Managing the Risk of Leachables from Container Closure Systems

Part One

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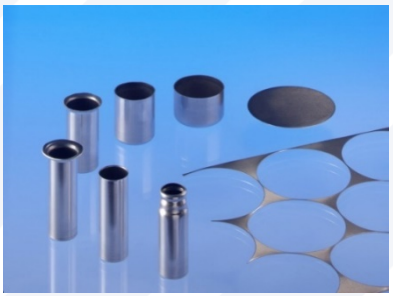
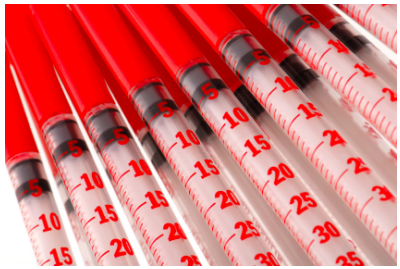
Leachables

- Chemicals that can migrate from packaging into the drug product or the patient under normal conditions of use
  - Packaging – During normal storage temperatures and delivery into the patient

All Materials Can Produce Leachables!





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Extractables

- It is very difficult to detect leachables in the drug product matrix at low concentrations (ppb / ppm) without knowing what to look for.

Extractables Testing

- Generates “Target Chemicals” to look for in the leachables testing.
- Determined in laboratory experiments using pure solvents under conditions that predict the “Worst Case” conditions of exposure.

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Worst Case Conditions of Exposure

The conditions used for the extractables testing are developed based on:

- **Contact time with the drug (For example shelf life for packaging)**
- **Storage Temperature**
- **Solvating Power of Drug**
  - **These parameters include:**
    - **pH**
    - **Polarity**
    - **Ionic Strength**

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Modified FDA/CDER/CBER Risk-Based Approach for Leachables

Degree of concern associated with the route of administration	Likelihood of packaging component-dosage form interaction		
	High	Medium	Low
Highest	Inhalation Aerosols and Sprays	Injections and Injectable Suspensions; Inhalation Solutions	Sterile powders and powders for injection, inhalation powders
High	Transdermal Ointments and Patches	Ophthalmic Solutions and Suspensions; Nasal Aerosols and Sprays	
Low	Topical Solutions and Suspensions, topical and lingual aerosols, oral solutions, and suspensions		Oral tablets and oral (hard and soft Gelatin) capsules; Topical powders, oral powders

SOURCE: USP <1664> "ASSESSMENT OF DRUG PRODUCT LEACHABLES ASSOCIATED WITH PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS"

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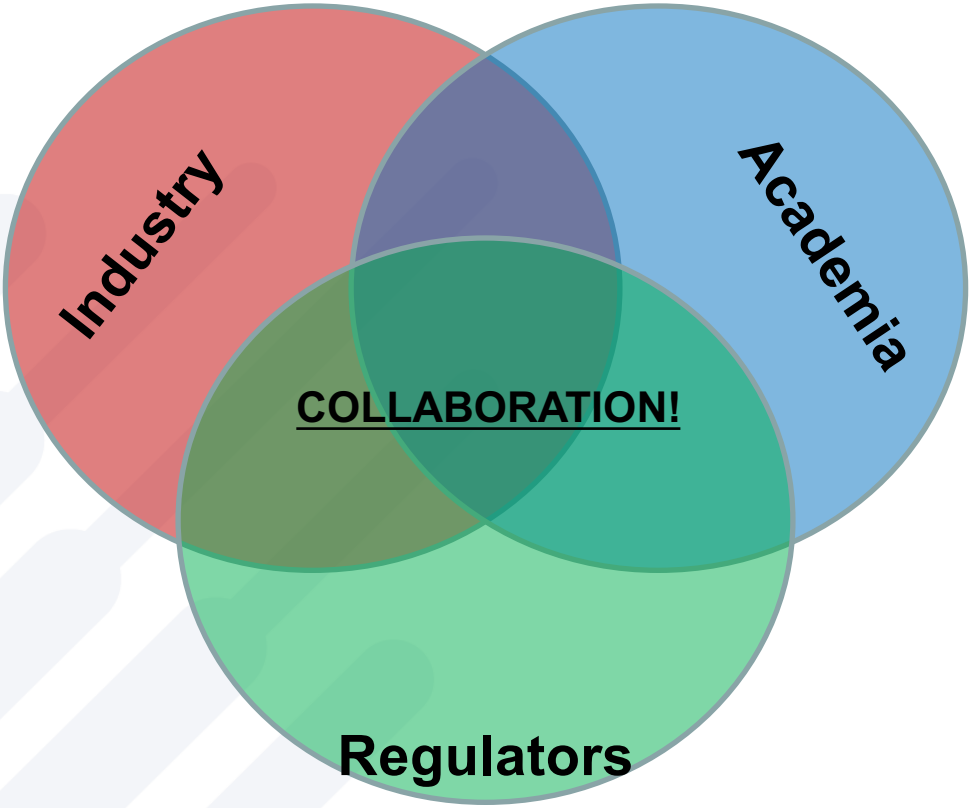
Best Practices for E&L Testing



