Insight into the design of optimal extractable and leachable studies for regulatory compliance and accelerated drug development

GatewayAnalytical

Aptar pharma

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Abstract

Every New Drug Application must include an extractables and leachables study to demonstrate that the drug formulation is fit for purpose. Several guidance and recommendations documents provide insight on how to perform these analyses and which methods to use, but as each drug combination product is unique, Pharma manufacturers must adapt to the requirements of their drug.

In this poster, we dwell into the process to follow to perform robust extractables study and leachable studies. We describe the method used to perform semi-quantitative and quantitative studies while allowing for identification of the leached compounds, to provide pharma partners with a complete dataset that demonstrates the drug's safety while supporting regulatory filing.

We also present a case study demonstrating how extractable and leachable studies can be adapted by drug delivery partners to created simulated leachable studies. Such approaches can greatly support pharma partners in anticipating the result of their actual leachable studies and support them in choosing the most appropriate closure solution for their drug.

Introduction

As the cost of drug development continues to rise and regulatory expectations become more stringent, pharmaceutical companies are under increasing pressure to mitigate risks associated with their products. It is incumbent upon these companies to demonstrate that their combination products, including packaging, are safe for patient use. This involves proving that the packaging is fit for its intended purpose and does not adversely affect the drug formulation.

A critical factor in this assessment is the chemical compatibility of the drug formulation with its packaging. Many injectable drugs are packaged in glass vials sealed with rubber stoppers, materials that are known to release extractables and leachables. Therefore, understanding and managing these potential compatibility issues is essential.

To address this need, pharmaceutical companies must anticipate potential compatibility problems and be prepared to provide comprehensive data to meet regulatory requirements. This proactive approach ensures that all potential risks are identified and mitigated, thereby supporting successful regulatory submissions and ensuring patient safety.

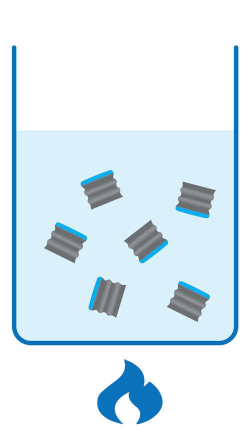
Extractables and Leachables (E&L) studies are essential for ensuring the safety and effectiveness of drug products. **Leachables** refer to chemical substances that migrate from packaging into the drug during storage or use, potentially impacting its safety or efficacy. **Extractables**, on the other hand, are chemicals that leach from packaging materials into a solvent under controlled lab conditions, which might eventually end up in the drug product.

For the study design, it is crucial to simulate conditions that reflect the product's actual storage and use environments. Setting an **Analytical Evaluation Threshold (AET)** helps establish the concentration at which a detailed safety review is needed.

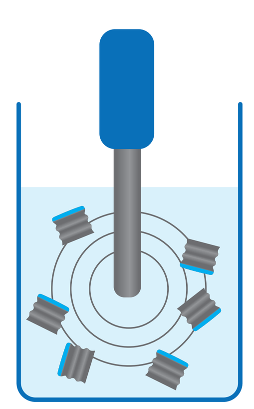
Though not always required by regulations, **simulation studies** are invaluable. They help predict potential issues and reduce development risks, especially for products with coatings, like PremiumCoat®, where conventional extractables testing might not capture all the real-world performance aspects. This is illustrated with a case study perform by Aptar Pharma, focusing on evaluating the effect of the ETFE film in mitigating the transfer of leachables into the drug product. Through a custom experimental design and leveraging state-of-the-art analytical methods, we allowed the demonstration of the barrier effect of the ETFE film. This result can support drug manufacturer in anticipating the final leachable profile with their drug products, and mitigating risks of incompatibility are earlier stages of the development process.

