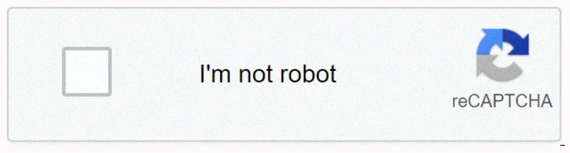

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Leachables and extractables guidelines ema

By Alan Wood, Reading Scientific Services Ltd - Pharmaceutical Analyst (LC-MS) Introduction A crucial task when launching pharmaceuticals to the market, is to determine the purity of the final product, necessitating the need to determine its impurity profile. Traditionally, this was concerned only with impurities arising from the manufacture and degradation of the pharmaceutical product. Currently, the migration of mobile chemical species of components used in the manufacture and storage of pharmaceutical products should be evaluated. Regulators such as the U.S. Food and Drug Administration (FDA) and the European Drug Administration (EMA) are increasingly focused on interactions between various manufacturing components, drug delivery devices and container closure systems (CCS) and the final pharmaceutical product. The objective is to identify and assess any toxicological risks that may arise through such interactions. The FDA has previously stated that containers and closures of drug products should not be reactive, additive or absorbable in order to alter the safety, identity, strength, quality or purity of the drug beyond official or established requirements. 1 Therefore, extractable and sandable studies (E&L) are now a crucial component of product release. Extractable and sandable: definitions and sources The FDA defines extractable and sandable as follows:2 Extractidic: Organic and inorganic chemical species that can be released from the surfaces of components used in the manufacture and storage of medicinal products under laboratory conditions (accelerated or exaggerated temperatures, solvents or surface exposure). Leachables: Organic and inorganic chemical species that can be released from the surfaces of components used in the manufacture and storage of medicinal products under normal use conditions. Extractibles represent the worst-case scenario in relation to the release of mobile chemical species from manufacturing and packaging components during forced extraction. The leachables should then include a subtale within this set of mobile chemical species, released under the softer storage conditions on the shelf. In practice, however, the lixachables study identifies species that were not all observed during the study of previous extractables. Thus, the set of leachable species is not fully included within the extractable set, but there is strong overlap between both sets (figure 1). Figure 1: Relationships between extractable and sandable There are multiple sources that may contain leachable species, and some common examples are detailed below:ManufacturingFiltersSingle-use bagsTubingPrimary packaging - External componentsContainer-closure system (vials, caps, caps and sheets)Single-use systems (syringes and intravenous bags)Primary packaging - Internal componentsGaskets and O-ringsValvesSpringsSecondary terciary packagingLabels and adesivosInks and coloringsLeachable species to consider consider and stabilizers Anti-static coatingsLubricants, sliding agents and emulsifiersDises and colorantsVulcanising agentsResidual monomer, polymer and oligomer speciesPhtatos, nitrosamines and polyaromatic hydrocarbons (PAHs)Toxic elements – for example, mercury, lead, arsenic, cadmiumThe multitude of component parts used during the manufacture and storage of the product, combined with the potential number of leachables, requires a structured and thorough study of E&L. E&L studies – a route for toxicological evaluation Leachables migrating to pharmaceuticals from the manufacturing and packaging system should be identified and monitored throughout the life of the product. The data collected allow a toxicological evaluation to be made in relation to any leachs found, ensuring patient safety. The key to this is to determine the Security Concern Limit (SCT) for the product under investigation. SCTs were introduced by the Product Quality Research Institute (PQRI) sandpaper working group, and are defined as the dose below which an individual lixachable would not cause effects, carcinogenic or not, which could constitute a safety concern.3 Two factors that significantly impact ctS are the route of administration and the degree of contact between products and packaging. To attribute risk of leachable species to the pharmaceutical product under investigation, the FDA developed the following matrix: 4 Degree of concern associated with the route of administration Probability of component-dosing interaction of high medium low lower aerosol sosols and solutions; injections and suspensions for injectionSOs powders and powders; inhalation of high ophthalmic solutions and suspensions; transdermal onnasal aerosols and spraysLow Solutions and topical suspensions; topical aerosols and languages; oral solutions and post-celtic suspensions; Oral powder Oral tablets and oral capsules (hard and soft gelatin) Products such as aerosols and injectables have the highest associated risk, while tablets and oral capsules have the lowest risk. The PQRI recommended that the high-risk CTS be set at 0.15 µg/day, while low-risk CTS is set at 1.5 µg/day, both of which have been justified from toxicological and safety perspectives.3 Under certain conditions, such as short-term exposure or in the treatment of a life-threatening condition, CTS can be elevated above 1.5 