November 2022

Is it Ever Too Soon To Start Your Extractables and Leachables Assessment?

A Step-Wise Approach for Emerging Companies to Meet Submission Timelines

Donald DeCou
Technology Manager,
Extractables and Leachables

Matthew Woods
Manager,
Extractables and Leachables

Executive Summary

Extractables and leachables assessments of pharmaceutical packaging and delivery systems are critical to both your development and regulatory submissions. This white paper summarizes what you need to know about planning for your extractables and leachables testing programs to mitigate delays to your drug development timelines.

Is it Ever Too Soon To Start Your Extractables and Leachables Assessment?

A Step-Wise Approach for Emerging Companies to Meet Submission Timelines

Demonstrating the compatibility of any material that comes in contact with a drug product throughout its lifecycle (manufacture, containment, and delivery) is a requirement for any regulatory submission. Agency expectations on this material evaluation, defined as extractables and leachables (E/L), continue to evolve and expand. These expectations are well beyond a check box activity that can be quickly and mindlessly completed at the end of Phase III. These newer companies are often at a disadvantage from larger companies as they do not have the ability to leverage historical E&L data or the advantage that comes with a platform approach to containment needs. Unfortunately, West sees a pattern where new and emerging pharmaceutical companies wait until the end of Phase III to start planning their E/L testing program. Waiting this late in development can lead to increased costs and delays, stemming from poor assessments that are questioned by the reviewer, or incomplete submissions that require the drug company to redo or execute additional work. In order to meet regulatory expectations, the mindset around E/L testing must change from "How quickly can we get extractable and leachables testing done?" to "Is it too soon to start my extractables and leachables assessment?"

WHY DOES E/L TESTING TAKE SO LONG?

Referring to an E/L assessment as a singular "test" drastically underrepresents regulatory expectations. Extractables and leachables assessments, or chemical characterizations, are multistep processes where a sponsor must use knowledge of their drug product and manufacturing process, along with data from vendors, analytical labs, and toxicologists to demonstrate material compatibility. Guidance documents from the United States Pharmacopeia (<1663>, <1664>) and the Product Quality Research Institute (Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Parenteral Drug Products [Intravenous, Subcutaneous, and Intramuscular]), as well as ISO standard 10993-18 provide sponsors with a framework of how to execute this assessment. The framework is as follows:

STEP 1 **Educated Component Selection**

- Use established materials from reputable vendors
- Review initial materials provided by the vendors

STEP 2 **Generate Extractables Profile**

- Ascertain compounds that could migrate from components – also known as extractable compounds

STEP 3 **Risk Assessment**

- Evaluate the risk to the patient and the product associated with the compounds that comprise the extractables profile

STEP 4 **Demonstrate Efficacy and Safety**

- Execute leachables study

In order to understand the significant time required to execute an E/L assessment, let's look at the same framework expanded (Figure 1) which outlines the required activities requirements in greater detail.

Although component selection can be considered the most important part of this process, it has been excluded from timeline because it is typically completed before proceeding to the actual assessment.

FIG 1

Example Extractables and Leachables Study Timeline for New and Emerging Companies

GENERATE EXTRACTABLES PROFILE

Before any extractables and leachables assessment can start, a sponsor must first gather pertinent data around the materials of use and the drug product. Examples of pertinent data include contact time, temperature, and proximity to final product for processing materials; storage conditions and desired shelf life for primary packaging components; and pH range and constituents of the drug product. Additionally, the sponsor should take the time to contact vendors and assess the availability and applicability of any available extractables data packages.

At this stage any extractable information gathered from vendors will aid the sponsor in planning and executing an extractable study. For example, West can provide Theoretical Material Extractable lists (TMEs) and Material Characterization documents to aid sponsors in this regard.

After this information is gathered and assessed, an extractables assessment can be designed. Using the applicable guidance documents (examples include USP <1663> for packaging materials, USP <665> for polymeric manufacturing components, ISO10993 for medical devices or delivery components on a combination product) studies must be designed (leveraging any available vendor data) to appropriately stress at risk materials to understand what could migrate from these materials.

Additional time for ancillary tasks related to the execution of an extractables study should be factored into your timeline. Some examples of these activities include:

- Vendor (external lab) approval, CDA and/or other agreements
- Study design with external lab
- Quote/PO process
- Protocol generation
- Sourcing, shipping materials

At the completion of a properly executed extractable study a sponsor should have a complete list of extractable species along with their semi-quantitative concentrations. This information is required for a thorough risk assessment.