Technique Used

Extractable techniques

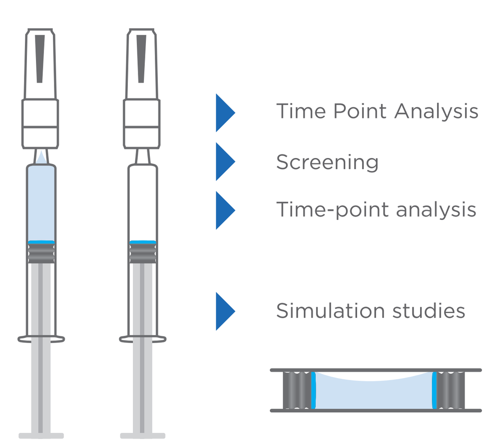


Refluxing



Sonication

Leachable Techniques



Real-life packaging

Simulated packaging

Analytical methods

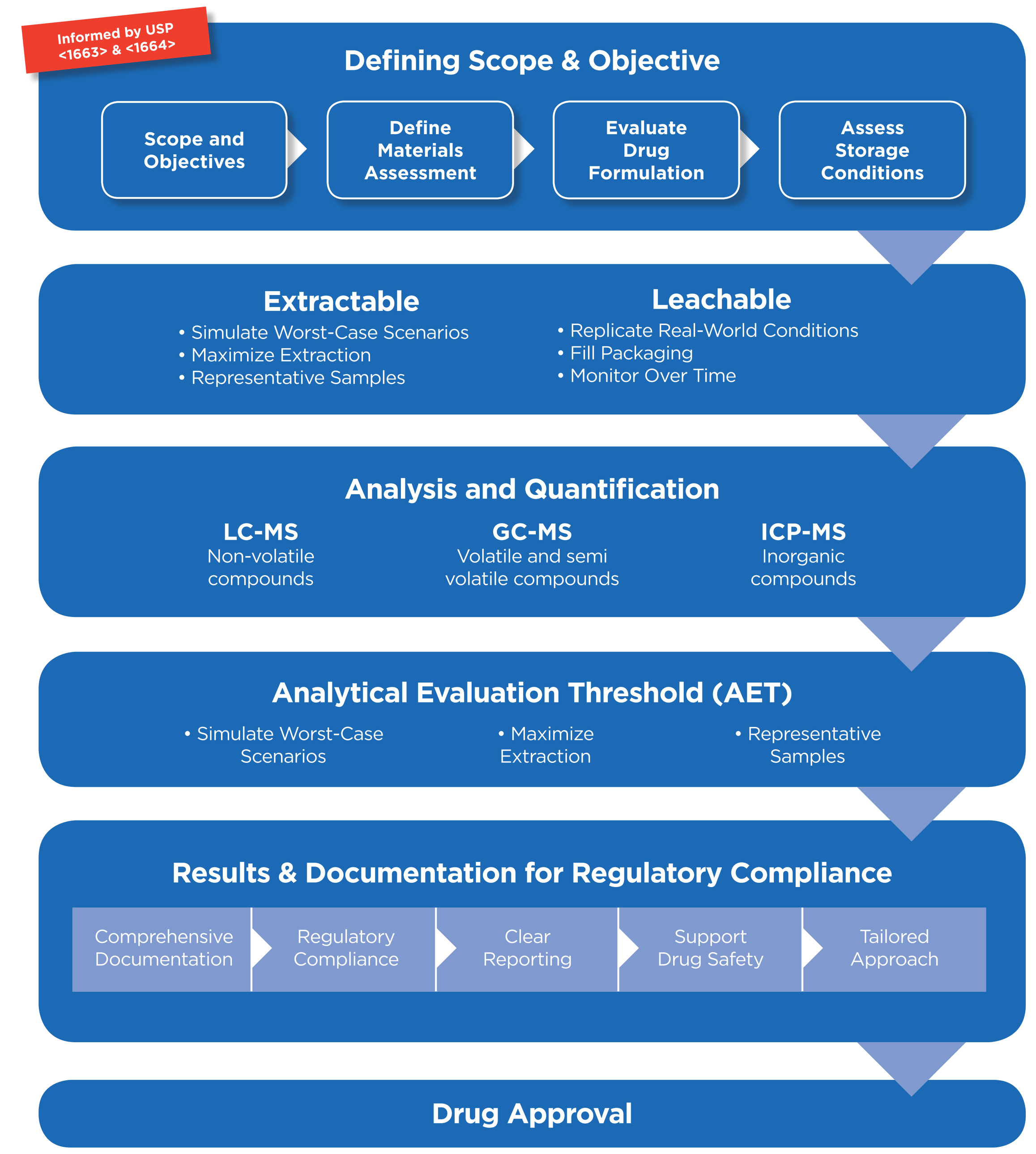
Gaz Chromatography Mass Spectrometry (GC-MS)

Liquid Chromatography Mass Spectrometry (LC-MS)

Inductively Coupled Plasma Mass Spectrometry (ICP-MS)

References: USP Chapter <1663>: "Assessment of Drug Product Packaging for Extractables and Leachables."
USP Chapter <1664>: "Assessment of Drug Product Packaging for Leachables and Extractables."
PQRI (Product Quality Research Institute).

