Extractables & Leachables: Solutions for Risk Management and Analytical Testing

Extractables and leachables ("E&L") studies are an essential component of regulatory filing to demonstrate product safety. Depending on the container-closure system or medical device being evaluated, E&L studies can be very complex. Choosing a CDMO with expertise is critical to successful delivery of robust E&L data that you can trust.

Extractables are the chemical species that are released (extracted) from the container closure/delivery/packaging system in a controlled laboratory study.[1] Leachables however, refer specifically to the compounds that are present in the drug product matrix as a direct result of their migration ("migrant") or leaching ("leachable") into the formulation under normal storage conditions, including accelerated stability conditions.[2] The read-out of the extractables study may serve as a guide where the potential analytes are already characterized –in a 'worst case' scenario from over-exposure to pH, chemical solvents and temperature extremes –prior to being reported (if observed) as a leachable in a cGMP quantitative study of the drug product. These studies encompass a complex array of individual experiments that often require specific material handling procedures and separate analytical approaches according to the physical properties of the analytes (i.e., volatiles, semi-volatiles, non-volatiles and elementals).

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During the drug development process, it is important to identify any risks of product adulteration that could present a risk of toxicity or affect stability and/or efficacy. It is widely accepted that drug makers must eliminate impurities in the drug product itself, but more recently, regulatory agencies have scrutinized the impact of impurities that may arise from the packaging of materials. In 1999, following extensive studies on the propellants used in metered dose inhalers, the FDA mandated that pharmaceutical manufacturers demonstrate the safety of materials used in production systems, container-closure systems and drug delivery devices. To comply with these standards, E&L testing is

About Cambrex

Cambrex is a leading global contract development and manufacturing organization (CDMO) that provides comprehensive analytical and IND enabling services, as well as drug substance development and manufacturing across the entire drug lifecycle.

With over 40 years of experience and a team of 2,000 experts servicing global clients from North America and Europe, Cambrex is a trusted partner in branded and generic markets for API development and manufacturing.

routinely performed to evaluate the potential for various chemicals to migrate from the primary packaging containers into the formulation matrix of drug products and biologics to be administered.[3]

For example, consider a typical drug product that is packaged in a glass bottle and sealed with a rubber stopper. The articles of construction are evaluated first to predict what is expected and to design targeted experiments. One aim of the study would be to extract as much heavy metal as possible since this class of impurities poses a high risk to the patient. A medical device presents a more complicated scenario because it is likely to contain many different components, and each component may have several articles of construction to consider. A single device might house chambers holding the drug product, as well as needles and sealants that all require analysis to ensure no exposure to leachables impairs the product or reaches the patient during use.

E&L studies seek to answer a fundamental problem of whether the materials used in the containment-closure system impact patient safety due to the impurity profile potentially contaminating the sample. The results from these studies have considerable importance in the protection of patients and for documentation destined for regulatory authorities. Failure to demonstrate material safety could result in failure to receive FDA approval for a product or result in a clinical hold. E&L studies enable manufacturers to identify, quantify and assess the risk of leachable impurities to demonstrate the safety of their container-closure systems, processing equipment or medical devices.

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Any change to the immediate packaging materials of a Drug Product would prompt the regulatory requirement to assess the impact of the change, but typically these studies are performed once the container-closure system has been selected and the manufacturing process is in the final stages of development. Control and monitoring of extractables and leachables is an important component in building Quality by Design principles into the product and process development. By choosing a CDMO that offers comprehensive and robust E&L studies, the insights gained can be directly integrated into other development activities. Cambrex offers both capabilities under one roof, which can facilitate a smooth product launch by ensuring minimal impact from impurities, all while mitigating risks associated with the final product.

Cambrex Approach – A Strategic Partnership for CMC Solutions to Your Product

Risk Assessment - Potential to Form Leachables in the Drug Product Packaging Configuration

At Cambrex, we work collaboratively with our clients to define all the parameters necessary for your E&L studies. As part of the project, our scientists may provide a risk assessment in the form of an Extractables Study for your Drug Product, if not already performed, to identify potential sources of leachables in your primary packaging configuration. Our analytical services offerings include from-scratch development of the analytical methodologies needed for Extractables studies and cGMP transfer or validation (or transfer of existing) methods to support Leachables studies. If a controlled Extractables study has not already been performed, we offer procedural designs using common representative glass vessels and chemical solvents for extractions of your primary packaging components. Typical examples of these include Soxhlet extractors and sealed glass vessels, or glass vessels capped with syringe-pierceable septa for headspace extractions.

