White paper

GMP lab

Ensuring pharmaceutical product safety: The critical role of extractable and leachable testing in development and regulatory compliance

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Introduction

When developing pharmaceutical products, pharmaceutical container closure systems, process equipment, and medical device packaging must have extractable and leachable (E&L) testing in order to determine the impurities and assess any associated risks. E&L studies evaluate the potential migration of chemicals from material components into the pharmaceutical product or patient. They are specifically designed for each pharmaceutical product based on the container closure system, administration and manufacturing process. Extractables are chemical compounds which are pulled out of the container closure or manufacturing material during studies which often include strong solvents or techniques that aid in the extraction process. Extractable studies, which are conducted on materials, can be used to assess and help predict risk from leachables, which are chemical substances that have migrated from manufacturing, storage, and/or administration systems into pharmaceutical products, during the normal, expected conditions of storage or exposure. Leachables therefore may potentially compromise the drug product safety, quality, purity, identity, and/or strength. An assessment of leachables is fundamental in the regulatory application process for applicable pharmaceutical products and medical devices. By identifying and quantifying the potential chemical substances that may migrate into the product, companies can assess the potential risks associated with these compounds and take appropriate measures to mitigate any potential harm.

The drug substance, product packaging (primary and secondary), and manufacturing process can introduce leachables into products. They consist of various materials, such as plastics, rubber, silicone, glass, and metals and often contain certain additives like plasticizers, antioxidants, dyes and other substances incorporated to improve the physicochemical properties of these materials. E&L studies are an essential part

of a comprehensive evaluation and analytical testing package for pharmaceutical products, medical devices, and packaging regulatory submissions. They allow companies to comply with regulatory requirements for successful product approval submissions. Regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) require thorough evaluation of E&L for applicable product types, to ensure patient safety and product quality. While E&L is a critical part of the pharmaceutical or biopharmaceutical development process, fully understanding what is needed can be a challenge for companies. The process of submitting a product for FDA review can be both time-consuming and costly. Pharmaceutical companies also often face challenges in navigating the evolving E&L landscape, particularly when the FDA identifies issues with E&L testing methods with little notice. Regulatory guidelines for E&L testing may be general, leading to interpretation: navigating evolving standards and differing expectations can complicate compliance efforts. Manufacturers of drugs and biologic products are responsible for conducting assessments for the detection of leachables in a finished product. For example, the EMA guidelines require evaluation and corresponding data from extraction studies for critical packaging materials, in addition to interaction studies (which include sorption and migration studies) as well as toxicological information and documentation.[1]

Companies needing E&L studies should work with a partner that can help confirm the safety of their products, as well as verify material consistency and quality by assessing product needs, type of testing, correct instrumentation, and planning. This white paper highlights how a lab with experience in E&L testing can successfully work with drug products in development and navigate regulatory requirements.

1. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-plastic-immediate-packaging-materials_en.pdf

E&L testing applicability

While E&L testing is applicable to a variety of products, not every drug product requires a full assessment. The need for testing is based on the relative risk plus the extent and likelihood of dosage form/product interaction and the route of administration. For instance, solid oral dosage forms do not typically require E&L evaluation. Below are the types of products/routes of administration that present higher risks and therefore require more complete E&L testing.

1. Parenterally administered (injectables/ transdermal)

This is a very broad category of drug products which includes a majority of the FDA approved biopharmaceutical products. A vast majority of biologics are parenterally administered, and there is a heightened focus for biologics due to product chemical composition and special concerns of leachables.

Parenteral is categorized in mainly two groups: Small volume parenteral and larger volume parenteral. Parenteral drugs fall into the US FDA's highest risk categories, as they are directly administered into the blood stream. Furthermore, the likelihood of interaction between this dose form type and packaging is high for liquid-state drugs. Even lyophilized drugs will have a propensity to collect volatile and semi-volatile leachable compounds upon storage, such as in a glass vial with rubber stopper. Therefore, the CCS (container closure system) should be assessed for its E&L interactions

2. Orally inhaled and nasal drug products

Like parenteral drug products, orally inhaled and nasal drug products (OINDP) represent a high E&L risk for the potential introduction of leachable impurities due to the container closure contact and route of administration. Inhalation aerosol formulations typically include organic liquids as the propellant and can exhibit a strong interaction with container closure system. Therefore, potential leaching of compounds from these polymeric materials into the drug formulation is considered as a very serious concern that should be addressed, as OINDP devices such as pMDI, DPI and nebulizers directly introduce the drug product to the patient circulation through the lungs.

