Extractables and Leachables Testing
A Risk Based Approach

White Paper

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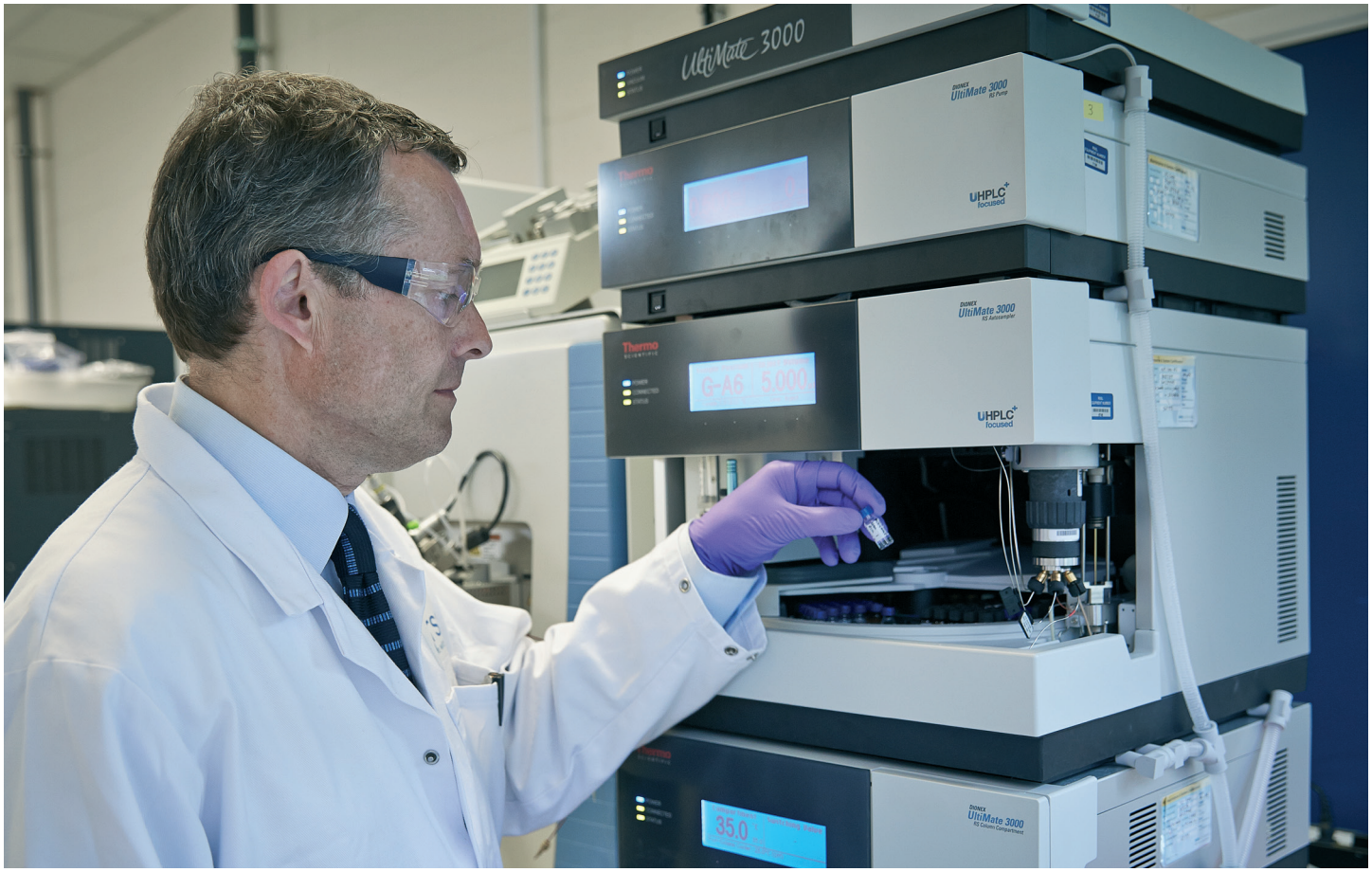
Introduction

Pharmaceutical products are in contact with many external components during both manufacture and usage and small amounts of chemicals may leach from these components with a potential health risk to the patient. Extractables and leachables (E&L) studies therefore play an important role in verifying the safety of a drug product over its lifetime.

Regulatory organisations such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) are taking an increased interest in the interactions of various drug delivery devices, pharmaceutical product containers and medical devices with drug product and/or patient and this field is therefore growing in importance.

Regulatory guidelines indicate that an extractables profile should be determined for all materials that contact the drug product. Once established, this profile can be used to determine whether any of these extractables are present as leachables within the product. If a leachable is detected, amounts can be determined using validated analytical methods, after which a biological risk can be established based on the exposure.

