# INTRODUCTION TO LEACHABLES AND THE RELATED TOPIC OF EXTRACTABLES – Pharmaceutical Packaging

# Trainer

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Triad Scientific Solutions, LLC

Principal Consultant, Nelson Labs - Europe

- 30 + years of experience in chemical characterization (E&L) of pharmaceutical packaging, manufacturing systems and medical devices, largely spent at Baxter Healthcare.
- Nearly 170 journal articles, numerous book chapters and one book on the topics of analytical chemistry, ion chromatography, theory and practice of chemical characterization.
- If there is something that you do not like about an E&L Standard, Monograph or Recommendation, then chances I am probably to blame.

# Participant Introductions

1. Name
2. Company
3. Department
4. Learning Expectations

# Training Course Outline

- Introduction to Pharmaceutical Packaging
- Suitability for Use Expectations for Packaging
- Packaging – Drug Product Interactions
- Impurities, Leachables and Extractables
- Guidance, Standards, Recommendations and Advice for Chemical Characterization of Packaging
- The Chemical Assessment Process
- The Anatomy of a Chemical Characterization Study
  - Extraction
  - Testing
  - Impact Assessment
- Re-cap
- Q&A

# Learning Objectives

- Understand the suitability for use expectations for pharmaceutical packaging
- Extractables and Leachables – Definitions and Correlations
- Review of the Regulatory, Compendial and Scientific Landscape
- Leveraging the Three Step Chemical Assessment Process for Qualifying Packaging
- Theory and Practice of the Simulation Study
- Designing an Extraction Study for the Purpose of Forecasting Leachables
- Properly Testing an Extract for Extractables or a Drug Product for Leachables
  - Identification
  - “Quantitation”
- A Dummy’s Guide to Toxicological Safety Assessment

# What is Pharmaceutical Packaging?

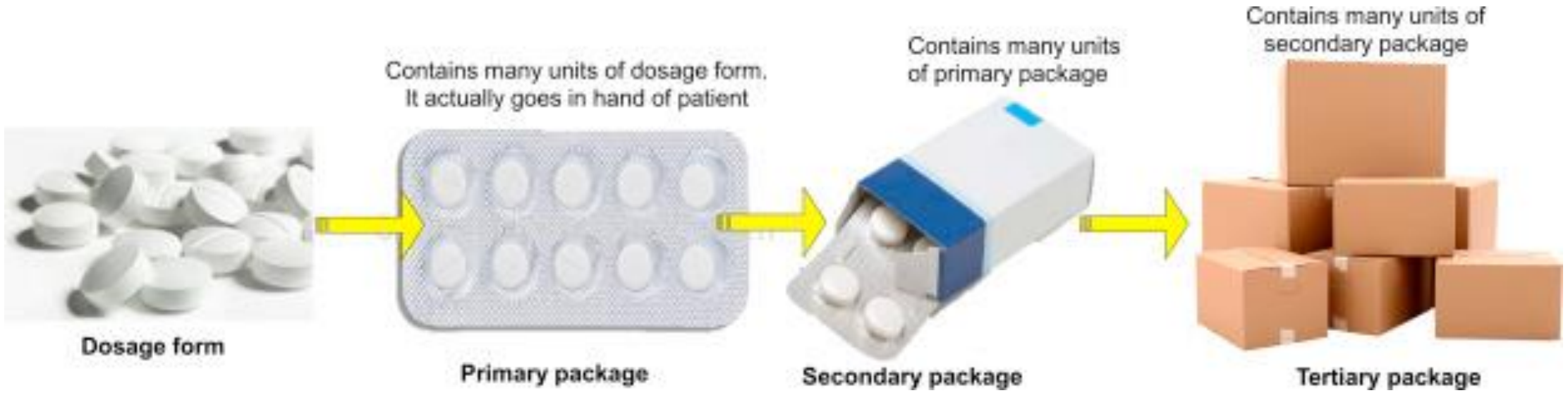
***From the FDA, EMEA and USP:***

A container closure system refers to the sum of packaging components that together contain and protect the dosage form.

A packaging system is equivalent to a container closure system.




# “Layers” of Pharmaceutical Packaging



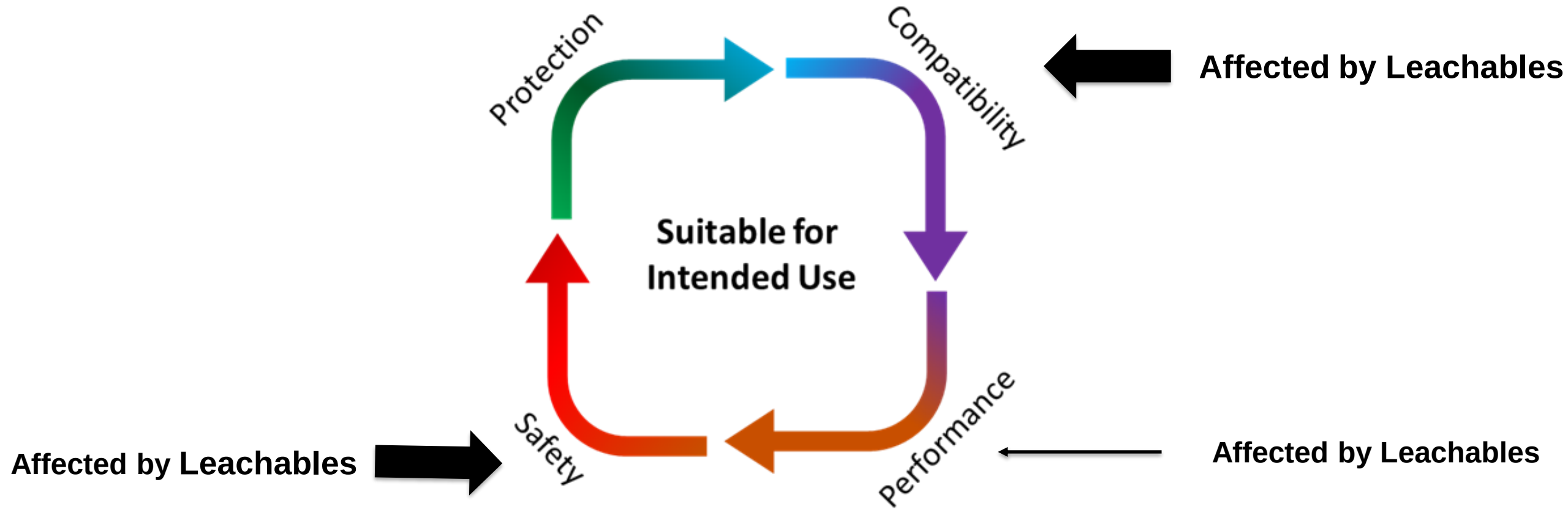

**Number of barriers between dosage form and packaging:**

| | **0** | **1** | **2** |
|---|---|---|---|
| **“Nature” of Contact:** | Direct | Indirect | Remote |

# What is Expected from Pharmaceutical Packaging?

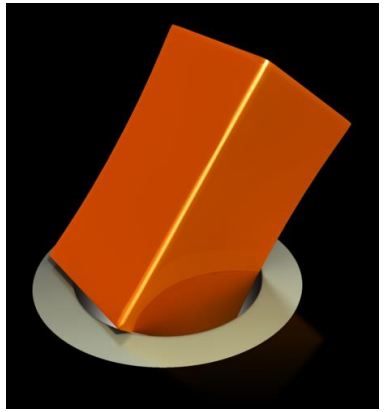
The selected Container / Closure system must be

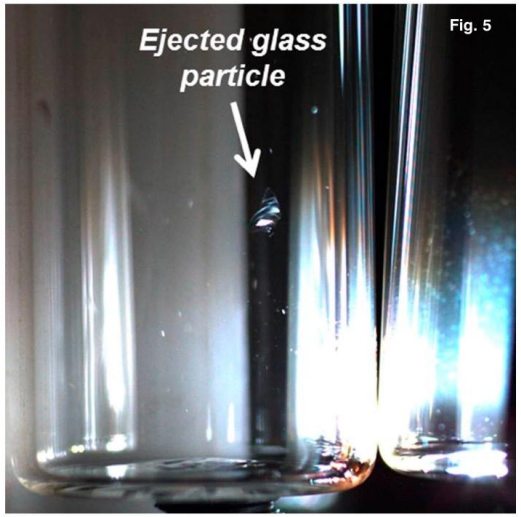
**“suitable for its intended use”**



# What is Expected from Pharmaceutical Packaging?

## Compatibility






Packaging components that are compatible with a dosage form will not interact sufficiently to cause unacceptable changes in the quality of either the dosage form or the packaging component.

## Safety


The Federal Food, Drug, and Cosmetic Act (the Act) mandates the need for adequate information related to packaging materials. Section 501(a)(3) of the Act states that a drug is deemed to be adulterated "if its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health...."

Packaging components should be constructed of materials that will not **leach** harmful or undesirable amounts of substances to which a patient will be exposed when being treated with the drug product.

# So Why do we Care about Leachables??

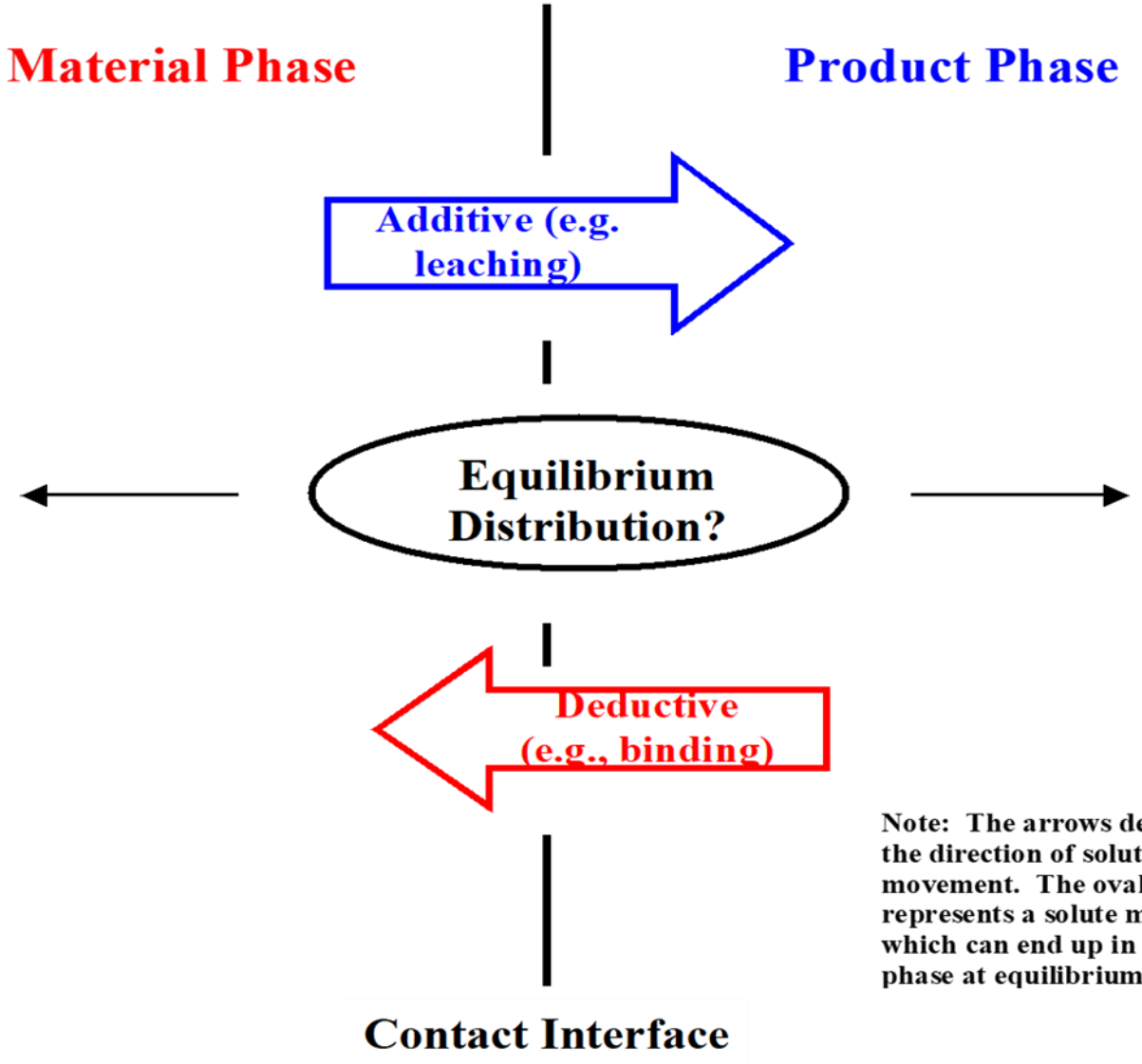
- **Adverse safety effects**
  - The leachable itself may adversely affect patient health and safety
  - The leachable, because of its behavior in the drug product, may cause a safety issue
    - Particulate formation
    - Reaction with drug substance and/or excipients to produce unsafe entities
- **Adverse drug product effects**
  - Drug substance potency reduced
  - Drug product stability reduced
  - Drug products no longer comply with specifications and/or compendial requirements
  - Leachables complicate drug product testing
  - Leachables have “unpleasant cosmetic” effects
- **Adverse packaging effects**
  - Packaging no longer functions properly