3. Devices and drug-device combination products (pre-filled syringes autoinjectors, infusion pumps)

Drug-device combination products are increasingly becoming a container of choice for storing and administering the drug product. Identification and quantitation of extracted/leached chemicals is critical for assessing toxicological and drug quality risks.[2] A high extractable/leachable risk assessment may simply disqualify a device and eliminate the need to conduct further resource intensive qualification assessments.

4. Ophthalmic products

Ophthalmic products, mainly eye drops, are more prone for leachables. This is partially attributed to the commonly used semipermeable low-density polyethylene (LDPE) storage bottles that do not provide a complete barrier to migrating chemical moieties from secondary packaging or label adhesives, inks, sanitization, varnish, etc. There is a higher risk of leachable contamination to these products.

5. Implants, catheters, syringes, and surgical instruments

Many invasive devices such as implants, surgical instruments, and syringes, etc., which have only short-term contact time to the body and the product during their use, can deliver an extensive set of leachables into the blood stream. Often these types of components can be evaluated using in-use simulation leachable studies.

6. Biopharmaceuticals or biologics

Most biopharmaceuticals are injectable products and, therefore contaminants enter the systemic circulation directly. Many biologics are produced in complex liquid formulations. These formulations provide the higher risk of leachable contamination of the product. Biologics pose numerous unique characteristics and challenges regarding E&Ls. For instance, certain leachables may not be directly toxic to the patient, but they may include chemical moieties that can interact with the drug formulation to alter its critical biologic attributes, negatively impacting its function and/or safety profile.

Biologic formulations often exhibit amphiphilic properties, possessing both hydrophilic (water-attracting) and hydrophobic (water-repelling) characteristics. This dual nature can facilitate the solubilization of leachables, rendering them more likely

2. A key consideration for drug-device combination products is based on which FDA regulatory body will eventually review the product submission. Either FDA CDER or CDRH may review certain E/L drug-device combination product submissions and the study design expectations may be different based on the submission body.

Thermo Scientific™ Orbitrap Exploris™ 240 Mass Spectrometer

to be present in the stored sample. Moreover, many biologic formulations include solubilizing agents, such as polysorbate, to enhance the solubility and stability of the active ingredients. However, the presence of such solubilizing agents can also accelerate the leaching process, potentially leading to an increased presence of leachables in the formulation. This is an important consideration in the development and storage of biologic formulations, as the presence of leachables can affect product safety, efficacy, and stability.

7. Manufacturing process components

During the manufacturing of a drug product, manufacturing systems can be partially or completely constructed from plastic materials that includes tubing, connectors, O-rings, gaskets, check valves, filters, and mixer bags etc. During contact of the liquid process stream with the component materials, substances could leach from the manufacturing component and become incorporated into the process stream as process equipment-related leachables (PERLs). PERL testing is crucial for ensuring pharmaceutical product safety and quality by identifying and quantifying leachables from manufacturing equipment. Higher risk process components are evaluated by simulating worst-case conditions (e.g., maximum exposure time and temperature) using solvents that mimic the drug product formulation, followed by analysis of test samples versus controls using analytical techniques like LC-MS and GC-MS to detect leachables. The results are compared against safety thresholds, and a risk assessment is conducted to evaluate the impact on product safety, efficacy, and stability. Comprehensive documentation supports regulatory compliance, helping to mitigate risks and ensure informed decision-making in material selection and process design.

E&L study types

Here are three types of testing for E&L studies, for which the instrumentation types utilized vary:

Controlled extraction study

A controlled extraction study conducts extractable compound profiling / identification using MS detection – multiple methodologies utilized to obtain a complete compound profile – HSGC/MS, DI-GC/MS, LC-UV/MS/MS for organics and ICP-MS for inorganics. Ion chromatography (IC) may also be incorporated for anion evaluation.

Leachable simulation study

A leachable simulation study during controlled extraction assesses potential leachables by simulating storage conditions and using solvents that mimic the drug product. This involves identifying materials in contact with the drug, extracting leachables under controlled conditions, and employing analytical techniques like LC/UV/MS and GC-MS to detect and quantify them. Performing this alongside controlled extraction studies provides a comprehensive understanding of leachable profiles, ensuring drug safety, efficacy, and stability. The advantages include early identification of harmful leachables, informed decision-making for packaging materials, and enhanced regulatory compliance, ultimately leading to a more robust and reliable drug product.

