Spinco Biotech-CuttingEdge
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Extractable/Leachables studies – Impact on Pharmaceutical Packaging.

I) Introduction:

A pharmaceutical company was surprised to find Benzophenone (a suspected carcinogen) appearing as an impurity during stability testing (6 month accelerated sample) of an ophthalmic product. Further investigation revealed benzophenone leaching from the adhesive used to fix the label on the outer surface of the ophthalmic bottle.

In another case, large levels (> 100 ppm) of a phthalate was found in a lipophilic drug product used for oral application which was found to have migrated from the adhesive used in multi-layer laminate used to pack the formulation.

In an extractable study conducted on a blister pack, a powerful sensitizer was discovered which had originated from the glue. As the product was pulmonary product this was a great risk to patient safety and the package had to be modified.

These examples show that impurities leaching out from packaging materials is indeed a serious concern. Pharma companies need to have a robust risk assessment strategy in place to detect these impurities as early as possible so that there is no risk to the patient.

Extractable/Leachable (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 product packed inside.

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

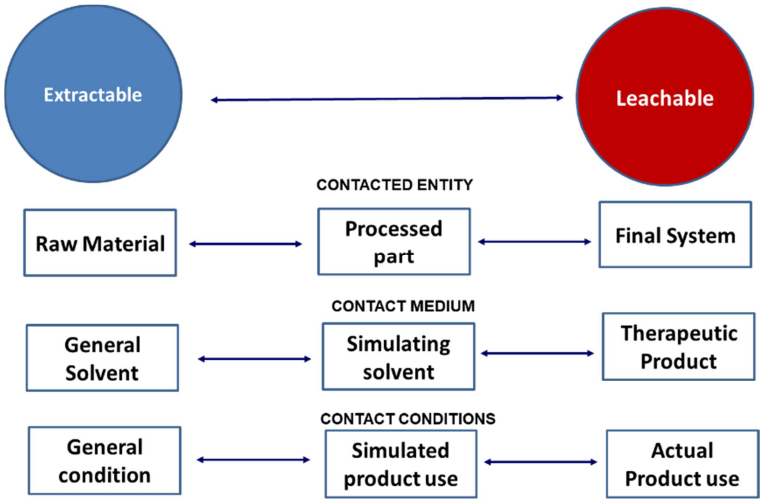
- *Leachables: Those substances that are present in the drug product due to its contact with a material, component, system etc.*

	Patient Safety	Container
EXTRACTABLE	Possible Impact	Test Material
LEACHABLE	Actual Impact	Test Product

Fig 1: **Extractable v/s leachable**

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

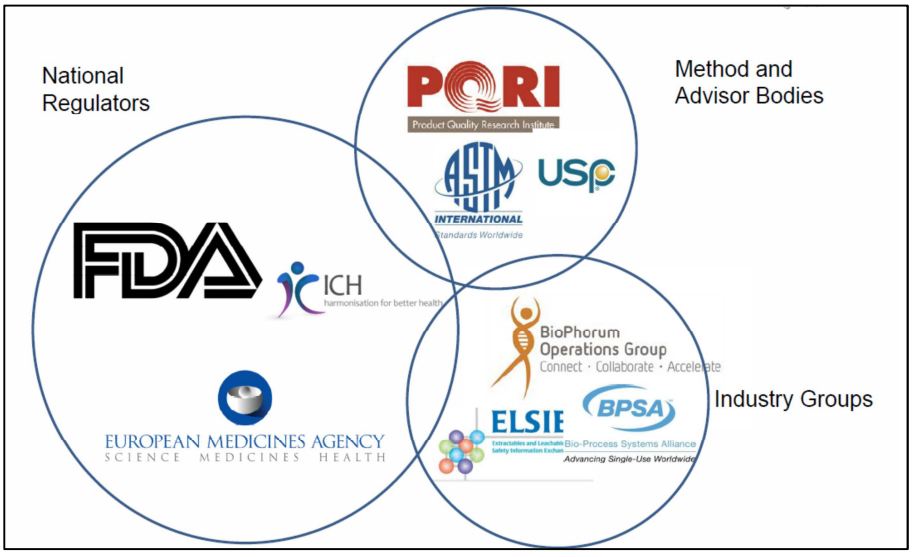
patients having adverse effects and even fatalities that were suspected due to impurities leaching from the packaging material into the drug product. These were initially for Orally Inhaled and Nasal Drug Products (OINDP) and the Product Quality Research Institute (PQRI) was tasked with developing guidelines. 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 2: Relationship between extractable and leachable.

