Introduction to E&Ls

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Overview

- What industries need to determine E&Ls
- Define extractables and leachables
- Basic overview of an E&L study
- Regulatory landscape

Jordi Labs

A leader in plastics analysis

- Founded in 1980
- Over 1000 projects completed annually
- State of the art facilities and instrumentation
- 80% of staff are degreed chemists (Ph.D., M.S., B.S.)

Extractables and Leachables Analysis

- Identification/Quantification
- Comprehensive Databases
- Pharmaceutical
- Food Contact
- Medical Device

Investigative Analyses

- Deformulation/Reformulation
- Polymer and Additive Identification
- Discoloration
- Off-odors
- Cracking, brittleness

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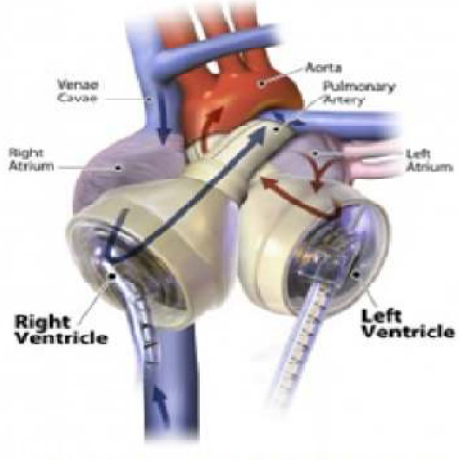
Who Needs E&L's

Biomedical Devices



Total Artificial Heart

Food Packaging

Pharmaceutical Packaging

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What are Leachables & Extractables?

Leachables are :

Trace amounts of chemicals originating from packaging, containers, medical devices or process equipment that end up as contaminants in medicinal products or food resulting in exposure to patients or consumers.

Extractables are:

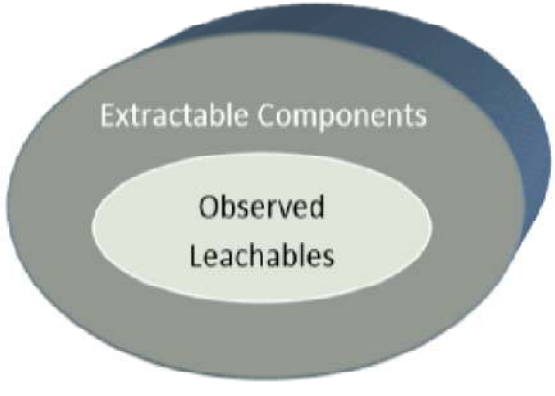
Substances that can be released from a medical device, pharmaceutical packaging or food contact surface using extraction solvents and/or extraction conditions that are expected to be at least as aggressive as the conditions of use.

ISO-10993-12

Introduction to Es and Ls

Examples of E&Ls

- Small molecules present in a polymer system including:
  - Antioxidants
  - Surfactants
  - Slip agents
  - Plasticizers
  - Acid scavengers
  - Cross linking agents
  - Residual monomers and *oligomers*
  - *Polymerization side products*
  - *Process Impurities*



- Extractables may not be leachables depending on their solubility and the use conditions of the device.

