Cambrex

Case study
Analytical services

Mitigating hidden risks: Extractables and leachables

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Expert detection of impurities can improve product safety and regulatory success.

Safety first: Extracting value from packaging components

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 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, testing of extractables and leachables (E&L) is routinely performed to evaluate the potential for various chemicals to migrate from containers into drug products and biologics.

The aim of these studies is to identify, quantify, and ultimately minimize any impurities that can make their way into a final product. In general, any material that is in direct contact with an API is considered for E&L analysis. Secondary or tertiary packaging, such as labels, are also evaluated for any potential impact.

Everything from glass or plastic bottles to foil pouches and the ink used in labels has the potential to leach unwanted contaminants. From a practicality perspective, the first challenge chemists address is to narrow the focus on the most likely suspects. Experience from previous studies is a critical advantage when designing a targeted analysis of a product containment system that may have unknown materials. Expert knowledge of materials improves the ability to predict which chemicals might be present in order to begin detection. At Cambrex, our E&L analysis leverages the experience of our experts and the libraries of available data to conduct thorough examination of containment-closure systems and medical devices.

Gathering the suspects: Designing a targeted analysis

Rising costs have driven manufacturing preferences toward modern synthetic materials, including plastic and rubber container-closure systems. These materials may permit leachants such as antioxidants, heavy metals, curing agents, or compounds like bishphenol A to contaminate the drug product. Chemists give careful consideration to

Detective work.

The best detectives know what they're searching for.

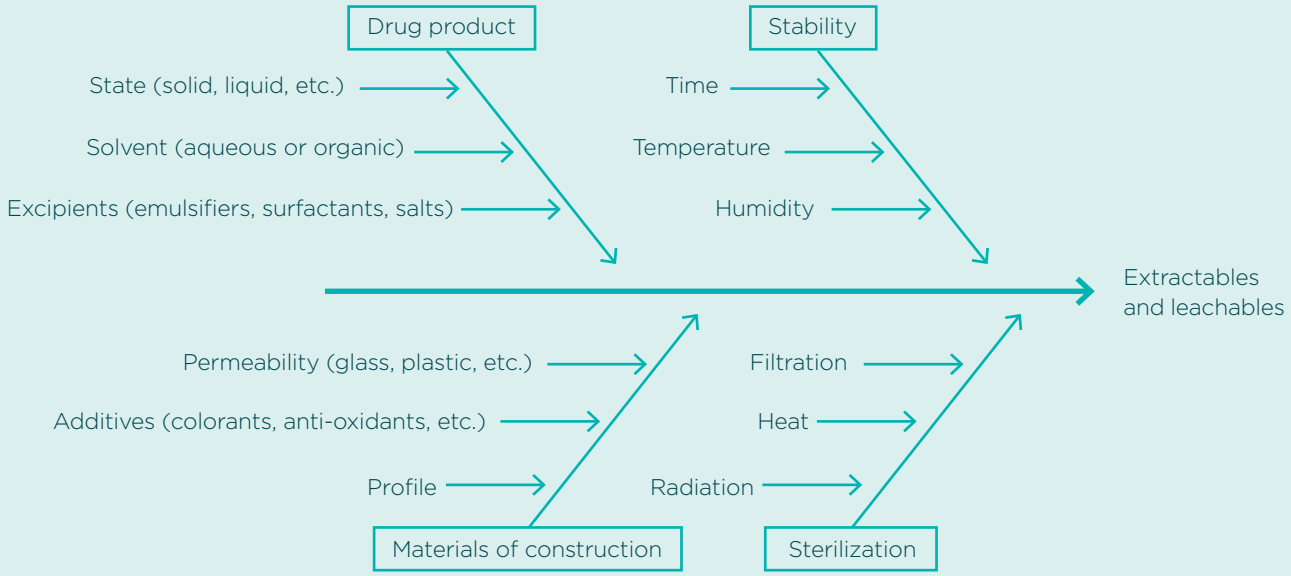
At Cambrex, our E&L studies target all suspected impurities in your material.

About Cambrex

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

With over 40 years of experience and a growing team of over 2,200 experts servicing global clients from North America and Europe, Cambrex is a trusted partner in branded and generic markets for API and finished dosage form development and manufacturing.