Leachables and Extractables Working Group

Orally Inhaled and Nasal Drug Products Drug Products (OINDP)

Parenteral and Ophthalmic Drug Products (PODP)

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E&L Studies - <1663> and <1664>

- <1663> Assessment of Extractables Associated with Pharmaceutical Packaging / Delivery Systems
- <1664> Assessment of Leachables Associated with Pharmaceutical Packaging / Delivery Systems
  - <1664.1> Orally Inhaled and Nasal Drug Products
  - <1664.2> Parenteral and Ophthalmic Drug Products
    - (Future Chapter)
- Framework for Design, Justification, & Execution of the Assessments
- Not Prescriptive
- Does not Establish Specifications or Acceptance Criteria

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High Risk Drug Products

Injectables

Inhalation

Transdermal

Ophthalmic

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Packaging-
Container Closure Systems (CCS)

Simple Systems

Bottle – Glass or Plastic
Closure – Rubber or Plastic

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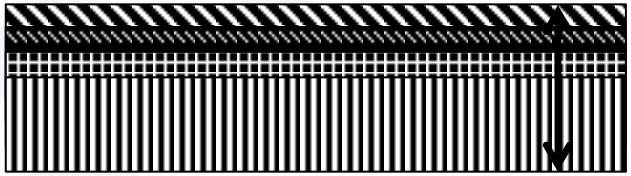
Packaging – Container Closure Systems (CCS)

Complex Systems

Multi-layered Systems



Leachables can diffuse from the outer layers and into the drug

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Combination Products

Very Complex Systems
Store and Deliver the Drug

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Materials Used In Pre-Filled Syringes

Primary Packaging

- Barrel
  - Glass or Plastic
- Plunger Stopper
  - Rubber
- Tip Cap / Needle Shield
  - Plastic, Rubber

Secondary Packaging

- Over Wrap / Container
  - Plastic
- Spacers
  - Foam or Plastic
- Labels
  - Paper
  - Ink
  - Adhesive

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Associated Components

- **Associated Components**
  - **intended to deliver the dosage form to the patient but not stored in contact with the dosage form**

- IV Bags
- Disposable Syringes
- Syringe Filters
- Extension Set
- Catheters
- Connectors

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Diffusion

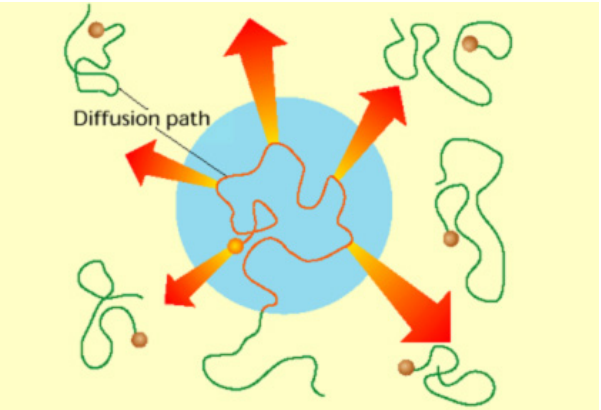
Migration of a chemical through a matrix is proportional to the square root of time.

$$X = \sqrt{\frac{2kTt}{6\pi\eta r}}$$

- X – Mean Square Displacement
- t – Time
- k – Boltzmann constant
- T – Temperature
- η – viscosity
- *r* - radius

What factors influence diffusion?

