eurofins | BioPharma Product Testing

Developing a Phase-Appropriate Extractables & Leachables Program

by Wayland Rushing, Ph.D.

Abstract

Until recently, the evaluation of extractables and leachables (E&L) in drug products has been performed almost exclusively during late-phase development. These requests can put clinical trials on hold and be expensive and time-consuming.

It is possible to Identify products and their attributes likely to be questioned by the FDA during early-phase clinical trials. For these products, a streamlined E&L study design can help answer or avoid requests for early-phase data. The study design helps companies be proactive about gathering information, builds Quality by Design (QbD) principles into the drug development pipeline, and reduces the cost and time of development.

Introduction

Patient safety and drug potency depend on minimizing the risks posed by leachable compounds migrating from container closures, manufacturing equipment, and drug delivery systems into pharmaceuticals. Over the past 20 years, E&L evaluations have evolved and taken on a larger role in the drug development process. The first drug products to require E&L studies were orally inhaled and/or nasal drug products (OINDPs), followed by parenterals, then ophthalmics and dermal products. E&L studies of manufacturing equipment have increased with the advent of single use systems, due to the presence of plastic components that replace traditional stainless steel in the manufacturing environment. Each of these evolutions have focused on the data required for registration of a drug. During each of these evolutions, regulatory guidance and industry best practices have evolved that provide a framework for what is required. However, these have always been focused on what is required for final approval and none provide any information on what is or may be required during the early phases of the development process.

The FDA provides general guidance about E&L but hasn't stipulated what needs to be measured, how to measure it, or at what level extractable and leachable compounds are a safety concern. Vendors rely, instead, on industry groups for best practices that they can use to support their submission for a final drug registration.

In the past five years, drug sponsors have seen a marked increase in requests from the FDA for detailed E&L data during Phase 1 and Phase 2. These requests are not only for clinical trial materials including container closure systems, but also for manufacturing equipment and dosing components. Several programs were placed on clinical hold until this data was gathered, leading to delays and increased costs.

The expense and time consumption of undertaking E&L studies can be an onerous burden on a drug development program. Managers in charge of the CMC portion of a regulatory filing, analytical development managers, and heads of manufacturing and processing struggle with how to acquire E&L information without increasing development time and expense.

Fortunately, there are commonalities in the questions regulators are asking and the types of programs receiving these requests for additional E&L data. Typically, it is non-aqueous formulations, unique syringe configurations, biomedical devices and drug delivery systems that receive these requests.

In response to the growing need for E&L studies during early phases, and the need for evaluations to be cost-effective and brief, Eurofins BioPharma Product Testing created a condensed experimental design to identify extractables and leachables in early phase clinical trial materials. Eurofins BioPharma Product Testing has used it successfully many times for a variety of drug products, helping drug development teams answer or avoid regulatory requests.

Definitions

Extractables: Compounds that migrate out of materials under aggressive laboratory conditions.

Leachables: Compounds that migrate into the drug product under actual conditions of usage, such as during production. These are normally a subset of extractables.

Safety Concern Threshold (SCT): The level below which there is negligible risk associated with the toxicity of the compound based on dosing. It is used for leachables with unknown risks, as compounds with known risks have toxicology data.

Analytical Evaluation Threshold (AET): The level at or above which a leachable or extractable needs to be reported for potential toxicological assessment. It is based on SCT.

Sources of Extractables & Leachables

- Primary packaging components
- Vials
- Stoppers
- Syringes
- Secondary packaging components
- Foil overwraps
- Labels
- Inks and dyes
- Associated/dosing components
- Medicine droppers
- Infusion sets
- IV sets
- Processing components
- Single use systems
- Manufacturing equipment
- Shipping materials

Regulations & Guidance

The FDA has similar requirements for container closure systems and equipment, for both pharmaceuticals and biologics but has provided only limited additional guidance:

- Guidance for Container Closure Systems for Packaging Human Drugs and Biologics (1999)

- Reviewers Guidance for Nebulizers, Metered Dose Inhalers, Spacers and Actuators (1993)

- Metered Dose Inhalers (MDI) and Dry Powder Inhalers (DPI) (1998)

- Nasal Spray and Inhalers Solution, Suspension, and Spray Drug Products (2002)

- Drug Products Packaged in Semipermeable Container Closure Systems (2002)

With the limited available guidances from the agency, companies typically rely on advice from CRO's and best practices document published by the PQRI, BPSA and BPOG along with the new USP chabters.