What factors drive design of E&L experiments



Complex study design

Variables in an E&L study require a complex series of experiments using a variety of conditions and instruments. Coupled with our world class expertise, Cambrex is equipped to consider each of these factors in their design.

the materials of construction in preparation for E&L studies. All known materials can be searched across libraries of existing data to guide appropriate experiments. When it's available, data from material suppliers can also provide insight into the expected extractables and leachables. The more data that can be gathered beforehand, the better the chemists can predict what extractables and leachables might be present, and analytical techniques can be targeted accordingly. For materials that are not already known or characterized, experience plays a critical role in devising a strategy for analysis. Our expert chemists at Cambrex have conducted studies on a broad range of materials to provide confident identification of extractables and leachables for containment-closure systems and medical devices.

Once extractables are identified, chemists determine whether trace amounts of these chemical entities might make their way into the drug product. These trace amounts of chemicals originating from containers or packaging, medical devices, or process equipment can leach into the final product as a result of direct contact with the material, and may ultimately result in exposure to patients. Naturally, the leachables of highest concern are those that are classified as a high risk to patients, and E&L studies must provide quantitative evidence to demonstrate they exist at safe levels, or not at all.

The overall concept of E&L studies is simple – expose the material to 'worst case' extremes of pH, solvents and temperature to reveal all potential extractables, and follow with analysis of the subset of extractables that may leach into the drug product. However, in practice, these studies encompass a complex array of individual experiments that require their own specific conditions. Instrument settings, spiking solutions and other conditions have to be modified according to each impurity studied.

Drilling down: A peek into the E&L toolbox

In a typical extractables study, chemists design experiments to study the critical components of the primary packaging. Broad experience is essential in choosing the best techniques to give a full picture of the relevant extractables for a given drug product and container system. Once chemists have identified which extractables are present, they can begin to quantify the substances and assess the potential risk they may pose to the integrity of the material. Next, the detected extractables can be examined against the literature to identify target leachables.

During leachable studies, Cambrex delivers beyond the industry standard by developing validated methods to assess leachables in the drug product. The Safety Concern Threshold (SCT) is used to determine the detection threshold during analysis and to provide context for the quantitative analysis. Comparative analysis against the correct toxicological standard is complex and requires the expertise of seasoned chemists.

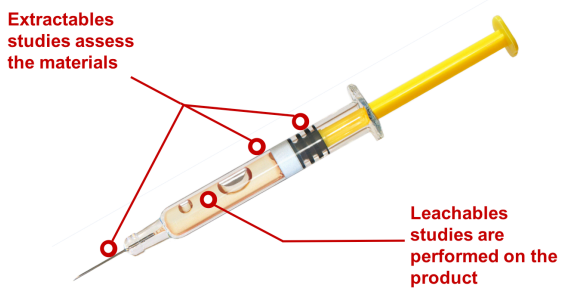
There are numerous analytical techniques used for E&L studies, including many forms of chromatography combined with mass spectrometry for identification. One of the tools that Cambrex relies on for optimal precision is Inductively Charged Plasma – Mass Spectrometry (ICP-MS), which is highly sensitive and ensures detection of metals at low levels. Samples are dissolved in an acid such as HCl or HNO3, and the dissolved sample is introduced into the inductively charged plasma which generates ions for analysis. Then, mass spectrometry is used to determine the exact signature of the metals present in the sample. Stability studies are also performed to analyze leachables over the shelf life of the drug product. Accelerated environmental conditions expose the material to elevated temperature to simulate the normal shelf life.

Confident identification.

Cambrex has the experience, expertise, and facilities to extract accurate data from your materials.

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: Test the material; test the product



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

Integrating capabilities: Building product safety into process design

E&L studies seek to answer two questions: whether the materials used in the containment-closure system impact patient safety, and if the materials have an effect over time on the efficacy of the drug product. 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.

Any change in a drug product's immediate packaging materials would prompt the regulatory requirement to assess the impact of the change, but typically these studies are performed once the container-closure system is chosen 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 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.

Extractables study: A new intravitreal implant

Cambrex worked with a customer for an Extractables study for an implant. The implant is a plastic biocompatible tube that is 3.5mm in length that is designed to deliver drug substance in the eye. This intravitreal application is designed to release the drug substance for three years for the treatment of the target chronic condition. During the submission process, the FDA requested that the customer perform an E&L analysis. Under tight timelines, Cambrex was able to provide the data that the agency requested so that the customer was able to receive an approval for their implant.

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