- Time
- Solvent
- Temperature
- Physical properties of the polymer



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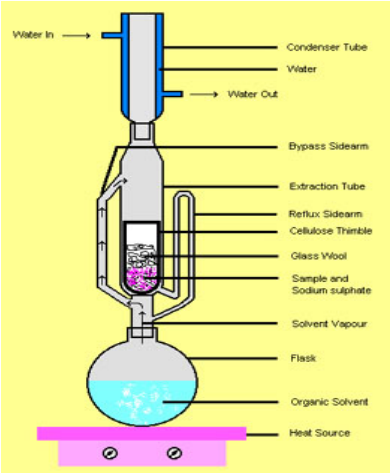
Controlled Extraction Studies

- **Goal:**
  - **To extract compounds under conditions which will model the leaching of compounds into a final product.**

- **Requires multiple…**
  - **Extraction Temperatures**
  - **Extraction Times**
  - **Extraction Methods**
  - **Extraction Solvents**
  - **Analytical techniques**



- **…to identify and quantify the possible leachables**

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Selecting the Extraction Solvents

- **Consider the solvating properties of the drug product**
  - **Oil versus Aqueous**
  - **pH Range**
  - **Salt Content (Ionic Strength)**

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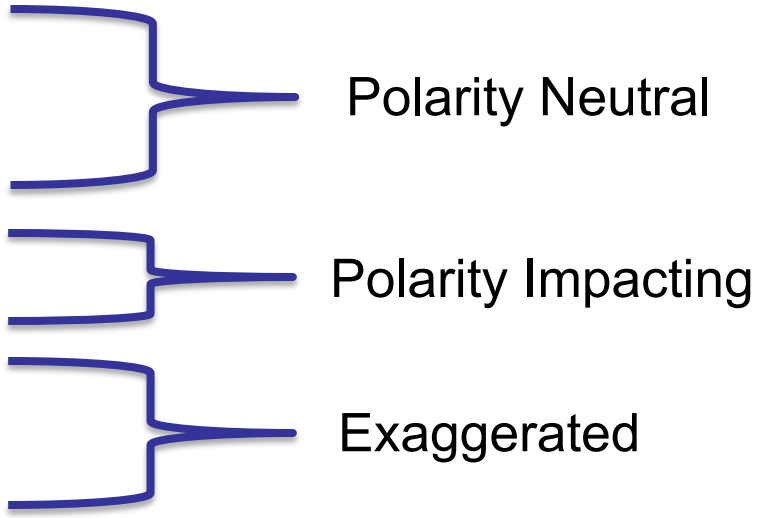
Controlled Extractables Study

- Aqueous - pH 2.5
- Aqueous - pH 9.5
- Mixed – IPA / Water
- Organic – IPA
- Organic – Hexane
- Technique
  - Aqueous: Sonication and Sealed Vessel
  - Mixed: Reflux
  - Organic: Soxhlet and Reflux