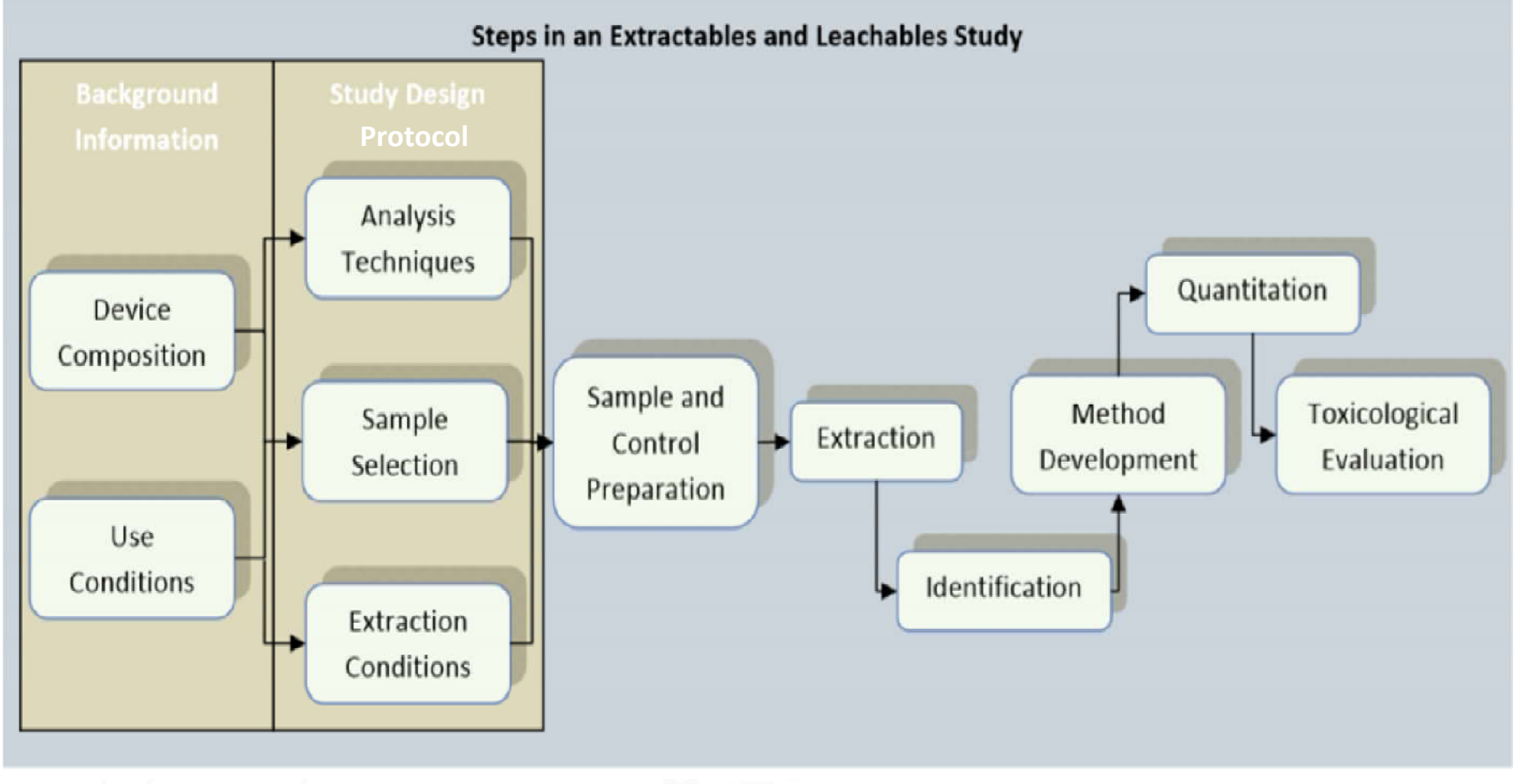
Reasons for Examining Ls

- Allows determination of the actual species expected to leach under the clinically relevant conditions
- Used to perform the toxicological evaluation and to establish product safety

Reasons for Examining Es

- Establish the worst-case leachables
- Identify accumulation levels over the shelf-life of a product
- Development of safe and effective packaging/delivery systems, manufacturing systems, and processes
- Facilitate investigations into the origin(s) of identified leachables whose presence causes out-of-specification (OOS) results for a marketed product.

E&L Study


Steps in an Extractables and Leachables Study
Background Information
Study Design Protocol
Device Composition
Use Conditions
Analysis Techniques
Sample Selection
Extraction Conditions
Sample and Control Preparation
Extraction
Identification
Method Development
Quantitation
Toxicological Evaluation

E&L Study Breakdown

Quality Control in an E&L Study

- The accuracy and reliability of an E&L study should be confirmed using rigorous quality control measures.
- This includes:
  - Analysis Blanks
  - Negative Control
  - Positive Controls and Spiking Studies

