DALTON

PHARMA SERVICES

Top 7 Considerations When Conducting Extractable And Leachable Studies

Extractables and Leachables Testing Services at Dalton

Gisel Murillo

Peter Pekos

01. Extractables & Leachables Definition

Extractables are compounds that migrate out of components of a manufacturing or packaging system into a solvent under experimental conditions, such as extreme time, temperature, and pressure.

Leachables are organic or inorganic compounds that can migrate into the drug product via direct contact with manufacturing systems, container-closure systems, and drug delivery device components at normal conditions.

Sources of extractables and leachables include:

- Plasticizers and oligomers
- Stabilizers
- Antioxidants
- Ink from labels
- Elastomers and adhesives from labels
- Migrants from secondary packaging
- Reaction products between the drug formulation and the container closure system
- Photo-initiators
- Degradation of products from processing, storage, and sterilization
- Elemental impurities

02. Importance of Extractables & Leachables Analysis

Extractable and leachable studies are performed to stimulate intended use and worst-case scenario conditions to reveal potential contaminants to a drug formulation. These contaminants may compromise the safety of a drug product. The identification and quantitation of extractables and leachables makes it possible to determine the long-term stability and safety of the product, ensure regulatory compliance, and avoid drug recalls.

03. Principles of Extractables & Leachables Study Design

The first step in an extractable and leachable study design is to collect information regarding the composition of the product, the delivery system, the packaging materials, and the intended use conditions. This information will determine the different extraction procedures and techniques that must be conducted to detect potential extractables. The identification of extractables involves extensive data interpretation, library searches, data comparisons, confirmation by several analytical techniques, and analytical expertise. Any extractables which are detected at levels above the analytical evaluation threshold (AET) value must then undergo toxicity evaluation. All extractables below the AET can be regarded as not harmful. The toxicity quantification and assessment will define the safety concern threshold levels for the extracted compounds. Evaluation of the toxicity of extractable compounds from the drug container closure systems is performed using a risk-based approach outlined by the FDA. This approach considers the route of drug administration, the potential for interaction between formulation and container systems, and patient population. The quantitation of any potential leachables is then undertaken based on the substances of concern that have been identified from extractable studies.

04. Extractables & Leachables Regulations & Guidelines

Title 21 of the eCFR Part 211.65, states that "Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."

Additionally, regulatory guidelines indicate that an extractable profile should be determined for all materials that contact the drug product. The corresponding guidelines depend on the governing regulatory agency:

- FDA: Guidance For Industry: Container Closure Systems For Packaging Human Drugs And Biologics (1999)
- EMA: Guideline on Plastic Immediate Packaging Materials (2005)
- HC: Guidance For Industry: Pharmaceutical Quality Of Inhalation And Nasal Products (2006)
- ICH: ICH is expected to release a guideline in November 2024 on the control of E&L, Q3E EWG Impurity: Assessment and Control of Extractables and Leachables for Pharmaceuticals and Biologics
- United States Pharmacopeia:
  - Plastic Packaging Systems for Pharmaceutical Use
  - Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems
  - Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems
  - Orally Inhaled and Nasal Drug Products

05. Analytical Evaluation of Extractables & Leachables

Extractable and leachable testing is achieved by the complementary use of a variety of analytical procedures and techniques:

- Headspace Gas Chromatography-Mass Spectroscopy (GC-MS) is used for the analysis of volatile and semi-volatile organic compounds that are given off by the sample after heating or over time. This technique can also screen for oligomers, additives, additive break-down products, and unknowns.
- Inductively Coupled Plasma (ICP)-MS ionizes the sample to detect metals and non-metals in liquid samples. This technique can also screen for catalysts, dyes, and pigments.
- GC with Flame Ionization (FID) and Thermal Conductivity (TCD) is used to define the total extractable material.
- High-Performance Liquid Chromatography (HPLC)-UV, HPLC-Evaporative Light Scattering Detection (ELSD), or HPLC- Charged Aerosol Detector (CAD) are all techniques used to separate molecules based on a variety of different properties such as size and surface charge.
- Ion Chromatography is used to measure concentrations of ionic impurities.
- Fourier Transform Infrared (FT-IR) is used to obtain an infrared spectrum of absorption or emission of a solid, liquid, or gas.
- UV-Vis-NIR Spectrometer is used to determine the optical properties of liquids and solids.
- Thermoanalysis Differential Scanning Calorimetry (DSC) determines the difference in the amount of heat required to increase the temperature of the sample.

