WHITE PAPER

Assessment of Extractables and Leachables Associated with Pharmaceutical Packaging

Introduction

Extractables and leachables studies are critical for maintaining the quality of your drug product during drug development and final batch release in accordance with GMP compliance. The testing process assesses whether the drug products could be exposed to any harmful leachable contaminants which could have a detrimental impact upon the safety and efficacy of the drug. Potential sources for leachable contaminants include: process equipment, primary packaging, label adhesive, printing inks or secondary packaging.

'Extractable' vs. 'Leachable'

Extractables are chemical compounds that can be a volatile, semi-volatile, non-volatile and elemental impurity, they can be extracted from a packaging system in a suitable solvent under optimum extraction conditions of time and temperature. Not all extractables end up as leachables. Extractables testing will be on the materials that will come in contact with the drug product during the manufacturing process.

Extractables are derived from a variety of sources and exhibit extensive chemical diversity such as chemical additives, monomers, secondary and tertiary packaging component migrants, hindered amine, hindered phenol or chemical substances on the surfaces of component fabrication machinery or other drug product manufacturing systems.

Leachables are volatile or non-volatile chemical compounds that leaches into the drug product formulation from a packaging component over the shelf-life of the drug product. They can be assessed under normal conditions or during accelerated studies. Leachable testing will be performed on final product up to and including end of shelf life.

USP <1663> and <1664> emphasize the quality of packaging systems used to store drug products. Initially, only the final packaging systems were the focus, but it was later extended to include packaging system, packaging components and also their materials of construction.[1-3]

From the characterization studies of these Extractables and Leachables, specific controls for a packaging system, its components and the materials of construction can be achieved. The General Chapters for packaging systems have undergone changes over the years with incorporation of a new regulatory approach each time.

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Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems <1663> and Leachables <1664>

Establishing the suitability of plastic packaging systems for therapeutic products involves multiple tests and testing procedures, as briefly outlined below:

- **Material screening:** Characterization of a packaging system's materials of construction to evaluate ingredients as probable extractables and potential leachables. Such a characterization facilitates the identification of materials that are suitable for use in packaging systems.
- **Controlled extraction (simulation) study:** Worst-case controlled extraction (simulation) study to determine the extent to which extractables may become probable leachables (for additional information.
- **Product assessment:** Actual-case measurement of confirmed leachables in the therapeutic product in the pharmaceutical packaging/delivery system intended for the commercial market.

Analytical techniques for extractables and leachables testing include:

- **Volatile and semi-volatile compounds:** Headspace Gas Chromatography Mass Spectrometry (HS GC-MS, e.g. TurboMatrix™ Headspace Clarus® SQ 8)
- **Non-volatile organic compounds:** Liquid Chromatography Mass Spectrometry (LC-MS, Flexar™ HPLC/UHPLC)
- **Elemental Impurities:** Inductively Coupled Plasma Mass Spectroscopy (ICP-OES or ICP-MS, e.g. Avio® 200, NexION® 2000)

Any impurity crossing the limit of Analytical Evaluation Threshold (AET) during extraction study requires attention during leachable study and this need to be calculated by following Formula:

AET = 1.5 ug/day x 1 day/No. of dose x 1 container/fill volume x uncertainty factor (0.5)

For semi-volatile and volatile extractables and leachables compounds, the inlet of a standard GC/MS is modified to allow for direct desorption of solid samples.

This method is efficient enough that multiple packaging options could be screened. The limits of detection here are often less than 1 ppm. This requires an instrument with high sensitivity, increased stability and above all, flexibility. Keeping this in mind, PerkinElmer designed an approach that provides the necessary trust across the entire workflow for volatile and semi-volatile compounds.[2]

HPLC or UHPLC are preferable method for non-volatile compounds. PerkinElmer Flexar HPLC systems provide robust, trouble free-operation and are perfect for routine analysis. You also have flexibility in your CDS (Chromatography Data Systems) of choice with either Chromera® or TotalChrom®. With the powerful, easy-to-use Chromera control and data handling software, you get increased range of configurations and the ability to fit your laboratory's application needs.

Elemental Impurities in leachables and extractables are best determined by ICP-OES or ICP-MS. These techniques are referenced in USP <233> [4] to detect trace metals in pharmaceuticals. Chapter <661.1> also introduces specifications for the elements aluminum, calcium, germanium, manganese, titanium, zinc and zirconium that are not identified as elements of toxicological concern in <232>/ICH Q3D. PerkinElmer offers a complete, integrated solution to elemental impurity testing including:

- Fast, safe, and cost-effective sample preparation equipment
- Intelligent sample handling that includes automated auto-dilution systems for elemental impurities methods
- Choice of best-in-class ICP-MS/ICP-OES and software solutions
- Enhanced Security™ ICP-OES and ICP-MS software to assist with 21 CFR Part 11 compliance and data integrity
- Complete analytical instrument qualification and validation services

References

1. <661.2> Plastic Packaging Systems for Pharmaceutical Use.
2. <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems.
3. <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging Delivery Systems.
4. USP <233> Elemental Impurities - Procedures.

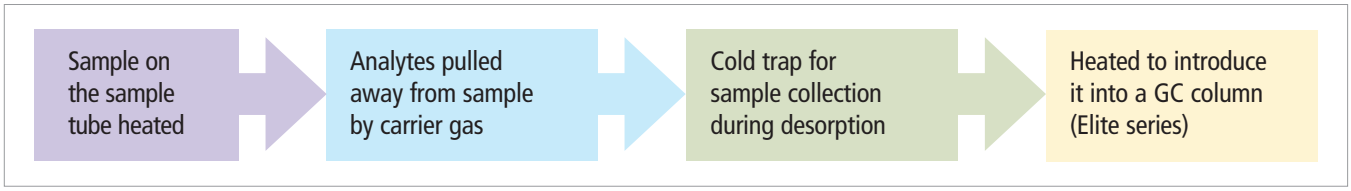

Figure 1. Inlet of a standard GC/MS.

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