

# Due Diligence for Leachables and Extractables in a Modern GMP Environment



## Introduction

Nearly two decades have passed since extractables and leachables have become a primary consideration for qualifying packaging intended for pharmaceutical use. The complexity of medicines and associated delivery systems continues to evolve, challenging approaches for identifying and quantifying leachables. Regulatory guidance for extractables and leachables exist, but only provide general recommendations for ensuring patient safety. Step-by-step instructions are impractical as dosage form, materials of construction, configurations and dosing are unique for each product; thus, potential impact to the patient must be reviewed case by case. Modern GMP advocates risk-based approaches starting at the drug product development stage, and determining the potential for leachables should be a priority to ensure patient safety. A comprehensive leachable study is a qualitative and quantitative evaluation of constituents that have the potential to migrate from packaging materials into a particular drug product over the proposed shelf-life. Dilemmas remain, including questions of how much testing needs to be done, when and at what sensitivity, and how to determine the process for qualifications. Methodology for extracting contact materials and assessment of the extracts is employed in food, drug and medical device industries, with the common goal of understanding what can migrate from these materials and potentially cause harm. While it is desirable to have definitive methods with identified sensitivity and specifications to fit all cases, it is not realistic; this article will look at extractable and leachable science and discuss approaches, applications and risk-based strategies.

## Background

Extractables are compounds that can migrate from components of a container closure system when in the presence of a solvent. These extractables have the potential to become leachables, compounds that can migrate into the dosage form from the container closure system over time in storage. It is critical to evaluate components used in the manufacture, containment and shipping of drug products that have direct or indirect contact with the medicine for potential leachables in all types of dosage forms. Several healthcare industry recall cases dating back to 1990 have cited the migration of 2,4,6-tribromoanisole (TBA) and 2,4,6-trichloroanisole (TCA) in tablets due to diffusion and permeation of these molecules from indirect contact with shipping pallets.<sup>1</sup> A number of different leachable cases

involving metal cations, tungsten, bromine, butylated hydroxytoluene and organic solvents originating from primary containers and prefilled syringes have been reported in various biologic protein products.<sup>2</sup> In order to ensure confidence when moving into scale-up and commercial phases, pharmaceutical manufacturers should identify potential leachable substances during drug development and assess the potential impact to medicinal product and patient. Investigation of packaging components will provide the knowledge needed to establish quality control points throughout the drug product lifecycle that are specific for the components' application. Unfortunately, the package configurations, manufacturing processes, dosage formulation and dosing - all of which can have an impact on leachables - are not entirely defined

**Table 1: Examples of Dosage Forms Materials and Associated Risks**

Risk Category Route of Administration	Dosage Forms	Components	Common Materials of Construction
Highest	Inhalation Injectables	Actuators, Canisters Pump/Valves Assemblies, Vials, Prefillable Syringe Components, Stoppers, IV Bags, Auto-injectors	Polyester, Polyacetal, Epoxy Coatings, Metals, Cyclic Olefin Polymers, Polypropylene, Polyethylene, Glass, Elastomers, Polyvinyl Chloride, Thermoplastic Elastomers/Rubber
High	Ophthalmic Transdermal Patches Nasal Sprays	Bottles, Closures, Tip Caps, Labels, Overwrap	Polyethylenes. Polypropylene, Polyesters Adhesives, Inks, Paper, Lacquer, Foil Laminates
Low	Topical Oral	Lined Tubes, Closures, Coatings, Bottles, Blister Packs	Metal, Epoxy Coating, Polyethylenes, Polypropylenes, Cyclic Olefins, Foil Laminates

early in the development process.<sup>3</sup> The degree and type of evaluation for each of these components is dependent on many interrelated factors. Many types of materials are used in the pharmaceutical and medical device industry, including those shown in Table 1: Examples of Dosage Forms, Materials and Associated Risks.<sup>4,5</sup> All types of materials can contribute to a leachable profile; metal, glass, rubber and plastic can present a risk to patient safety and drug product quality. Particulates have been reported due to leaching or sloughing of constituents from product contact materials, such as glass or roughing in stainless steel, that impacted drug product purity and safety.<sup>6</sup> Polymer materials, especially when subjected to heat and solvents, are at risk of migration of constituents from component materials that directly or indirectly contact medicinal products and should be carefully investigated.