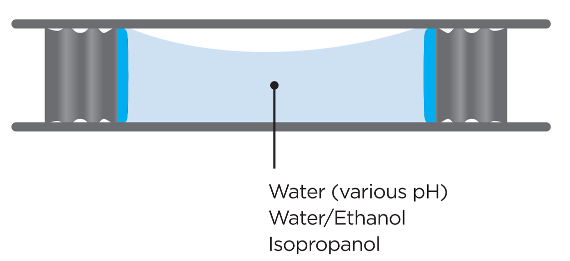
How to Design E&L study



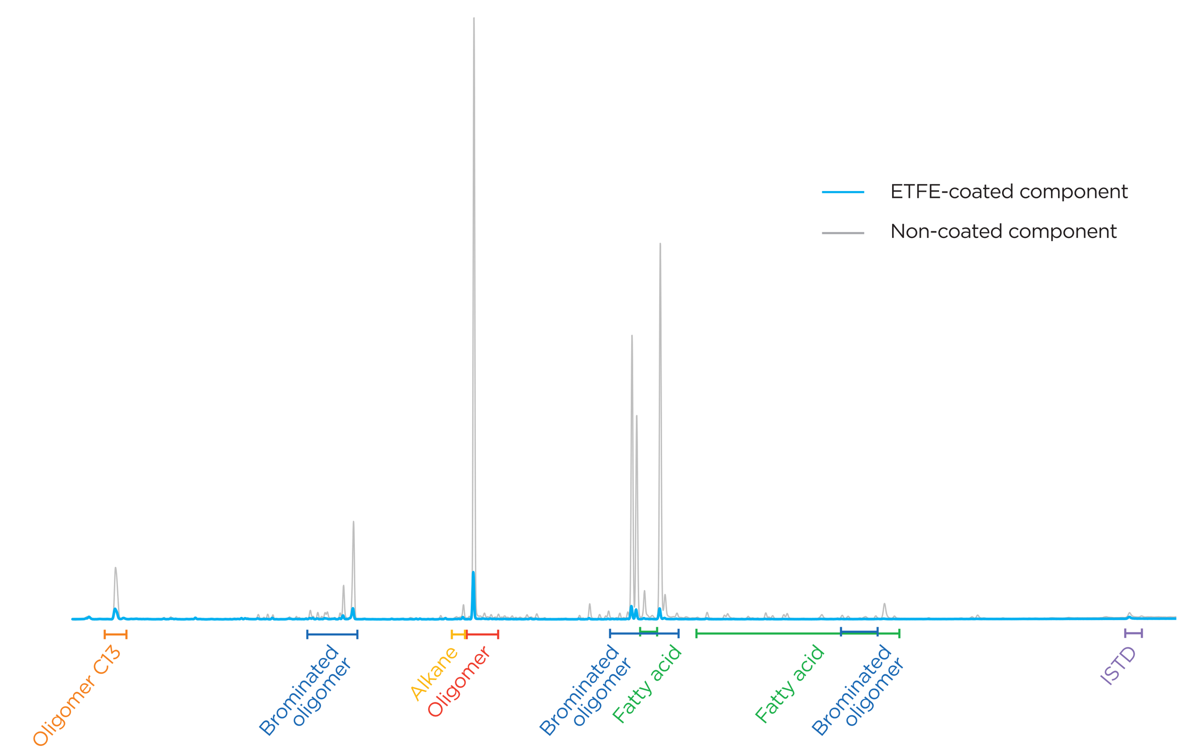
Case study

Simulation study to assess the efficiency of the ETFE film coating on bomobutyl PFS plungers.

Simulated packaging setup and model extraction solvents to investigate potential leachable from closure component only.



Example of simulated leachable profile and compound identification



Conclusion

Extractable and Leachables studies are mandatory steps that every drug developer have to perform before getting its product approved on the market. Though several guideline exist and formulate recommendation on how to perform these studies, the responsibility of choosing the right strategy and method lies with the drug developers. Whether it is in the planning phases, for the choice of the extraction method, the choice of analytical method, the analysis of data or generation of documentation, drug developers can rely on the expertise of Gateway Analytical to perform GMP studies that are suitable for regulatory filing.

Extractable and simulated leachable studies can also be used as a risk-mitigation tool and help drug developer select the right packaging for their formulation. In this case study, Aptar Pharma performed simulated leachable studies to demonstrate that PremiumCoat® ETFE film-coated pre-filled syringe plunger outperforms its uncoated counterpart. Qualitative analysis allowed to identify the main class of compounds that were leached from the components, while quantitative analysis demonstrated that all compounds detected were drastically reduced with PremiumCoat®. These information are now readily available for drug developers to anticipate probable leachables and derisk their drug development process.