DALTON Pharma Services

EXTRACTABLES AND LEACHABLES IN THE PHARMACEUTICAL INDUSTRY

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ABOUT DALTON

Dalton Pharma Services is a leading cGMP contract service provider of integrated drug discovery, development, and manufacturing services to the pharmaceutical and biotechnology industries. We are FDA Inspected and Health Canada approved and bring over 30 years of experience to every project. We deliver fully integrated solutions with an emphasis on speed, flexibility and quality.

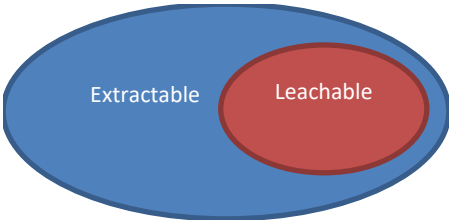
REGULATORY CONSIDERATIONS OF EXTRACTABLES AND LEACHABLES

What are Extractables and Leachable?

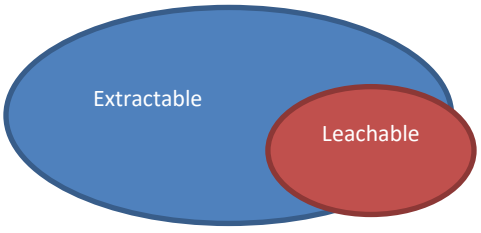
Extractables and Leachable (E&Ls) are often used interchangeably in the industry, referring any chemicals that migrate from the packaging material into the drug product. However, this is a misnomer.

- **Extractables** are chemical compounds that can be "extracted" from the product enclosure system using various stress conditions in the laboratory setting (USP<1663>).
- **Leachables** are chemicals that leach from the product enclosure system into the drug product under conditions that are representative of drug lifecycle (USP<1664>).

Ideal Scenario



Reality



Generally, Leachables are a subset of Extractables. However, in some instances the drug product can react with an extractable to form a reactive leachable. Thus, a well-designed E&L study is essential to properly evaluate all potential leachables that may arise during the product life cycle.

Importance of Extractable and Leachable Testing?

For regulatory submission for both Drug Products and Medical Devices a robust extractable and leachable study is expected. Extractables and leachables can potentially be very harmful to humans. For example, Bis(2-ethylhexyl) phthalate (DEHP) is a used as a softener in the commercial production of various plastics and it was found to leach. Since 1994 DEHP has been listed as toxic under Canadian Environmental Protection Act, 1999, and has been banned in cosmetic products and is strictly regulated in pharmaceutical products in Canada.

Product	FDA Definition	Regulatory Chapter	Example of Product
Medical Devices	An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them.	**ISO-10993-1** **ISO 13485**	**Pacemakers** **Hip Replacements** **Bandages** **Infusion Pumps***
Drug Product or Substance	Intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and articles (other than food) intended to affect the structure or any function of the body of man or other animals	**USP<1663>** **USP<1664>** **USP<1469>** **USP<232>**	**APIs** **Drug formulation** **Infusion Pumps***

*__Note:__ For combination devices both Medical Devices and Drug Product regulations apply.

ANALYTICAL CONSIDERATIONS

Safety Concern Threshold (SCT)/ Analytical Evaluation Threshold (AET)

The Safety Concern Threshold (SCT) is a toxicological limit (µg/day) that an E&L will not have an adverse effect on human health. The SCT varies in concentration depending on the risk of Dosage Form Interaction. Generally, lower risk dosage forms have SCT = 5.0 µg/day while higher risk dosage forms have a lower SCT = 0.15 µg /day.

Degree of Concern with Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	**Medium**	**Low**
Highest	Inhalation Aerosols and Sprays	Injectables Suspensions Inhalation Solutions	Sterile Powders Powders for Injection Inhalation Powders
High	Transdermal Ointments and Patches	Ophthalmic Solutions and Suspensions Nasal Aerosols and Sprays	N/A
Low	Topical Solutions and Suspensions Topical and lingual Aerosols Oral Solutions	N/A	Oral Tablets and Capsules Topical powders Oral powders

Note: This table is simply a guideline and the risk of leachables should be evaluated on a case by case basis for each drug product. Table Adapted from USP<1664>.