### Science of Migration

The likelihood that extractables will result in leachables can be viewed in terms of migrant interactions related to permeation of volatile components into drug products, or accumulation of a migrant at the package product interface and partitioning into drug product or precipitation. The phenomenon of migration encompasses a range of physical and chemical processes that include extractable rates of diffusion, solubility, permeation and chemical structure. The area of exposure will have an effect on the potential for migrating species. Time, temperature and type of contact media/solvents also may affect the rate of migration. In the end, it is the actual exposure over the shelf life of the product that will serve as proof of impact on patient safety because it relates to accumulation of leachables and dosing per day. Although predictive models maybe employed, there are many contributing factors to multicomponent systems in which models can lead to great uncertainty. There are also conditions in which model extraction studies may not capture all potential leachables, or maximum concentrations are not fully represented. Protection of patients relies on properly designed extraction studies followed by full shelf-life

leachable studies.

Ingredients used in the manufacture and forming of the materials such as additives, processing aids, residuals and cleaning agents can all be suspected extractables, as well as associated with their potential contamination or degradation of products. A controlled extraction study will provide potential for leachables as a first step. These studies should include extraction after final processing (e.g. sterilisation and assembly) to reveal the actual potential leachables, because this is the system that will be in contact with the drug product over the shelf-life. Migration of additives in polymer materials and impact on food safety have been widely investigated in both the United States and Europe. Legislation has been enacted to protect consumers based on positive lists for indirect food additives. There are examples of regulations that have threshold limits for safety associated with allowable amounts to be added to manufacture the packaging materials and, in some cases, specific migration limits.<sup>7,8</sup> While thresholds are important for leachable assessments, there is limited utility for specifications listed in the food additive regulations with respect to qualifying packaging for pharmaceutical use. Migration of additives or chemical constituents from polymers related to the pharmaceutical and medical device industries consider other routes of exposure and impact assessments, which do not necessarily translate to the same type of alerts.

Once leachables can be confirmed through appropriately conducted

studies, the impact on the patient and medicinal product can be evaluated. There are many conceivable substances that have the potential to leach, but it is only those that leach above an acceptable level that are of priority. Leachable thresholds have been recommended by the Product Quality Research Institute for orally inhaled and nasal drug products; other dosage forms are still being considered.<sup>9,10</sup> The challenge of identifying and prioritising leachables relies on a thorough understanding of packaging component chemistry; however, extractables data alone cannot predict the impact on patient safety. Understanding the chemistry of components and the mechanics of migration will aid in developing suitable extractables and leachables methodology to provide the rationale for control strategies based in science.

Extractables can be classified in terms of molecular weight and other aspects to associate probability of extraction by taking into consideration parameters influencing migration. This information is useful to identify appropriate test methodology. The potential safety impact of a given leachable is greatest for those constituents that have evidence of toxicity, but often these occur at trace levels and are not always readily detectable. Classes of potential leachables can indicate potential for a migrant's diffusivity, and surface interaction leading to appropriate investigations of chemical entities should be considered for developing

**Table 2: Physical Chemical Indicators for Potential Leachables.**

<b>Molecular Weight</b>	<b>Classes of Potential Leachables</b>
Low < 250 Da	Unreacted Monomers, Degradation Products, Additives
Medium	Monomers, Additives, Reaction Products, Impurities, Low Molecular Weight Oligomers
High >1000 Da	Additives, Oligomers, Condensation Products, Polymeric Additives
<b>Other Aspects</b>	<b>Influencing Factors</b>
Material Type	Nature of Material, Molecular Weight and Structure, Crystallinity, Glass Transition Temperatures, Orientation, Cross-linking, Permeability
Additive	Chemical Nature, Concentration, Molecular Weight, Size, Shape, Interaction, Diffusion Coefficient
Co-Additive	Fillers, Solvents, Monomers, Reactive Chemistry Co-Diffusants
Processing	Morphology, Homogeneity, Forming Conditions, Cleaning, Packing, Storage Time and Conditions
External Environment	Compatibility with Contact Media, Temperature, Pressure Humidity, Length of Exposure, Area of Contact, Sterilisation Methods
Experimental Conditions	Contact Time, Type of Solvent, Temperature, Physical Geometry, Area, Extraction Techniques, Introduction for Analysis

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analytical methodology.<sup>11</sup> Influencing factors for potential leachables are referenced in Table 2: Physical Chemical Indicators for Potential Leachables.

