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How to Evaluate Manufacturer-Provided Extractable Information

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Abstract

Purpose

Extractables and leachables (E&L) is a challenging topic to address during product development. A successful E&L program depends on Container Closure Integrity system design. The first critical step is the initial material characterization (of the container/closure system) to understand what can migrate into the final drug product as a leachable. If the data from these studies is insufficient or not applicable for a sponsor's product, it can lead to regulatory delays or recalls. Most of the container/closure systems used today are not proprietary and are purchased from component manufacturers. As part of a service to their clients, many providers offer extractables information on their products. However, the usefulness of this information can vary widely from manufacturer to manufacturer. The challenge for sponsors is to understand what information is needed, what questions to ask vendors, and how to evaluate information for the specific application. This whitepaper will walk through the process for ensuring the correct questions are asked and how the information should be evaluated.

Methods

A step-by-step process will be presented that will enable companies to ensure they are asking the correct questions when interacting with their container/closure vendors. An example risk assessment and gap analysis process will be presented that cover how data can be evaluated against a sponsor's specific drug product.

Results

Representative case studies will be presented in applying the process to data provided by the component manufacturer.

Sources of Extractables & Leachables

- Primary packaging components
- Secondary packaging components
- Associated/dosing components
- Processing components
- Shipping materials

Regulatory Basis for Evaluation of Extractables & Leachables

The regulatory requirements for the evaluation of extractables and leachables are found within the Code of Federal Regulations (CFRs) The regulations indicate that the requirements for all contact materials) are the same.

Regulatory Guidance

Several guidances are available from the FDA which addresses extractables and leachables:

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

While the above information from the FDA addresses E&L studies, it does not go into specifics on how the studies need to be performed. For guidance on performing E&L studies, industry best practices documents can be used for designing studies. Some of the groups that have guidances available are Product Quality Research Initiative (PQRI), Bio-Process Systems Alliance (BPSA), and Biophorum Operations Group (BPOG).Additionally, the United States Pharmacopeia (USP) has drafted new chapters for guidance on E&L studies, including USP <1163> and USP <1164>

Background

Given the rise in E&L expectations, many component manufacturers have started providing extractables data on their materials. These data packages vary in the level of detail and in how the information is collected. This is not unexpected given the lack of regulatory guidance of requirements, no regulatory requirements for the component manufacturers to perform studies, and the manufacturers do not know all possible products and dosing regimens a company might use.

As a result, the usefulness of these packages can vary significantly. It is important for a company to have a process in place to evaluate the information provided by the manufacturer, and to determine whether the information is applicable to their product or if additional studies are necessary. The following is a summary of a detailed process which can be used as the main questions to ask and in how to evaluate the collected information.

Evaluation Process

Step 1: Questions to ask the Vendor
The key to starting an evaluation is to ensure you have the correct information. This requires going to the manufacturer and obtaining as much information as possible on the contact materials and materials of construction.

Is there a DMF?
Drug Master Files (DMFs) can provide a level of confidence in vendor materials. However, it needs to be understood that the FDA does not approve DMF's. A DMF suitable for one use, does not mean it will be found appropriate for other compounds.

Is there an extractables data package?
Some manufacturers have started extractables programs on their materials and have made these packages available to clients. Some manufacturers provide a limited package free of charge, while others have packages available for purchase.

Has the component been used in a successful filing?
This allows for some comfort that the material is being used commercially. As with the DMF caveat, the FDA will review the component in regards to your specific drug product (DP) and application.

Are multiple resin sources available for polymeric components?
Some manufacturers allow for the use of polymeric resins from multiple sources. This can complicate the extractables profile, as each source is unique. Extractables data on each resin will be needed.

Are there different grades of resins?
Grades of polymeric resins can have a direct impact on extractables profiles. When choosing a polymeric component, ensure that the decision is based on quality, not solely on pricing.

Are all components made in the same facility/line?
If components are made in multiple lines or facilities, then an extractable package should be performed on each material.

What testing is performed on the components for release? How is variation controlled? Does the vendor test the components for extractables as part of a release test?
These can be important, especially if your product has a high risk for potential leachables. It can help minimize variations in observed peaks.

Will they implement a supply agreement?
This is critical so the customer is notified of any changes in the process. Polymeric components are not manufactured in accordance to cGMP in many cases, as a result more variation can be tolerated.

Step 2: Perform Risk Assessment and Gap Analysis on the Information Provided. Once the information from the above questions is received, it is important to evaluate the data with regard to the specific drug product and application. Without a good evaluation process, it can leave the company open to higher risk that there could be delays or surprises in development.

Were chemical extractions performed or list of "possible" extractables given based on manufacturing process?
Some vendors do not perform testing on their components, but rather provide information based on the formulation of the component. Information based solely on formulation is of limited use, as the specific extractables are often not easily predicted and impurities in the formulation products are not well characterized even though they can often be a source of leachables.

How were the chemical extractions performed?
A typical extraction profile is as follows:

- **Multiple Solvents:** These cover a broad range of solvent polarities, including ones representative of the drug formulation.
- **Multiple Extraction Techniques:** Consider the proper extraction techniques to use, such as reflux, microwave, soxhlet, and various sample preparation approaches (whole, cut, ground).
- **Asymptotic Extractions:** Samples are taken from the extractions over time and analyzed to ensure that the maximum level of extractables are being removed. Care should be taken to avoid being too aggressive on the extractions, to

avoid physically or chemically altering the product being extracted.

