Table 30: Extractable and Leachable Studies: Best Practices to Support New Products and Process Changes

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Key Words:

Extractable and Leachable Studies, Best practices

Scope:

Extractables - compounds that extract out of a component under harsher conditions than actual use. Typical conditions are higher solvent strength, higher temperatures, extreme pH, etc. Manufacturers of a component may have an extractable study already performed under standard conditions such as USP, ICH, BPOG. Methods to analyze extractables are simpler because the sample matrix solvents are simple well-defined solvents that give little interference in the analytical methods.

Leachables - compounds that passively make their way into the product under normal conditions of use. Leachables should be a subset of the extractables. Methods to analyze leachables are more complex because they need to reduce interference from protein and complex excipients of the drug substance/ drug product formulation.

Extractable and leachable (E&L) studies are required for successful registration of parenteral biologics. The E&L profile is monitored from a safety perspective and for the potential impact to biological product stability, quality, and efficacy. There are new challenges for the pharmaceutical industry due to the introduction of single-use manufacturing, novel primary container closure systems, and new modalities. There exist gaps on agreed standards for overall risk management and application of QbD principles for E&L studies. Therefore, the roundtable will discuss best practices for extractable and leachable studies to support new products and process changes.

Questions for Discussion:

1. How much E&L data on the primary container closure system is typically required for BLA filings? a. How much data at recommend storage conditions? How much data at accelerated and stressed conditions?
2. How much E&L data on the product contact materials is typically required for BLA filings? a. When is leachable data required for product contact materials?
3. When can prior knowledge or a risk assessment be used in lieu of actual E&L studies?
4. How much E&L data is needed to support primary container systems changes? Product contact material changes?
5. What special E&L considerations are required for new modalities (cell & gene therapy, ADC, mRNA, protein degrader, etc)
6. Are there region-specific E&L expectations?
7. Where is the dossier is E&L data provided?

Notes:

The content of Extractables and Leachables ("E&Ls") in the final product container is of critical importance, but Applicants should not ignore upstream contribution of E&Ls (i.e. filters, single-use bags, intermediate containers, etc.). If providing a toxicological assessment, Applicants/Sponsors should provide their own toxicological calculations as part of the data package.

The approaches vary by companies - some rely solely on a risk-based assessment, others routinely conduct product-specific stability-based studies; While accelerated stability based studies are informative and may be supportive of the overall risk assessments, Sponsors should still consider that data to real-time long-term conditions. If risk is considered low by the company but no data was generated, it is not uncommon for a Post Approval/Marketing Commitment to result. Overall, the requirement for Leachables data but will depend on the totality of the submission package. If unexpected results are obtained (i.e. detection of a new leachable that increases PQ risk), Applicants should notify the agency immediately.

To leverage Vendor data as part of a risk-based approach: Start with vendor data, how the study was conducted, and perform a product/process specific risk-assessment. Full documentation and Vendor study data is typically provided in DS section of BLA, accompanied by a summary of the risk assessment; The Applicant/Sponsor should compare results of Vendor data from a toxicicological and PQ point of view to inform further product-specific studies that are fit for purpose.

As regards Elemental Impurities - data is generated from testing the final product; elemental impurities can come from raw materials, product-contacting surfaces, and all the way through to the final vial/labeling (i.e. ink leaching from the label onto container has been observed).

As regards the DS storage container vs DP Container: for post-approval (i.e. filter change) - typically treated less stringent, but a risk-assessment should still be provided as supportive information.

Regarding regional differences in the data packages presented in a Marketing Application - nitrosamine risk assessment is required - the EU Guideline on Nitrosamines is a valuable reference.