These sources deal with the data and information required to submit a final registration for an NDA, BLA or NADA, but do not outline the requirements that might be necessary earlier in the development process.

Clinical Trial Material: The Next Step in E&L Studies

Companies typically start an E&L analysis at the end of Phase 2, as the container closure system had been chosen and the manufacturing process has been finalized with the leachables stability data being generated during Phase 3. A thorough E&L program can take six to eighteen months to generate the data necessary for registration filing. This timeline makes it challenging to do a complete E&L study during the short length of Phase 1 and 2 trials.

Eurofins BioPharma Product Testing saw the first request for E&L data for Phase 1 material in 2012, for a non-aqueous formulation using a nonstandard vial/stopper configuration. Since then,Eurofins BioPharma Product Testing worked with a large number of programs that received regulatory requests for E&L evaluations and/or data during Phase 1 or pre-IND. In some cases, the FDA stated that USP testing was insufficient for performing a risk assessment. A significant portion of these programs were placed on clinical hold pending generation of this data.

Regulations for Clinical Trial Material

While specific regulatory requirements are vague, Dr. Ingrid Markovic of CBER stated, "E&L and other impurities are deemed to be controlled in the IND phase because the clinical outcomes are closely monitored; therefore, E&L studies are generally not required, unless so deemed warranted… However, from a manufacturing perspective, it is advisable to be cognizant of E&L during component and packaging selection in early development to avoid possible problems in late development."[5]

This comment underscored the challenge associated with performing E&L studies in the early phase. Typically, it may be a good idea to generate the data for future challenges and qualityimprovement, it is not required for a safety evaluation "unless so deemed warranted." The question is, *"what do regulatory authorities consider 'warranted?'"*

Which products get questions?

Using internal data from our experience with many different drug products at various stages of development, along with information from colleagues and pharmaceutical companies, we are able to predict whether a particular product will receive a request from the FDA for E&L data in Phase 1.

Products receiving requests tend to be high-risk as identified in the FDA guidance document for container closure systems. The only exception to this is inhalation products, because the information is made available to the FDA by manufacturers.

Category 1: Products with a Material Qualification Program

Drugs that have been assessed for quality and safety through a material qualification program typically receive no requests for additional E&L data. A company's material

qualification program establishes a standardized testing protocol to assess the risks of all materials. The extraction uses as many as ten solvents, a range of pH and ionic strength, alters the organic/aqueous ratio and uses common additives such as surfactants to mimic the conditions of the process. They are tested with a variety of analytical methods, such as HPLC. It allows a comparison of two possible components in compatibility and leachability.

This testing comes with a low risk that an unknown leachable will appear later on. It requires significant up-front time and cost to generate the data and internal resources to maintain and perform the testing. As such, it is best used in companies with large development pipelines, such as those that might have a dozen vial/stopper configurations to test.

Category 2: Vendor Supplies Extractables Package for a Standard Formulation

If a product was not qualified with a material qualification program, but the vendor supplied a thorough extractables profile for formulations that are standard in commercialized products, it is not likely to see a request for additional E&L data. The information gathered prior to selecting a material includes whether there is a DMF, whether the component has been used in a successful filing, and the testing performed on the components for release.

This is the recommended route for for early phase products. Vendors should be evaluated to assess which offers the best extractables package. If two components are equal in terms of functionality, it makes sense to pick the product with the better extractables package because it lowers the risk. It is also advisable to choose well-characterized materials. The one drawback to this is that there could be unknowns above the SCT.

If leachable studies are desired, the vendor's extractable methods might be available. Some CROs that do E&L testing have in-house generic screening methods that can be used. It should be kept in mind that extractable unknowns could show up as leachables, although vendor's data should catch these.

