image

Piramal
Pharma Solutions

INTEGRATED SOLUTIONS FOR EXTRACTABLES AND LEACHABLES

piramal**pharmasolutions**.com

INTRODUCTION

Studies of extractable and leachable components (E&L) within packaging systems and pharmaceutical container closures have become mandatory to meet the safety requirements for marketed medicines over the past two decades. The regulatory guidance for E&L provides only general recommendations to ensure safety. The development and analysis of E&L for inhalation, ophthalmic, and injectable drug products is challenging since studying them depends on the type of formulation and packaging material being used.

Background:
Extractables are compounds that can be extracted from the container closure system in the presence of a solvent. Leachables are compounds that leach into the drug product from the container closure as a result of direct contact with the formulation.

According to US Food, Drug and Cosmetic Act Section 501(a)(3): 'A drug is deemed to be adulterated if its container is composed in whole or part of any poisonous or deleterious substance which may render the contents injurious to health'.

Example of dosage from materials and associated risks:

DEGREE OF CONCERN ASSOCIATED WITH ROUTE OF ASMINISTRATION	PACKAGING COMPONENT DOSAGE FROM INTERACTION		
	High	Medium	Low
Highest	• Inhalation Aerosols & Solutions • Injections & Injectable Suspensions	• Sterile Powders & Powders for Injection	
High	• Ophtalmic Solution, Suspensions • Transdermal Ointments & Pathces • Nasal Aerosols & sprays		
Low	• Topical Solutions & Suspensions • Topical & Lingual Aerosols • Oral Solutions & Suspesions	• Topical & Oral Powders	• Oral Tablets & Capsules

The initial phase of the lyophilization process is the freezing procedure. Usually, the product is frozen beyond its freezing point. The lyophilizer then enters the sublimation procedure, also referred to as the primary drying phase, followed by desorption or the secondary drying phase. During this process, a vacuum is applied to the chamber and the shelves are heated in order to evaporate the water from the frozen state. The vials are then fully stoppered and removed from the lyophilizer.

The process is complicated and lengthy, but the benefits of a lyophilized product are well worth it. Aseptic handling is simplified with the ease of processing a liquid product. In a dry state, the product has enhanced stability which helps it resist degradation and transports easily. Another benefit of lyophilization is the rapid and easy dissolution of the reconstituted product. In all, PPS can provide complete lyophilization services beginning with formulation and ending with an attractive and cost-effective product.

ASSESSMENT OF EXTRACTABLES AND LEACHABLES

For the assessment of E&L, there are chapters in United States Pharmacopoeia and European Pharmacopoeia, which deal with the testing of plastic materials, including extraction tests. Since there are limited guidelines on E&L for final dosage forms, PQRI (Product Quality Research Institute) gives regulatory guidance for E&L analysis which is recognized by the FDA. PQRI has developed guidelines called OINDP for orally inhaled and nasal drug products and PODP for parenteral and injectable drug products.

Extraction of packaging material needs to be done at high temperatures, to obtain all possible compounds which can be extracted out from packaging material using polar, mid-polar and, non-polar solvents to mimic the drug product properties.

FACTORS TO BE CONSIDERED

- Construction materials of the system; surface treatments and/or processing aids; dosage form active ingredients and excipients; sterilization and/or other related processing; and storage conditions.
- Review composition of primary packaging components with vendors, obtain certificates of compendia compliance.
- Identify potential E&L with assistance from vendors, literature search – material safety data sheets (MSDS), technical data sheets
- Use of clean raw materials with minimal processing additives.

ANALYTICAL TECHNIQUES TO QUANTIFY DIFFERENT CATEGORIES OF COMPOUNDS

- Headspace Gas Chromatography Mass Spectrometry (HS-MS): Quantification for highly volatile compounds
- Gas Chromatography Mass Spectrometry (GC-MS): Quantification for semi-volatile compounds
- Liquid Chromatography Mass Spectrometry (LC-MS): Quantification for non- volatile compounds
- Ion Exchange Chromatography (IC): Quantification for anions and cations (inorganic or organic)
- Inductively Coupled Plasma Mass Spectrometry (ICP-MS): Quantification for elements including heavy metals

FACTORS TO BE CONSIDERED

Any impurity crossing the AET limit during extraction study requires attention during leachable study which can be calculated using the below formula:

$$\text{AET} = \frac{1.5\text{ug}}{\text{Day}} \times \frac{1\ \text{Day}}{\text{No. of dose}} \times \frac{1\ \text{Container}}{\text{Fill volume}} \times \text{Uncertainty factor (0.5)}$$

Currently the toxicological database of extractables is being compiled by ELSIE (The Extractables and Leachables Safety Information Exchange) starting with 15 priority compounds: antioxidants, cross-linking agents, lubricants, anti-slip agents, plasticizers, monomer, surfactants, acid scavengers, and starting material. Many times toxicological information is not readily available for specific substances.