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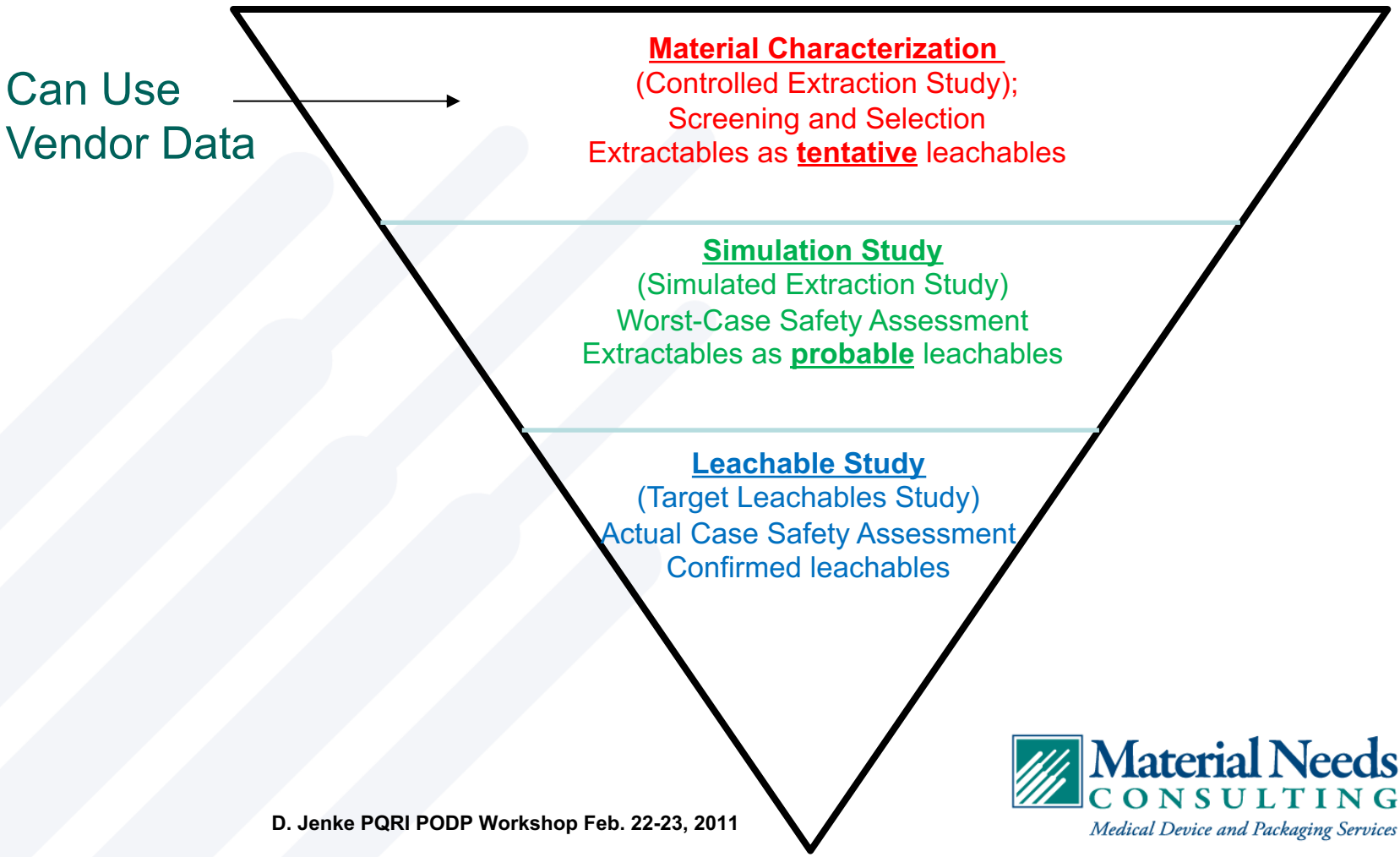
Consider the Safety Assessment Triad



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Analysis of the Extracts

Multiple Separation and Detection Techniques

- Volatiles
  - Headspace GC/MS
- Semi-Volatiles
  - GC/MS
- Non-Volatiles
  - LC/UV/MS
- Inorganics
  - ICP-MS

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Leachables Method Development and Validation

- Select Targets From Extractables Testing
  - Chemistry
  - Toxicology
  - Compounds of Concern
- Develop Leachables Methods in Drug Product
  - Volatiles
  - Semi-Volatiles
  - Non-Volatiles
  - Inorganics
- Method Validation
- Study Exposure Conditions Vary by Application

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Leachables Testing –CCS Application

- **Monitor leachables in drug formulation during product stability testing**
  - **Run real-time, long-term studies over proposed shelf-life**
  - **Run accelerated tests**
  - **Upright and Inverted containers (exposure to seals during storage)**
  - **Sampling Points – T_0, 3, 6, 9, 12, 18, 24, and 36 Months**
  - **Assess impact on product quality, safety, and efficacy**
    - **Especially for Biologics!!!**
  - **Correlate leachables to extractables profile**