This white paper will provide an overview of the processes used to determine extractables and leachables from plastics.



Extractables definition

These are chemical compounds and inorganic elements that can be forced to migrate from the contact material (container, syringe, tubing etc.) under aggressive conditions such as extreme surface exposure, elevated temperature and/or strong solvents.

Leachables definition

These are chemical compounds and inorganic elements that migrate from the contact material into the product of concern under normal conditions of use. Leachables are usually a subset of extractables.

Why do we need extractables and leachables testing

The FDA has previously stated that "Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements[1]".

With the introduction in 1999 of the industry guidance document: Container closure systems for packaging human drugs and biologics[2] this has led to the formalised testing for extractables and leachables from container closure systems.

A number of industry guidance documents have since been issued by bodies such as the EMEA[3] and the Product Quality Research Institute (PQRI[4]) providing valuable information when carrying out extractables and leachables studies.

Taking a look at some specific leachables examples, there have been a number of high profile incidents over the years regarding food and pharmaceutical products contaminated by leachables.

In 2010, a product recall was launched for 28 million boxes of breakfast cereal[5] after consumers reported a strange taste and odour, with some complaining of nausea and diarrhoea. These symptoms were subsequently found to be caused by elevated levels of methylnaphthalene in the product packaging.

Also in 2010, a product recall was launched for a medical product, Tylenol (paracetamol)[6], used for pain relief and the relief of cold and flu symptoms, after consumer reporting of a strange odour coming from the bottles in which the product was stored. The odour was later linked to 2,4,6-tribromophenol, a wood preservative, that was present within wooden pallets that were used to transfer the product.

In the same year another medical product, Lipitor (atorvastatin)[7], used to lower blood cholesterol, was also recalled due to contamination with a 2,4,6-tribromophenol related compound.

These examples and many like them therefore highlight the need to understand potential sources of leachables and to proactively look for and control them.

A typical approach to extractables and leachables studies

There are five main stages to conducting an extractables and leachables study and these will be discussed in more detail over the following pages. The stages include:

1. Sample assessment
2. Vigorous extraction of the material under test
3. Analysis of the extracts
4. Assessment of the extractables data
5. Conducting the leachables study

Before beginning though, a brief word on what extractables and leachables are chemically. These are typically small molecules (molecular weight under 1500 amu) and they originate from a variety of sources. Examples include, but are not limited to plasticisers, lubricants, stabilisers, pigments, surface residues from component fabrication processes, emulsifiers, anti-oxidants, reaction products, anti-static agents, slip agents, label glue/ink components and residual monomers and oligomers of the plastic polymer. Many of these compounds may be detected as extractables due to the aggressive conditions used during the extractables phase of the study, but will not necessarily be leachables.

Sample assessment

Before beginning an extractables and leachables study it is important to determine the leachables risk associated with a particular product. This risk will be dependent on two factors; route of administration and likelihood of a packaging component-dosage form interaction. Risk can be summarised in the following table 2 and will determine future safety thresholds for all 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 solutions; Injections and Injectable Suspensions	Sterile Powders and Powders for Injection; Inhalation Powders	
High	Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays		
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions	Topical Powders; Oral Powders	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules

The PQRI leachables and extractables working group have recommended a safety evaluation threshold for highest risk routes of administration e.g. Orally Inhaled Nasal Drug Product's (OINDP's)[4] which has been justified from a toxicological and safety perspective.

This threshold is called the 'Safety Concern Threshold' (SCT), has a value of 0.15 µg/day and is defined as the threshold below which an individual leachable would have a dose so low as to present negligible safety concerns from carcinogenic and non-carcinogenic effects.

For lower risk routes of administration e.g. Oral solutions, a SCT of 1.5 µg/day can be used. This represents a lifetime risk of cancer of 1:100,000 and could theoretically be increased further under certain circumstances e.g. short term exposure, treatment of a life-threatening condition.

The European Medicines Agency (EMA) guidance document 'Guideline on the limits of genotoxic impurities[8]' contains further details as does the FDA draft guidance document, titled 'Guidance for Industry, Genotoxic and carcinogenic impurities in drug substances and products: recommended approaches[9]'.

These thresholds represent absolute exposure, expressed as total intake per day. There is therefore a need to convert this value into an amount of leachable per drug product. This threshold is known as the 'Analytical Evaluation Threshold' (AET) and is determined by consideration of the SCT and the specific drug product configuration. The AET can then be used to assess instrument suitability for a particular project.

Vigorous extraction of the material under test

Extractables studies are conducted to determine what chemical substances are contained in materials that are in contact with the drug product and thus have the potential to leach. Study design will depend on the composition of the material to be tested and its conditions of use and the intention would be to exaggerate these conditions in order to generate more extractables than what would potentially leach into the drug product.