µg/day.5 Projecting an E&L study An E&L study consists of two individual projects still interconnected. The extractable study identifies species of manufacturing components (where applicable) and the packaging system that could migrate to the pharmaceutical product through storage under normal conditions. This establishes a baseline for the following leaching study, a series of tests performed at predefined time points on the pharmaceutical product the duration of its useful life. Study of extractibles The components under investigation are extracted in pharmaceutical product. The key points to consider are the number of components and types of materials to be tested, and the solvents with which to perform the extractions. Simple storage systems, for example, glass ampoules or plastic bottles with screw caps, will have a limited number of components. However, more complex units, for example pump dispensers containing O rings and springs, will contain multiple components that require investigation. Secondary and tertiary packaging also needs to be considered at this stage. Extractions should be carried out with a range of solvents of varying solvency power to ensure that a pool representative of extractable organic and inorganic species is generated. In the case of liquid formulations, those chosen should better mimic the composition of the pharmaceutical product to provide a profile of extractables at worst. The use of overly powerful solvents is discouraged. This could destroy component materials, creating an unrealistically large set of extractables. Two or three solvents are typically chosen, but more can be used if considered appropriate. Common examples include: Water (neutral, acidic or basic if pH ≠ 7)Organic solvent (ethanol, isopropanol or n-hexane)A final aspect to consider is the type of material under investigation. Plastics and rubbers must be extracted by all solvents chosen. However, there is little value in performing organic extraction of solvents from metal springs, which would only produce inorganic impurities. Such considerations shall be made between the solvents used and the components under investigation. Study of leachable time points are predefined before starting an E&L study, and can be performed concomitantly with a stability test. Samples are screened for sanders, including those identified during the study of extractables and any new species found during the leaching study. Those found to exceed ctS are identified and evaluated for toxicity. Crucial to a successful study is the creation and storage of appropriate controls and leaching sample. The control sample should be stored in such a way that there is a minimal risk of leaching, and carefully labeled avoiding the use of paints and adhesives directly into the container. For leaching samples, inverted and upright (e.g. bottles equipped with lids or lids) and storage conditions (e.g. 4°C, 25°C/60% RH, 40°C/75% RH) should be considered. Analysis of extracts and samples In general, extractable and leachable can be divided into three broad groups: nonvolatile leachablesVolatile and semivolatile lixachablesInorganic / elemental leachables. Validated analytical methods are required to analyze all samples and can be used in both studies. The 2 exemplifies the typical analytical strategy employed. Figure 2: Generalized approach to e&l sample analysis The liquid chromatography-mass spectrometry (LC-MS) analysis allows the analysis of larger, nonvolatile sanding species. Volatile. the analysis of gas chromatography (GC-MS) mass spectrometry allows the analysis of volatile and semivolatile sandable species. Gc-MS analysis in head space is an option where a large amount of volatile species can be expected. Elementary impurities are analyzed and quantified by inductively coupled plasma mass spectrometry (ICP-MS). The methods must be validated before the start of work, but can accommodate a wide range of pharmaceutical products. Normally, the feasibility of the method only needs to be demonstrated before the start of leaching studies. This ensures that the pharmaceutical product under investigation does not cause effects of the injunction matrix, and that the extractables can be recovered from the sample matrix, avoiding the redevelopment and revalidation of the method. Conclusions The complex nature of the E&L study requires thorough planning and access to a variety of complex analytical hardware by executing validated methods. The investigative nature of the work requires a team of analysts with capabilities in all method validation, molecular identification and toxicological evaluation, to ensure that the study runs without problems and that the data is interpreted correctly. With thorough planning, adequate analytical hardware and in-depth knowledge from the start, the E&L study can be performed without problems and successfully to completion, ensuring that patient safety is maintained. References 1. U.S. FDA, Code of Federal Regulations, 21CFR211.94 - 2. Fda's current perspective on leachable impurities in parenteral and ophthalmological drug products, 2011 - 3. Development of Safety Qualification Limits and Their Use in the Evaluation of Products of Oral Drugs Inborn and Nasal - DOI: 4. Industry Orientation: Container closing systems for packaging human and biological medicines - 5. Evaluation and control of reactive DNA impurities (muteers) in drugs to limit potential carcinogenic risk, M7 -