Extractable/Leachable studies – Challenges & Upcoming Trends

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The importance of Extractable and Leachable studies came to light probably in the 90s. It was the time when when uncoated rubber stoppers in a PFS had leached compounds into the Erythropoietin thereby triggering an adverse immune response. Today, Extractable and Leachable studies have become an important part of the drug approval process.

Extractable and Leachable risk assessments are now centre stage for pharmaceutical companies, packaging manufacturers and regulatory agencies.
Thousands of studies are conducted, expert articles are published, books are written, multitudes of seminars are organised and yet outcomes cannot be predicted when it comes to E/L risk assessments.

Analytical science has progressed over the past 2 decades and we are able to access instruments & techniques that can detect compounds at ever lower concentrations. Yet the pharmaceutical & medical device industry continues to grapple with several challenges…

– Is my E/L risk assessment complete? Have I interpreted the guidelines properly?
– Have I been able to reliably detect all leachable compounds?
– Am I sure that the compounds I am reporting are coming from packaging materials/contact surfaces?

Although the industry is much more aware and understands the real risk that leachables pose, what is the way ahead which can improve the situation and lead to more reliable outcomes for E/L risk assessments…??

This article is anattempt to give an idea on thedirection in which the E/L assessments are expected to move over the coming years, We will also look into the the current challenges that pharma companies face.

Regulatory landscape

Currently there are no universally accepted standards for assessing the risk of extractables and leachables. Investigators and regulators need to piece together a mix of:

- Regional guidelines
- Pharmacopeial standards (that are evolving e.g., USP)
- Publications e.g., PQRI, some of which are in draft form

Absence of a harmonized guidance on the evaluation and control of E&L substances can result in:

- Disparate filing requirements at regional and country levels
- Protracted reviews and approval of marketing applications
- Requests for additional studies without a clear scientific foundation
- Expensive and time-consuming post-approval commitments

Below is a list of common deficiencies/queries raised by the USFDA when reviewing EL submissions:

1. If the packaging components have been approved for another product, you can't claim approval for your product, even if your product is similar.
2. A DMF letter of authorization doesn't not exempt you from performing E/L studies.
3. Performing risk assessment only on Extractable data and not doing leachable study is not permitted Only submitting vendor extractable data is not sufficient.
4. LOQ of method is higher than the AET which is not acceptable.
5. Method suitability for leachables not addressed especially when AETs are very low and extracts are concentrated by a large magnitude to achieve the AET.
6. Compounds above AET not tox assessed.
7. Correlation between extractables and leachables not provided.

Advice:

- Provide justifications for methods (time, solvent, temperature etc)
- Ensure AET is appropriate. AET must be able to address SCT recommended or if AET cannot be met with suitable justification safety assessment will be based on LOQ.
- Obtain leachable date from mutliple batches. (at least 3)
- Include leachable assessments at multiple timepoints over the course of stability. Identify trends.
- It is important to do a tox risk assessment of leachables if above AET. You can always qualify leachables with a toxicology study.
- Determine if E and L correlations make sense.
- Plan ahead to obtain your E/L data in parallel with long term stability studies.
- Provide an integrated summary explaining why you chose the methods you employed and how you leveraged the E data to inform your L studies

Challenges in E/L study design

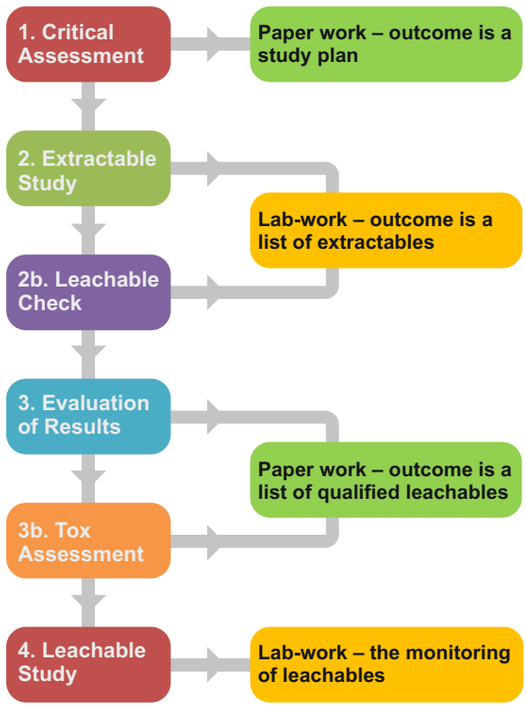
The E/L study is not a limit test nor has a defined standard to evaluate the results. When we start an E/L study we are not even sure of what compounds to expect. So it is a risk assessment where knowledge and creativity of the analysts is very important.