# What do we Expect from Pharmaceutical Packaging?

## We expect Pharmaceutical Packaging to be INERT[1]!


[1]Chemically inactive and unreactive

# What do we Experience from Pharmaceutical Packaging?




**Interactions are the norm rather than the exception!**

Note: The arrows denote the direction of solute movement. The oval represents a solute molecule, which can end up in either phase at equilibrium.

# The Perfect versus the Imperfect World of Drug Products


## In the Perfect World:

A drug product would be 100% pure, meaning that it contains no impurities.

## In the Real (Imperfect) World:

A drug product is unavoidably impure, meaning that it inevitably contains impurities.

## In the Perfect World:

A drug product would only produce the desired therapeutic effect.

## In the Real (Imperfect) World:

A drug product produces both desired and undesired clinical effects.

# The Problem with Impurities

## An Impurity in a Drug Product could:

- Prevent the drug product from having its desired therapeutic effect
- Produce an undesired clinical effect

# The Big Picture – Impurities in Drug Products

## What is an Impurity?

Any component of the new drug product that is not the drug substance or an excipient in the drug product.[1]

## What is a Contaminant?

A substance whose introduction to a drug product renders the drug product impure, inferior, unsafe, or otherwise unfit for use.

## What is an Adulterant?

A foreign or inferior substance which, when added to a drug product corrupts[2], debases[3] or otherwise makes the drug product impure.

## What is a Degradation Product?

An impurity resulting from a chemical change in the drug substance brought about during manufacture and/or storage of the new drug product by the effect of, for example, light, temperature, pH, water, or by reaction with an excipient and/or the immediate container closure system.[1]

[1]Official definitions from Guidance for Industry Q3B(R2) Impurities in New Drug Products. 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). July, 2006.
[2]Corrupts: alters from the original or correct form
[3]Debases: lowers in quality, intrinsic value or character

# What is a Leachable?

No definition although the term is used throughout the document.

Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics. 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, 1999.

GUIDELINE ON PLASTIC IMMEDIATE PACKAGING MATERIALS; European Medicines Agency. London, 19 May 2005. CPMP/QWP/4359/03: EMEA/CVMP/205/04.

Leachables (in OINDP) are compounds which are present in the drug product due to leaching from container/closure system components.

*From:* Safety Threshold and Best Demonstrated Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products. Product Quality Research Institute (PQRI). August, 2006.

Leachables are foreign organic or inorganic entities that are present in a packaged drug product because they have leached into the packaged drug product from a packaging/delivery system, packaging component or packaging material of construction under normal conditions of storage and use or during accelerated drug product stability studies.

*From:* USP <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems.

# What is a Leachable?

For a medical device: A leachable is a "substance that is released from a medical device or material during its clinical use".

*From:* ISO/DIS 10993-18:2018(E). ISO/TC 194/SC /WG 14. Biological evaluation of medical devices — Part 18: Chemical characterization of medical device materials within a risk management process

For a component used to manufacture a drug substance or product: A leachable is "a foreign organic or inorganic chemical entity that is present in a manufactured biopharmaceutical DS, or pharmaceutical or biopharmaceutical DP because it has leached from a component used in the manufacturing system and has persisted through the entire manufacturing process."

*From:* USP ⟨1665⟩ CHARACTERIZATION OF PLASTIC COMPONENTS, AND SYSTEMS USED IN THE MANUFACTURING OF PHARMACEUTICAL DRUG PRODUCTS AND BIOPHARMACEUTICAL DRUG SUBSTANCES AND PRODUCTS (draft).

# The First Common Factor to all Leachable's Definitions:

## The patient!

**A leachable is a substance (impurity?) that patients are unintentionally exposed to when they are medically treated with a drug product or a medical device.**

# The Second Common Factor to all Leachable's Definitions:

## Leaching!

**All the definitions of a leachable talk about the donor item (such as packaging) being leached by the receiving item (such as a drug product).**

## Question:

Can a substance be a leachable if there is no chemical interaction between the donor phase and the receiving phase?

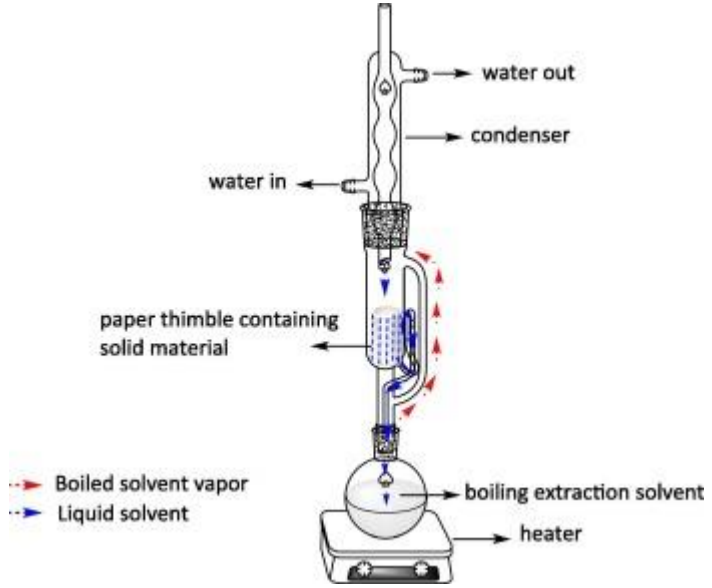
# The Third Common Factor to all Leachable's Definitions:

## Conditions of Actual Use

**All the definitions of a leachable talk about the leaching occurring under conditions of actual use.**

**Versus**


**Versus**



# So What Exactly is a Leachable?

**Is it a(n) …**

- Impurity,
- Contaminant,
- Adulterant,
- Degradation Product,
- All of the Above,
- Something Else?

# The Most Important Point I Learned about Leachables:

**If your analytical team is able to screen your drug product, medical device or manufacturing component for unspecified leachables down to the AET, then do it and be on your way. Do not think, Do not re-consider, Do not ask "how much" or "why" …**

# What is an Extractable?

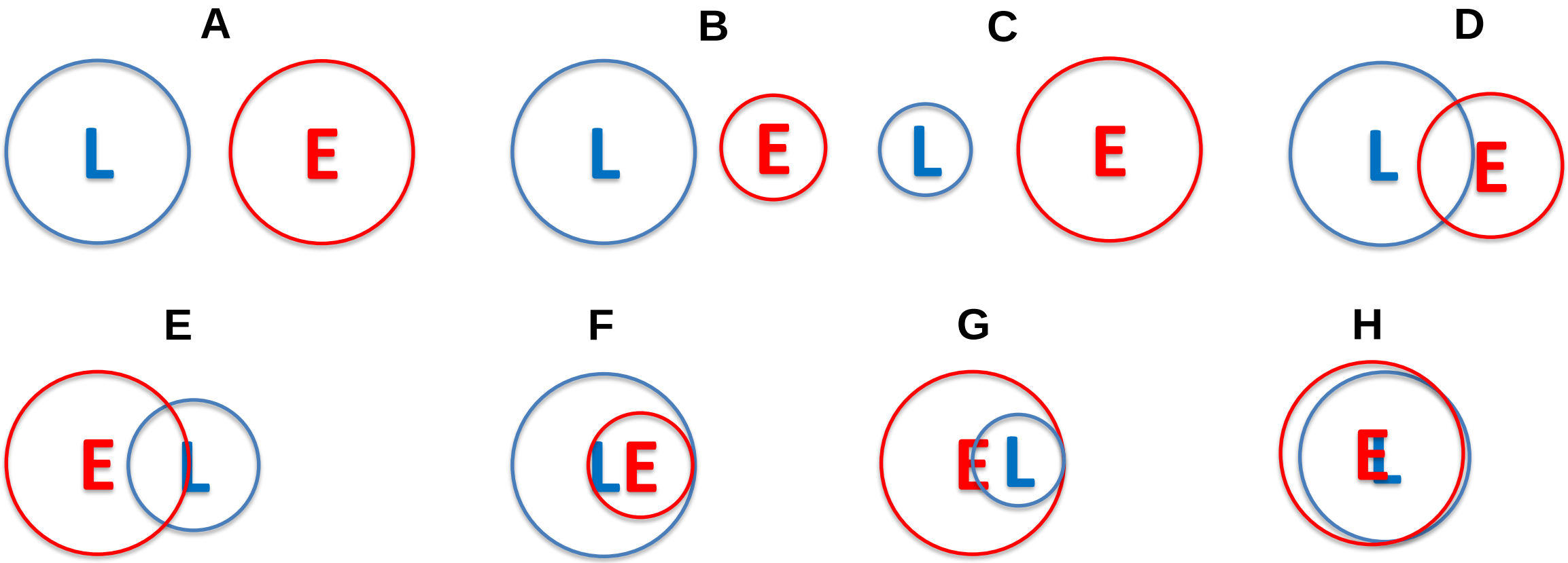
Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics. U.S. Department of Health and Human Services: Food and Drug Administration; Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). May, 1999: No definition although the term is used throughout the document.

GUIDELINE ON PLASTIC IMMEDIATE PACKAGING MATERIALS; European Medicines Agency. London, 19 May 2005. CPMP/QWP/4359/03: EMEA/CVMP/205/04: No definition although the term is used throughout the document.

Safety Threshold and Best Demonstrated Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products. Product Quality Research Institute (PQRI). August, 2006: **Extractables are compounds that can be extracted** from (OINDP) device components or surfaces of the (OINDP) container/closure system in the presence of an appropriate solvent(s) and/or condition(s).

USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems: **Extractables are** organic or inorganic entities that are **released** from a pharmaceutical packaging/delivery system, packaging component or packaging material of construction and into a extraction solvent **under laboratory conditions**.

# The Extractables – Leachables Continuum




There is a whole continuum of extractables and leachables relationships, as depicted by the size and intersection of the E & L populations (circles)!