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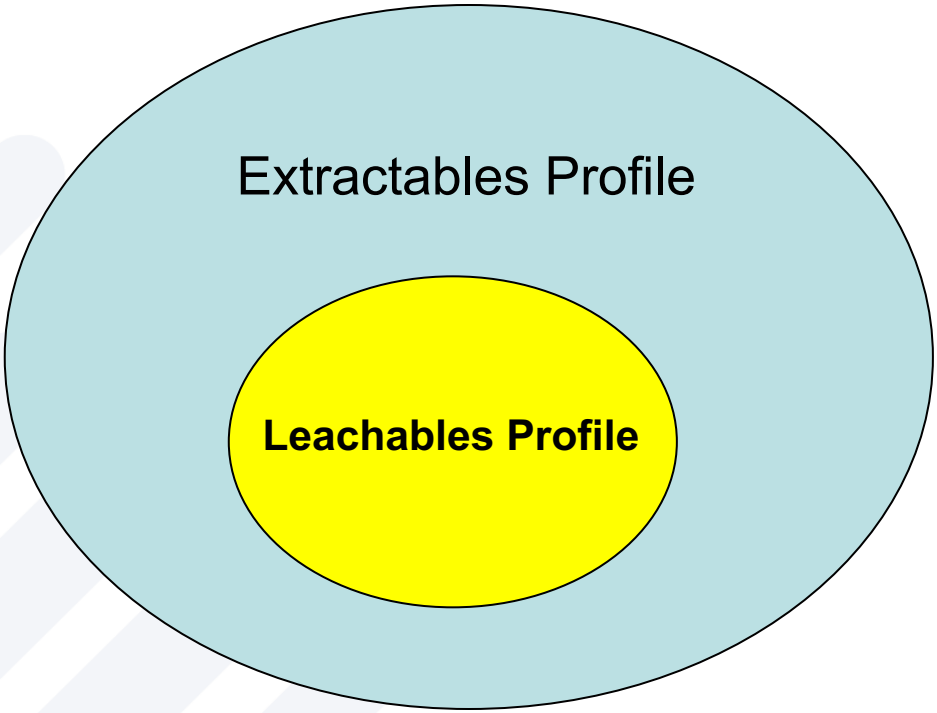
Leachables Testing – Correlation (1)



