

HOW DO YOU DEVELOP A PHASE-APPROPRIATE EXTRACTABLES AND LEACHABLES PROGRAM?

WHITE PAPER

Developing a Phase-Appropriate Extractables and Leachables Program

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ABSTRACT

Until recently, the evaluation of extractables and leachables in drug products has been performed almost exclusively during late-phase development. Regulators are now increasingly requesting additional E&L data for early phase clinical trial material, especially when the products are nonstandard or lack a vendor-provided extractables package. These requests, which can put a hold on clinical trials, can be time-consuming and expensive.

Identification of the products and their attributes that are more likely to receive questions from the FDA during early phase clinical trials is possible. For these products, a streamlined E&L study design is described that helps companies answer or altogether avoid requests for early phase data. The study design helps companies to be proactive about gathering this 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 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 (SUS), due to the presence of plastic components that replace traditional stainless steel manufacturing environment. Each of these evolutions has focused on the data required for registration of a drug (e.g. NDA, ANDA, BLA). 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 extractables and

leachables 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 advice 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 phases 1 and 2. These requests are not only for clinical trial material including container closure systems, but also for manufacturing equipment and dosing components. Several programs were placed on clinical hold until this data is gathered, leading to delays and increased costs.

Given the expense of undertaking E&L studies and the length of time it takes to perform them, this 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 this E&L information without significantly increasing development time and expense.

Fortunately, there are commonalities in terms of 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 requests. These are more likely to require E&L studies at an early phase when they have uncommon components, proprietary packaging, the vendor has not supplied an E&L data package or components have not yet been used in an approved product.

In response to the growing call for E&L studies during early phases and the need that these evaluations be cost-effective and as brief as possible, we created a condensed experimental design to identify extractables and leachables in early phase clinical trial material. We have 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.

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

Extractable ≠ Leachable: Extractables don't always leach, leachables don't always extract.

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; compounds with known risks have toxicology data to refer to.

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 the SCT.

SOURCES

- **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**
- **SUS**
- **Manufacturing equipment**
- **Shipping materials**

REGULATIONS AND GUIDANCE

The FDA has similar requirements for container closure systems and equipment, for both small molecule drugs and biologics. To date, other than to say that companies need to perform E&L analyses, the agency 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)**

Instead, for what to measure, how to perform the studies and levels at which leachables become a safety concern, companies rely on industry best practices and CROs for advice. These

include PQRI, which has best-practices documents for inhalation devices, parenterals, and ophthalmics, ICH, USP, and BPSA and BPOG, with guidance about bioprocessing equipment and SUS.

Taken together, these sources deal with the data and information required to submit a final registration for an NDA, PLA or NADA, but don't outline the requirements that might be necessary earlier in the development process.

CLINICAL TRIAL MATERIAL: THE NEXT STEP IN E&L STUDIES

A company typically starts its E&L analysis at the end of phase 2, as the container closure system is chosen and the manufacturing process is being finalized. It then generates leachable stability data during phase 3. A thorough E&L program can take six to 18 months to generate the data necessary for registration filing. This timeline makes it challenging to do a complete E&L study during the much shorter length of phase 1 and 2 trials.

We 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, we've worked with a large number of programs that received regulatory requests for E&L evaluations and/or data during phase 1 or, in some cases pre-IND. In some cases, the FDA stated that USP testing was insufficient for performing a risk assessment. A significant portion of these programs was placed on clinical hold pending generation of this data.

REGULATIONS FOR CLINICAL TRIAL MATERIAL

While specific regulatory requirements are vague, a Dr. Ingrid Markovic of CBER said, in a 2014 presentation, "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."

These comments underscore the challenge associated with performing E&L in the early phase. Typically, while it may be a good idea to generate the data to have a better understanding of potential future challenges and improve quality, it is not required for the purposes of evaluating safety "unless so deemed warranted." The question is, what do regulatory authorities mean by "deemed 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 is likely to get a request from the FDA for E&L data during phase 1.