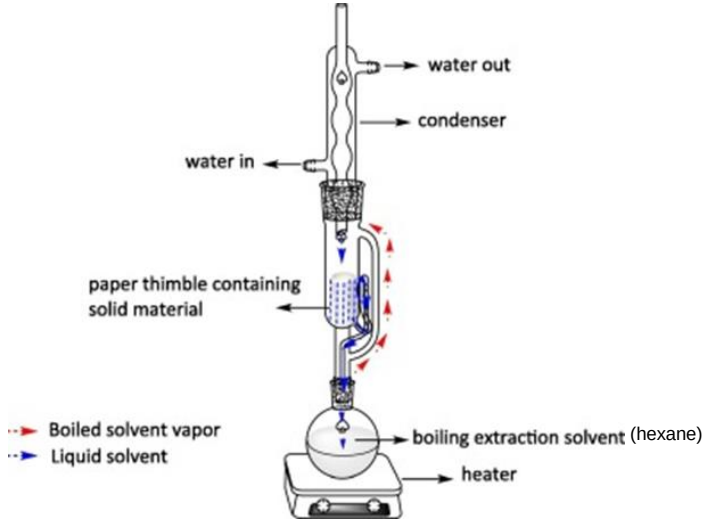
# How well do Extractables and Leachables Correlate?

The extent to which extractables and leachables correlate depends on:

1. How closely the extraction conditions match the clinical conditions of use (leaching conditions), and

2. How liberal one is in the definition of leachables.


**Versus**




Unfortunately, wood pallets don't just pose a health risk to food safety. The same health risks that are present with food loads are also present with pharmaceutical loads.

**Contaminants --- Yes!**
**Leachables --- ???**

# The “Big Five” Events that Keep Interest in E&L High

## 1. DEHP and BPA (The “Bad Actors”).

- Bisphenol A and DEHP – (in)famous examples of impurities from plastic

**Leaching of the plasticizer di(2-ethylhexyl)phthalate (DEHP) from plastic containers and the question of human exposure.**

*Di(2-ethylhexyl)phthalate (DEHP) is a widely used plasticizer to render poly(vinyl chloride) (PVC) soft and malleable. Plasticized PVC is used in hospital equipment, food wrapping, and numerous other commercial and industrial products. Unfortunately, plasticizers can migrate within the material and leach out of it over time, ending up in the environment and, frequently, the human body.*

**BPA, chemical used to make plastics, found to leach from polycarbonate drinking bottles Into humans - Exposure to BPA May Have Harmful Health Effects**

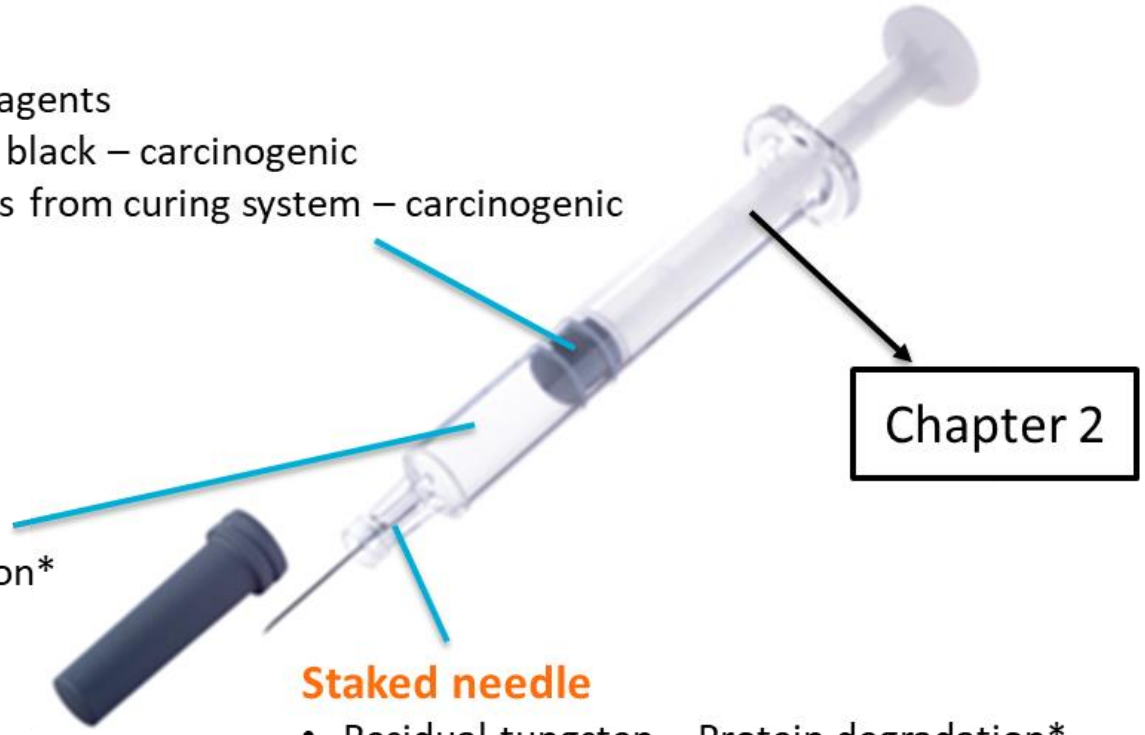
*Boston, MA — A new study from Harvard School of Public Health (HSPH) researchers found that participants who drank for a week from polycarbonate bottles, the popular, hard-plastic drinking bottles and baby bottles, showed a two-thirds increase in their urine of the chemical bisphenol A (BPA). Exposure to BPA, used in the manufacture of polycarbonate and other plastics, has been shown to interfere with reproductive development in animals and has been linked with cardiovascular disease and diabetes in humans. The study is the first to show that drinking from polycarbonate bottles increased the level of urinary BPA, and thus suggests that drinking containers made with BPA release the chemical into the liquid that people drink in sufficient amounts to increase the level of BPA excreted in human urine.*

# The "Big Five" Events that Keep Interest in E&L High

## 2. The Emergence of the Pre-filled Syringe

**Rubber stopper**

- Halogenated rubber oligomers – alkylating agents
- PolyNuclear Aromatics (PNA's) from carbon black – carcinogenic
- Nitrosamines and sulfur-holding compounds from curing system – carcinogenic
- Iron – oxidative degradation of proteins*
- Aromatic antioxidants – toxic




**Glass barrel**

- Barium and Aluminum – particle formation*
- Silicon oil – protein aggregation*

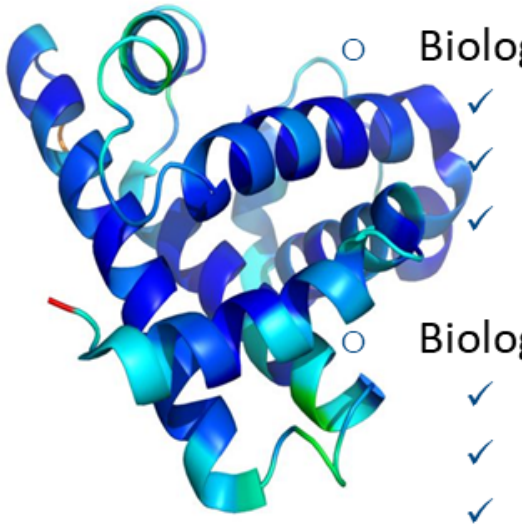
**Staked needle**

- Residual tungsten – Protein degradation*
- Acrylates from incomplete curing – reactive and toxic*

** Presented By I. Markovic, "Regulatory Perspective on Extractables & Leachables for Biologics, Quality Perspective" PDA E/L-Workshop, Brussels , 2014*

## 3. The Emergence of Biopharmaceuticals

- Protein drug products require special care
  - Administration by injection is among those of highest concern
  - Likelihood of interaction between packaging component and injectable dosage is high
  - Biologics are complex
    - ✓ Large molecular weights
    - ✓ Abundance of binding sites on the surface (hydrophilic and hydrophobic)
    - ✓ Heterogeneous mixtures
  - Biologics are sensitive to structural modifications
    - ✓ Safety considerations (immunogenicity)
    - ✓ Efficacy considerations (loss of activity, formation of neutralizing antibodies)
    - ✓ Quality considerations (protein aggregates, stability)



# The “Big Five” Events that Keep Interest in E&L High

## 4. Biocontainers that Adversely Effect Cell Growth

Some cytotoxic compounds such as **bis(2,4-di-tert-butylphenyl) phosphate (bDtBPP)** have been found to leach from single-use films used in culture and media bags. This specific compound was responsible for reduced cell growth in a Chinese hamster ovary (CHO) process and inconsistent cell viability due to varying leachable amounts per bag per lot, even from the same manufacturer.

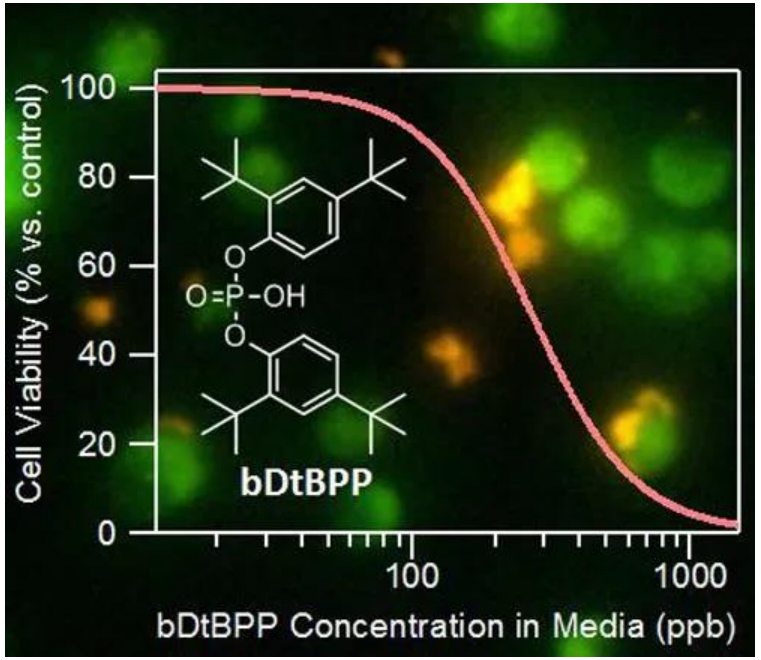
bDtBPP is formed from the degradation of a common antioxidant stabilizer (Irgafos 168), which is added to many flexible polymers such as those used in biomanufacturing.

**Identification of a Leachable Compound Detrimental to Cell Growth in Single-Use Bioprocess Containers**

MATTHEW HAMMOND[2,*], HEATHER NUNN[3], GARY ROGERS[3], HANS LEE[1], ANATOLIA-LILIANA MARGHITOIU[1], LOURDES PEREZ[1], YASSER NASHED-SAMUEL[1], CARL ANDERSON[4], MICHAEL VANDIVER[1], and SALLY KLINE[5]

[1]*Product Attribute Sciences;* [2]*Product Contact Assessment;* [3]*Materials Science, Amgen Inc., Thousand Oaks, CA;* [4]*Cell Sciences & Technology, Amgen Inc., Seattle, WA; and* [5]*Pilot Plant Operations, Amgen Inc., Bothell, WA. ©PDA, Inc. 2013*

*ABSTRACT:* Out of the plethora of chemical species extractable at low levels from the materials of construction of single-use bioprocess containers, we have identified one particularly conspicuous compound and shown it to be highly detrimental to cell growth. The compound, *bis*(2,4-di-*tert*-butylphenyl)phosphate (bDtBPP), is derived from the breakdown of *tris*(2,4-di-*tert*-butylphenyl)phosphite crude name Irgafos 168®), a common antioxidant additive present in many formulations of polyethylene (one of the polymers commonly used in the material contacting process fluids in bioprocess containers). Cell growth experiments using several mammalian cell lines and growth media spiked with bDtBPP show harmful effects at concentrations well below the parts-per-million range. Cellular response to bDtBPP is rapid, and results in a significant decrease in mitochondrial membrane potential. The migration of bDtBPP from polyethylene-based films is shown to be time- and temperature-dependent. Further, experiments suggest that exposure of oxidized Irgafos 168 to ionizing radiation (such as gamma irradiation) is an important condition for the generation of significant amounts of leachable bDtBPP.