Robust studies should be designed with several key parameters in mind. The components of the primary packaging must first be defined, followed by calculation of the Analytical Evaluation Threshold (AET), Together, these criteria define the boundaries of the scope for each study. The material components represent the source of potential compounds to profile, and the AET defines a suitable cutoff for identification of any extractables to be profiled, but also is used for the reporting limits if leachables are observed for downstream toxicological assessment. To maximize coverage of potential compounds, the analytical

laboratory needs to be outfitted with highly sensitive instrumentation and an experienced team capable of designing and executing the study plan. Our veteran team of scientists has extensive experience with performing controlled laboratory extractions with access to our state-of-the art analytical facilities that house the industry standards in a variety of mass spectrometry (MS) based detection platforms (Refer to Table 1).

Development and Validation of the Analytical Methodology

The low-level sensitivity requirement (often low ppm or below), driven by the AET (typically ≥ 10 Qg/g), also necessitates high degrees of specificity/selectivity, and therefore the MS detection platform must be maintained in optimal operating conditions free of contaminants that may impact the analysis. Additionally, methods will require specificity from potential interferents such as residual solvents, impurities or matrix components present in the material. Sample preparation also must be carefully controlled as it is often necessary to perform a solid-phase extraction, liquid-liquid extraction and/or evaporative concentration step to enhance the method sensitivity; however, these steps have the potential to lose volatile analytes in the process and contribute to false negative results.

The instrumental setup utilized depends on a variety of factors, primarily which analytes are pursued, the specific composition of the sample matrix and limits of detection and quantitation needed. Headspace and direct-inject GC-MS approaches may appear to offer advantages over LC-MS based on the ability to prepare samples sometimes at significantly higher concentrations than what is typically used for ESI LC-MS approaches as a means to enhance method sensitivity. However, this is not always practical for all

E&L Category	Common Culprits	Specific Examples	Common Analytical Approach	Available Technologies
Volatiles	• Solvents • Adhesives	• tert-Butanol • Pentane • Heptane	Gas Chromatography Mass Spectrometry (GC-MS)	Headspace with EI source and single quadrupole (HSGC-MS)
Semi-Volatiles	• Plasticizers • Lubricants • Parabens	• Polysiloxanes • Benzoic Acids • Hexadecane • Tridecane	Gas Chromatography Mass Spectrometry (GC-MS)	Direct Injection with EI source and single quadrupole (DIGC-MS)
Non-Volatiles	• PEGs • Surfactants • Inks	• Palmitic Acid • Stearic Acid • Linoleic Acid • TBEP • Stearamide	Liquid Chromatography with Ultraviolet Detection or Mass Spectrometry (LC-UV or LC-MS)	• UPLC with ESI source and single quadrupole detector • UPLC with ESI or APCI sources and triple quadrupole tandem MS/MS detectors • UPLC with ESI source and single quadrupole time-of-flight (Q-ToF) high resolution detector
Elementals	Heavy Metals	• Lead • Arsenic	Inductively Coupled Plasma Mass Spectrometry (ICP-MS)	Screens per ICH Q3D or validated product-specific methods

Table 1: List of Common E&L Substances Quantitated by Cambrex Analytical Services