In theory, the leachables profile should be a subset of the extractables profile

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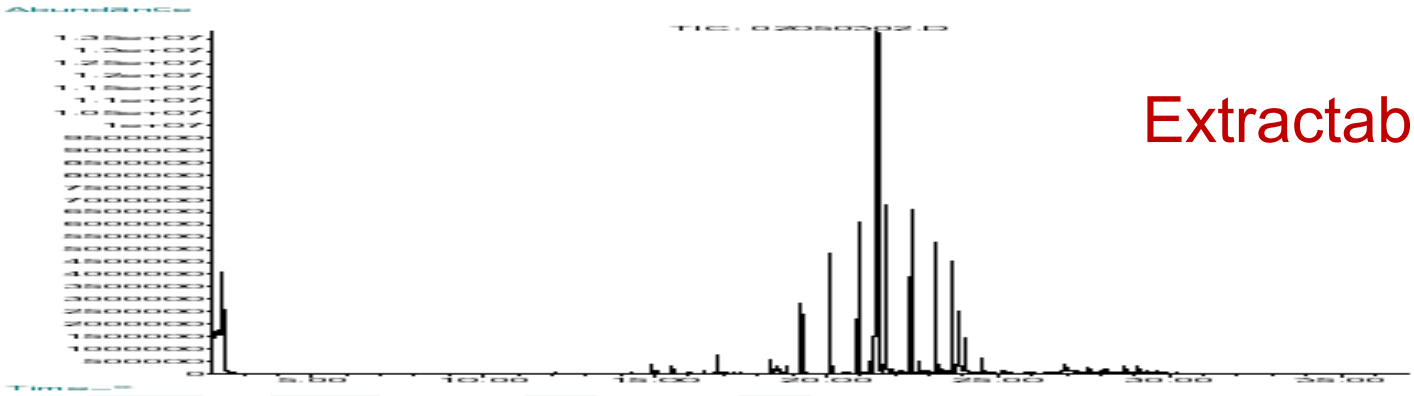
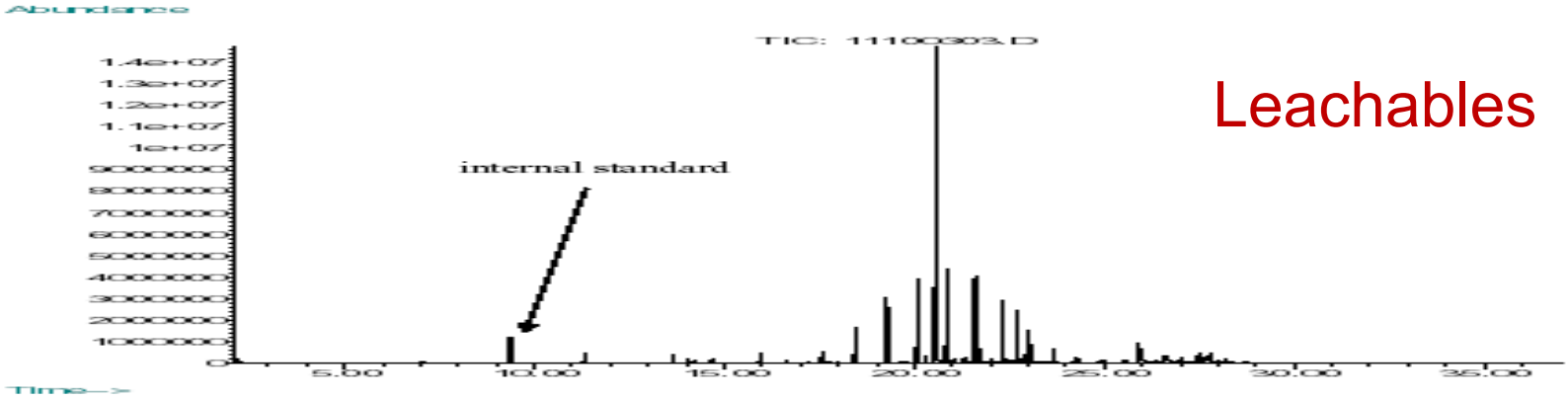
Similar Methods Ease Correlation Establishment



Extractables



Leachables

Courtesy of PQRI

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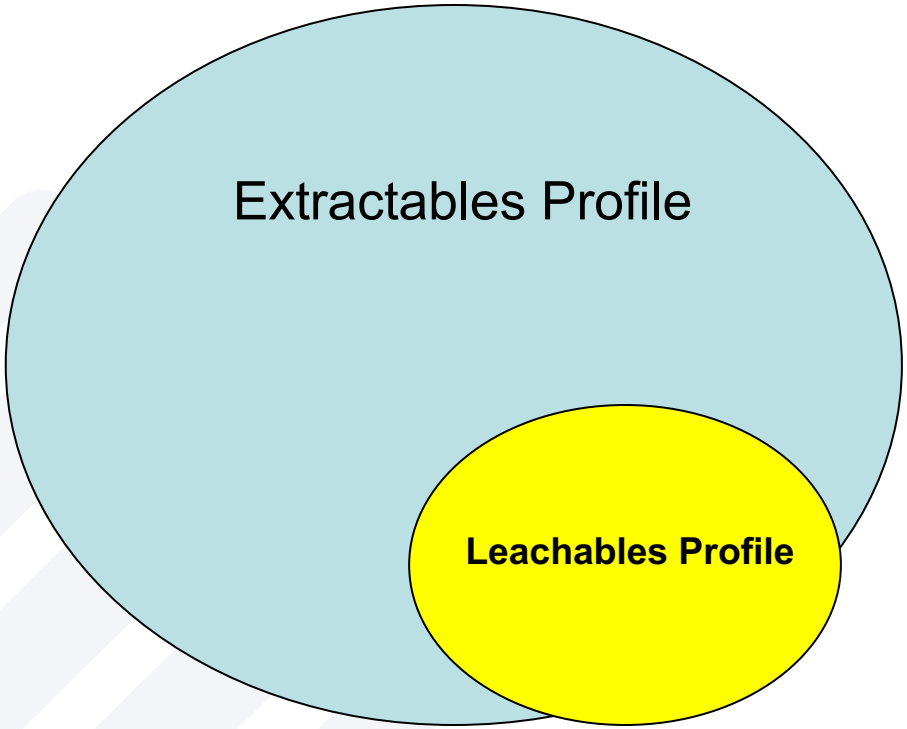
Leachables Testing – Correlation (2)