# The “Big Five” Events that Keep Interest in E&L High


## 5. Eprex.

- Eprex = Human Recombinant EPO
- introduced in late ‘80 early ’90 – Janssen Cilag
- Increase Hematocrit (RBC-count) in CKD Patients
- Until ’98: no side effects
- From ‘98 onwards: increased incidence of PRCA
  - *Caused a drop in Hematocrit (instead of an increase)*
  - *Immune response*

- **Cause** (certain): Changed the Eprex formulation from Serum Albumin to Polysorbate 80
- **Cause** (certain): Altered leachables profile (vulcanizing agent from stopper)
- **Cause** (hypothesis): Leachables cause adjuvant-like properties
- **Solution** (certain): Coated plunger

**First example of “reactive” leachables – leachables which exert an indirect effect**

# Regulatory Guidance

*There is none!!!!!!!*

**The documents exist but the regulators no longer use the concepts and requirements contained therein as the basis for an acceptable E&L submission strategy.**

## Guidance for Industry

**Container Closure Systems for Packaging Human Drugs and Biologics**

CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION

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 1999


European Medicines Agency
*Inspections*

London, 19 May 2005
CPMP/QWP/4359/03
EMEA/CVMP/205/04

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)
COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

**GUIDELINE ON PLASTIC IMMEDIATE PACKAGING MATERIALS**

| | |
|---|---|
| DRAFT AGREED BY QUALITY WORKING PARTY | October 2003 |
| ADOPTION BY CPMP/CVMP FOR RELEASE FOR CONSULTATION | February 2004 |
| END OF CONSULTATION (DEADLINE FOR COMMENTS) | 31 August 2004 |
| AGREED BY QUALITY WORKING PARTY | February 2005 |
| ADOPTION BY CHMP/CVMP | April/May 2005 |
| DATE FOR COMING INTO EFFECT | 1 December 2005 |

This guideline replaces the Guideline on Plastic Primary Packaging Materials (Rules Governing Medicinal Products 3AQ10a).

Public

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# Regulatory Guidance: A Universal Concept for Packaging Qualification

| Degree of concern associated with the route of administration | Likelihood of packaging component-dosage form interaction | | |
|---|---|---|---|
| | High | Medium | Low |
| Highest | Inhalation aerosol and sprays | Injection and injectable suspension; inhalation solution | Sterile powders and powders for injection; inhalation powders |
| High | Transdermal ointment and patches | Ophthalmic solutions and suspension; nasal aerosol and sprays | |
| Low | Topic solutions and suspensions; topical and lingual aerosol; oral solutions and suspensions | | Oral tablets and oral (hard and soft gelatin) capsules; topical powders; oral powders |

**The greater the risk, the greater the amount and rigor of testing required!**

# Compendial Monographs

## European Pharmacopoeia (EP)

**3.1 *Materials* used in the manufacture of containers**

3.1.1.1 **PVC** for human blood (components) containers
3.1.1.2 **PVC** for human blood (components) tubing sets
3.1.3 **Polyolefines**
3.1.4 **PE without additives** containers for parenteral/ophthalmic preps
3.1.5 **PE with additives** containers for parenteral/ophthalmic preps
3.1.6 **PP** containers for parenteral/ophthalmic preps
3.1.7 **EVA** for containers and tubing for parenteral/ophthalmic preps
3.1.9 **Silicone elastomer** for Closures and Tubing
3.1.10 **Non-plasticized PVC**
3.1.14 **Plasticized PVC**
3.1.15 **PET**

**3.2 *Containers***

3.2.1 **Glass** containers for pharmaceutical Use
3.2.2 **Plastic** Containers/Closures for Pharmaceutical Use
3.2.2.1 **Plastic** Containers for aq. solutions for parenteral infusion
3.2.3 **Sterile plastic** containers for human blood (components)
3.2.4 Empty Sterile **containers of plasticized PVC** for human blood
3.2.5 Sterile **containers of plasticized PVC** for human blood, containing anticoagulant
3.2.6 **Sets for the transfusion** of Blood and Blood components
3.2.8 Sterile single-use **plastic syringe**
3.2.9 **Rubber** Closures

**General tests that are not safety or suitability indicating, therefore *not* useful for E&L**

# Compendial Monographs - Chemistry

## US Pharmacopoeia (USP)


- Enforceable Packaging and Packaging-related Monographs
  - ⟨381⟩ Elastomeric Components in Injectable Pharmaceutical Product Packaging/Delivery Systems (revised)
  - ⟨660⟩ Containers – Glass (revised)
  - ⟨661⟩ Plastic Packaging Systems and Their Materials of Construction (new)
    - ⟨661.1⟩ Plastic Materials of Construction (new)
    - ⟨661.2⟩ Plastic Packaging Systems for Pharmaceutical Use (new)
  - ⟨662⟩ Metal Packaging Components and Systems (in development)
- Enforceable E&L-related Monographs
  - ⟨665⟩ Plastic Components and Systems Used to manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products (in development)
- Informational Monographs
  - ⟨1663⟩ Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems
  - ⟨1664⟩ Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems
  - Informational Monographs associated with each Enforceable Monograph (e.g., <1665> for <665>) (in development)

# Industry Group Recommendations

PQRI
Product Quality Research Institute

8 SEPTEMBER 2006

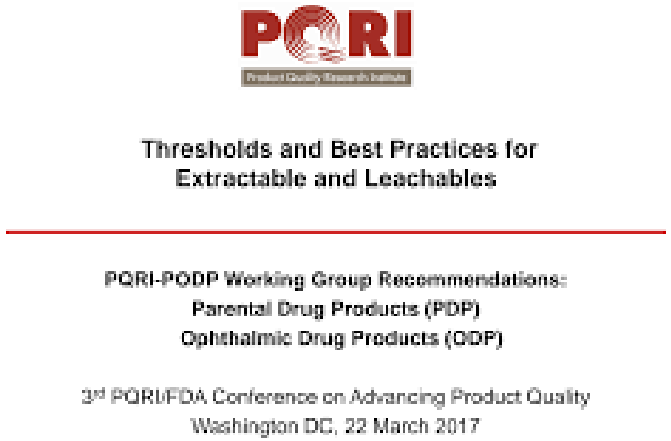
**SAFETY THRESHOLDS AND BEST PRACTICES FOR EXTRACTABLES AND LEACHABLES IN ORALLY INHALED AND NASAL DRUG PRODUCTS**

Submitted to the PQRI Drug Product Technical Committee,
PQRI Steering Committee, and U.S. Food and Drug Administration
by the
PQRI Leachables and Extractables Working Group

| | |
|---|---|
| Daniel Norwood (IPAC-RS), Chair | Timothy McGovern (FDA) |
| Douglas Ball (IPAC-RS) | Diane Paskiet (PDA) |
| James Blanchard (IPAC-RS) | David Porter (USP) |
| Lidiette Celado (AAPS) | Michael Ruberto (Lab) |
| T.J. Deng (Lab) | Alan Schroeder (FDA) |
| Fran DeGrazio (PDA) | Mark Vogel (PhRMA) |
| Bill Doub (FDA) | Qingxi Wang (PhRMA) |
| Thomas Feinberg (AAPS) | Ronald Wolff (IPAC-RS) |
| Alan Hendricker (Lab) | Melinda Munos (IPAC-RS) |
| Jeff Hrkach (AAPS) | Lee Nagao (IPAC-RS) |
| Roger McClellan (University of New Mexico) | |

The views expressed in this document are not necessarily those of the US Food and Drug Administration.

**Generalities**



PQRI
Product Quality Research Institute

Thresholds and Best Practices for Extractable and Leachables

PQRI-PODP Working Group Recommendations:
Parental Drug Products (PDP)
Ophthalmic Drug Products (ODP)

3rd PQRI/FDA Conference on Advancing Product Quality
Washington DC, 22 March 2017

**Generalities**


**Cookbook**

# E&L Guidance, Standards, Recommendations and Advice

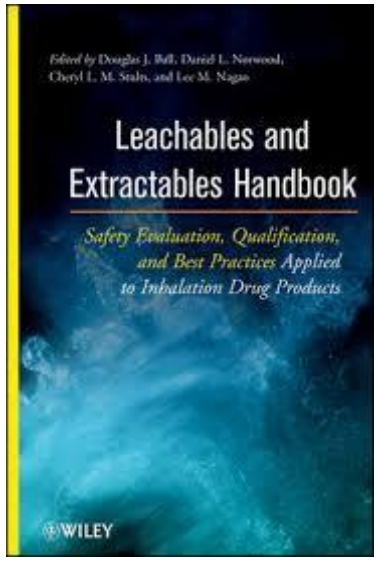
## General Advice

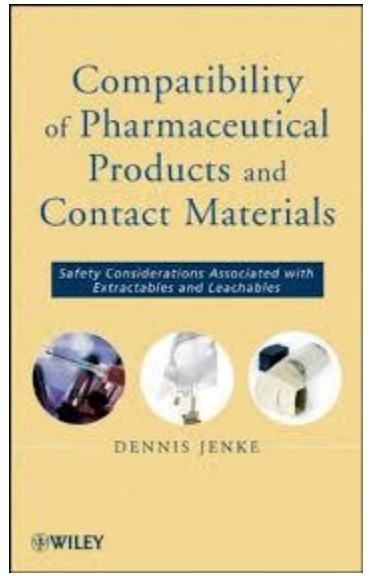
FDA U.S. FOOD & DRUG ADMINISTRATION

**Nonclinical Review of Extractable Leachable Studies: Practical Advice from an FDA Reviewer**

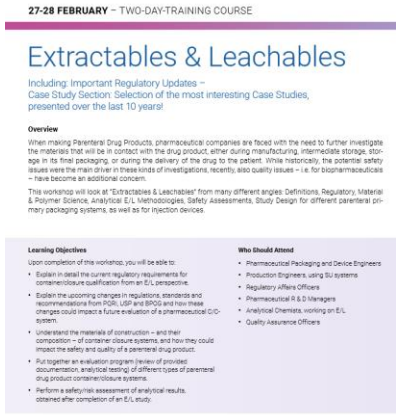
Dan Mellon, PhD
Pharmacology Toxicology Supervisor
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Center for Drug Evaluation and Research (CDER)
U.S. FDA

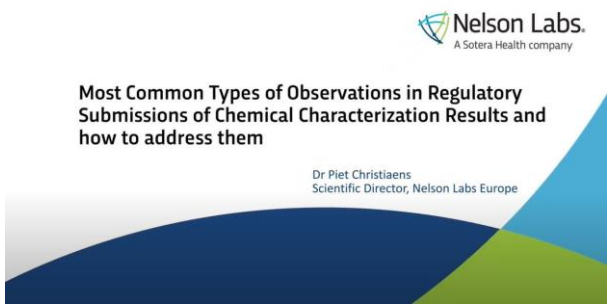
Extractables & Leachables USA
Arlington, VA
May 9, 2019