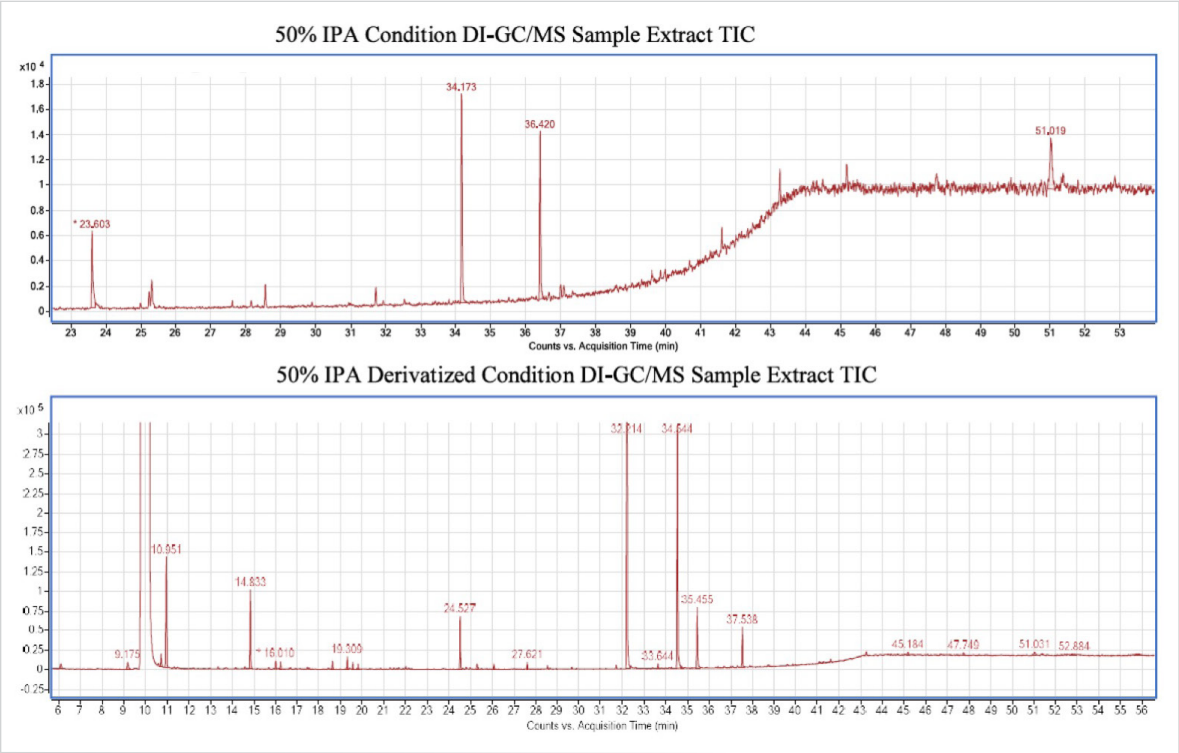

Figure 1: Direct Inject GC-MS Total Ion Chromatograms of Sample Extracts (Extractable Study) using Native vs. Derivatized Reaction Chemistry for Select Semi-Volatile E&L Compounds

analytes, as many non-volatiles may only be observable by LC-MS. Cambrex has extensive experience with derivatization chemistry to enhance volatility of many semi-volatile and non-volatile analytes, making their derivatives quantifiable down to AET levels using GC-MS based approaches when LC-MS sensitivity may not be feasible (refer to Figures 1-3). For elemental analytes, we recommend ICP-MS analysis, but also have validated several methods using ion chromatography with conductivity detection. All of these platforms are available to our customers and are fully compliant with U.S. FDA 21 CFR part 11 for cGMP use.

The simulated study is typically conducted for a timeframe of two to three months rather than 12-24 months for ICH studies, but may still utilize the same methodological approaches.

As part of the leachables study, the analytical methodologies developed may be validated for use following ICH Q2, if not already performed prior. Often, our customers ask for a simulated non-GMP/R&D leachables study prior to performing an ICH stability study for leachables under cGMP, both of which are available and performed under an appropriate study protocol with pre-determined acceptance criteria. The simulated study is typically conducted for a timeframe of two to three months rather than 12-24 months for ICH studies, but may still utilize the same methodological approaches. If selected, the simulated study still may require a verification of the accelerated results with standard ICH stability based on FDA guidance after filing an NDA, if not already performed prior to registration.

When you partner with Cambrex, our team provides you with access to state-of-the art technology, veteran industry experience, and creative approaches to problem solving while maintaining the highest degree of quality in the process to ensure your products meet your desired specifications and ultimately advance to your next regulatory and commercial milestones.