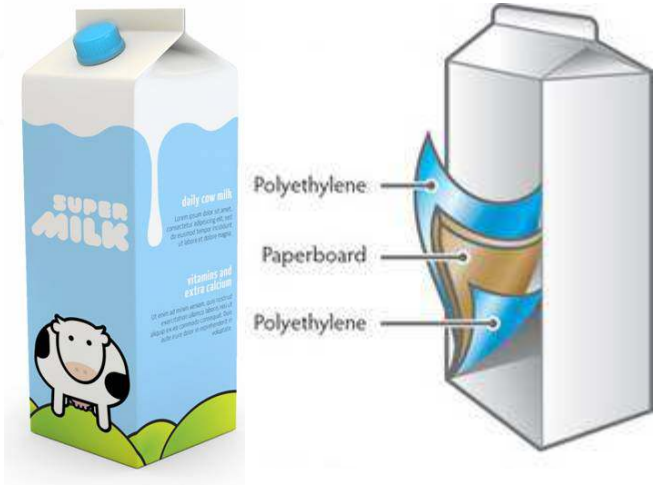
E&L Study Breakdown

Sample Selection

- The primary consideration in sample selection is that the specimen is representative of the final product as applied to the patient.

Sample Preparation

- Analysis of an entire device or package is often used
  - Full Fill
  - Cut & Cover
- If this is impractical or not appropriate
  - Composite Samples
  - Single Sided Extraction



E&L Study Breakdown

Types of Extractions

Simulated-use Extraction

- *An extraction conducted using a method that simulates the expected use conditions.*

Exaggerated Extraction

- *An extraction which uses conditions which are expected to cause a greater amount of extractable material to be released than using the simulated use extraction.*

Exhaustive Extraction

- *An extraction which is repeated until the total amount of extractables is less than 10% of the amount obtained during the initial extraction.*

E&L Study Breakdown

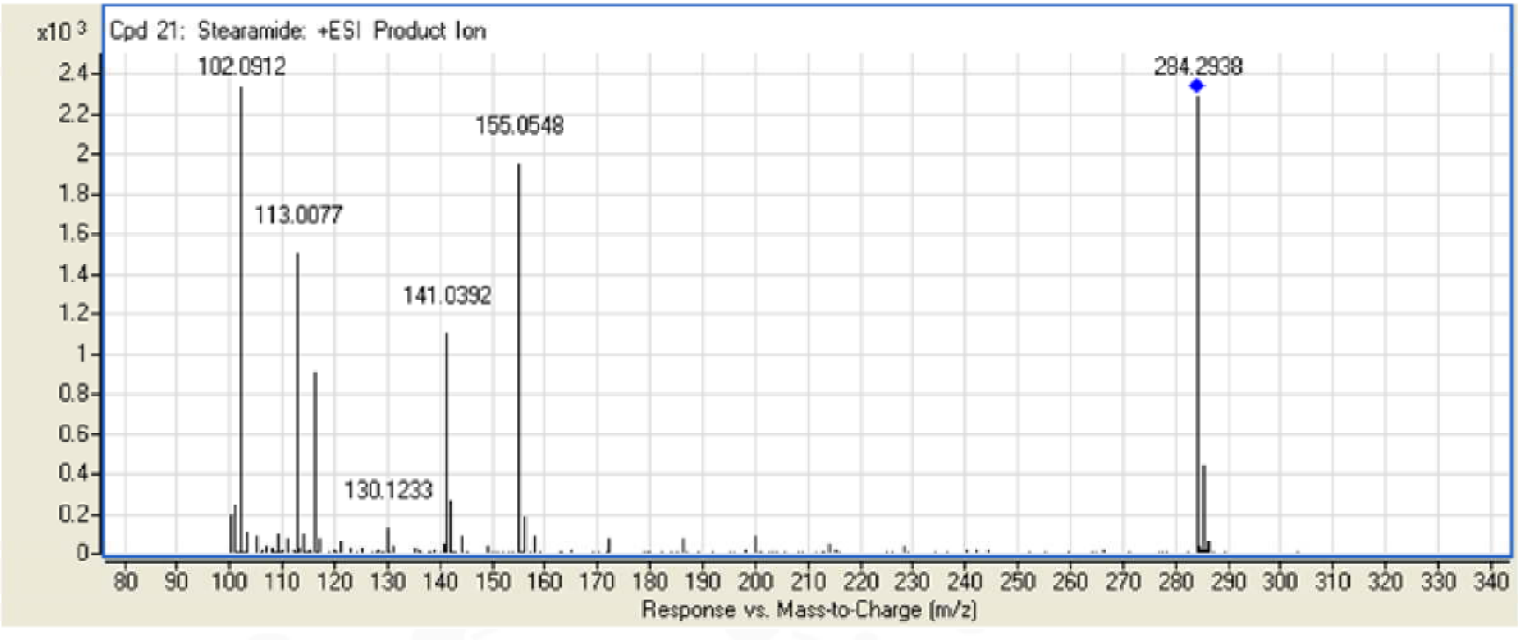
Identification of E&Ls (Qualitative Analysis)