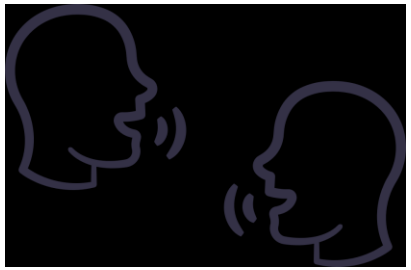




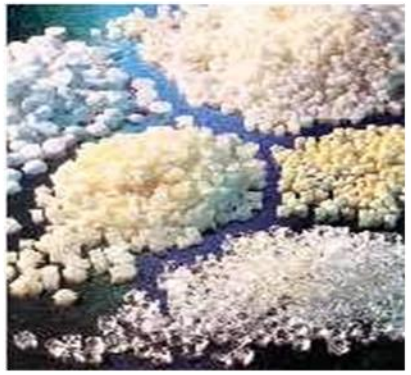



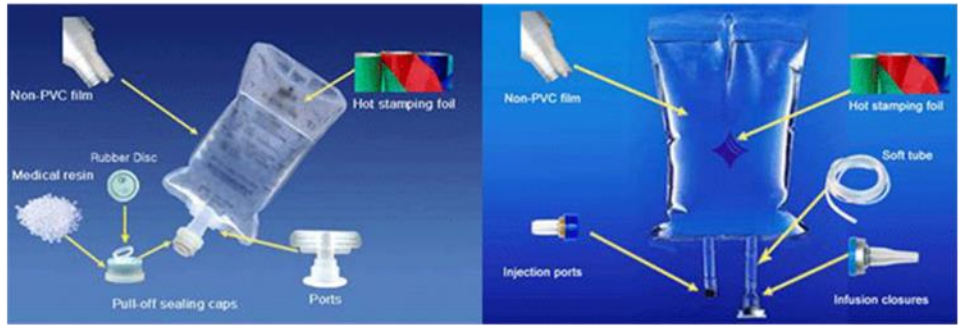



# Understanding the Chemical Assessment Process

| | | |
|---|---|---|
| Ingredients | → Extractables | → Leachables |
| Materials | → Systems | → Packaged Products |
| Material Screening & Selection | → Controlled (simulation) Extraction Study | → Packaged Product Testing |






# A Systematic Approach to Chemical Characterization

## Before you run to the lab …..

***… Collect available safety information!***

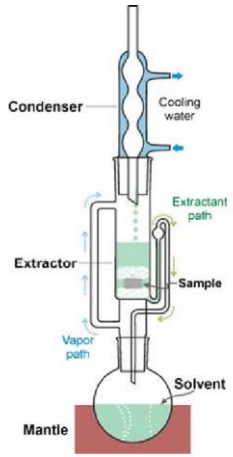
1. **Compendial Compliance**
2. **Biological Reactivity Testing**
3. **Use in Food Contact Applications**
4. **Conformance to Compositional Standards**
5. **Formulation**
6. **Processing**
7. **Extraction testing**

**When making and supporting a claim of safe for its intended use, these types of information create a preponderance of evidence, which may make up for gaps in extractables or leachables testing.**

# Level 1 Assessment:

## Material Characterization:

**Establish the total amount of all constituents, intentionally and unintentionally added**




Complete and exhaustive extraction or dissolution

**Absolute Worst Case Assessment** based on a patient being dosed with each ingredient's total amount

Typically more suited to permanently implanted medical devices and less suited to packaging

# Level 2 Assessment:

## Extractables Testing:

**Establish the extractable amount of all extractable substances**

Realistic and simulated extraction, typically accelerated and appropriately exaggerated

**Practical Worst Case Assessment** based on a patient being dosed with each extractable at its measured level. As an exaggerated study, the extractables profile exaggerates the leachables profile.

Well suited for externally communicating medical devices and pharmaceutical packaging

# Level 3 Assessment:

## Leachables Testing:

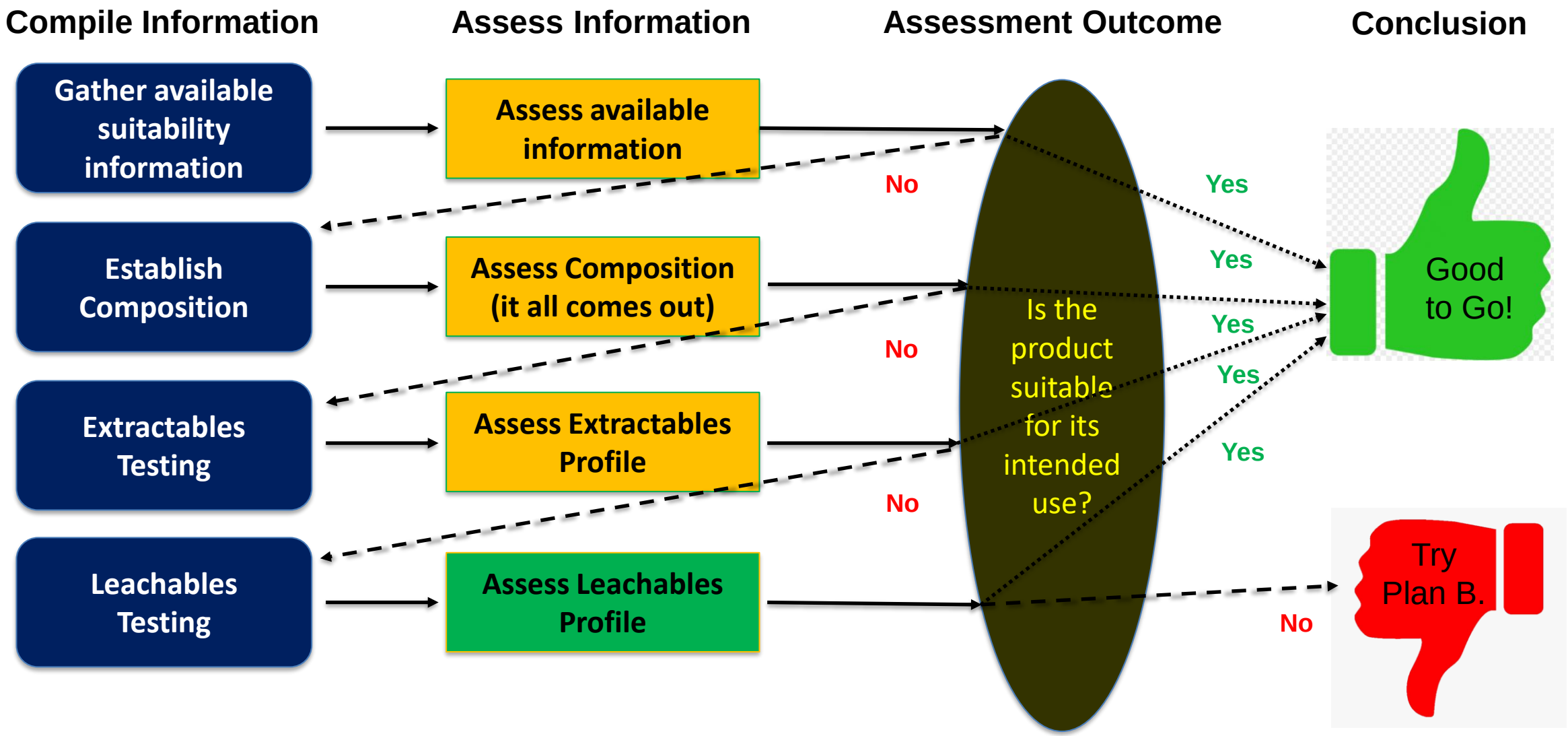
**Establish the amount of all leached substances**

Testing of the packaged drug product over shelf-life

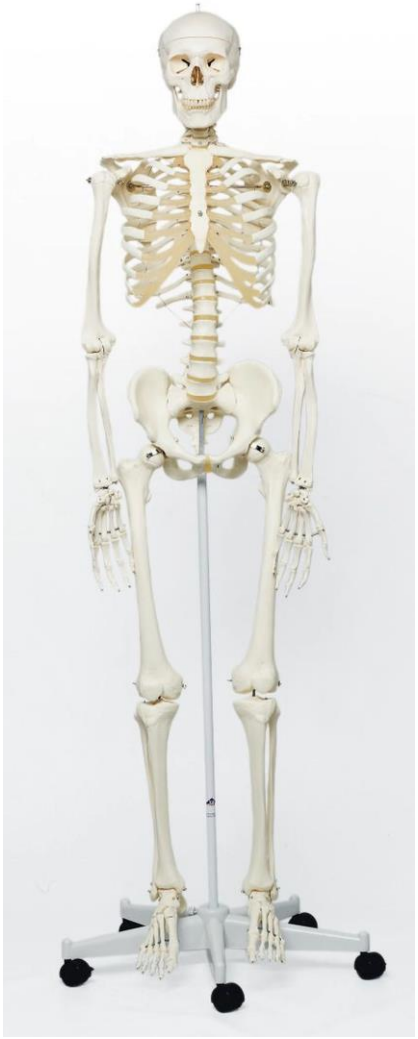
**Actual Case Assessment** based on a patient's actual clinical exposure to the packaged drug product and all substances present therein.

Well suited for pharmaceutical packaging, recognizing potential analytical issues involved

# Chemical Characterization as a Process



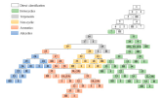
# The Anatomy of A Chemical Characterization Study



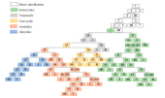
**Chemist**

**Toxicologist**

Collect and Review Background Information



Design Study



Secure Needed Test Articles and Test Equipment

Implement Study - Perform Extraction (if necessary)

Prepare Extracts (or drug product) for Analytical Testing

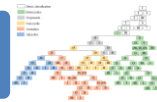
Instrumental Analysis of Prepared Samples