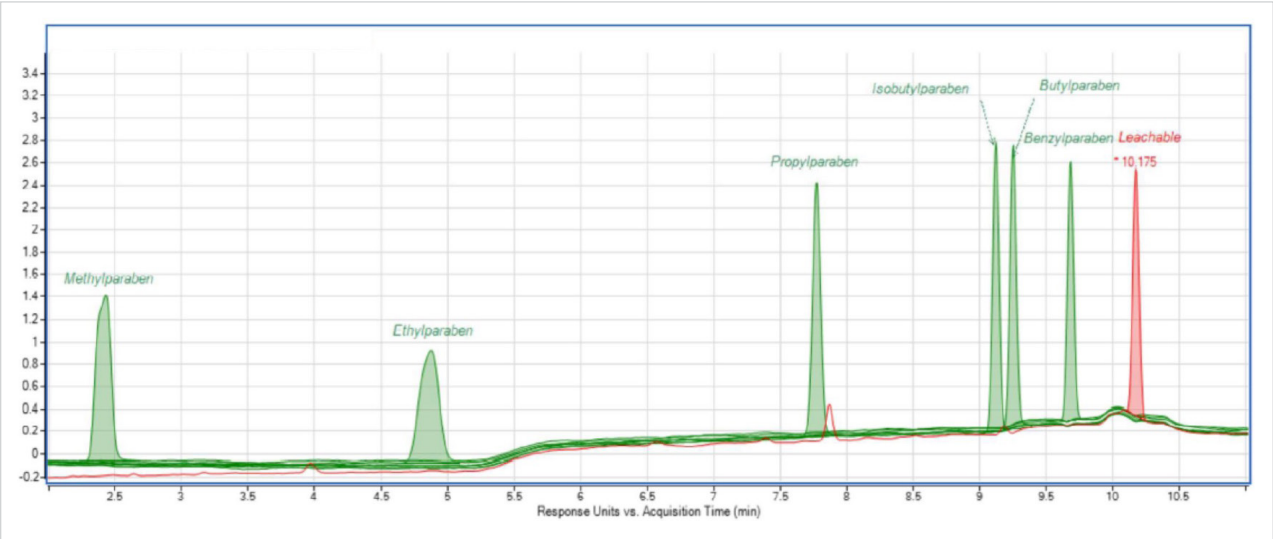

Figure 2. LC-MS Overlay of UV and MS (Q-ToF) Chromatograms (Leachables Study) for Select Semi-Volatile E&L Compounds

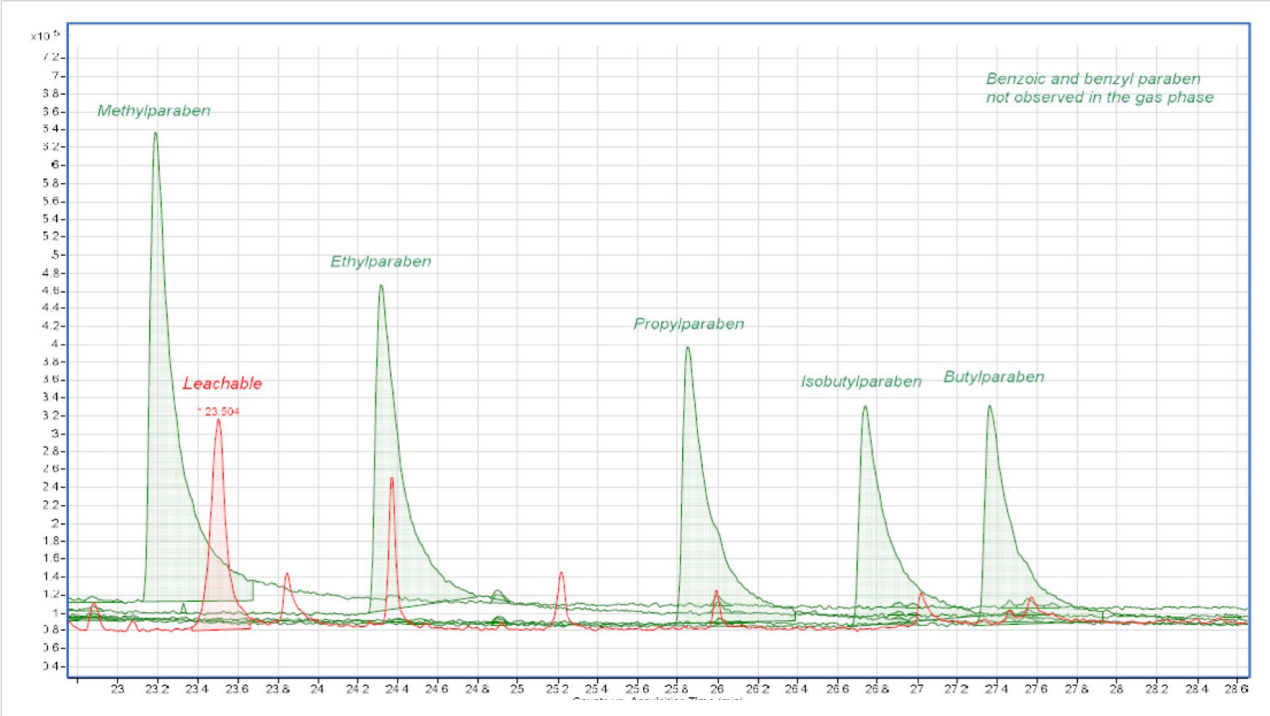

Figure 3. GC-MS Total Ion Chromatogram (Leachables Study) of Select Semi-Volatile E&L Compounds

References

1. USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems
2. USP <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems
3. Container Closure Systems for Packaging Human Drugs and Biologics, FDA Guidance for Industry

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