!

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