Data Reduction

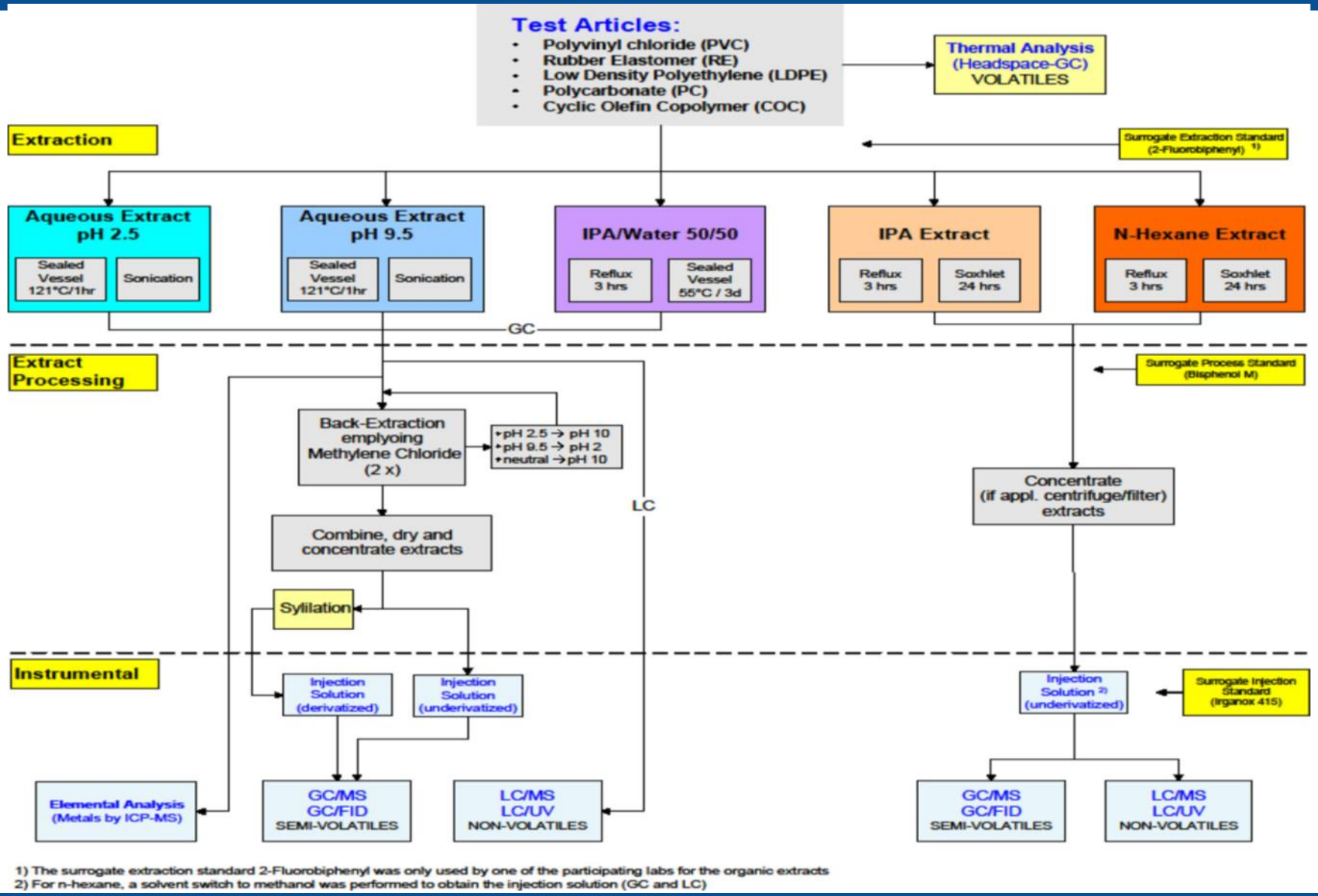
Data Review

Data Reporting

Impact Assessment



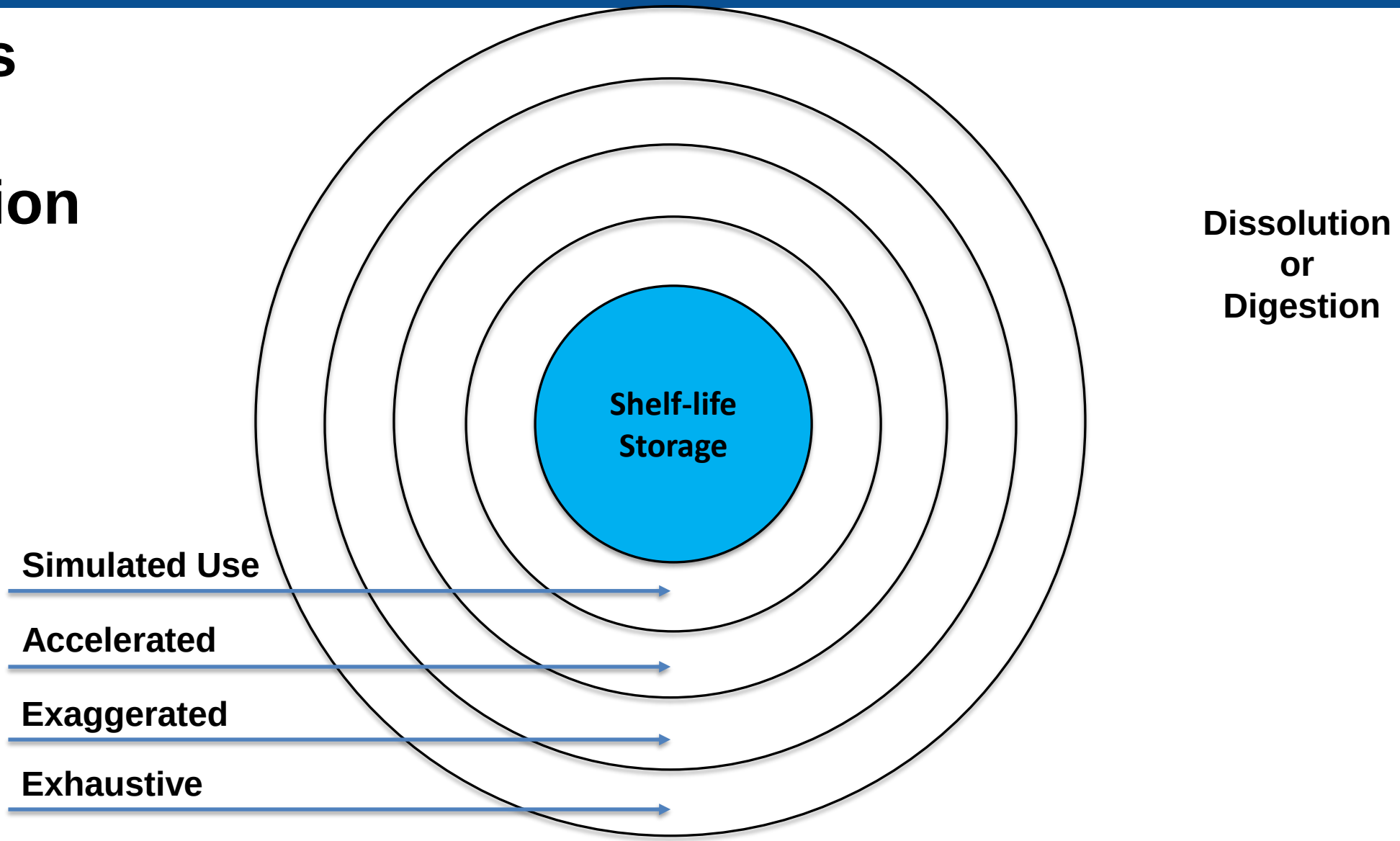
# The Anatomy of A Chemical Characterization Study




1) The surrogate extraction standard 2-Fluorobiphenyl was only used by one of the participating labs for the organic extracts
2) For n-hexane, a solvent switch to methanol was performed to obtain the injection solution (GC and LC)

# Extraction: The Heart of an Extractables Study

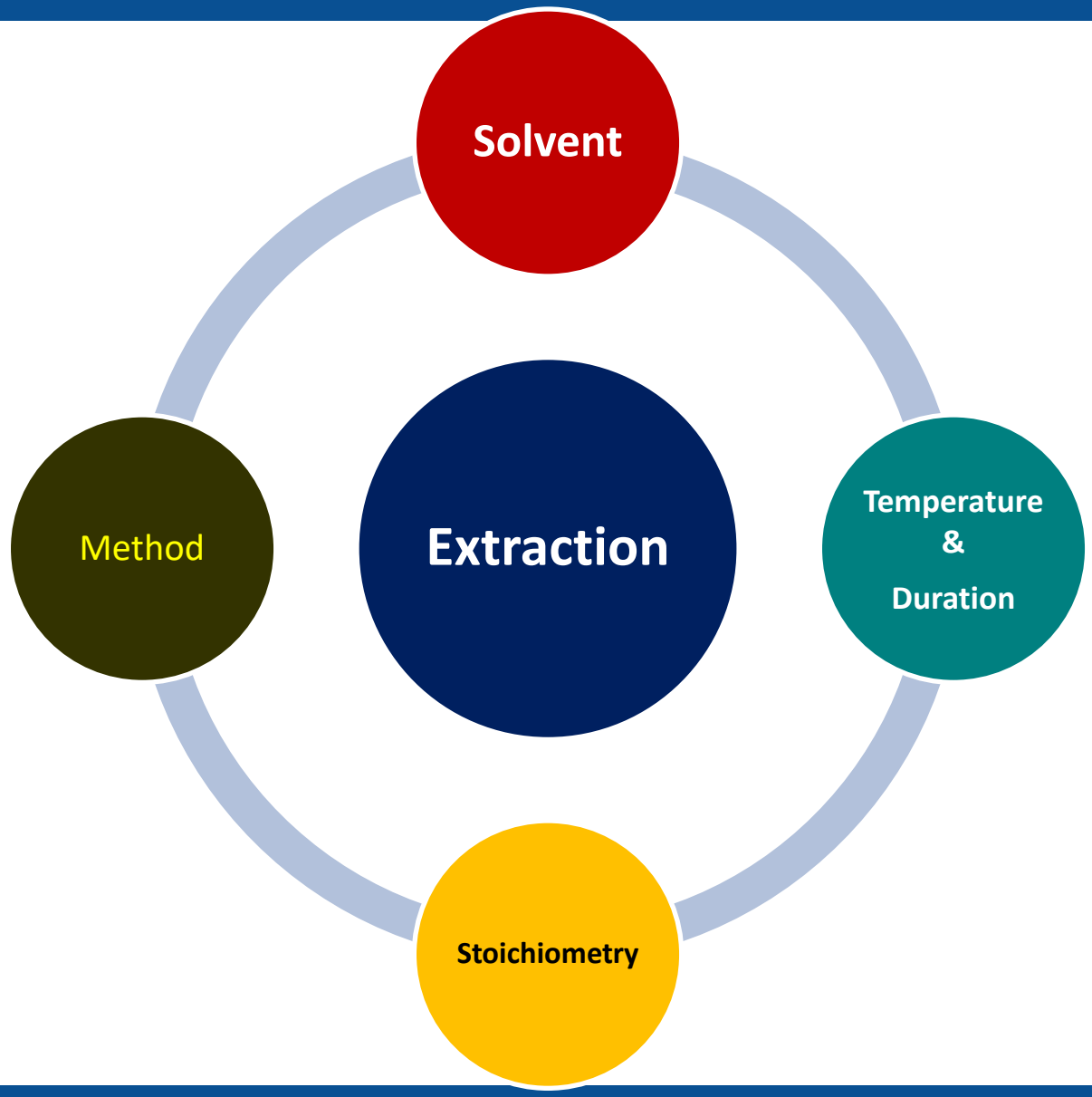
## Types of Extraction




**Dissolution or Digestion**

# Extraction: The Heart of an Extractables Study

## Dimensions of Extraction



# The "Golden Rules" of Extraction

**Rule #1:** The extraction conditions employed cannot materially change the nature of the extractable profile.

Corollary 1A: No new extractables can be produced, and no existing extractables can be lost, due to the extraction.

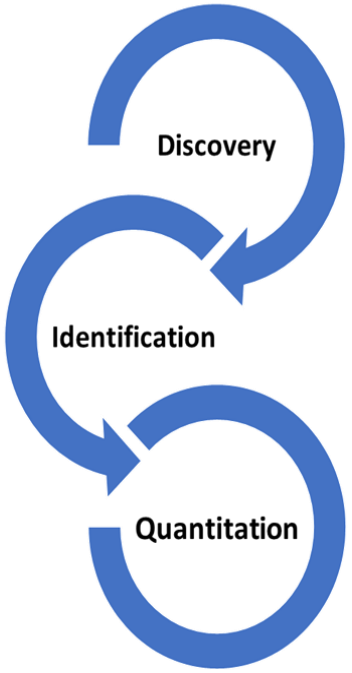
Corollary 1B: There can be no change in the number, identity and concentration of extractables due to the extraction

**Rule #2:** An extraction process must be technically justified in terms of its ability to produce an extractables profile that is the same as the leachables profile.

# Testing: The Hands of an Extractables or Leachables Study

## Methods of Testing

### Screening




1. Are there substances unique to the sample (versus an appropriate blank) that are present in the sample above a certain concentration threshold?
2. If yes, what are they identities of those substances?
3. If yes, what are the concentrations of those substances?