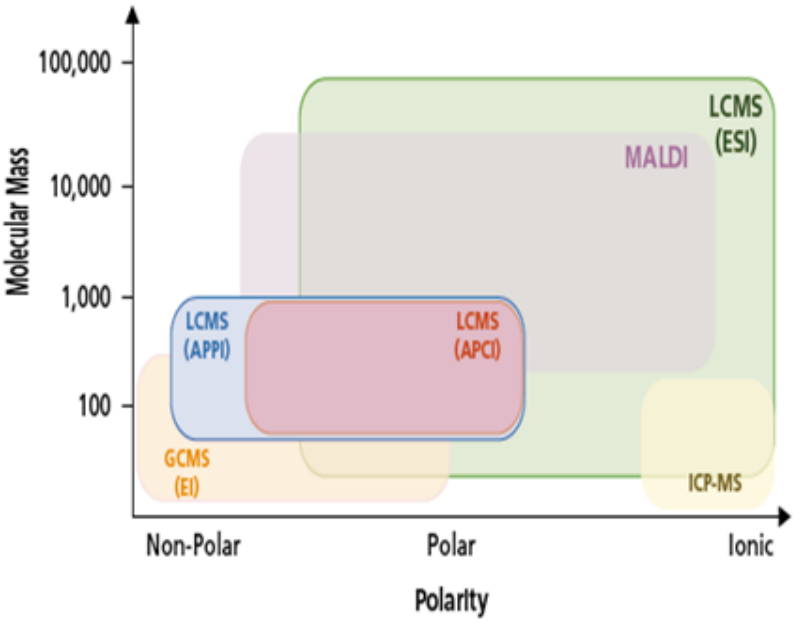
$$AET = \frac{\text{SCT ug/Day}}{\text{\# Actuations/Day}} \div \frac{\text{Drug Product (g)}}{\text{\# Actuation}}$$

The SCT is than converted into Analytical Evaluation Threshold (AET) which is an analytically relevant concentration. Any E&L above this limit should be characterized to determine their risk to human health.

Analytical Techniques

Due to the sheer diversity of E&L compounds and the differences in chemical and physical properties, there is no one size fits all method. As such Regulatory bodies recommends a variety of different analytical techniques to properly characterize individual E&L compounds. E&L compounds are categorized under 4 general categories:

- **Non-Volatiles:** Compounds generally higher weight and polar usually analyzed by (ESI/APCI) LC-MS.
- **Semi-Volatiles:** Compounds with medium weigh and polarity usually analyzed by GC-MS.
- **Volatiles:** Compounds with low weight and non-polar usually analyzed by HS/GC-MS.



- **Elemental Impurities:** Elemental impurities usually analyzed by ICP-MS.

At Dalton we have full complement of GC-MS, (ESI and APCI) LC-MS/MS, and ICP-MS that meet the needs of any E&L study for drug products.

EXTRACTABLE AND LEACHABLE STUDY

E&L studies are complicated, and often require significant amounts planning, controls, knowledge in-depth knowledge the drug manufacturing and packaging process. Currently, there are no universal guidelines on how to conduct an Extractable and Leachable Study, however a robust E&L study can be divided into 4 phases.

Dalton has qualified several final product enclosure systems in an Extractable Study.

Solid Dosage Form	Liquid Dosage Form (Light Protection)	Liquid Dosage Form

Material Characterization

In Material Characterization, it is important to gather background information on the drug product, delivery mechanism, packaging material (Primary, Secondary, and Tertiary), composition of the device, storage condition and duration. Ideally, this occurs early in the drug design process to avoid any potential issues.

Examples of Material

- Rubber Stoppers
- Plastic Liners
- Rubber Tubbing
- Anti Slip Agents
- Markers on Labels
- Blister Packaging
- Tyvek Bags
- Glass Containers

Generally, plastics are at the highest risk for E&Ls. To limit the potential leachable, it is best to use glass or high-quality plastic material especially in high-risk formulations. Several different product enclosure systems can be chosen to determine which produces the least amount of E&L.