II) 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.

Degree of concern associated with the route of administration	Likelihood of packaging component-dosage form interaction		
	High	Medium	Low
Highest	Inhalation Aerosols and Sprays	Injections and Injectable Suspensions; Inhalation Solutions	Sterile powders and powders for injection, inhalation powders
High	Transdermal Ointments and Patches	Ophthalmic Solutions and Suspensions; Nasal Aerosols and Sprays	-
Low	Topical Solutions and Suspensions, topical and lingual aerosols, oral solutions, and suspensions	-	Oral tablets and oral (hard and soft Gelatin) capsules; Topical powders, oral powders

Fig 3: **Modified FDA/CDER/CBER Risk-Based Approach for Leachables**

SOURCE: USP <1664> "ASSESSMENT OF DRUG PRODUCT LEACHABLES ASSOCIATED WITH PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS"

Fig 2 shows the relative risk of various dosage forms related to extractables/leachables. Inhalation products, injectable represent the highest risk and E/L data will be required to prove compatibility whereas on the other end solid orals have the lowest risk and may not require detailed E/L studies.

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? (Identification)

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

3. Why: Why are these compounds leaching?

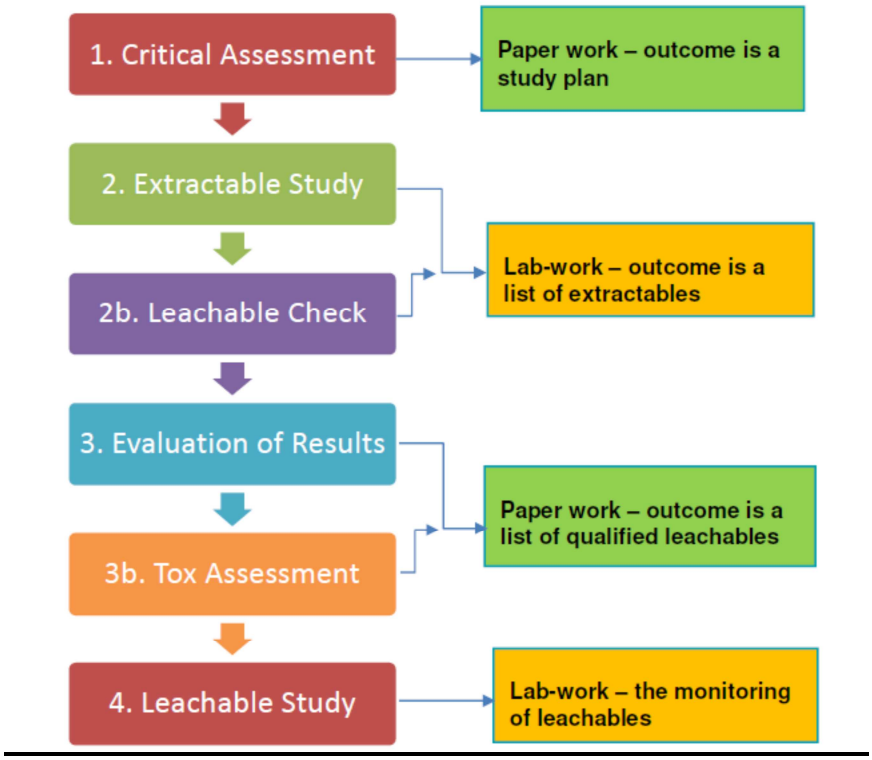
Questions 1 and 2 are generally answered as a part of any E/L study, but rarely is the 'Why' aspect looked into, as this requires material and packaging expertise which usually the pharmaceutical companies lack.

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 are no leachables that can cause a patient safety concern.

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:



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 irrespective of the toxicological nature of compound.*
- 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.*

V) Challenges in performing E/L Study

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, knowledge and creativity of the analysts is very important.

A few common issues that the pharma industry encounters in doing E/L studies are:-

1. Expertise – Far too often Pharmaceutical companies look at E/L as a merely analytical issue and the packaging team is not sufficiently 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. However packaging manufacturers are generating quality Extractable data which could prove very valuable to pharma companies as they can directly proceed to the leachable assessment.

3. Guidelines – There is no standard way or a one size fits all approach for E/L. The dosage form, route of administration, the daily dose, nature of primary and secondary packaging, etc have to be taken in to consideration which is precisely why there are several guidelines that have to be adapted to the current situation. However this creates confusion in designing a good analytical strategy and interpretation of results.

