Extractable/Leachables – Pharmaceutical Packaging

I) Introduction:

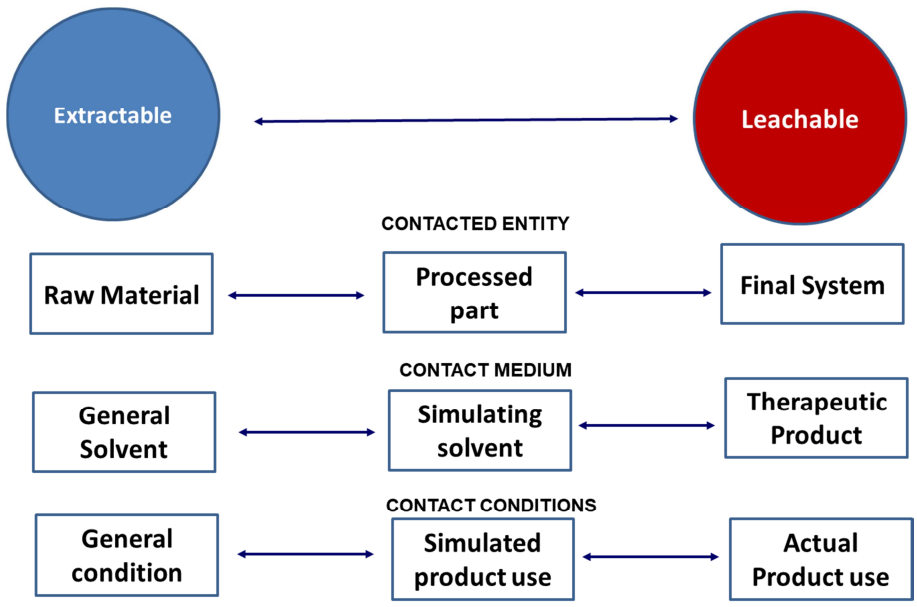
E/L studies are Qualitative and Quantitative investigations which ensure that a pharmaceutical packaging or contact material is safe with regard to chemical components and which does not negatively influence the drug.

- *Extractables: Those substances that are present in the material, component, system that can be extracted from that material by a solvent.*

- *Leachables: Those substances that are present in the drug product due to its contact with a material, component, system etc.*

Amongst the various functions that packaging is supposed to perform – compatibility with the product is one of them. For Pharmaceutical products which typically have a shelf-life from 1 year to 3 years, this is particularly an important and sensitive aspect. No primary packaging material can claim to be totally inert and some interaction with the drug product (formulation) is to be expected. Back in the late 90s regulators were increasingly concerned about patients having adverse effects and even fatalities that were suspected due to impurities leaching from the packaging material into the drug product. These were initially for Orally Inhaled and Nasal Drug Products (OINDP) and the Product Quality Research Institute (PQRI) was tasked with developing guidelines. Over the past 15 years several guidelines covering wide variety of packaging materials and devices have been published and the packaging and pharmaceutical community is required to demonstrate the compatibility of packaging material for any new drug product which are especially going to be sold in the regulated market.

Fig 1: Relationship between extractable and leachable.



II) How to perform E/L Study?

An E/L study is a risk assessment. Knowledge about the packaging materials, the chemistry, the conversion process and drug product are critical in making the right assessment.

With a wide variety of materials, devices, drug products, what are the factors to be considered in coming with the correct assessment and study design?

An E/L Study should answer these three fundamental questions

1. What: What are the compounds that can leach from the packaging material?

2. How Much: What is the quantity in which these compounds are leaching?

3. Why: Why are these compounds leaching?

Questions 1 and 2 are generally answered as a part of any E/L study, but rarely is the 'Why' aspect looked into, as this requires material and packaging expertise which usually the pharmaceutical companies lack.

The packaging suppliers can play an important part in characterising the materials used which can be of value to the pharma company. But finally it is the responsibility of the pharma company to test the stability samples of the drug product to prove there is no leaching.

III) Interpretation of results and regulatory landscape

There are several guidelines that deal with E/L. This presents a huge challenge to the industry on performing the study and interpreting the results. However the one that is widely accepted is the PQRI guideline and science based study design with co-relation between extractable and leachables and coverage of all potential extractable type will usually be sufficient. It is important to bear in mind that despite whatever extractable data is available the regulatory agency is always interested to see the results of study in the drug product i.e. for potential leachables.