For example, 2 different types of stoppers (Bromo Butyl Rubber and Fluoride Coated Rubber) were chosen for a lyophilized drug product. An extraction study showed that Bromo butyl Rubber contained higher amounts of extractables when compared to the Fluoride Coated Stoppers. At Dalton we have already qualified several lyophilized product enclosure systems, with respect to E&Ls.

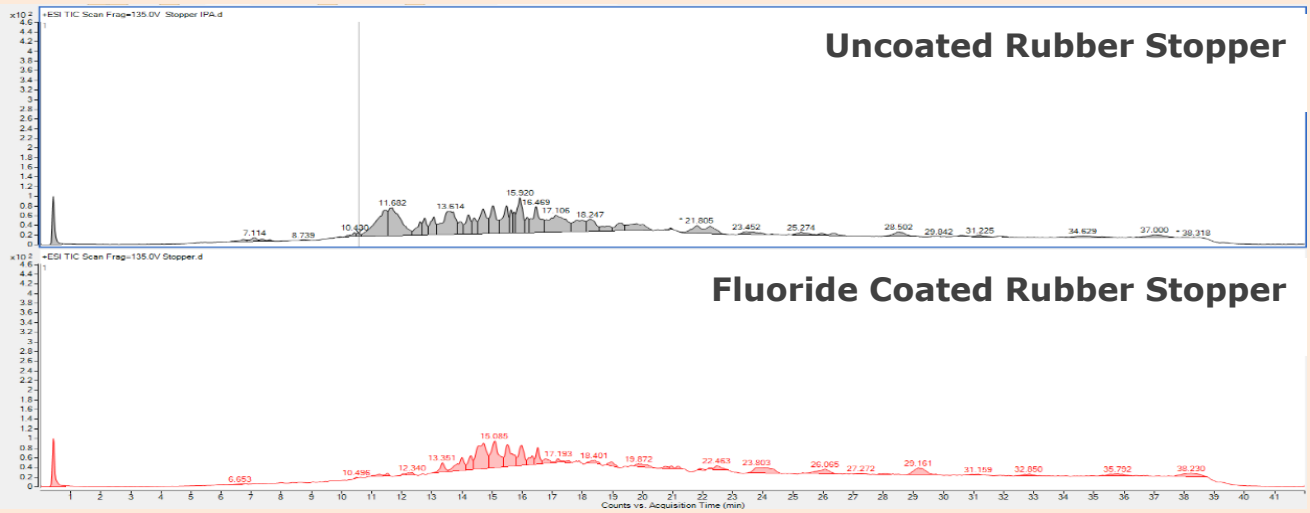
Example of Product Enclosure for Lyophilized or Liquid Drug Product

Extractable Study

The purpose of the Extractables Study is to determine the potential of leachable in each of the product enclosure system. The Extractable Study represents the worst-case scenario for potential E&Ls. It is an exaggeration of the ambient environmental and may not be representative of the drug product life cycle. However, a robust extraction study is beneficial for choosing the product enclosure system with the lowest potential of leachate.

Scenarios	Solvent
Non-Polar Extractables	100% IPA
Semi-Polar and Polar Extractables	1:1 Water and IPA
pH Buffered Drug Product	Water Buffered 1± Target pH

Due to the wide range of physical and chemical properties of E&L, it is recommended to extract target article with wide solvent mixtures covering a wide range of polarities. Careful planning with respect to the ratio of test articles to solvent used and duration of the extraction should be considered. This ensures the that the majority of the extractables are captured.

