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E&L Programs for Complex Dosage Forms and High-Risk Drug Products

Understanding the regulatory requirements for Extractable & Leachable (E&L) studies can lead to confusion, and if the inappropriate path is taken, it could result in delays in getting a drug into the market. Deficiencies most commonly arise when the expectations for material characterization or "simple" E&L studies are applied to the more complex drug delivery systems. Much of the confusion stems from the varying requirements and expectations based on a drug's route of administration, formulation, dosing requirement, container/closure system, and drug delivery device requirements. This leaves many companies asking if they need to follow PQRI, ISO 10993, USP 661/662, USP 1663/1664, EMEA, BPOG, BPSA, or any other number of regulatory guidance publications. As a result, inadequate E&L information in filings has continued to be a significant source of deficiencies cited in Complete Response Letters such as[1]:

- Presence of E&L compounds above the Qualification Threshold (QT) that have not been identified
- Inadequate sensitivity to be able to detect compounds at the requested Analytical Evaluation Threshold (AET)
- Inadequate stability data to examine trends in leachables over time
- Inadequate descriptions of how extractable data were used to design leachable assessments
- Inadequate E&L correlations

With over 20 years of experience performing E&L studies, Eurofins BioPharma Product Testing has developed and validated over 1,000 leachable methods and has experience with every route of administration and common container-closure system on the market. We have completed over 50 inhalation programs (pMDI, DPI, Nasal Sprays and nebulizers), and over 100 complex drug/device programs (Transdermal patches, implantables, auto-injectors, etc.).

[1]Mellon, Dan (May, 2019) Nonclinical Review of Extractable Leachable Studies: Practical Advice from an FDA Reviewer, Extractables & Leachables USA, Arlington, VA.

Why Choose Eurofins BioPharma Product Testing?

We provide full E&L program support, including controlled extraction studies, leachable method development/validation, extractable/leachable identification, toxicological evaluations, risk assessments, and leachable stability studies.

We custom design E&L programs to meet clients' specific needs and that also meet current regulatory standards and expectations.

We use a proprietary HPLC-MS identification database, Eurofins Extractable Index, with over 1,500 compounds (including common plasticizers, antioxidants, stabilizers, elastomers, lubricants, and accelerants) to identify extractables and/or leachables in products.

We provide regulatory consultative services to help our clients navigate the regulatory expectations and perform risk assessments of their manufacturing chains and/or container/closure systems.

We have a successful regulatory track record with no rejections or delays in approval from a Eurofins designed E&L program.

E&L studies can generally break down into three categories listed below. The flow chart helps to outline the basic steps required to successfully complete an E&L study for the most complex products.

Material Characterization Studies

- Extractable only studies
- USP 661.1, BPOG, BPSA
- Used most commonly for vendor selection and qualification

"Simple" E&L Studies

- Reduced testing, typically only requiring extractables and leachables correlation
- Oral Solutions, simple parenterals

Complex E&L Studies

- Full E&L studies required including stability assessement
- Inhalation devices
- Complex drug/device combinations
- Transdermals

1. Gather Information/ Risk Assessment	2. Study Design
• Assess manufacturing process/container closure system for contact points and potential sources of leachables • Collect information on components: materials of construction, supplier testing, manufacturing process for components	• Determine AET based upon the applicable SCT/TTC, route of administration and dosing requirements • Determine the material requirements for testing • Custom designed program to meet client needs and compliant with applicable guidances : USP <1663>, USP <1664>,PQRI, BPOG, etc
3. Controlled Extraction Studies	**4. Determine Probable Leachables**
• Multiple solvents based on drug product characteristics • Multiple analytical techniques to cover the range of potential extractables • Standard turnaround time: 6-8 weeks	• Aged/Stressed product analysis • If product is not available,a simulation study may be performed • If neither available, extractables from CES are treated as probable leachables • Standard turnaround time: 2-4 weeks (may be run concurrently with Controlled Extraction Studies)
5. Leachable Identification	**6. Leachable Toxicological Evaluation**
• If the observed leachables/ extractables are not identifiable with databases, additional testing can be performed to identify them • Standard turnaround time: 1-2 weeks per compound	• Identified Leachables above the AET/SCT are evaluted for potential toxicological concerns • Standard turnaround time: 1-2 weeks
7. Develop/Validate Leachable methods	**8. Leachable Stability Study**
• Methods developed against pre-defined performance expectations for identified leachables • Methods are validated in accordance with ICH Q2 • Standard turnaround time: 10-12 weeks (multiple methods can be run in parallel)	• Performed in compliance with ICH Q1 guidelines • Typical turnaround time: 3-4 weeks per release or stability time point