Extracted components are identified using a combination of spectroscopy methods including LCMS, GCMS, headspace MS, NMR, FTIR and ICP-MS.

Jordi Identification Process

- MS is the prince of the analytical methods!
- Accurate Mass analysis for elemental formula determination (QTOF)
- Database searches to correlate mass spectra to known reference compounds
  - NIST and Wiley Mass Spectral Libraries
  - Jordi Proprietary Polymer Additives and Oligomer Database
- MSMS, HPLC-NMR and HPCL-FTIR analysis for structure elucidation
- Verification with an authentic reference material for retention time matching

QTOF-LCMS Identification of E&Ls



Compound Name	Precursor Ion	Match Score	Rev Score	Fwd Score	Collision Energy	Ionization Mode
Stearamide	284.29400	90.842	100.000	81.684	30	ESI

Identification Confidence Level

- Mass Spectral Identification
  A. Mass spectrometric fragmentation behavior
  B. Confirmation of molecular weight
  C. Confirmation of elemental composition
  D. Mass spectrum matches automated library or literature spectrum
  E. Mass spectrum and chromatographic retention index match authentic reference compound

Confirmed identification = A *and* B or C *and* D or E have been fulfilled

Confident identification = Sufficient data to preclude all but the most closely related structures (combination of D with any of A, B, or C)

Tentative Identification = Data consistent with a class of molecules only

E&L Study Breakdown

Quantitative Method Development

- Identified components must be quantitated to allow for toxicological evaluation
- Methods must be developed to allow for accurate quantitation
  - Chromatographic methods and spectroscopy methods

Validation of Analytical Methods

- Method validation should be performed to verify the performance characteristics of a method and to confirm that the method is suitable for the intended purpose.

E&L Study Breakdown

Determination of E&L Concentration (Quantitative Analysis)

- Two primary approaches are applied for quantitation.
    1. Formal Quantitation (authentic reference compound)
    2. Relative Quantitation (surrogate standard)
- Techniques commonly applied include ICP-MS, LCMS, HPLC, NMR and GCMS

E&L Study Breakdown

Acceptable Levels for Leachables

- Acceptable level of leachables depends on:
  - route of exposure
  - treatment duration
  - daily exposure
- Approaches to determine the safety threshold include:
  - Threshold of toxicological concern (TTC)
    - 1.5 µg/day Total Daily Intake (TDI) for Genotoxic impurities
  - Safety Concern Threshold (SCT) –
    - 0.15 µg/day TDI in Orally Inhaled Nasal Drug Products (OINDP)
  - Qualification Threshold (QT)
    - 5.0 µg/day TDI in Orally Inhaled Nasal Drug Products (OINDP)

E&L Study Breakdown

Analytical Evaluation Threshold (AET)

- The TTC or SCT can be converted to an analytical threshold

- AET is the threshold at or above which a chemist should identify a particular leachable and/or extractable and report it for potential toxicological assessment.

$$AET\left(\frac{\mu g}{container}\right) = \left(\frac{0.15\mu g/day}{doses/day}\right) x \left(\frac{labeled\ doses}{container}\right)$$

E&L Study Breakdown

Analytical Evaluation Threshold (AET) Examples

– Metered Dose Inhaler: 200 labeled actuations per canister, a recommended dose of 12 actuations per day, and a critical component elastomer mass per valve of 200 mg.

