Extractables and Leachables for Inhaled Medicines

How risk assessments can improve E&L strategies

Regulatory agencies such as the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) are encouraging a more structured approach to product development, such as using Quality by Design (QbD) principles.

The structured approaches encouraged by the FDA, EMA, and other regulatory bodies require additional upfront resources compared to a more traditional approach. Performing an initial assessment of materials used in the product and developing a more thorough understanding of products earlier in their development allows more appropriate experiments on the higher-risk aspects rather than generic approaches covering all materials.

Benefits of Performing a Risk Assessment

Extractables and leachables (E&L) risk assessments are valuable processes that can identify and highlight the risks of potential leachables from both the container closure system and the manufacturing processes. The risk assessments also include the level of risk that leachables might present to user safety and product quality.

By performing a risk assessment, manufacturers can better understand the product, whether a medical device or the container closure system, and the manufacturing processes. Identifying risks and scoring them based on that understanding allows for subsequent E&L studies to be more focused. Therefore, decisions around the E&L aspects of the project can be more appropriate.

Risk Assessment Lifecycle

Quality risk management is a systematic process. The lifecycle can be split into Assessment, Control, and Review stages, and there should be regular communication with stakeholders throughout the lifecycle. A typical quality risk management process is described in ICH Q9 with a flowchart, and it is a good place to start when designing a strategy. An initial assessment can be performed based on previously mentioned tables and decision trees from the FDA and EMA guidelines. This can inform stakeholders early in the assessment about the studies that might be required for the project.

The first step of the process is the Risk Assessment, which is further divided into a series of sections:

- Risk Identification involves identifying the parameters that might affect the leachables by reviewing and brainstorming processes and materials.
- Risk Analysis collates information to understand identified failure modes.
- Risk Evaluation uses information gathered during the Risk Analysis to score the failure modes.
- Risk Control covers where the risks are either accepted or experimental studies are planned based on mitigating risk appropriately.
- A Risk Review reassesses the failure modes and re-scores them following any risk mitigations. Risk review can also be part of lifecycle management.

Inhaled Medicines

In the UK, pressurised metered dose inhalers (pMDIs) are a commonly prescribed treatment for the 5.4 million people with asthma and the 1.2 million with chronic obstructive pulmonary disease (COPD). A 2019 study found that based on a sample of 85 patients, switching from dry powder inhalers (DPIs) to pMDIs was associated with decreased asthma exacerbations and improved asthma control. Despite alternatives such as DPIs being available, pMDIs still represent the foundation of asthma control in the UK.

pMDIs consist of a drug formulation (in suspension or solution) with a closure that delivers the required dosage efficiently and consistently. A pMDI usually consists of a pressurised canister that contains the active substance and propellant and is capped with a metering valve, along with a plastic holder consisting of the actuator, mouthpiece, expansion chamber, and mouthpiece.

Compared with other pharmaceutical products, pMDIs have a much greater risk of the packaging impacting drug delivery. The formulation includes the API in a hydrofluorocarbon (HFC) liquified gas, which acts as an effective solvent for leaching. Furthermore, pMDIs often consist of multiple materials and plastic components with a range of polymerisation catalysts, antioxidants, pigments, and slip agents used in their manufacture that may leach, all of which may carry varying toxicological risks.

Extractables Studies

Having identified the risk parameters, manufacturers can design their E&L studies accordingly. Extractable studies are chemical analyses that expose a sample of the container closure system or part of the manufacturing system to selected solvents and conditions that either simulate the product formulation or aggressively extract from (but do not destroy) the material to inform the potential for leachables under normal use. Extractable studies can help assess the risk of leachables in the finished product and help design the leachables studies.

Extractable studies are intended to identify potential leachables from a material. Several solvents are used to extract substances from components; the range of solvents should span a range of polarities and pH that may be observed in the finished product.

Solvents commonly used are water, isopropyl alcohol (IPA), and hexane to span solvent polarity. These can also be

modified to span a relevant pH range. Solvents that simulate your product's formulation can also be used.