The execution of an extractables study typically involves the following steps:

1. Extraction of the materials
2. Preparation and analysis of resulting extractions on various analytical instrumentation
3. Data interpretation (including assigning identifications in untargeted screening analyses)
4. Reviewing and Reporting

Typical analytical techniques for the analysis of the generated extracts include:

1. High Performance Liquid Chromatography with Ultraviolet and Mass Spectrometer detectors (HPLC/UV/MS) for the analysis of non-volatile extractables.
2. Gas Chromatography with Mass Spectrometer detection (GC/MS) for the analysis of semi-volatile extractables.
3. Headspace Gas Chromatography with Mass Spectrometer detection (HSGC/MS) for the analysis of volatile extractables.
4. Inductively Coupled Plasma with Mass Spectrometer detection (ICP-MS) for the analysis of elemental extractables.
5. Ion Chromatography (IC) for the analysis of anionic species.

Risk Assessment

After the extractables data has been generated, the sponsor must review this data to assess if any of the extractable compounds could pose a risk to the patient or the product. This assessment can be daunting for sponsors due to significant data that may have been generated during the extractables assessment. Typically, additional studies or resources are necessary to help sponsors digest the extractables data and determine an appropriate way to demonstrate safety to the regulatory bodies. West can aid in this by performing an E2L™ risk-based evaluation of data generated during an extractables study. West's E2L risk-based evaluation is used as a tool to help sponsors progress from the extractable stage to the leachable stage of a project.

During the transition from extractables to leachables, a simulated leachable study can be extremely helpful. The purpose of a simulated leachables study is to provide the sponsor with data generated using actual use conditions. Typically, the study design involves drug product or placebo in contact with packaging at conditions mimicking actual storage.

Although accelerated conditions can be used to expedite sample aging, these studies can require significant time to allow for the appropriate samples and controls to be generated for analysis. In comparison to the steps listed above, steps 2-4 remain comparable. However, that initial extraction time can take months. To provide context, using the Arrhenius equation conservatively it would take 2-3 months of aging at 40°C to mimic a storage condition/shelf life of 2-8°C for 2 years. The extractables data should be leveraged in this study due to the analytical challenges the constituents of the drug product can present to the analytical techniques commonly used. For example, the active pharmaceutical ingredient and/or excipients may interfere with the detection of leachable compounds. In cases where interreferences will occur, other solvents that simulate the drug formulation solvent strength or properties without introducing interferences may be used. The resulting data provides the sponsor with a clearer understanding of what compounds could migrate into their specific drug product.

A toxicological assessment is necessary to evaluate the potential risk the compounds observed are to the patient. Extractables and leachables guidance from the Product Quality Research Institute (PQRI) suggests the use of appropriate analytical thresholds when generating extractables data by combining a concept they created called the Safety Concern Threshold (SCT) (which is defined as "the threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and non-carcinogenic toxic effects") with the dosing information of the product. Compounds observed above this threshold aren't automatic issues, but rather need to be evaluated on a case by case basis to understand the risk to the patient.

The result of the sponsor's extractables risk assessment must be a clear rationale of how the sponsor progressed from identifying the materials in contact with the product and patient to their risk assessment conclusion. The conclusion should include a list of compounds to target during a leachables study and/or how the product will be monitored for leachables throughout the shelf life.

Demonstrate Compatibility with Leachables Study

The leachables study is the final step in demonstrating compatibility between the materials of use and the final drug product. Based on the risk assessment in the previous step, methods must be developed and validated targeting any potential problematic compounds in the final drug product at appropriate concentrations. A complete and low-risk leachables study involves the use of both targeted and screening methods. Targeted methods will quantify compounds identified in the risk assessment. Non-targeted screening methods (similar to those used during extractables studies) are used to monitor the packaged drug product for unanticipated leachables throughout the shelf life of the drug product. This further supports the decisions/ inclusions of targeted compounds.

Time requirements in the final step are at the highest for the entire E/L assessment process due to the need to evaluate the final packaged drug product throughout the shelf life. Additionally, resource heavy development and validation activities are required to establish targeted methods specific for the drug product under evaluation.

Conclusion

A complete extractables and leachables assessment is a significant process. Starting the assessment as soon as manufacturing and packaging components are finalized is critical to allowing a sponsor's team time to demonstrate to the regulatory authorities that all materials used for the manufacturing, containment, and delivery are compatible with the drug product.

Compressing the timeline can, at best, impact the sponsor's confidence in their own risk assessment or, at worst, impact a regulator's confidence in the risk assessment. As long as the materials are finalized, it's never too soon to start your extractables and leachables assessment!

To find out more about options and offerings available in support of extractables and leachables in your drug development visit West's **Extractables and Leachables** Analysis landing page where you can find a range of resources such as information sheets and case studies. We invite you to reach out **Contact Us** so that we can connect you with an account manager in your region.

West Pharmaceutical Services, Inc.
530 Herman O. West Drive, Exton, PA 19341 USA
610.594.2900

www.westpharma.com

0922