$$AET\left(\frac{\mu g}{container}\right) = \left(\frac{0.15\mu g/day}{12}\right) x(200)$$
$$= 2.5\mu g/canister$$

$$AET\left(\frac{\mu g}{g}\right) = \left(\frac{2.5\ \mu g/canister}{0.2\ g\ elastomer}\right) x(1\ canister)$$
$$= 12.5\ \mu g/g$$

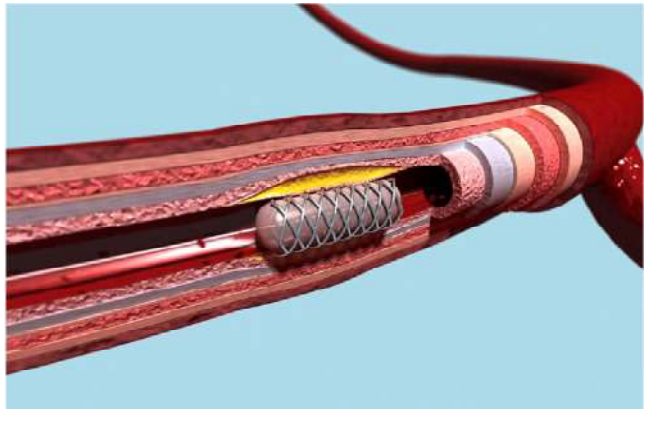
E&L Study Breakdown

Analytical Evaluation Threshold (AET) Examples

– Inhalation Solution with 3 mL of drug product contained in a low density polyethylene (LDPE) container weighing 1 g, with a recommended dose of 3 containers per day.

$$AET\left(\frac{\mu g}{container}\right) = \left(\frac{0.15\mu g/day}{3\ doses/day}\right) x(1\ dose/cont.)$$
$$= 0.05\frac{\mu g}{container} = 0.05\frac{\mu g}{g}$$

E&L Regulations



Biomedical Devices

- ISO 10993
- FDA Memorandum - #G95-1

Food Packaging

- FDA: Guidance for Industry: Preparation of Premarket Submissions for Food Contact Substances: Chemistry

Pharmaceutical Packaging

- USP <661>
- USP <1663>
- USP <1664>

Pharmaceutical Packaging Regulations

Regulations

USP <661> Plastic Packaging Systems and Their Materials of Construction

USP <661.1> Plastic Materials of Construction

USP <661.2> Plastic Packaging Systems for Pharmaceutical Use

Informational Chapters

USP <1663> "Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems"

USP <1664> "Assessment of drug product leachables associated with pharmaceutical packaging/deliver systems"

Pharmaceutical Packaging Regulations

Additional Informational Chapters

USP <1664.1> “Orally Inhaled and Nasal Drug Products”

USP <1665 > “Toxicological Assessment”

Future Chapters

USP <661.3> “Plastic Systems Used for Manufacturing Pharmaceutical Products”

USP <661.4> “Plastic Medical Devices used to Deliver or Administer Pharmaceuticals ”

Leachables Specifications in Individual Monographs

Pharmaceutical Packaging Regulations

High level view!

Three Tiered Approach

- material-of-construction characterization
- packaging system characterization
- pharmaceutical product characterization

USP U.S. Pharmacopeial Convention™

Global Expertise
Trusted Standards
Improved Health

Well Characterized Materials:

1. Identity
2. Physiochemical properties
3. Extractable metals
4. Additives
5. Bio-compatibility

Suitable Materials:

1. Uses well characterized materials <661.1>
2. Physiochemical properties
3. Compatible with packaged drug product
4. Chemical assessment (21 CFR Indirect Food Additives, 661.1 and E&Ls)
5. Bio-compatibility (USP <87>, <88>)

Pharmaceutical Packaging Regulations

USP <661> Plastic Packaging Systems and their Materials of Construction

Purpose: Chapter <661> is the primary chapter which establishes the rationale behind the testing requirements and specifications that appear in its subsequent sections.

Specific Polymer Requirements for:

1. Polyethylene (HDPE and LDPE)
2. Polypropylene
3. Polyethylene Terephthalate

Under Revision: Subchapters are being added that are relevant for a particular type of test article.