Leachable study

For long-term drug product container-closure systems, leachable methods are typically developed and validated based on the results of controlled extraction and simulation studies. These methods are then employed to monitor the presence and concentration of leachables in the drug product over the product shelf-life storage. This approach ensures that any potential leachables are identified early, allowing for continuous monitoring and control throughout the product's stability period, thereby maintaining product safety, efficacy, and compliance with regulatory standards. Leachable methods developed and validated for specific, targeted leachable compounds may be utilized, with follow-on leachable screening for unspecified unknown leachable monitoring, or in certain cases, optimized screening methods may be utilized for the stability testing at each timepoint, study and used for monitoring targeted compound and unspecified leachable compounds.

- For primary container/closure systems for long-term product storage, leachable testing through product shelf-life is expected, with a minimum of early, middle, and late timepoints at appropriate orientation to maximize CCS and product contact.

Main considerations

It is important to consider both when to begin planning and what kind of services you need.

When to start your E&L plan

Early engagement is recommended for E&L testing. Planning ahead is better than starting a late engagement, since E&L studies take time to complete and starting too late can result in product approval delays.. E&L studies are typically required in Phase II (it's recommended to not start too early, and especially not too late). If the design or materials of construction of container/closure or device components changes due to development modifications, E&L testing may need to be repeated. Conducting these studies too late in the development process can delay product approvals, as comprehensive evaluations require significant time to ensure safety and compliance. Early and proactive E&L testing is crucial to identify and mitigate potential issues, thereby facilitating timely regulatory submissions and approvals.

A tailored approach

Different approaches can be tailored to specific scenarios in E&L assessments. For instance, in situations where the product has transient contact with components, the E&L assessment can be conducted by exposing the product or a product-simulating solvent to the components under conditions that mimic the worst-case scenario of actual use. This includes simulating the maximum duration and temperature the product would experience in real-world conditions. After exposure, the sample is analyzed alongside a control to identify and quantify potential leachables. This approach helps ensure that even brief interactions are thoroughly evaluated, maintaining the safety and integrity of the drug product.

Solutions and services to request

The following is a quick checklist of E&L testing a provider can offer:

- Thorough and robust study design
- Experienced E&L guidance and support
- Platform methods for extractable and leachable screening and for special case compounds, as required.
- The E&L testing lab should have dedicated and suitable sample preparation areas for minimizing the potential for cross contamination and the personnel should possess extensive, demonstrated experience and expertise in this area
- The E&L testing lab should have available appropriate tools for effectively conducting an E&L study, such as high-resolution accurate mass spectrometry GC and HPLC instrumentation and database libraries for compound identification and the personnel skillsets to competently evaluate and process the complex data that is generated. A Thermo Scientific™ Orbitrap Exploris™ MS is shown as an example.
- Complete client confidentiality
- Complete lifecycle support needed for E&L studies and variations.
- Toxicological evaluation and Regulatory Query Support

Overcoming E&L challenges with PPD Laboratory services

- We are a leader in E&L studies, offering extensive expertise and state-of-the-art instrumentation. Our team has more than 20 years of experience supporting the pharmaceutical industry, including inhaled, parenteral, transdermal, oral, medical implants, drug-device combination products, and biopharmaceuticals. Commitment to scientific rigor, regulatory compliance, and patient safety is why we're a trusted partner for E&L studies in the pharmaceutical and medical device industries.

Key capabilities and services:

- Comprehensive E&L study design and execution
- Controlled extraction studies for container closure systems (CCS) and manufacturing components
- Development and validation of E&L methods for various dosage forms
- Leachable stability testing and batch extractables testing
- Identification and quantification of unknown impurities
- Elemental impurities screening or method development, validation, and routine testing by ICP-MS
- Nitrosamines testing, with validated GC-MS and LC-MS methods

Track record and expertise:

- More than 1,500 E&L full programs completed across small molecules and biologics
- Annual support for multiple drug products approved for market
- Expertise in handling complex formulations and ultra-low level impurity detection

Collaborative approach:

Our locations in Europe and the US serve as hubs for conducting comprehensive E&L studies. Close scientific collaboration between these sites ensures seamless knowledge sharing and a holistic approach to E&L assessments. This collaboration, paired with our advanced analytical capabilities, ensures thorough evaluation and compliance with regulatory requirements.

Conclusion

E&L studies are critical for ensuring the safety, efficacy, and regulatory compliance of pharmaceutical products and medical devices. These studies help identify potential interactions between the product and its packaging or delivery system, providing essential data for risk assessment and mitigation. It is important to partner with a lab that can provide comprehensive E&L studies and has had years of experience and advanced analytical capabilities. The collaborative approach between the PPD™ clinical research business of Thermo Fisher Scientific's GMP lab locations ensures robust and accurate assessments, leveraging state-of-the-art instrumentation and deep expertise. By partnering with us, companies can be confident in achieving scientific rigor, regulatory compliance, and a commitment to patient safety and product quality.

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