### Extractables

Selection of critical components (individual components of manufacture, containment or other material contacting the drug product) and extraction of the test material are the foundations of an extractable study. Adequate component sampling is necessary to establish a comprehensive profile as variability of trace level constituents is inevitable. In addition, suitable sample preparation, material-to-solvent ratio, type of solvent and extraction conditions are critical for acquisition of proper data. The function of the critical components, along with knowledge of the component composition and drug product formulation, should be used to guide solvent selection. Multiple extraction techniques and analytical techniques should be employed.<sup>12</sup> The course of the study should be planned to achieve the outcome that will support the study objective and lead to appropriate leachable studies. Extractables assessments have been used to serve multiple purposes, such as overall chemical characterisation, to understand potential for leachables in severe conditions or model systems to represent intended use to indicate probability for leaching under specified conditions. Model systems are intended to mimic products under accelerated conditions, and are typically employed by the food industry and certain medical devices.<sup>13,14</sup> Regardless of the conditions chosen for the extraction study, the outcome of the test should provide results that correlate and confirm the type and amount of leachables for pharmaceutical packaging, which is needed to judge patient safety.

An example of data generated for a polypropylene sample for the purpose of characterisation compared to that of an accelerated condition to simulate migration is illustrated in Figure 1: Material Characterisation GC/MS Data Compared to GC/MS Data Simulating Actual Use Conditions.<sup>15</sup> Conditions for characterisation will

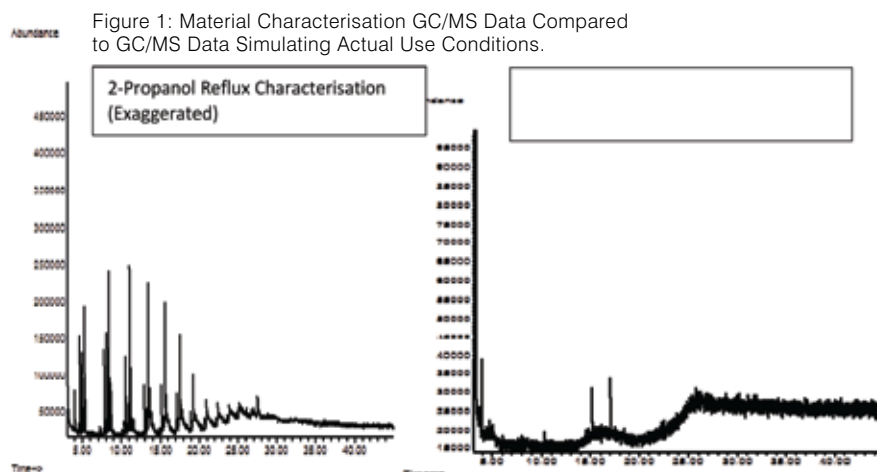
provide information to understand the chemistry of extractables through maximisation of migrants, while a model extraction study employs simulated conditions intended to indicate or predict actual use. It can be realised from the GC/MS chromatograms that the simulated conditions alone would not provide adequate background to establish a comprehensive extractable profiles or leachable assessment; however, they can be a gauge for migration behaviour.

The generation of extracts, and identification and measurement of extractables or migrating substances, are time-consuming and should follow a systematic approach of investigation. Understanding the migration behaviour can provide insight into the selection of study parameters and analytical methodology. Polymer characteristics to consider are:<sup>16</sup>

- Polymer effects (morphology, molecular structure surface energy, entropy)
- Physical loss of chemical constituents and conversion to associated degradation products
- Chemical reactions within complex mixtures, formation of by-products or interaction products
- Migration of chemicals to the surface
- Solubility in contact media, precipitation, blooming effect
- Extractive loss and mass transport based on molecular motion (diffusion rate or volatilisation)
- Outgassing (evaporation of rest constituents) in headspace or accumulation in solution
- Permeability or transport of chemicals through a material

### Leachables

Leachable studies are often not conducted until later in the pharmaceutical development programme. In these studies a drug product is stored in stability under a variety of controlled environmental conditions and analysed for leachables, both qualitatively and quantitatively, at multiple time points over the anticipated shelf-life of the drug product.<sup>17</sup> Extractables serve as an indicator of potential leachables, but the probability for migration of chemical entities in a drug product can be unexpected, proceeding slowly and/or under unique, unpredictable conditions. When parameters influencing migration (such as temperature) are accelerated, there are possibilities for anomalies to occur. If conditions or contact media are too mild, it is possible leachables can be missed. Drug product impurity analysis may reveal leachables, but often at high levels, and independent studies are necessary to trace back and correlate to a source. An example of a leachable detected in an impurity assay was demonstrated for an ophthalmic product. Changkang described the methodology used to trace the 0.19 percent impurity back to a lacquer coating.<sup>18</sup> To mitigate the risk of chasing abnormalities or missing a critical leachable, targeted studies should be conducted throughout stability while early assessment can warn of potential hazards. Drug stability is a key property to be monitored during development and throughout the drug product lifecycle, but impurity assays cannot always be optimised for suitable concentrations of potential leachables. Drug degradation products, impurities