CHALLENGES

- Method development of volatile, semi-volatile, and non-volatile compounds
- Development of extraction procedure for partially coated and non-coated stoppers
- Development of leachable method for non-aqueous products by GC-MS and LC-MS

Piramal Pharma Solutions has developed an extraction procedure for non-coated rubber stoppers using the Soxhlet extraction technique and an extraction procedure for partially coated rubber stoppers has been developed using incubation and direct heating techniques.

There are separate methods available with known scholarly papers to detect and quantify phthalates, hydrocarbons, volatile, and semi-volatile compounds. The analytical methods mentioned in various published articles recommend using GCMS column having 5%-phenyl, 95%-dimethylpolysiloxane as a stationary phase with physical dimensions as 30m (0.25µ × 0.25 mm).

To overcome the challenges with minimum analysis time and cost, Piramal Pharma Solutions has developed a single method on GCMS column having 5%-phenyl, 95%-dimethylpolysiloxane as a stationary phase with physical dimensions as 50m (0.33µm, 0.20mm) to detect all categories of compound in a single run by using GC-MS/MS.

This method is capable of detecting all possible potential extractables at a level of ~0.06 µg/mL and identifying unknown compounds using the NIST library.

A highly sensitive method has been developed on LC-MS/MS to quantify geno-toxic compounds like nitrosamines and toxic compounds like fatty acids at a level of ~0.001 µg/mL.

SUPPORT FOR EXTRACTABLES AND LEACHABLES STUDY

At Piramal Pharma Solutions, we believe in providing services with high quality and fast turnaround. With our mission of “Quality on time”, we aim to augment the human knowledge for evaluating and solving E&L-related challenges.

Development Strategies:

We understand the latest trends, requirements and pitfalls that potentially occur during development of E&L. Development includes:

- Packaging material COA evaluation
- Solvent extraction studies (varying polarity)
- Screening and identification with LCMS/MS & GCMS/MS
- Qualifying extractables as per vendor COA, PQRI, PODP, and USP guidelines
- Validation/verification of analytical methods
- Toxicity evaluation as per Derek Nexus updated software
- Conducting leachable studies

RESEARCH CAPABILITIES

Piramal Pharma Solutions has developed analytical methods for quantification of the below potential extractables by various techniques.

- Phthalates
- Nitrosoamines
- Elements
- Volatile /Semi-volatile organic compound
- Polynuclear aromatic hydrocarbons
- Antioxidants and elastomer additives
- Fatty acids

The scientists at Piramal Pharma Solutions reveal their knowledge and expertise in developing and validating methods not only for E&L but also for different types of finished dosage forms. Analytical instruments like GC/MS-MS, LC/MS/MS, UPLC and HPLC combined with 21 CFR part-11 helps to identify and quantify the E&L of packaging systems in drugs products. The stability chambers are maintained as per ICH guidelines to carry out leachable studies. Highly recommended software like the NIST library helps to identify unknown compounds which can leach out from the drug product during the shelf life.

In addition, qualified toxicologists assist to identify the toxic compounds and safety threshold with the help of Derek Nexus software. As a result of many years of experience, Piramal has developed a strategy for performing E&L studies which satisfy the PQRI and PODP requirements, presenting the client with a highly cost effective and efficient approach.

Contact our team today to learn more about Piramal Pharma Solutions' extractables and leachables capabilities for your next project.

Piramal Pharma Solutions is a contract development and manufacturing organization (CDMO), offering end-to-end development and manufacturing solutions across the drug life cycle. We serve our clients through a globally integrated network of facilities in North America, Europe and Asia. This enables us to offer a comprehensive range of services including Drug Discovery Solutions, Process & Pharmaceutical Development services, Clinical Trial Supplies and Commercial supply of APIs and Finished dosage forms. We also offer specialized services like development and manufacture of Highly Potent APIs, Antibody Drug Conjugation and are well versed in technologies such as Bio-catalysis, Route Scouting etc. Our capability as an integrated service provider & experience with various technologies enables us to serve Innovator and Generic companies worldwide.

Piramal Pharma Solutions

Piramal Pharma Solutions, Agastya Corporate Park
Kamani Junction, Kurla (West). Mumbai 400 070. India.
Email: contactus@piramal.com
Call: +91 (0)22 3802 3000

piramal**pharmasolutions**.com