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Your Challenges Require Smart Solutions.

Extractables and Leachables Studies Outsourcing Guide

Pharmaceutical manufacturers are obliged to conduct extensive studies on Extractables and Leachables (E&L). Health authorities thus want to ensure patient safety and make sure that no harmful organic or inorganic substances migrate from the primary packaging materials (such as stoppers, blisters or pump systems) into the pharmaceutical formulation.

Besides best practice guidelines e.g. by FDA, EMEA and PQRI, there are also compendial regulations (USP chapters <1663>, <1664>, and <1664.1>). Nevertheless, there is often uncertainty on the strategy and methodology of conducting E&L studies among those who are just getting started with this topic.

Only a qualified laboratory such as GBA Pharma Labs, where the relevant expert knowledge is available, can guarantee that the E&L study is thoroughly planned, the appropriate methods are competently chosen and the experimental phase is carried out by experienced and well-trained staff.

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An E&L study is usually carried out in four steps:

1. Planning and Risk Assessment

The first step is a risk-based assessment of the packaging material, in particular the components being in contact with the product and their potential interactions with the pharmaceutical formulation. Getting detailed information from the packaging material supplier about the additives contained in the plastic material is extremely helpful in this assessment phase.

2. Extractables Study

Based upon this information and on the given regulatory guidelines, the study plan for an extractables study is set up in close cooperation with the customer.

In the course of this extractables study, the primary packaging material is extracted under stress conditions (high temperature, strong solvent concentration (polar and nonpolar solvent), extreme pH values). The extracts obtained are analyzed systematically using our inhouse methods which are individually matched with your product.

Semi-volatile substances are analyzed by GC-FID and, if necessary, their structure is identified by means of GC-MS and comparison to NIST data base. Semi quantitative target analysis for non-volatile substances is performed by means of HPLC-MS. Screens for unknown non-volatile substances are performed by LC-HRMS (Orbitrap Exploris 240) including a Compound Discoverer E&L database query and FISh algorithm. Headspace-GC-MS is used to identify highly-volatile extractables, such as isoprene, directly from the plastic component being in contact with the product. This well-structured approach assures that potentially migrating substances are determined qualitatively and/or quantitatively above a previously defined AET (analytical evaluation threshold).

3. Toxicological Assessment

The next step is the toxicological assessment of the results of the extractables study. The challenge for the toxicological assessment is in many cases the absence of toxicological data. The typical solution in such cases is the consensus of a minimal concentration considered safe even with life-long exposure. The applicable threshold orientate on the general concern for systemic toxicity, which by itself is addressed by classifying substances into “Cramer Classes”. If your company does not have a toxicological department, we could offer our services in this field, too.

4. Leachables Study

The final step is the leachables study as part of the stability study according to ICH Q1A(R2). Here the compounds that had been identified as toxicologically relevant in the preceding extractables study are quantified, using highly sensitive and validated methods (adapted to your matrix) under GMP conditions, typically on stability samples of your product. It should be kept in mind that interactions between leachables and the pharmaceutical formulation could lead to reaction products which had not been detected in the preceding extractables study.

If you should need our expertise and support for the complete qualification of a packaging material, the identification of leachables or the response to a letter of deficiency, please do not hesitate to contact your Business Development Manager at GBA Group Pharma or

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