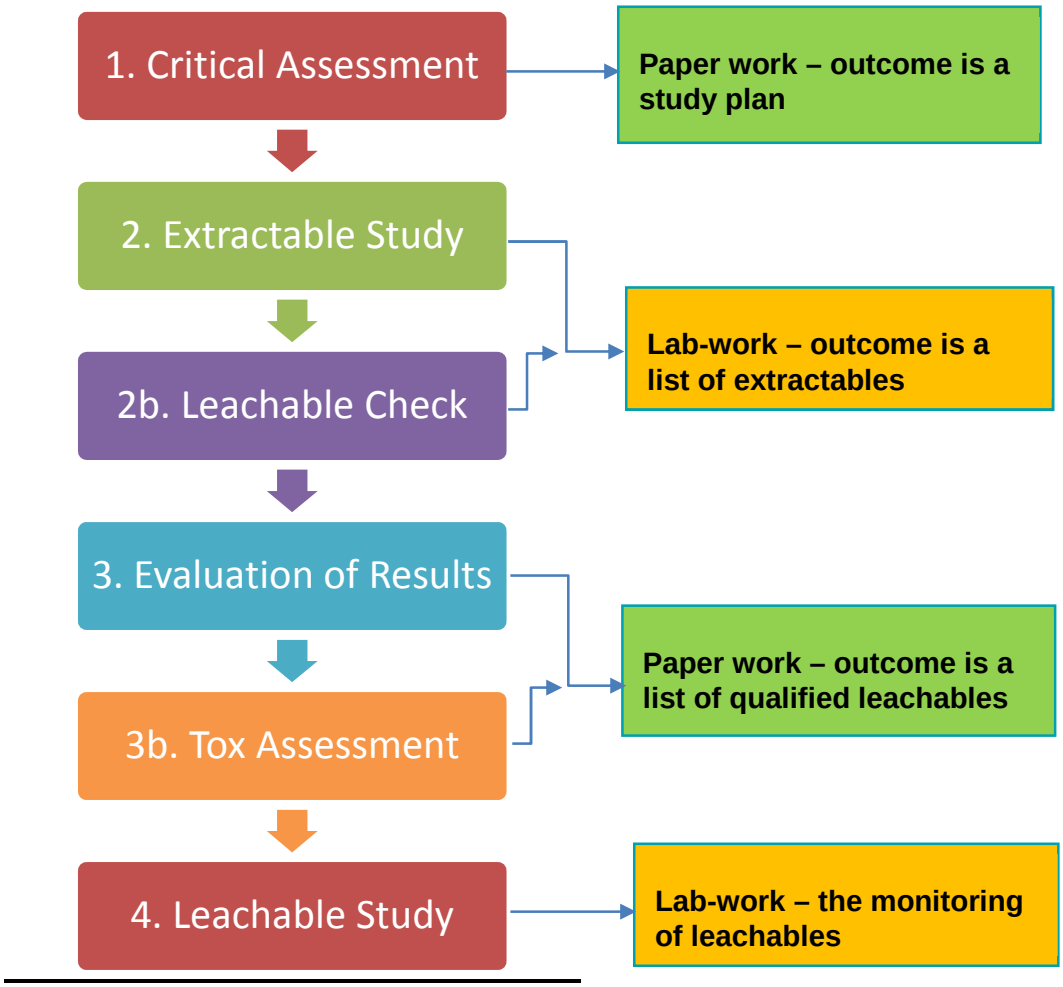
The thresholds for interpreting the results of E/L studies are:

- 1.5 µg/day is Safety Concern Threshold (SCT) – *If leachable exposure is below this value no further action is required.*
- 5 µg/day for sensitizer and irritants – *If compound is not a sensitizer/irritant then leachable exposure up to this limit is acceptable.*
- 150 µg/day for General toxicity (QT) – *For compounds more* 5 µg/day *apply the general rules of toxicological and perform the risk assessment accordingly.*

These limits are for Parenteral products, while for Orally Inhaled and Nasal Drug Products the SCT is 0.15 µg/day and QT is 5 µg/day

IV) Steps in an EL Study

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



Step 1.) The critical assessment of the packaging system and the properties of the pharmaceutical formulation plus an evaluation of the guidelines.

Step 2.) The Extractables Study is a set of forced lab experiments to extract as much as possible out of the packaging material & the printing (but not to destroy the material). In this case the chemists & polymer chemists "creativity" is necessary to design reasonable experiments.

Step 3.) The data evaluation of the extractable study, including a tox.- assessment. Selection of critical leachables.

Step 4.) The Leachables Study is finally performed as part of the stability study for the drug product after appropriate method optimisation & validation for the selected leachables.

V) Challenges in performing E/L Study

The E/L study is not a limit test or 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 and knowledge and creativity of the analysts is very important.

A few common issues that the pharma industry faces are:-

1. Expertise – Far too often Pharmaceutical companies look at E/L as a merely analytical issue and the packaging team is not sufficient involved which creates problems later on. A combination of packaging knowledge, material science and drug product is essential for a successful E/L assessment.

2. Supply Chain – Pharma customers expect their packaging vendors to supply extractable data which although in theory is good, but practically is a challenge for vendors as more often than not they are not aware about the drug product that will be packed. Also a typical packaging supply chain may involve inputs from several vendors and as such this limits the ability of the convertor to give accurate and reliable information.

3. When to do the study – Pharma companies tend to underestimate the importance of E/L and leave it too late in the development process. Any surprises in the E/L study then leaves very little time to take any corrective action. Ideally once the packaging material specifications are fixed or the device has been finalised an extractable study can be done and the risk of E/L assessed.

V) Conclusion

It is mandatory for Pharmaceutical companies to demonstrate compatibility of the device/packaging with the drug product by submitting E/L study data to the regulatory agencies. Hence it is advisable to give due importance to E/L during the drug development and packaging selection process and involve all stakeholders as early as possible.

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

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