MediZap

Advanced Sterilization

Navigating the Complexity of Extractables and Leachables Studies in Drug Regulatory Compliance

Extractables and leachables (E&L) studies constitute a pivotal element of regulatory submissions aimed at validating product safety. The complexity of E&L investigations varies depending on the container-closure system and drug product under scrutiny. Selecting a Contract Research Organization (CRO) endowed with expertise is imperative for the meticulous generation of reliable E&L data. The ISO certification for contract research labs that conduct microbiology and analytical chemistry testing on pharmaceutical products is ISO/IEC 17025. This standard specifies the general requirements for the competence, impartiality, and consistent operation of laboratories. It applies to all organizations performing laboratory activities, regardless of the number of personnel or the extent of the scope of testing and/or calibration activities.

Leachable and extractable testing is performed on pharmaceutical products to identify and quantify any substances that may leach out of the container or packaging and into the product. This is important to ensure the safety and efficacy of the product. The testing process typically involves exposing the container or packaging to a variety of solvents under controlled conditions, and then analyzing the solvents for the presence of leachable and extractable substances using analytical techniques such as gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-mass spectrometry (LC-MS). The specific testing methods and conditions may vary depending on the product and its intended use. Extractables denote the chemical entities liberated (extracted) from the container closure, delivery, or packaging system in a controlled laboratory setting. Conversely, leachables specifically pertain to compounds present in the drug product matrix as a direct consequence of migration ("migrant") or leaching ("leachable") into the formulation during normal storage conditions, including accelerated stability conditions. The outcomes of extractables studies may serve as a reference point, whereby potential analytes are preliminarily characterized, typically in a 'worst-case' scenario involving over-exposure to pH, chemical solvents, and extreme temperatures, prior to being identified (if observed) as leachables in a Current Good Manufacturing Practice (cGMP) quantitative assessment of the drug product.

These investigations encompass a multifaceted array of individual experiments often necessitating specific material handling procedures and distinct analytical methodologies corresponding to the physical properties of the analytes (e.g., volatiles, semi-volatiles, non-volatiles, and elementals).

Throughout the drug development trajectory, it is imperative to identify any potential risks of product adulteration that could pose toxicity hazards or compromise stability and/or efficacy. While the elimination of impurities from the drug product itself is widely acknowledged, regulatory agencies have increasingly scrutinized the impact of impurities originating from primary packaging materials. In 1999, subsequent to extensive studies on propellants utilized in metered dose inhalers, the FDA mandated pharmaceutical manufacturers to validate the safety of materials employed in production systems, container-closure systems, and drug delivery devices. To adhere to these standards, E&L testing is routinely conducted to evaluate the potential migration of various chemicals from primary packaging containers into the formulation matrix of drugs and biologics intended for administration. For instance, consider a typical drug product packaged in a glass vial and sealed with a rubber stopper. Preliminary assessments of the construction materials are conducted to anticipate expected outcomes and design targeted experiments. A single drug unit encompasses both the primary packaging and the drug product, all necessitating analysis to ensure that exposure to leachables does not compromise product integrity or patient safety during usage.

E&L studies endeavor to address a fundamental query regarding whether primary packaging materials employed in the container-closure system of the drug product influence patient safety through the potential contamination of the sample by impurities. The findings from these studies carry substantial significance in safeguarding patients and formulating documentation intended for regulatory authorities. Failure to substantiate drug safety under FDA regulatory requirements risks general population safety. E&L studies empower drug manufacturers to identify, quantify, and evaluate the risk posed by leachable impurities, thereby demonstrating the safety of their container-closure systems, processing equipment, and drug products.

Any alteration to the immediate primary packaging materials of a drug product necessitates a regulatory assessment of its impact. However, such studies are typically undertaken once the container-closure system has been finalized, and the manufacturing process is in its concluding stages. Vigilant control and monitoring of extractables and leachables constitute pivotal elements in incorporating Quality by Design principles into product and process development. By selecting a CRO offering comprehensive and robust E&L studies, the insights garnered can be seamlessly integrated into other development endeavors.

MediZap, in the drug development of the R&D phase, supports E-Beam | X-Ray terminal sterilization of samples required for E&L studies after a primary packaging system is selected.