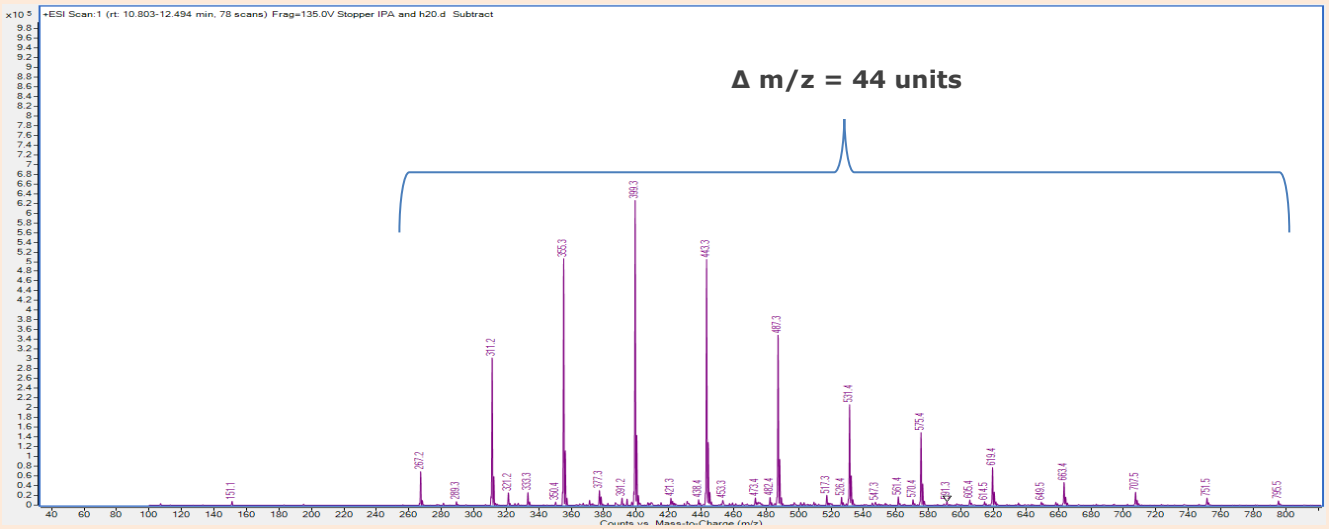


Extraction of 2 different stoppers with IPA, as a preliminary test to determine the "worst case" scenario for total extractables. The Fluoride Coated Stopper is preferred as it has less observed total extractables in the TIC compared to the Uncoated Stopper. Generally, during leachable testing EIC should be used when peak resolution is an issue.

Simulation Study/ Method Validation

Simulation Studies highly recommended as they provide invaluable information on the potential leachables that could arise during the Leachable Stability Study. Simulation studies are analogous to how force degradation study may identify impurities that might occur during a conventional Stability Study. In the Simulation Study, the drug product is incubated with a solvent that closely mimics the drug formulation and placed under accelerated conditions. The goal of the simulation study is to identify potential leachables prior to the Leachable Study. This is especially true for leachables with low AET that may not be detected at the initial T=0.

In any leachable testing, the sample matrix is the drug product instead of the product enclosure system in the extractable study. It may be challenging to properly resolve each leachable peaks due to matrix interference and co-elution. At Dalton using our technical expertise and wide array of advance Mass-spectroscopy equipment these issues are mitigated. However, small changes to mobile phase gradient or source condition may still be required depending on the drug matrix in question. All drug product matrixes should be validated on a case-by-case basis.



The Mass Spectrum of the leachable peaks in a simulation study. This leachable is likely a rubber polymer due multiple equidstant peaks with guassian distribution.

Leachable Study

The leachable study can be done concurrently with the stability study for said drug product. At this stage the respective validated leachable method for the respective drug product should be used. It is important prior to the start of the Leachable Study that proper controls are in place to help distinguish what is a true leachable or an API related degradant.

Any leachable above the AET should be identified as to determine its relevant toxicological effect on humans. In many cases these leachable could be novel compounds or have minimal toxicology data. In these cases (Q)SAR models or toxicology testing may be required.

CONCLUSION

The FDA, EMEA, and other regulatory authorities are taking an increased interest in the interactions of various drug delivery devices, pharmaceutical product containers, and medical devices with a drug product and/or patient.

E&L studies can be a daunting task, as no internationally harmonized guidelines exist yet on the assessment and control of E&Ls. This current gap generates uncertainty for industry and regulators, creating potential delays in the approval process by regulators. At Dalton we can use our expertise to eliminate these gaps and reduce potential approval delays.