In reality, new components can be present if the leachable reacts with the drug product.

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Leachables Testing – Correlation (3)

- **Establish correlation between Leachables and Extractables**
  - **Qualitative – No new peaks in leachables profile**
  - **Quantitative – Lower concentration of common chemicals in leachables profile**
- **Direct or Indirect Correlation**
  - **Component identified in extraction study**
  - **Component linked to extraction study**
  - **Component a reaction with drug product**

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Thresholds

- **SCT (Safety Concern Threshold)**
  - **< 0.15 µg / day for OINDP**
  - ***< 1.5 µg / day for Parenterals***
  - **Carcinogens and irritants are generally safe at this level**
- **QT (Qualification Threshold) < 5.0 µg / day**
  - **Other compounds without Carcinogenicity or Irritation markers**
- **Define an AET (Analytical Evaluation Threshold)**
  - **Based upon potential patient exposure**
- **Peaks above AET should be identified and quantified**

"Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products", Product Quality Research Institute, Arlington VA, September 8, 2006

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Calculating the AET (1)

Example AET Calculation for a Metered Dose Inhaler (MDI):

Consider an MDI with 120 labeled actuations per canister and a recommended dose of 8 actuations per day. For an individual organic leachable in this MDI formulation considering an SCT of 0.15 µg/day (for Orally Inhaled and Nasal Drug Products), the estimated AET would be:

$$AET = \left(\frac{0.15\ \mu\text{g/day}}{8\ \text{actuations/day}} \times 120\ \textit{labeled}\ \text{actuations/canister} \right)$$

$$AET = 2.25\,\mu\text{g/canister}$$

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Calculating the AET (2)

Example AET Calculation for a Prefilled Syringe (Insulin Pen):

Consider an insulin pen with 100 units/mL, a recommended dose of 10 units per day, and a total volume of 3.0 mL. For an individual organic leachable in this formulation considering an SCT of 1.5 µg/day (PODP), the estimated AET would be:

$$AET = \left(\frac{1.5\ \mu\text{g/day}}{10\ \text{units/day}} \times 100 units / mL \right)$$

$$AET = 15\,\mu\text{g/mL}$$

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Calculating the AET (3)

Example AET Calculation for a Large Volume Parenteral (LVP):

Consider an LVP with 1L of drug product packaged in a container/bag of appropriate polymeric material, with a recommended dose of 1 container per day. For an individual organic leachable considering an SCT of 1.5 µg/day (PODP), the estimated AET would be:

$$AET = \left(\frac{1.5\ \mu\text{g/day}}{1\ \text{bag/day}} \times 1\text{dose/bag} \right)$$

$$AET = \left(\frac{1.5\ \mu\text{g/bag}}{1\ \text{L/bag}} \right) = 1.5\,\mu\text{g/L} = 0.0015\,\mu\text{g/mL}$$

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Qualification of Leachables

- The substances identified as actual leachables will undergo toxicological evaluation.
- This evaluation will be based on an estimation of total daily dose of each leachable under the use conditions of the drug product.
- Total daily intakes for leachables will be assessed using the proposed thresholds.
- Based on this evaluation, conclusions and/or next steps are described.

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Any Questions?

Webinar Series

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