It should be noted that some regulatory agencies recommend three solvents, e.g., polar, non-polar, and semi-polar. Standard extraction techniques typically considered are reflux, sonication, autoclave, and solvent soaking; each has advantages and limitations. When choosing the extraction technique, consideration should be given to the objectives of any extractable study, i.e., aggressively extracting compounds from the sample without degradation of compounds extracted or damage to the material. Characterisation of the extract solutions is principally carried out using mass spectrometry techniques because of their sensitivity, selectivity, and low sample requirement; examples are headspace GC-MS for volatile species, direct injection GC-MS for semi-volatile species, LC-MS for non-volatile species and ICP-MS for elemental species.

Every effort should be made to identify extractable compounds above a previously determined analytical evaluation threshold (AET) using spectral libraries, test mixes, and trained analysts' expert knowledge and experience. Guidance such as USP <1663> and ISO 10993-12 are good places to start when designing extractable studies, and the risk assessment process allows studies to focus on the highest-risk areas. Following an extractables study, a toxicological assessment of the observed extractable species is required to inform whether any species must be targeted in long-term leachables studies due to their toxicity risk.

Leachable Studies

Leachables studies are chemical analyses of the finished product. Leachable studies can detect the release of compounds that are either washed from the surfaces of the container closure system or manufacturing equipment, or migrate from materials into the product under normal storage conditions.

Leachables are a potential risk to product quality and patient safety. Leachables studies are often run as part of a long-term stability program to observe the levels of migrating species over the product's intended shelf life. Depending on the product being tested, the sample matrix can introduce complexity to a leachable study compared to an extractables study, impacting both sample preparation and ease of analysis.

Formulation excipients such as flavours or drug substances can interfere with detecting the often trace level leachables, affecting the method sensitivity requirements. Simulant formulations, which simulate the final formulation's physical properties but may omit certain ingredients to aid the analysis process, are an option if sample preparation techniques cannot reduce interference. However, the use of simulant formulations must be robustly justified.

Storage of samples is typically based on ICH Q1A stability guidelines, and methods used can be targeted to analytes of concern, as determined by Toxicologists. Targeted methods must be validated as fully quantified or limit test methods (to ICH Q2), with limit test methods being justified if confidence exists that leachables will not be observed above a certain level. Extractable studies are routinely performed using clean solvents. Therefore, when product formulation is introduced in leachable studies, unforeseen leachables may occur due to the action of formulation ingredients or the interaction of these ingredients with previously observed potential leachables; this may result in leachable compounds being observed in the leachables studies that were not observed during extractables studies. These new leachables would not be detected if only specific targeted methods were employed in leachables studies.

As methods for targeted analysis are commonly based on the screening methods used for the extractables study, it is good practice and recommended that screening capability be retained during leachables studies.

Risk Review

A toxicological review of the data generated during E&L experiments is essential to the E&L risk assessment. A toxicological review of the materials and ingredients contributes significantly to the quality of the risk assessment.

Toxicological experts' contributions include assessing the materials and ingredients before the risk identification process and advising appropriate sensitivity levels for analytical methods to inform the leachables study design. Following any leachables studies, the Toxicologists assess the leachables compounds and levels observed and play a critical role in informing the group whether the risk has been reduced or possibly increased due to results.

Regulatory agencies have shown an increased requirement to show aspects of QbD when developing new products. E&L risk assessments demonstrate knowledge of the product and its manufacturing process, contributing to applying QbD principles during a product's development. They also focus efforts on E&L projects, which can be expensive when performed inefficiently. By following the risk assessment process, only required studies are performed, and these studies can be designed to de-risk several failure modes.

Working with a science or regulatory consultancy can help you design and implement an effective E and L risk assessment. Broughton has extensive experience of developing tailored E and L studies that combine technical and analytical expertise with integrated toxicological consultancy and regulatory compliance. To find out more and to speak to one of our scientific experts, visit the Broughton website at www.broughton-group.com.

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