Some issues that come up when designing and performing these studies are as listed below. This list is by no means exhaustive.

a. Dealing with low AETs of Large Volume Parenterals.
b. Nitrosamine risk assessment from packaging materials.
c. Identifying rubber oligomers in E/L studies.
d. How to design E/L studies for Lyophilised drug product?
e. Can screening methods be validated?
f. How to design study for Ophthalmic/Topical dosage forms when there are no guidelines?
g. Should control/blank samples be suitably aged? What if control samples are not available?

Advice:

An E&L investigation is not one single study, it is at least divided in 4 subsequent major steps:



- Giving attention and spending enough time for a critical assessment of the product and packaging system and reviewing available information is important. All too often there isn't enough time and the E/L study is rushed through, which can lead to undesirable outcomes.
- Adopt good screening techniques for both extractables and leachables so that it allows us to narrow down on targets which have a high probability of showing up as leachables.
- Ensure the methods are sensitive enough keeping the AET in mind.
- Perform method suitability if the product matrix is complex or AETs are low.
- Leverage vendor data to identify targets in extractable and leachable screening studies.
- Extractable studies have to be adjusted keeping in mind the container and the formulation.
- Interpretation of results of analytical studies is critical. Applying the right thresholds, correlating E and L data and justifying your choices for study design and selection of extractables and leachables must be done.

The Analytical Tool Box for a good E/L characterization

In the extractables study a standard set of analytical methods, which includes TD-GC/MS, GC/MS of derivatives, HS-GC/MS, LC/MS and ICP-MS/OES, allows the comprehensive identification and quantification of extractable compounds from container/ closure systems.

The criteria for these methods are that they must be exhaustive and comprehensive All potentially extractable analytes from polymeric materials of a container/ closure system can be covered qualitatively and (semi)-quantitatively.

Besides, this this set of methods should be generic in the sense that the methods are applicable for extractables studies on various different polymeric materials of container/ closure systems.

(a) Thermodesorption-GC/MS (TDS-GC/MS)

A very useful first experiment in an extractables study is the application of TDS-GC/MS on the raw polymeric materials of a container/ closure system.

With thermoplastic materials the TDS-GC/MS chromatogram can be very complex, because many saturated and unsaturated hydrocarbons are thermally stripped from the polymeric matrix.

Still, a detailed analysis of these chromatograms can strongly aid in the later identification of and search for analytes in the extracts of the material. Therefore, analytes found in extracts of polymers by GC/MS are often a subset of analytes that are found by TDS-GC/MS of the raw polymeric material.

A good example for these similarities is illustrated in figure 1, where the TDS -GC/MS chromatograms (ion traces of the most prominent fragment of one of the extractables

- Bisphenol A, the compound that is labelled with an asterisk in figure 1 of the raw polymeric material and extracts thereof are overlaid:

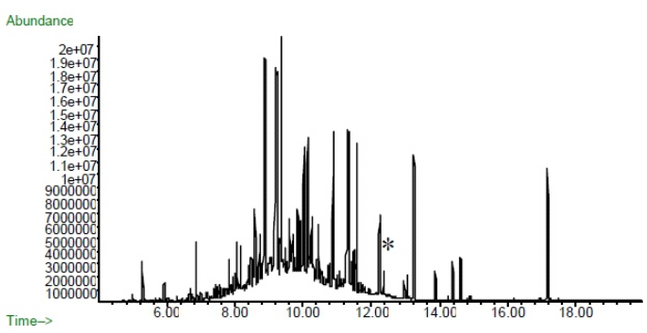


Fig 1: TDS-GC/MS chromatograms of polymeric part of a catheter system

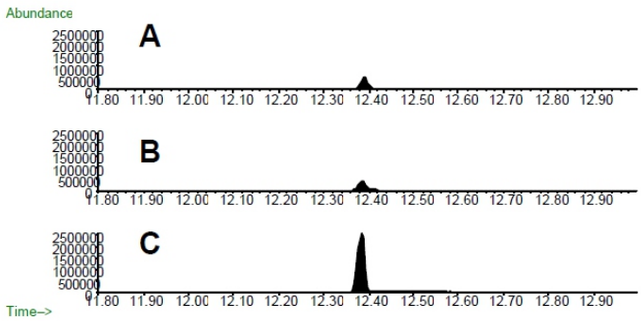


Fig 2: TDS-GC/MS chromatograms (ion trace) of A: raw polymeric material, B: ethanolic extract, C: aqueous extract after workup

The limitation of TDS-GC/MS is that it can only be applied for the identification and quantification of unipolar and (semi-)volatile compounds, whereas strongly polar and/ or high molecular weight compounds demand for different methods.

(b) Headspace-GC/MS (HS-GC/MS)

Volatile extractables are analytically accessible with the aid of HS-GC/MS. The application of this method is best exemplified by studying a case, where printing inks where used on the polymeric container/ closure system to indicate the date of filling, shelf life of the pharmaceutical product etc. One of the ingredients of the ink formulation was cyclohexanone, and this particular compound could easily be detected and later on quantified on a ~1 ppm level (in relation to the amount of extracted polymer) in the aqueous extracts of the container/ closure system, as illustrated in figure 3:

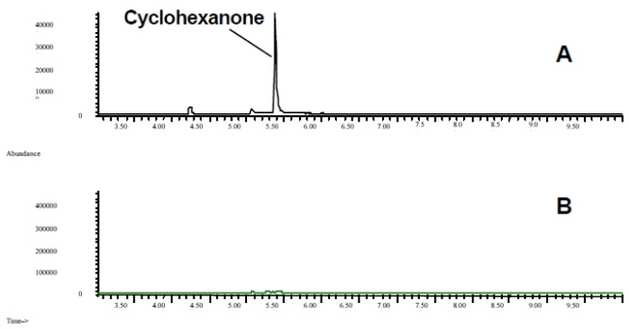


Fig 3: Overlay of HS-GC/MS chromatograms of aqueous extracts of a printed (A) and an unprinted (B) polymeric container/ closure system.

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The application of all GC/MS methods is limited to (semi)-volatile analytes. The analysis of polar and/ or high molecular weight extractables demands for the application of liquid chromatography coupled to the powerful tool of mass spectrometry.

(d) ICP OES or ICP- MS

Often inorganic additives and pigments are compounded into polymeric materials. The analysis of this class of chemicals demands for methods that can sensitively detect metals, and ICP -OES or ICP -MS are best suited for this.

(e) Analytical Methods for Leachable Studies

In contrast to extractables studies, leachables studies are performed under cGMP with drug product formulations that usually come out of stability testing. The methods that are used (and validated) for leachables testing underlie certain criteria: while on one hand they have to be very specific (because the leachable compound has to be extracted from or detected in the often very complex drug formulation), on the other hand the applied method should be very sensitive, because the specifications of the potentially leachable compounds within the drug formulation are usually very low. Additionally, as these methods will later on be applied in the routine quality control of the drug product, they should be as simple as possible.

Methods for the analysis of extractables require the complete qualitative and quantitative coverage of compounds with a broad spectrum of chemical structures and properties. After an extractable study the analyst should be confident that no other compounds than the detected ones can potentially leach from the container/ closure system into the pharmaceutical formulation. Once this confidence is established, specific methods for the quantification of the potentially leachable analytes in the drug formulation are developed and validated. These methods obviously strongly depend on the type of analyte and on the matrix. A leachable screening study may also be done which gives additional information and confidence in selecting the target leachables for monitoring during stability.

