DAICEL

DAICEL PHARMA SERVICES

ECONOMICAL • FAST • FLEXIBLE

EXTRACTABLE & LEACHABLE STUDIES

YOUR GLOBAL GMP
ANALYTICAL SERVICES PARTNER

www.daicelpharmaservices.com

OVERVIEW

In recent years, the U.S. Food and Drug Administration and European Medicines Evaluation Agency (EMEA) has expressed concerns over potential toxicity and efficacy effects of chemical entities, organic and inorganic, released into drug products through direct and indirect exposure to components used in manufacturing and packaging. These chemical entities are referred to as **Extractables and Leachables (E&L)**.

The USP has published several chapters regarding E&L studies for primary, secondary, and tertiary components in manufacturing and packaging. Due to the relatively short time a finished product is exposed to manufacturing components, manufacturing studies tend to focus on primary components involving Extractables. Packaging studies, as defined by USP, include individual parts of systems that have a specific function in delivering or storing the drug product. Because they have much longer exposures to finished drug products, Extractable and Leachable studies on primary, secondary and tertiary components are required.

EXTRACTABLES

Extractables are defined as any chemical entity, organic or inorganic, released from manufacturing and packaging components into an extraction solvent under exaggerated conditions of time and temperature. Extractables have the potential to leach into drug products, thus becoming a Leachable, and sources of such entities must be monitored. Customary manufacturing components include vessels, tubing, valves, connectors, and filters where PTFE, silicon, stainless steel, ceramic and various plastic polymers are most commonly used. Packaging components for containers and devices include glass, natural or synthetic rubbers, polyethylene, polyethylene terephthalate and polypropylene.

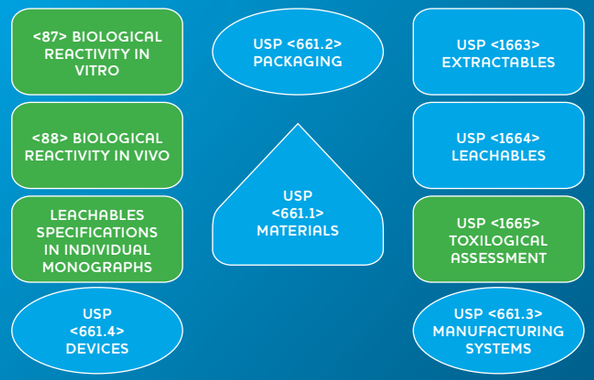
LEACHABLES (AND MIGRANTS)

Leachables are defined as any chemical entity, organic or inorganic, unrelated to, but present in a packaged drug product because it has leached into the drug product from a packaging/delivery system, packaging component, or packaging material under normal conditions of storage and use or during accelerated drug product stability studies.

Leachables involve the direct action of the drug product on the source of the leachable. Typically, this source is primary and secondary packaging, which serves as a barrier between the packaged drug product and other potential sources of foreign chemical entities (such as tertiary packaging and ancillary components).

Migrants are differentiated from Leachables in that they accumulate in the packaged drug product after crossing a physical barrier, such as that provided by primary and secondary packaging, not due to the direct action of the drug product on the source of the migrant. Typically, migrants are derived from secondary and tertiary packaging and ancillary components. Migrants are still foreign substances in the packaged drug product and must be assessed in the same manner as Leachables. However, the means by which Leachables and Migrants develop within the packaged drug product may be different, requiring different extractable studies to address and manage manufacturing and handling issues.

E&L TO SUPPORT USP CHAPTERS



GLASS DELAMINATION STUDIES

Packaging materials tested:

- ✔ Glass vials
- ✔ Rubber stoppers
- ✔ HDPE bags
- ✔ LDPE containers
- ✔ PP containers
- ✔ EPDM packaging
- ✔ Gaskets and O-rings

Drug products tested:

- ✔ Inhalants
- ✔ Ophthalmics
- ✔ HDPE bags
- ✔ Parenterals/Injectables
- ✔ Oral vaccines
- ✔ Topicals

Daicel Pharma Services E&L Studies are performed in a US-FDA audited analytical facility.

OUR APPROACH

KNOWN IMPURITIES

- All analytical activities will be performed according to customer approved protocol
- Sample preparation is formulated in accordance with approved protocol
- GCMS/MS: Screening is performed using a predominantly non-polar capillary column with a broad range temperature scan. EI (Electron Ionization) spectra are used for the identification of the individual extractable and leachable through the computerized library search
- A pre-developed method is used for screening during the extractable and leachable study
- LCMS: a reversed phase LC column with low to high organic solvent gradient is used for screening
- ICPMS: a linearity curve is used to determine the level of the elemental impurities in the samples
- IC: the level of the anions is determined in the samples

UNIDENTIFIED IMPURITIES

- Any unidentified impurity not matching the mass library, during the extractable scouting study through GCMS or LCMS analysis, will be monitored during the leachable scouting on the basis of mass fragmentation
- Volatility of the impurity is determined
- Non-volatile impurities are isolated and identified using 2D NMR studies
- LOD and LOQ are set for the predefined methods
- Identified impurity is quantified in the drug product using appropriate analytical techniques and included in the final report
- Solvent extractions are checked for the individual standard recoveries
- AET is taken into consideration during sample preparation
- If necessary, CCS extraction is performed at elevated temperatures and for a prolonged period of time

U.S. FOOD & DRUG ADMINISTRATION

INSPECTED FACILITY

ISO 17025:2017 CERTIFIED

ISO 9001:2015 CERTIFIED

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