Were the analytical methods used in the analysis appropriate/ validated?

The potential extractables in polymeric material can have a wide range of chemical properties. It is critical that the analytical methods used cover the full range of potential compounds

- HPLC – Semi-Volatiles and Non-Volatiles
- GC – Volatiles
- ICP – For metals
- Special Case Extractables
  - Poly-aromatic Hydrocarbons (PAH's)
  - Nitrosamines
  - 2-Mercaptobenzothiazole

Can the analytical methods detect low enough levels?

This is tone of the most challenging and common deficiencies of of data packages provided by manufacturers. Analytical methods do not detect low enough levels for a specific drugs product's formulation dosing regimen. See the following section for calculation of the Analytical Evaluation Threshold (AET) and the Case Study examples.

Evaluation of Supply/Shipping chain

While rare, shipping materials have been known to be the source of leachables. Additionally, how the materials are packaged and shipped from the manufacturer are important to understand.

Commonly Observed Gaps & Deficiencies

- Solvents used in extraction studies not representative of the Drug Product (DP) formulation.
- Asymptotic extractions were not performed.
- Reporting level of the data is higher than the determined AET.
- Insufficient number of analytical methods used in analysis of extracts.
- Inadequate detail in reporting extractables.

Safety Concern Threshold (SCT)

- SCT is the level below which there is negligible risk associated with the toxicity of the extractable or leachable compound based upon dosing. This only applies to unknowns and is presented as a Total Daily Intake (TDI). The PQRI recommends 0.15 µg/day for inhalation products and 1.5 µg/day for parenteral products

Using the PQRI's suggested Safety Concern Threshold, one can convert to an equivalent analytical level for a specific product. The conversion takes into account the drug's specific dosing regimen and the number of doses which are in each container/ closure system.

Case Study #1

One of the most critical issues in extractable evaluations is ensuring that the data used to make decisions meets the expectations based on best practice recommendations. This requires evaluating the information for the specific drug product formulation and the worst case scenario dosing regimen The following case study demonstrates that information provided by a manufacturer may be adequate for some cases but not acceptable for others.

The product is a parenteral with an aqueous formulation (same formulation for both scenarios) in a 20 mm glass vial with a 3.0 gram rubber stopper. The stopper manufacturer has provided an extractables package that used analytical methods with a quantitation limit (QL) of 5 ppm. Asymptotic extractions were performed using water and IPA. We will review the package against two different container closure scenarios: The first scenario will be 5 mL fill at one dose per day with one dose per vial. The second scenario will be 5mL fill at one dose per day with 20 doses per vial

1. Extraction Solvent(s) vs. DP Formulation

The extraction solvents used (water and IPA) cover the polarity range of the DP formulation (aqueous). In terms of extraction solvents used, the data provided by the manufacturer is applicable to the product.

2. QL of the extraction methods vs. AET needed

Applying a 1.5 µg/day SCT, based on the PQRI current recommendation for parenteral products, we are able to compare the expected reporting level against the data provided by the manufacturer.

As can be seen in the table, for scenario 2, we are able to use the data provided by the manufacturer for evaluating the extractables profiles, however in the case of scenario 1, the analytical methods used did not detect low enough levels.

Case Study #1 Summary

The data provided by the manufacturer can be used for the evaluation in scenario 2. However, the data is not adequate for evaluating against the dosing regimen in scenario 1. As a result, it is likely that additional studies would

be needed to achieve the lower QL required by the AET.

Case Study #2

For this example we will evaluate another parenteral product with an oil based formulation (cottonseed oil) in the same container/closure system as in Case Study #1. The stopper manufacturer has provided an extractables package that used analytical methods with a quantitation limit of 5 ppm. Asymptotic extractions were performed using water and IPA.

We will review the package against a configuration of 5mL fill at one dose per day and 20 doses per vial.

For the evaluation of the data we are going to evaluate the same two scenarios as we did in case study #1:

1. Extraction Solvent(s) vs. DP Formulation

The extraction solvents (water and IPA) are not representative, nor do they cover the polarity range of the formulation (cottonseed oil). As a result they would not be predictive of leachables in the product.

2. QL of the extraction methods vs. AET needed

Applying a 1.5 ug/day SCT, based on the PQRI current recommendations for parenteral products, we are able to compare the expected reporting level against the data provided by the manufacturer.

As can be seen in the table, the QL (5 ppm) and extractables data provided by the manufacturer does detect low enough compared to the AET required for the drug product.

Case Study #2 Summary

Based on the extraction solvent mismatch, the data provided by the manufacturer cannot be used in evaluation for the drug product. New studies would be required.

Summary

It is important to use the correct information and process to ensure that the development process is not delayed as a result of an E&L issue. By having the right information available, it is possible to avoid some of the most common pitfalls that can result in regulatory delays for products by having a well-defined process in place when choosing the container/closure system.

REFERENCES:

[1]Ng, Linda (CDER/FDA), "Current Regulatory Recommendations for Leachables in Ophthalmic Drug Products," Thresholds and Best Practices for Parenteral and Ophthalmic Drug Products, 22- 23 February 2011, Bethesda, MD.