Category 3: Lack of Extractables Data for a Nonstandard Formulation

These products are routinely getting requests from both CBER and CDER for early-phase data. While every product that received a request for additional E&L data fell into this category, not every product that falls into this category requires additional E&L evaluation. In one case, the company did not have a material qualification program, it was not supplied with an extractables package from the vendor and the product is a nonstandard formulation. Preemptive generation of early-phase data can benefit a company expecting questions from the FDA or to prevent getting those questions.

Category 4: Parenteral Dosing Devices

An exception to the scenarios above are infusion sets used during clinical trials. These tend to elicit requests from the agency to provide E&L data. Products that are dosed via this route during clinical trials are also at the highest risk of being placed on clinical hold if E&L risks are not addressed.

Challenges of Designing an Early-Phase Program

Study designs for early phase programs need to be shortened to take into account the time, cost and resource limitations inherent in

	PRODUCT TYPE	PRODUCT ATTRIBUTES
Additional requirements	• Non-aqueous formulations • Unique syringe configurations • Implantable devices • Injection cartridges • Infusion sets	• Specialty/uncommon components • Proprietary packaging • No supplier-provided E&L packages • Components not used in an approved product • No chemical control tests on the components
No additional requirements	• Aqueous based formulations • Typical stopper/vial configurations • pMDIs • Oral formulations • Lyo-based formulations	• Well-known suppliers • 'Characterized' materials • Supplier-provided E&L packages • Filed DMF • Already used for commercial products • Specific extractables control test • Companies had a Material Qualification program

early-phase trials. A thorough E&L evaluation can take 18+ months and cost as much as $500,000. So how do we design a study that is based on good science, focused on patient safety, and addresses the timeline and cost constraints of early-phase development?

Condensed Early-Phase E&L Study Design

The standard, late-phase E&L study design begins with information gathering, followed by a determination of SCT/AET of materials, extractable studies and then leachable studies. Eurofins BioPharma Product Testing has simplified this design to make it phase appropriate while still providing high-quality data that lowers risk and answers potential questions a company may receive from the FDA. We used this study design successfully, especially for products placed on clinical hold.

The first two steps are the same: gather information and set the analytical level. The third step has extractables and leachables studies performed in parallel instead of separately. It allows us to analyze all extractable samples, and simulation has extractables and leachables studies performed in parallel instead of separately. It allows us to analyze all extractable samples, and simulation or actual leachable samples to generate that data simultaneously. Then we identify potential leachables in all these samples that are above the AET. The final step is to perform the toxicology evaluations on these leachables.

Extractables Program: We perform controlled extractions as per the typical program with a minimum of three solvents, covering the polarity and pH range of the drug product. One of the solvents closely resembles the drug product placebo. We use reflux or sonication, making sure not to be too aggressive as this can produce spurious extractables that are unlikely to be leachables. Extractables are analyzed using HPLC, GC, ICP for metals and other techniques.

Leachables Program: Early phase drug products generally have a shorter shelf life, as little as one month, and infusion sets might only be used one or two days in a clinical study. This allows us to shorten the experimental design to simulate a quicker leachables profile.

We store the drug product and placebo in the container closure system to be tested under normal and accelerated conditions. Then we age, stress simultaneously, or start the leachables before initiating extraction studies to generate E&L samples that can be analyzed concurrently. Additionally, we test placebos and the forced degradation of the API.

Since testing everything together, Eurofins BioPharma Product Testing performs subtractive fingerprinting between the different samples for each analytical technique. For example, we generate our HPLC profiles for the E&L in the API. We may find 40 extractable peaks, but only three of those appear in leachables. That means we do not have to identify all 40 extractables because the data shows that 37 do not leach. Instead, we focus on the three that appeared in our samples.

Analytical Interpretation: Data interpretation is straightforward: comparing fingerprints between the extraction and placebo samples. Use of the API and drug formulation samples allows for removal of API and drug product-related peaks. Thus, we trace back peaks in the final drug product to determine whether they came from the API, the drug product formulation, or the leachables. Then we only focus on those that can be traced back to the extractables.