4. 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.

VI) 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-OES, allows the comprehensive identification and quantification of extractable compounds from container/ closure systems.
The criteria for these methods are that they are on the one hand exhaustive and comprehensive in the sense that all potentially extractable analytes from polymeric materials of a container/ closure system can be covered qualitatively and (semi)-quantitatively. On the other hand 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 5, 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 4 of the raw polymeric material and extracts thereof are overlaid:

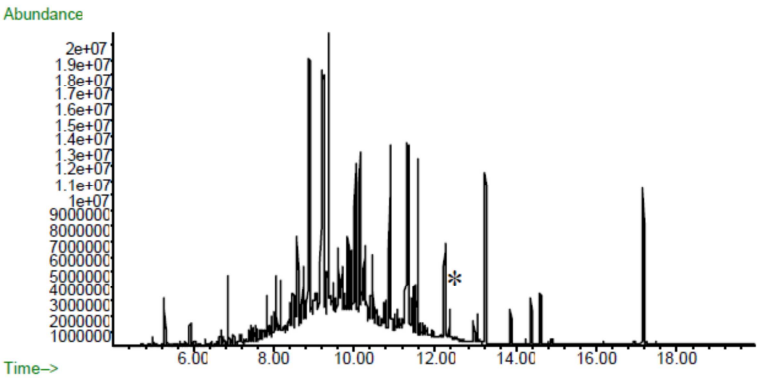


Fig 4: **TDS-GC/MS chromatograms of polymeric part of a catheter system**

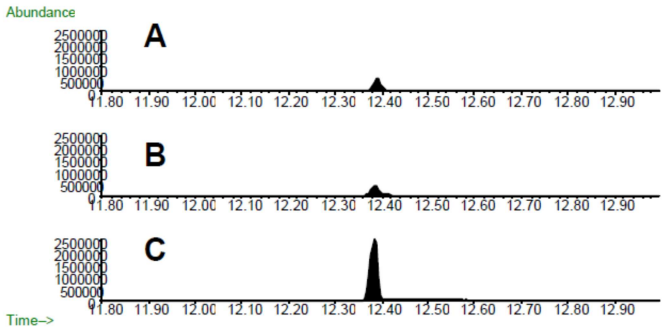


Fig 5: **TDS-GC/MS chromatograms (ion trace) of A: raw polymeric material, B: ethanolic extract, C: aqueous extract after workup**

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) <u>Headspace-GC/MS (HS-GC/MS)</u>

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 6:

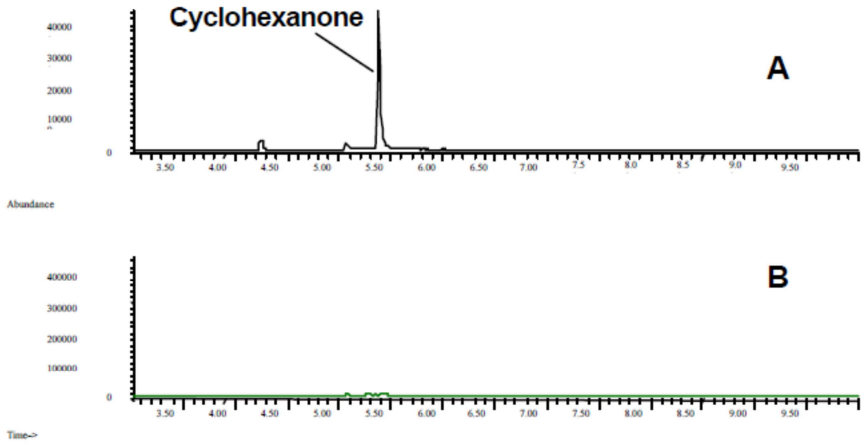


Figure 6: Overlay of HS-GC/MS chromatograms of aqueous extracts of a printed (A) and an unprinted (B) polymeric container/ closure system.

(c) <u>LC/MS</u>

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) <u>ICP OES or ICP- MS</u>

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: on the 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 - and these methods obviously strongly depend on the type of analyte and on the matrix.

VII) Key Messages and Summary.

- Limited direct regulation covering E/L.
- 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.
- 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.

It is mandatory for Pharmaceutical companies to demonstrate compatibility of the device/packaging with the drug product by submitting E/L 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 or improving packaging materials and devices which have lower leachability and hence better compatibility.

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