All extractable studies will be carried out on a representative portion of the material under study using multiple solvents of varying polarity. Typically two to three solvents will be used. These solvents will be chosen to mimic and exceed the solvating power of the drug product, however care should be taken to avoid solvents that are too strong as the final extractable sample may not be representative due, for instance, to extensive decomposition of the material under test.

The testing will be performed under exaggerated conditions of time and temperature using the chosen extraction technique. Examples include, reflux, soxhlet extraction and ultrasonic agitation.

Once samples are prepared, they can be concentrated, if necessary, and then analysed. If concentrated, care should be taken to avoid loss of unstable or volatile components.

Analysis of the extracts

Analytical techniques should be chosen to ensure detection of as many extractables as possible. Extractables fall into a number of broad categories and no single instrument is able to detect all of them. Extractables categories include volatiles, semi-volatiles and non-volatiles and these can be organic in nature or inorganic such as elements, including metals, or salts.

For this reason, a number of different analytical techniques are used and these would typically include Gas Chromatography Mass Spectrometry (GC-MS), Headspace GC-MS, Liquid Chromatography Mass Spectrometry (LC-MS) and Inductively Coupled Mass Spectrometry (ICP-MS) although additional techniques could be used if required. For instance Ion Chromatography (IC) for salts or Fourier Transform Infrared Spectroscopy (FT-IR) for non-volatiles.

Aqueous soluble extractables would normally be detected by LC-MS. Volatile and semi-volatile organic extractables would normally be detected by GC-MS or headspace GC-MS with elements, including metals, detected by ICP-MS.

Further work is then required to identify every extractable detected above the analytical evaluation threshold.

Assessment of the extractables data

As many extractables as possible will be identified in order to allow a toxicological assessment to be made prior to beginning any leachables studies. Identification would also provide the opportunity to buy in commercially available standards should method development/validation be subsequently required.

The identification process will typically involve extensive manual data interpretation, library searches, analyst expertise as well as the use of additional analytical techniques.

Identification can be a challenging process with full structural elucidation not always possible. If partial identification is achieved, then a closely related analogue may be used to aid with the quantitation of any potential leachables.

Only after a full assessment of all extractables has been conducted should a leachables study be undertaken.

Conducting the leachables study

A leachables study is conducted in order to detect any substances that may leach out of the material under investigation into the drug product and thus put patient safety at risk.

Substances of concern will have been previously identified during the extractables study and these will be screened for during the leachables study alongside representative standards in order to ascertain whether the analytical evaluation threshold has been exceeded.

Prior to conducting the study, method development would be conducted in order to ensure that all extractables of interest could be detected at acceptable concentrations in the presence of the product matrix with method validation to follow, if required.

Study design would involve placing the drug product on stability storage for a representative period (typically up to the expiry of the drug product). The drug product would be stored in the packaging under investigation, inverted or upright. Stability storage would be carried out under ICH conditions and 25ºC/60%RH real time, 40ºC/75%RH accelerated storage would typically be used although different conditions would be chosen should product storage warrant it.

Care should be taken in labelling and storage of the samples as secondary packaging is a potential source of leachables. For instance, inks and adhesives from in-house labelling may contain leachables that could migrate into the drug product.

Samples would be analysed at various time-points over the duration of the study, for instance 3 months, 6 months, 9 months and 12 months, with analysis typically carried out by GC-MS, Headspace GC-MS, LC-MS and ICP-MS. A leachables profile can then be established.

Any leachables detected above the analytical evaluation threshold would be quantified and assessed for toxicity before a final decision was made on product safety.

Conclusion

Extractables and leachables studies are predominantly complex and lengthy investigative studies. Study design is therefore critical in reaching a successful outcome, namely verification of the safety of a medical product.

A combination of laboratory expertise as well as access to a wide range of analytical instrumentation is essential before an extractables and leachables study can be undertaken due to the wide range of analytes that may be encountered.

Laboratory expertise includes an understanding of the materials in contact with the drug product as well as the drug product itself, strong investigative/identification skills as well as knowledge of how to develop and validate quantitative methods.

Despite these challenges, careful planning and execution will deliver a successful outcome with patient safety the final goal.

RSSL is an established expert in this field, we have performed controlled extractables and leachables studies on a wide variety of containers, closures and medical combination drug delivery devices using a range of analytical technologies (LC-MS, GC-MS, ICP-MS). To find out more about our extractables and leachables services, please contact us on: +44 (0)118 918 4076, email enquiries@rssl.com, or visit www.rssl.com

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Peter has over thirty two years of pharmaceutical industry experience, working both in the private sector and within a CRO environment. He has extensive knowledge of a wide range of analytical techniques and drug product matrices. Peter's primary areas of expertise include investigative LC-MS, method development and extractables/leachables testing.

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