. How will the E/L landscape be in 10 years from now? Listing down a few emerging trends which should hopefully further strengthen the E/L risk assessment process while making it relatively easier to perform these studies.

Emerging Trends for E/L

1. Modelling of leachables.
2. ICH Q3E – Will it achieve harmonisation?
3. Availability of public database of E & L compounds
4. Guidelines covering all dosage forms.
5. USP 665 for process components.
6. More attention on E/L studies for biopharmaceutical products and processes as they gain more dominance over small molecules.

A lot of work has been happening on coming up with a methodology to predict leachables. Since leaching is a physical process and equations can be defined to explain leaching, can a simulation or a tool predict the fate of leachables from various materials under specific conditions?

There are several organisations at work to come up with easy-to-use tool to predict leachables in a specific system. This could be a very good source of information when designing studies or interpreting results. Alogrithms and AI could be very well used for coming up predictive data and models on the fate of extractable and leachables. This could avoid unnecessary testing and allow for a better risk assessment.

Coming up with a robust database of leachable compounds seems to be the holy grail of the EL universe. If there could a ready list of compounds extracted from different materials with their safety assessment, this would be indeed wonderful. The ELSIE (Extractable Lecahable Safety Information exchange) has been at this task for the past few years and now has a list of 466 compounds with safety reports which is available for members of ELSIE.

An eagerly awaited development is the ICH Q3E. It is anticipated that the scope of such a guideline would include chemical,

biological and biotechnicological products, including drug-device combination drug products.

It would also include allassociated dosages forms and take into account the extracting/leaching conditions, the route of administration, drug indication and patient exposure. Hopefully the ICHQ3E will take into consideration all the work done in the past when coming up with this guideline.

Lastly, the biopharmaceutical world is expanding. Unlike small molecules, the process also plays an important part in EL especially with Single Use Systems (SUS) being used. With vaccine manufacturing expanding exponentially there is a renewed interest in also ensuring that the EL risk is addressed in both manufacturing and storage of vaccines. As the EPREX case highlights a reaction between a leachable and the protein can cause adverse immune reactions which would be very difficult to predict even if leachable studies are done properly. Hence there is a need to involve relevant experts to not only look at toxicity but also potential reactivity of leachables.

Key Messages and Summary.

- Limited direct regulation covering E/L but situation should improve in coming years.
- Science led risk-based approach is a key to which dosage forms are likely to require E/L testing and how much testing is to be done.
- A formal risk assessment is useful in determining where to aim the E/L testing.
- Thresholds for safety assessment are key in determining the limits to apply to E/L testing.
- Variety of analytical tools required for comprehensive coverage of potential extractables.
- Correlation between extractable and leachables should be part of any report.
- Control strategies and life cycle management are closely linked to supplier relationships which are important to identify and detect potential leachables as early as possible.

Finally, E/L can also be used as a tool for packaging development by developing or improving packaging materials and devices which have lower leachability and hence better compatibility.

References & suggested further reading

1. Sotera Health Academy – A collection of white papers, webinars and articles on relevant issues and topics on Extractable & Leachables.
2. ELSIE Data – www.elsiedata.org
3. Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Parenteral Drug Products(Intravenous, Subcutaneous, and Intramuscular) Product Quality Research Institute – www.pqri.org
4. USP 1663/1664 – Assessment of Extractables/Leachables Associated with Pharmaceutical Packaging/Delivery Systems.
5. USP 665 - A rational risk-based USP 1663/1664 – Assessment of Extractables/Leachables Associated with Pharmaceutical Packaging/Delivery Systems.
6. Principles of management of Extractables/Leachables in Ophthalmic Drug Products – PDA Journal of Pharmaceutical science and Technology – 2022 by Christopher Houston, Andrea Desantis Rodrigues, Brenda Birkestrand Smith, et al.

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