Case Study 1: Non-Aqueous Vial/Stopper

We used this compressed experimental design to analyze a non-standard vial/stopper configuration which had no vendor-supplied extractables information and used an unusual cottonseed-oil formulation. The FDA requested E&L data prior to the clinical study, which was scheduled to be two months long.

Study Design: We performed extractables on the stopper. Leachables were generated using only the placebo for two reasons: sufficient quantities API (a specialty compound) were unavailable; the API concentration in the drug product was low enough that it wasn't going to alter the leaching profile. We stored samples for two months at the normal storage temperature (25ºC) as a worst-case scenario, then analyzed the leachable samples concurrently with extractable samples, API, and drug product.

Results: There was a large number of extractables, which was expected as one of the solvents was

cottonseed-oil. Many other were unknowns. Fingerprinting revealed only two leachables above the SCT and both correlated with known extractables. At 25ºC, four leachables were observed, of which one was an unknown compound that we identified from a library match with its gas chromatography mass spectrum. Since they were all knowns with available toxicology data, risk assessment showed that there were no safety issues.

The program took three months from beginning to the issuance of our report. Our data satisfied the regulator's request and no additional questions were posed.

Case Study 2: Infusion Set

Evaluations of drugs infused by pump in clinical studies typically focus solely on drug product compatibility, asking whether the API is sticking to polymer or whether there is loss of potency. For this early phase study in which the drug was infused by a syringe pump for less than 24 hours, no E&L data had been presented in the IND. The FDA had questions about the infusion sets, not the syringe pump or syringe, and put the study on clinical hold until an E&L evaluation was performed.

Study design: We performed extractions on individual components of the infusion set using the drug product and placebo Then, we dynamically generated leachables under the actual. conditions of use, using the infusion pump over 24 and 48 hours at 37ºC, a temperature that mimics leachables under the actual. conditions of use, using the infusion pump over 24 and 48 hours at 37ºC, a temperature that mimics the state of having the equipment next to a patient.

Results: Given that the infusion sets were constructed of five different polymers, multiple extractables were observed. Many were unknowns. Fingerprinting showed that, even after 48 hours, there were no leachables above the AET, as expected given the low contact time. Risk assessment showed no safety issues even at twice the length of typical use. The study took six weeks until issuance of our report. The data was accepted and the clinical trial hold was removed.

Conclusions

There is growing regulatory scrutiny of extractables and leachables of clinical trial material. E&L evaluations are now part of drug development at all stages. Fortunately, we have been able to identify the specific early-phase products used in clinical trials and their particular attributes that make them more likely to face enhanced scrutiny from the FDA for E&L data.

To meet these growing requirements for phase-appropriate E&L evaluations, we have developed an abbreviated study design that is ideal for generating data in a cost-effective, time-efficient manner for early-phase clinical trial material. This experimental process has the added benefit of building Quality by Design principles into drug development from the early phases, thus lowering overall risk and ensuring patient safety. The study design helps companies answer and/or avoid questions from the FDA during Phase 1 and Phase 2 that could lead to a clinical hold on a study.

The two case studies presented represent the many companies for which we have successfully used this condensed plan to aid their drug development.

References

[1]. Norwood, D.L. and L.M. Nagao. "The Analytical Evaluation Threshold (AET)." PQRI. August 2015. http://pqri.org/wp-content/uploads/2015/08/pdf/PQRI_AET_Poster.pdf

[2]. US FDA. "Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics." May 1999. https://www.fda.gov/downloads/drugs/ guidances/ucm070551.pdf

[3]. PQRI. "Thresholds and Best Practices for Extractable and Leachables." 22 March 2017. http://pqri.org/wp-content/uploads/2017/02/CombinedPQRI-PODPSlides_PQRI-FDA_22Mar2017.pdf

[4]. BPSA. "Technical Guides." http://bpsalliance.org/technical-guides/

[5]. Markovic, I. CBER, ASTM E55 workshop. 21 May 2014