### Targeting


1. Is a specified substance present in the sample in reportable quantities?
2. If yes, what is the concentration of the specified substance?

**NET-FISHING**

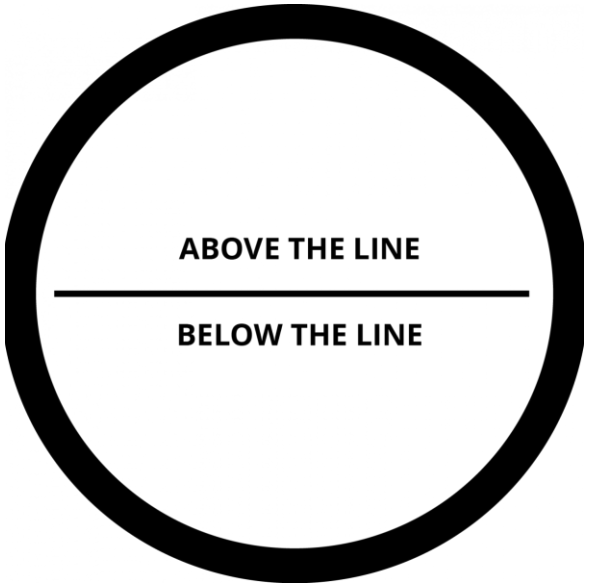
**FLY-FISHING**

# Discovery: "How Low Do You Go?"

# Discovery: "How Low Do You Go?"

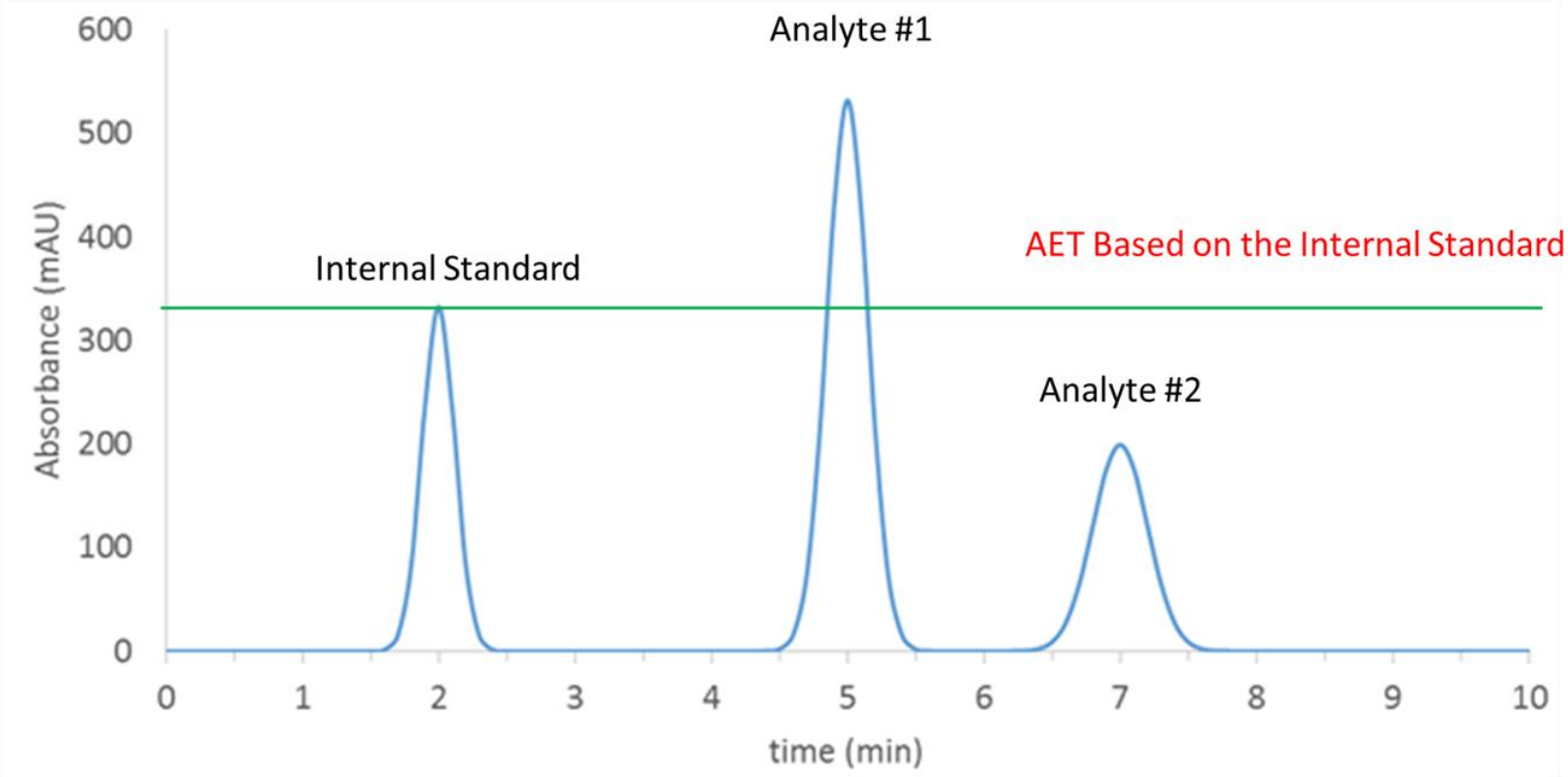
## *Down to the AET!*

The Analytical Evaluation Threshold (AET) establishes that concentration, of an extractable in an extract or a leachable in a drug product, above which the extractable or leachable must be reported for toxicological safety risk assessment.



# Discovery: "How Low Do You Go?"

## *Down to the AET!*



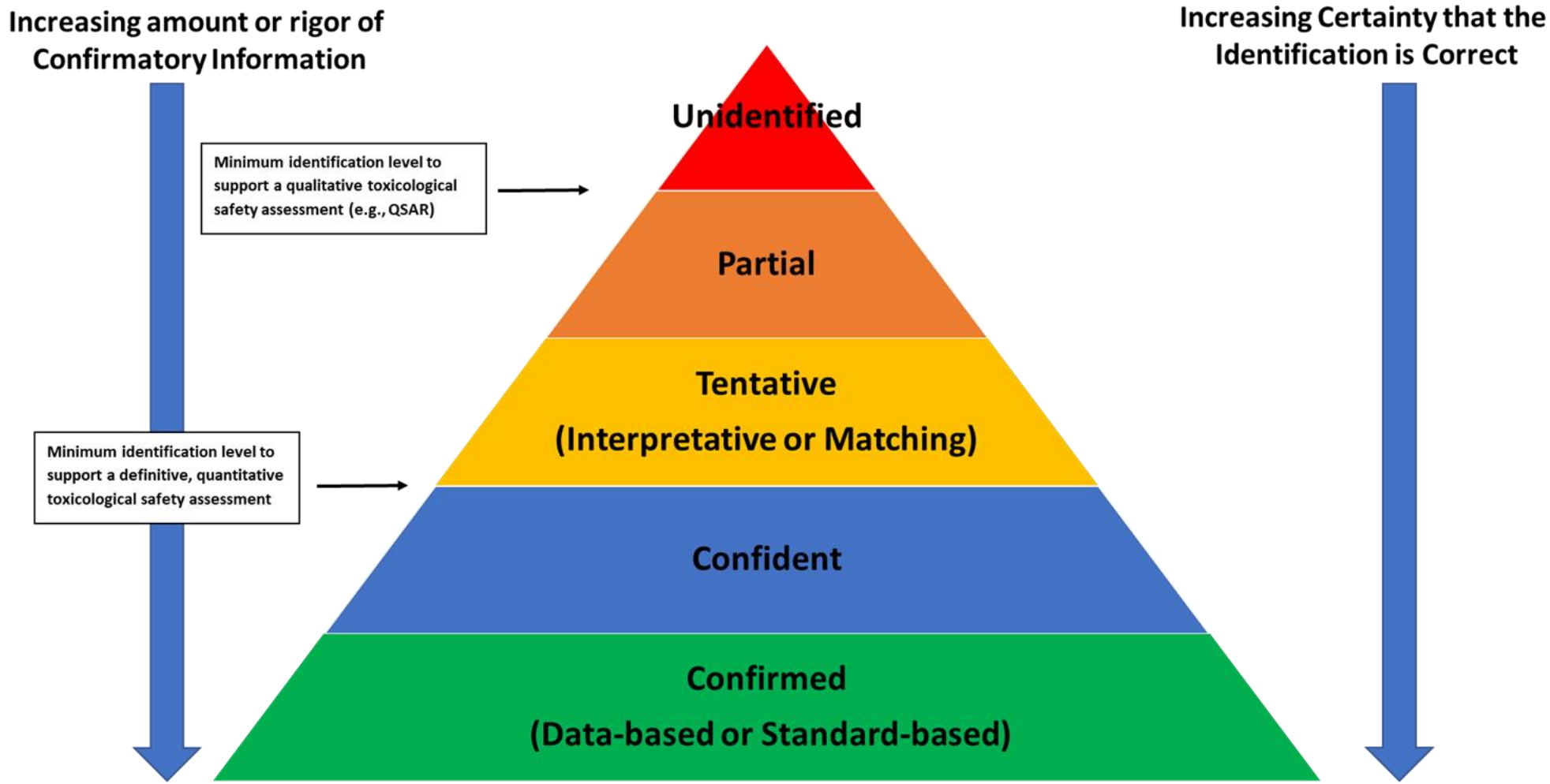

- The peak for Analyte #1 is above the AET line. Thus, Analyte #1 is reported for toxicological safety risk assessment.
- The peak for Analyte #2 is below the AET line. Thus, Analyte #2 is not reported for toxicological safety risk assessment.