Products getting requests tend to be in the high-risk category identified in the FDA guidance document for container closure systems.² The exception to this has been inhalation products, which tend not to get requests, possibly because of information that the manufacturer makes available to the FDA.

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	PRODUCT TYPE	PRODUCT ATTRIBUTES
Additional requirements	<ul style="list-style-type: none"> • Non-aqueous formulations • Unique syringe configurations • Implantable devices • Injection cartridges • Infusion sets 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Aqueous based formulations • Typical stopper/vial configurations • pMDIs • Oral formulations • Lyo-based formulations 	<ul style="list-style-type: none"> • 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

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. Then they are tested with a variety of analytical methods, such as HPLC. It allows comparison of two possible components (e.g. stoppers) in terms of compatibility and leachables.

This standardized testing comes with a low risk that an unknown leachable will show up later on. It requires significant up-front time and cost to generate the data and internal resources to maintain and perform 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 supplies 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 that should be gathered prior to selecting material includes whether there is a DMF, whether the component has been used in a successful filing and what testing was performed on the components for release.

This is the recommended route for early phase products. Vendors should be evaluated to assess which one offers the best extractables package. If two components are equal in terms of functionality, it usually makes sense to pick the product with the

better extractables package because it lowers risk. It is advisable to choose well-characterized materials. The one drawback is that there could be unknowns above the SCT.

The typical experimental design that manufacturers use to generate data requires a lot of effort. As with category 1, leachable data is not normally required as extractables are taken as worst-case leachables. If leachable studies are desirable, 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 such ‘bad actors.’

CATEGORY 3: LACK OF EXTRACTABLES DATA FOR A NONSTANDARD FORMULATION

These products are the ones 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. The company does 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 (INFUSION SETS, PUMPS, IV BAGS)

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 early phase trials. A thorough E&L evaluation can take 18+ months and cost as much as \$100,000-500,000, which doesn’t work with the shorter length and limited budget of an early phase program. So how do we design a study that is still based on good science and focused on patient safety while addressing the timeline and cost constraints of early phase development?

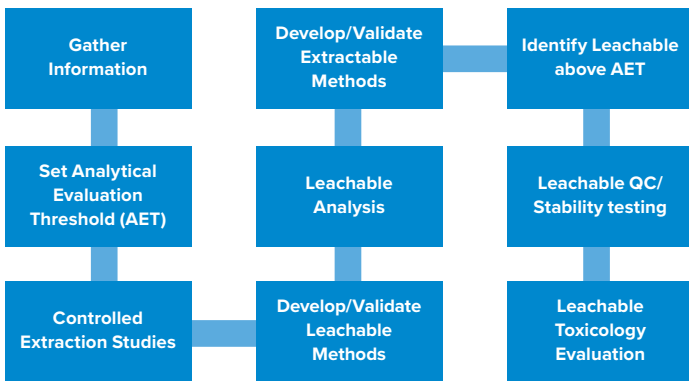
CONDENSED EARLY-PHASE E&L STUDY DESIGN

The standard, late-phase E&L study design begins with information gathering, followed by a determination of SCT/AET for materials, extractable studies and then leachable studies.

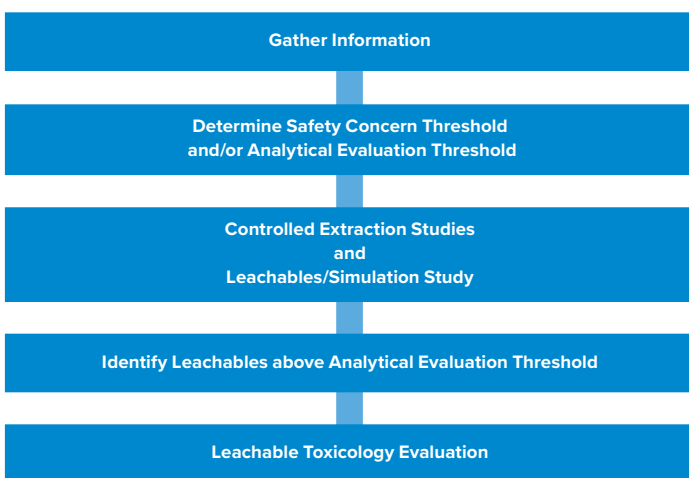
We have pared this design to make it phase appropriate while still providing high-quality data that lowers risk and answers the potential questions that a company might get from the FDA. We have used this study design successfully dozens of times, especially for those products placed on clinical hold.