Pharmaceutical Packaging Regulations

USP <661.1> Plastic Materials of Construction

Purpose: *Materials Characterization, a* material is <u>well characterized</u>:

1. Identity (FTIR, DSC)
2. Biocompatibility (USP <87>, <88>)
3. Physicochemical properties (Extraction, UV absorbance, pH, TOC)
4. Additives (Extraction, chromatographic analysis)
5. Extractable metals (Extraction, ICP-MS, AA)

<USP <661.2> Plastic Packaging Systems for Pharmaceutical Use

Purpose: *Packaging System Characterization*; packaging is <u>suitable</u>:

1. Biological Activity (USP <87>, <88>)
2. Physicochemical Tests (Extraction, UV absorbance, pH, TOC)
3. Extractables/Leachables
4. Safety Assessment

Pharmaceutical Packaging Regulations

USP <1663>

"Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems"

GENERATING THE EXTRACT

Experimental Design

EXTRACTION PARAMETERS

Chemical Nature of Extracting the Medium
Extraction Time and Temperature
Extraction Stoichiometry
Mechanism of Extraction-Extraction Technique
Extractions That are Not Solvent Mediated

Pharmaceutical Packaging Regulations

USP <1663>

"Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems"

CHARACTERIZING THE EXTRACT

- Objectives and Challenges
- Processes Involved in Extract Characterization
  1. Scouting
  2. Discovery
  3. Identification
  4. Quantitation
- Preparation of Extracts for Analysis

SUMMARY

- Assessing the Completeness of an Extractables Assessment
- Example Extractables Profiles and Materials Characterization

Pharmaceutical Packaging Regulations

USP <1664>

"Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems"

CONCEPTS

- General Concepts for Leachables Assessment
- Safety Thresholds
- Information Sharing

LEACHABLES STUDY DESIGN

LEACHABLES CHARACTERIZATION

- Analytical Thresholds
- Analytical Method Requirements
- Prepare the Drug Product for Analysis
- Analytical Techniques
- Quantitative Methods and Validation

Pharmaceutical Packaging Regulations

USP <1664>

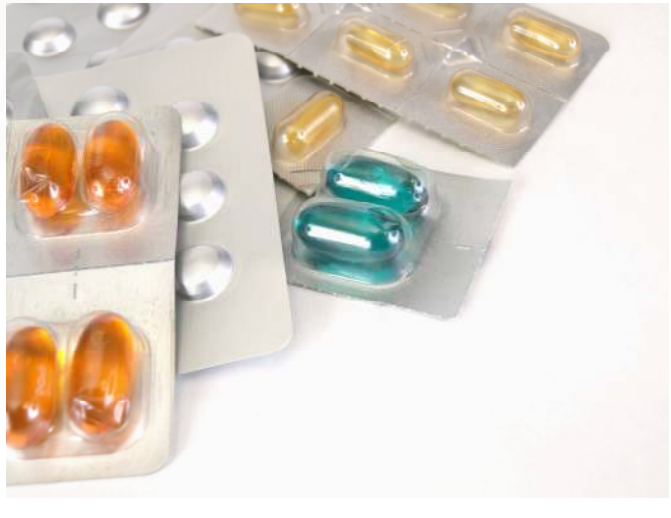
"Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems"

ESTABLISHING A LEACHABLES- EXTRACTABLES CORRELATIONS

CONSIDERATIONS IN DEVELOPING LEACHABLES SPECIFICATIONS AND ACCEPTANCE CRITERIA

ADDITIONAL CONSIDERATIONS

Simulation Studies
Inorganic (Elemental) Leachables



Degree of Concern Associated with Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	Medium	Low
Highest	Inhalation: Aerosols, Sprays	Injections and Injectable Suspensions; Inhalation Solutions	Powders: Sterile, Injectable, Inhalation
High	Transdermal Ointments and Patches	Ophthalmic Solutions and Suspensions Nasal Aerosols and Sprays	
Low	Topical: Solutions and Suspensions, Aerosols Oral: Solutions and Suspensions		Oral: Tablets, Capsules, Powders Topical: Powders

Revised table adapted from USP <1664>;
http://www.usp.org/sites/default/files/usp_pdf/EN/meetings/workshops/m7127.pdf

Thank you!

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