Emerging technologies, such ELSD, improve the sensitivity and expand the detection limits of conventional methods.

06. Assessment of Extractables Data

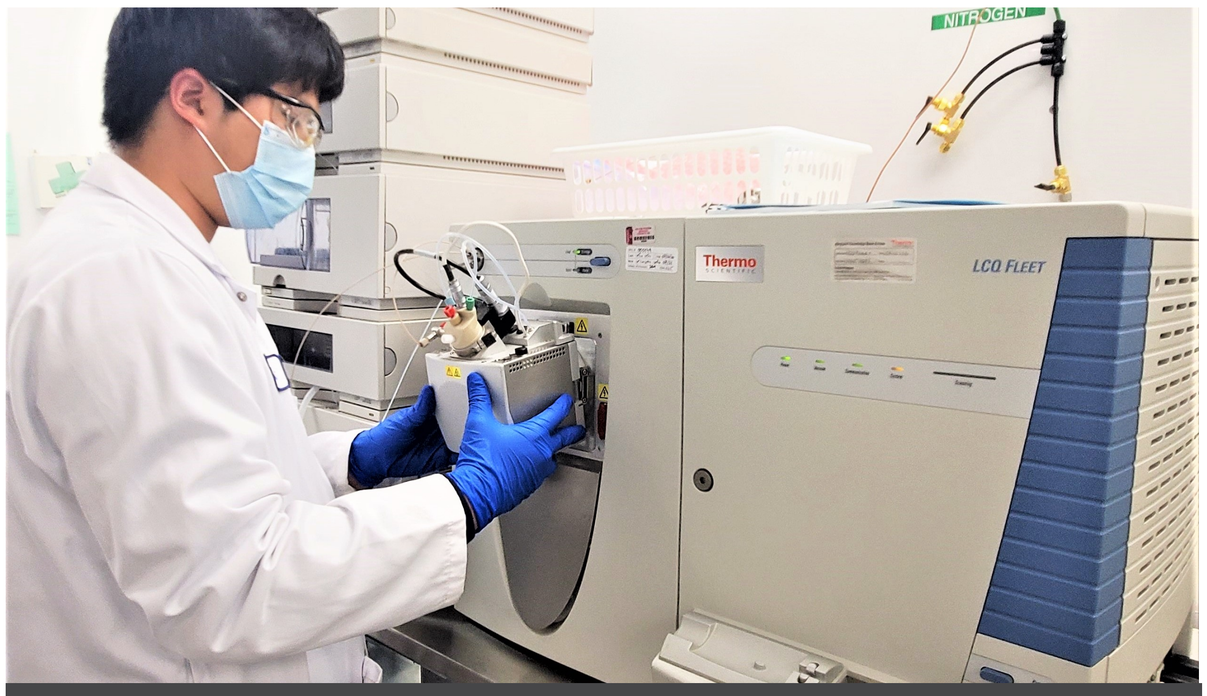
The identification of extractables involves extensive data interpretation, library searches, data comparisons, confirmation by several analytical techniques, and analytical expertise. Toxicity quantification and assessment must follow the identification of an extractable above AET.

Although the majority of leachables are a subset of extractables and are based on the substances of concern that have been identified through extractable studies, leachables can sometimes be secondary. Thus, a leachables analysis on any secondary packaging, labels or printings, is ideal. The toxicity assessment and quantitation of any leachables will determine the overall product safety.

07. Extractables & Leachables at Dalton

Dalton now offers extractable and leachable consultations, providing you with services including the determination of analytical evaluation thresholds, tailored study designs, validation of analytical methods, chromatography and spectroscopy, spectroscopic analysis, and thermal analysis. As an FDA, HC, and EMA (through MRA) approved company our team adheres to GMP and regional guidance and can help you identify the most challenging extractables and leachables. For our extractables and leachables testing services, please visit https://www.dalton.com/extractables-and-leachables.

DALTON
PHARMA SERVICES



DALTON
Pharma Services

CONTACT INFORMATION

Call Us
(416)-661-2102
(800)-567-5060

Write Us
Dalton Pharma Services
349 Wildcat Rd.
Toronto, ON M3J 2S3

Email Us
bd@dalton.com

Website
https://www.dalton.com/