The first two steps are the same: gather information and set analytical level. The third step has extraction and leachables studies performed in parallel instead of in stepwise fashion. It

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Process for conducting an Extractables and Leachables study



Process for conducting an early-phase Extractables and Leachables study.

allows us to analyze all of our extraction samples, along with simulation leachable samples or actual leachable samples (if the client already has some available from earlier R&D or preclinical work) to generate that data simultaneously. Then we identify potential leachables in all these samples that are above the AET. The final step is to do the toxicology evaluations on these leachables.

Extractables program: We perform asymptotic 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 unlikely to be leachables. Extractables are analyzed using HPLC, gas chromatography, ICP for metals and other techniques.

Leachables program: Early phase drug products generally have a shorter shelf life, perhaps 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 drug product and placebo in the container closure system to be tested under normal and accelerated conditions.

Then we age or stress simultaneously, or start the leachables even before initiating extraction studies, to generate extractable samples and leachable samples that we can analyze concurrently. Additionally, we test placebos and the forced degradation of the API.

Since we're running everything together, we perform subtractive fingerprinting between the different samples for each analytical technique. For example, we generate our HPLC profiles for the extractables and leachables in the API. We might see 40 extractable peaks, but only three of those peaks show up in the leachables. That means we don't have to identify all 40 of the extractables because the data show that 37 don't leach. Instead, we focus on the three that showed up 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, confident that those are the actual leachables.

CASE STUDY 1: NON-AQUEOUS VIAL/STOPPER

We used this compressed experimental design to analyze a vial/stopper configuration for which the stopper was nonstandard, 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 of the API, which was a specialty compound, were unavailable; the API concentration in the drug product was low enough that we assumed, from a risk standpoint, that it wasn't going to alter the leaching profile. We stored samples for two months at the normal storage temperature (5°C) and at room temperature (25°C) as a worst-case scenario, then analyzed the leachable samples concurrently with extractable samples and API and drug product.

Results: There was a large number of extractables, which we expected since one of the extraction solvents was cottonseed oil. Many of these were unknowns. Fingerprinting revealed only two leachables above the SCT and both correlated with known extractables. At 25°C, 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. The 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

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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, however, 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 37°C, a temperature that mimics the state of having the equipment next to the body.

Results: Given that the infusion sets were constructed of five different polymers, multiple extractables were observed, many of which 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. Extractables and leachables 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 QbD principles into drug development from the early phases, thus lowering overall risk and ensuring patient safety. The study design helps companies answer or, in some cases, altogether avoid questions

from the FDA during phases 1 and 2 that could lead to a clinical hold being placed 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.

ABOUT THE AUTHOR

Wayland Rushing, PhD, is director of scientific affairs at EAG Laboratories. He is a technical expert in CMC program design, analytical development and regulatory submissions. Dr. Rushing is a subject matter expert in HPLC and GC method development and validation, E&L program design and regulatory submission requirements. He has drafted IND and NDA submissions and assists EAG clients in responding to FDA deficiency letters.

Over his 16 years as a scientific advisor with EAG Labs, Dr. Rushing has led CMC development programs for biopharmaceuticals, including parenterals, inhalation drugs, and other medicines with complex delivery systems.

ACRONYMS

AET: Analytical evaluation threshold

DMF: Data master file

GC: Gas chromatography

SCT: Safety concern threshold

USP: US Pharmacopeia

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