# Ok, I'm above the AET. What does "must be reported for toxicological safety risk assessment" mean?

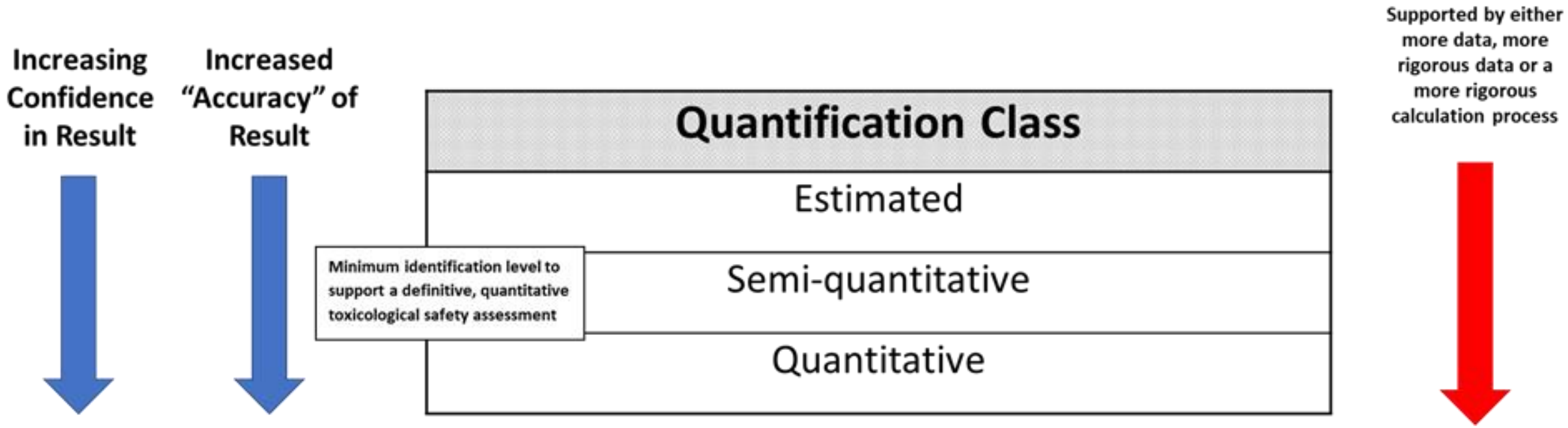
**Identify**
**(What is it?)**


**Quantify**
**(How much of it is there?)**

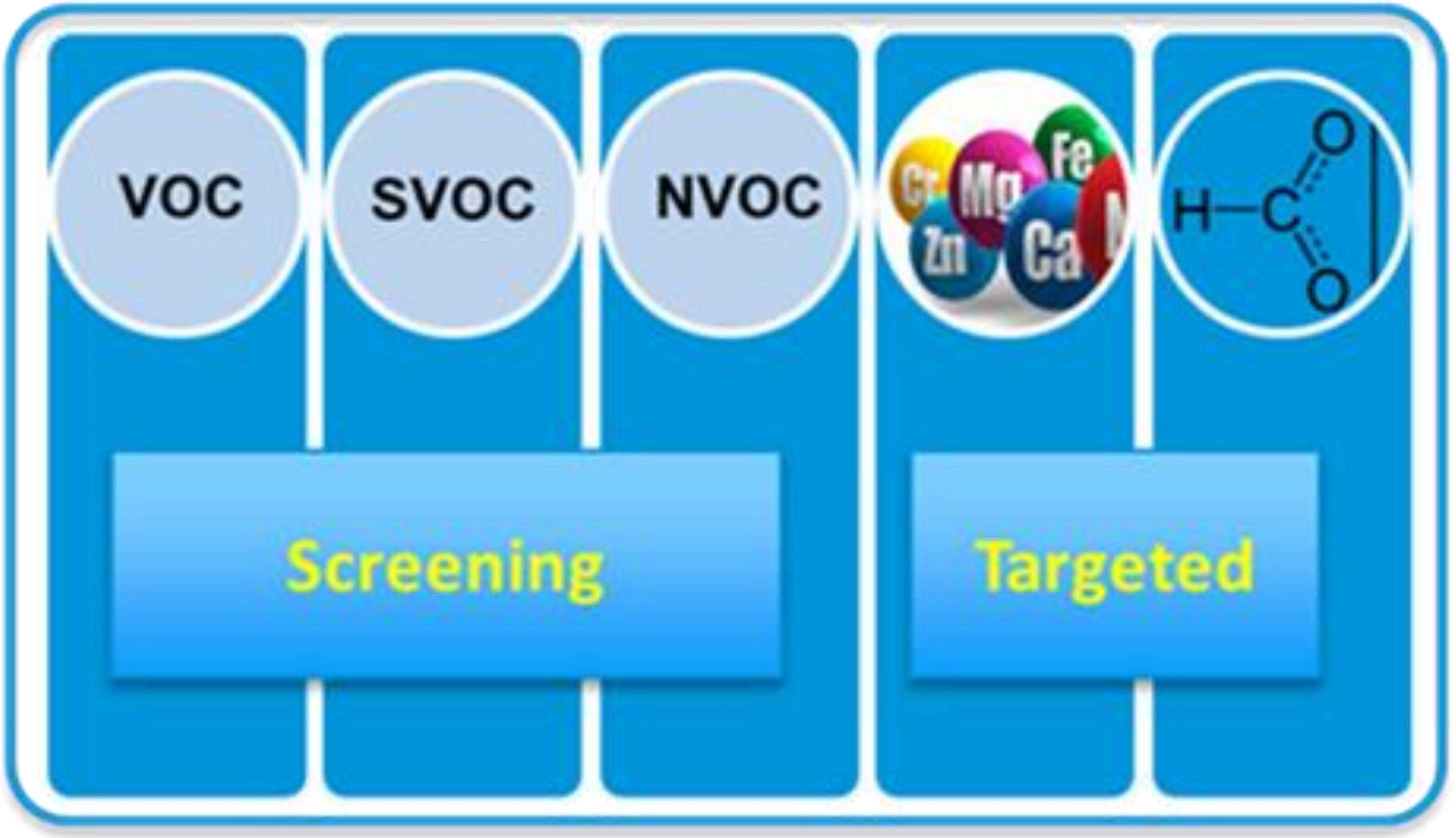
# Identification: A Matter of Confidence



# Quantitation: A Matter of Accuracy



# A Complementary and Orthogonal Testing Strategy



# Assessment: The Brain of an E/L Study

A leachable could affect multiple aspects of a drug product's quality and suitability for use.

**Assessment:** The evaluation or estimation of the effect a leachable will have on a drug product's quality and/or suitability for use.

- **Adverse safety effects**
  - The leachable itself may adversely affect patient health and safety
  - The leachable, because of its behavior in the drug product, may cause a safety issue
- **Adverse drug product effects**
  - Drug substance potency reduced
  - Drug product stability reduced
  - Drug products no longer comply with specifications and/or compendial requirements
  - Leachables complicate drug product testing
  - Leachables have "unpleasant cosmetic" effects
- **Adverse packaging effects**
  - Packaging no longer functions properly

# Assessment: The Brain of an E/L Study

*"The Dose Makes the Poison"*

**Paracelsus, Swiss MD (1492-1541)**

Hypothesis:

"All compounds are toxic, but below a certain dose – they are NOT"

➔ Concept of **NOAEL**

**N**o **O**bserved **A**dverse **E**ffect **L**evel

# Assessment: The Brain of an E/L Study

## Role of the Chemist (Data Procurement):

- Find every substance in the test sample (extract or drug product) that is present at a level of potential safety concern (for example, above the AET)
- Diffentiate between those found substances which are true extractables (or leachables) and analytical artifacts
- Reliably identify and accurately quantify all true extractables/leachables

## Role of the Toxicologist (Assessment):

- Procure credible information for each reported substance
- Judge the Quality of Data!!
- Calculate the Safe Daily Exposure Limit (PDE, TI, TE, ADI, ...)
- **Compare the Safe Daily Exposure Limit to the Patient Daily Exposure**
- Evaluate the Weight of Evidence
- Establish the patient health & safety risk associated with the reported substances

**Chemist**

**Toxicologist**

# Assessment: The Brain of an E/L Study

**From the pages of *Toxicology Safety Risk Assessment for Dummies***

**Important Terms in Toxicological Safety Risk Assessment**

**TDI = Tolerable Daily Intake (the maximum amount of a substance to which a patient can be exposed to in a day without an adverse health effect)**

**ADI = Actual Daily Intake (the actual amount of a substance a patient is exposed to in one day)**

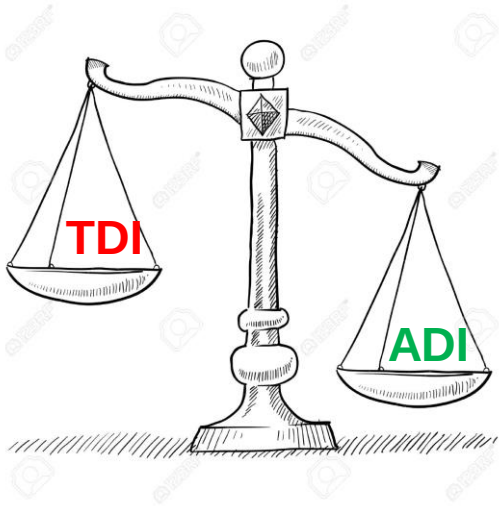
**ADI = Concentration of a leachable in a DP x Daily Dose Volume of the DP**

# Assessment: The Brain of an E/L Study

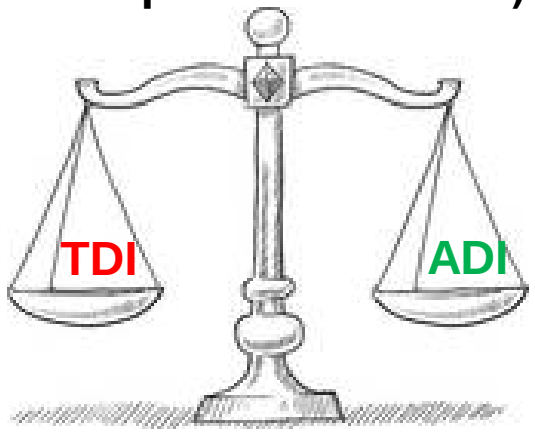
## From the pages of *Toxicology Safety Risk Assessment for Dummies*

## The Margin of Safety (MoS) = TDI/ADI

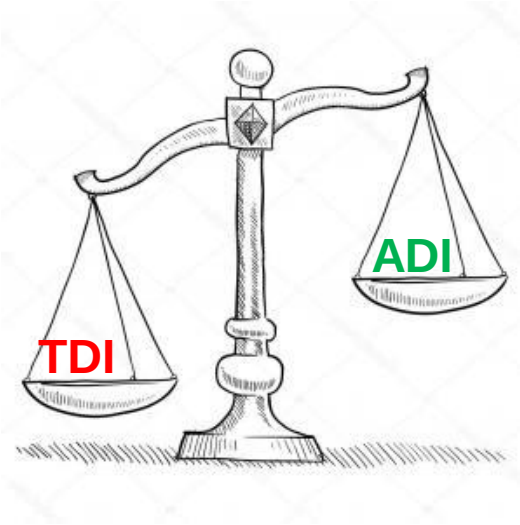
**TDI < ADI**
**MoS < 1**
**Leachable is potentially unsafe**




**TDI = ADI**
**MoS = 1**
**Leachable is likely safe**
**(but don't quote me on that)**




**TDI > ADI**
**MoS > 1**
**Leachable is likely safe**



# Recap

1. Pharmaceutical packaging must not interact with the drug product to the extent that either the drug product or the packaging becomes unsuited for it intended use.
2. The leaching of substances from the packaging and into the drug product is the primary means by which a drug product and its packaging interact.
3. Leachables are substances that are incorporated into the drug product due to its interaction with its packaging over production, storage, distribution and use.
4. Not every substance that is found when a drug product is screened for leachables in a leachable.
5. Extractables are substances that can be extracted from packaging under laboratory conditions.
6. Extractables are important based on their ability to predict leachables.
7. The ability of extractables to predict leachables depends on how well the extraction conditions mimic the packaged drug product's history and what one defines as a leachable.
8. If you can find published guidance that actually reflects how regulatory submission are reviewed, please send me the link.
9. Most recommendations for performing chemical assessment provide a general outline and suggest good practices, it is up to you to fill in (and justify) the details of performing a study.
10. Chemical characterization is a process involving three inter-related steps:
    a) Material Characterization
    b) Extractables Testing
    c) Leachables Testing

# Recap

11. IF YOU CAN SCREEN YOUR DRUG PRODUCT DOWN TO THE AET, THEN DO THIS!
12. Performing an Extraction to produce an extractables profile that reflects the leachables requires careful consideration of the extraction conditions including:
    a) Solvent(s)
    b) Temperature and Duration
    c) Stoichiometry
    d) Method
13. THE AET IS YOUR FRIEND.  Know it and Know how to use it.
14. Testing and Extract for Extractables or Drug Product for Leachables has three objectives:
    a) Discovery
    b) Identification
    c) Quantitation
15. Testing of extracts can either be screening or targeted (and each has its own specific purpose and requirements).
16. The calculation of the Margin of Safety (MoS) is an important part of Toxicological Safety Risk Assessment of leachables (and extractables as possible leachables) but it is not the entire assessment.

# Q&A


**Contact the presenter at:**
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www.triadscientificsolutions.com

## Thank you!