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Implementing Extractables & Leachables into Quality Control Testing Programs

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Introduction

One of the many challenges with Extractables & Leachables (E&L) programs is encountered when testing transitions from the lab to a routine QC environment. Initial E&L studies performed by specialized labs with equipment and personnel may not be conducive to routine QC testing. Understanding the limitations and challenges of the routine QC environment is key to avoiding issues down the road. This whitepaper will cover the following areas, along with representative case studies:

- **QC Method Development:** Designing the development with a QC lab ito ensure success.
- **Method Validation:** Performing validations for E&L methods & common challenges.
- **Stability Programs:** Implementing stability testing and interpreting data.
- **Release Testing:** Testing final product vs. testing incoming components.

Background

The initial steps of an E&L study are performed using generic scanning methods utilizing specialized equipment in an R&D lab environment. These methods are used for the determination and identification of the E&Ls observed. An E&L program will then be required to move from the R&D lab and into the QC lab. The two areas you may be required to institute for QC testing are incoming release testing of components and release and/or stability testing on your final product or API.

Incoming Component Release Testing

You may be required to set up incoming testing on the container or closure components depending on the results of the controlled extraction studies and the testing performed by the manufacturer. These methods should be validated in accordance with ICH guidelines:

Quantitative Method

- Accuracy, Precision, Linearity, Specificity, Sensitivity, & Limit of Quantitation

Limits Test Method

- Specificity & LOD

Leachable Test Method

Establishing a QC leachable method may not always be required. There are multiple cases where it may be possible to justify not establishing leachable QC testing, such as:

- No detectable extractable peaks. If no peaks are observed, it is possible to justify not pursuing additional testing.
- All extractable peaks are reported below the Analytical Evaluation Threshold (AET) and safety concern.
- No leachables are reported above reporting threshold.
    - Extractables and/or leachables found have no toxic concerns.
    - Extractables and/or leachables identified above the safety concern threshold were evaluated by QSAR analysis or a paper toxicology assessment.
- If QC leachable methods are required, the methods were validated in accordance with ICH guidelines. Leachables are considered impurities in the final Drug Product (DP) and the method should be validated identically as one would validate a DP impurities method.

Challenges of E&L Methods

Due to the unique nature of E&L and the methods typically employed, there are many challenges associated with establishing QC testing methods.

On challenge is that E&Ls may not behave as API/DP related impurities. Leachables can be a variety of compounds ranging from small polar solvents to large macromolecules. As a result, behaviors can be substantially different than the “normal” impurities.

Another challenge is setting “typical” acceptance criteria for the method validations based on similar criteria used for DP related impurities. Critieria should be set on the required performance of the method and the limitations associated with it. Method development may need to be extensive and complex, as all leachables may not be able to be identified.

The final challenge is analytical reporting levels can be significantly lower than ICH impurity levels. It is not uncommon for leachables to be 10-100X lower than impurity

reporting levels. API and formulation impurities may not be observable or could interfere with leachable peaks.

It is also not uncommon to perform sample concentration steps in order to obtain the needed AET. The concentration can range from 2-100X, which can lead to challenges with formulations. The identified leachables may not have any commercially available standards making validating methods difficult.

Method Validation Challenges

Specificity

API/DP degradants can cause significant issues due to the lower levels which leachables are required to meet. It is not uncommon to observe more API/DP related impurities than the normal impurity methods monitor. As a result, it is highly recommended that aged API/DP is used to track these impurities. If aged material is not available, stress the API/DP to artificially generate impurities.

Formulation/placebo impurities need to be accounted for as well. As with the API/DP impurities, it is not atypical to observe more excipient related peaks than expected.

Coelution of extractables/leachables can be a challenge. In some cases, the leachables monitored may have extremely similar chemical structures, making their chromatographic separation challenging. In some cases, it may not be possible to completely separate the leachable.

Accuracy/Precision

Non-homogeneous samples are a challenge. Whether testing DP, or extracts, the variance in the samples can be significantly greater than expected for API/DP related impurities. This can make performing sample precision tests more challenging as it can result in the variance of the samples rather than the method.

Traditional precision testing is typically performed by preparing multiple replications from lots of material. However, leachables may not be present in the lot until it has aged.

Using homogenized samples can be a preferred way to perform both accuracy and precision testing of the method. This would involve preparing three levels across the range of the method prepared in triplicate. The precision is determined by calculated the %RSD of the recoveries.

Standards

Standards of the leachables are not always available. As a substitute, internal or surrogate standards may be used.

Surrogate or internal standards may not mimic behavior of actual extractables and leachables and may cause issues for the method during routine testing.

Choose the appropriate standard based on known target compounds.

If a range of leachable is monitored, it may be appropriate to use multiple standards to cover the potential range of the various leachable compounds.

Wider acceptance ranges may be justifiable based on the method performance and the testing intent.

Linearity

Some of the analytical techniques are inherently non-linear and will require special treatment. This can be accomplished by transforming the responses to generate a linear curve, or fitting the curve with a non-linear regression analysis. These techniques may be able to fit with a linear regression under smaller ranges of use and approximate a linear response. Some of the common techniques which can generate non-linear curves are Mass Spectrometry, Corona Aerosol Detector (CAD), and Evaporative Light Scattering Detector (ELSD).

Solution Stability

Some extractables and leachables are unstable or reactive, making monitoring and setting solution stability ranges a challenge. For example, the antioxidant Irgafos 168® readily oxidizes. It is difficult to control or prevent the oxidation from occurring and is commonly accepted that if you observe one you will observe the oxidized form, as well.

Stability Programs

Stability programs for leachables should be established per ICH Q1 guidelines, testing under nominal storage and accelerated conditions. However, data interpretation can be more complex and may need to be evaluated separately from normal API/DP related impurities.

Migration kinetics and solubility/positioning are the two main forces which determine if a compound will leach into a drug product.

Regression analysis can be used to model the rate at which the leachable appears, but the resulting kinetic curves can be significantly different than typical reaction kinetics.

Extractable to Leachable Correlation

One of the main goals of an E&L program is to establish a correlation.

Enough data must be generated to directly relate the observed leachable level to the known extractable level of the component.

For example, based on the data sets, it may be possible to correlate that if a component has a compound that extracts 30 µg, this could equate to a total of 2 µg of the component leaching into the product.

If it is possible to establish an extractable to leachable correlation, it may be possible to either reduce or eliminate the leachable testing, and establish control of the leachable by controlling the extractable in the incoming material.

Summary

E&L methods can pose a series of challenges when they transition from the R&D environment into routine QC testing. It is important to understand these challenges and limitations prior to implementing to avoid costly delays. Eurofins BioPharma Product Testing can support E&L testing to help you overcome these challenges.