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and potential leachables require appropriate methodology for discovery and measurement. A trace level constituent can arise from multiple and/or obscure sources. Leachable methods should be robust enough to capture the expected, the unexpected and potential unknowns. Because methods can be very sensitive, it can be challenging to ascertain the identity of unknowns as well as the source. A substantial amount of time can be invested in isolating and confirming the unknown leachable compound. Comprehensive extractable studies should result in a better understanding of the component chemistry and facilitate the identification of unknown leachable compounds and potential mechanistic pathways.

Once the materials in contact with the drug product are understood in terms of their extractables or migrants, potential leachables should be assessed. Decisions are necessary to select which of the observed chemical species may be of concern for patient safety and drug product quality. Leachable studies require several steps before the leachables analysis can begin: compounds should be identified confidently, reference compounds made available for measurements, and appropriate instrumentation and analysis conditions developed, validated and optimised for adequate sensitivity. In addition, the drug product matrix can be anticipated to cause interference with detection techniques and recovery of analytes. Ingredients in drug product formulations often can obscure the response of low-level constituents of interest or bind to the matrix, which can also present quandaries. Targeted studies that use optimised/validated methodology for measurement of leachable analytes in the specific matrix offer more accurate information about leachables. The methodology that has been developed for appropriate specificity, recovery and reproducibility of the target analytes within the matrix produces a confident leachables study with correlation to extractables.

A “bridge” between extractables and leachables can be implemented using an approach from a theoretical perspective and/or additional extraction studies under a simulated or stressed



environment. The outcome of this assessment will provide background information to ensure development of appropriate leachable methodology or indicate a potential toxicological concern. These data can have a place in early development, especially when the specific drug product formulation has not been finalised. Solvents that most closely simulate the drug product matrix, placebo or the drug product itself are typically used under accelerated conditions. Often method optimisation is necessary for accelerated studies in complex matrices that may or may not be feasible for leachable development. The full process of material characterisation and understanding extractables through development of specific methodology and monitoring of leachables throughout stability is not a rapid process, but one rooted in Quality by Design (QbD).

The goal of QbD is to plan for quality attributes based on a quality target product profile (QTPP). The profile for components in contact with a dosage form should include acceptable levels of leachables. The risk of leachables should be assessed in relation to properties of dosage form, route of administration, patient population, dosing and patient daily exposure. Prior knowledge is useful to guide methodology for discovery and understanding of potential leachables derived from comprehensive extractables evaluations. A planned set of controls should be developed based on leachable studies and a current product and process understanding

to assure product quality with patient safety in mind.<sup>19</sup>

### Conclusion

Understanding the science of extractables and correlating to leachables using risk-based strategies will support drug development stages and continue throughout the drug product lifecycle. Application of risk-based strategies will provide rationalisation to influence decisions to assure drug product quality and patient safety related to materials in direct or indirect contact with dosage forms. Final component selection and drug formulation design should include information gathered in material characterisation studies and risk assessments with the aim of decreasing risk later in drug formulation development.

Approaches to extractables and leachables studies are varied and dependent on specific products and patient administration. Extracts generated under simulated conditions can be used to bridge the extractables study and subsequent leachables study, but have certain limitations and should not be perceived as a singular leachables study. Selection of target leachables based on risk and development of specific methodology to monitor for leachables over the shelf life of the drug product are consistent with QbD principles. Accurate measurement and assessment of leachables with full method validation is an essential element to protect the quality of the medicine and the safety of patients.

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### Diane Paskiet

is Director, Scientific Affairs at West Pharmaceutical Services, Inc.



Diane has more than 20 years' experience in polymer analysis relating to product failures, deformation and migration studies. A sought-after speaker, Diane has authored national and international papers on leachables and extractables and is a PDA Training Institute faculty member.

Email: [diane.paskiet@westpharma.com](mailto:diane.paskiet@westpharma.com)

Laura Stubbs is a senior chemist at West Analytical Services. She authors study protocols and analytical reports and serves as the technical contact for clients regarding extractables. Laura has 15 years' experience in the field of extractables and leachables, including managing an organic laboratory group focused on contract extractable and leachable testing of packaging components and drug product, method development and method validation.

Email: [laura.stubbs@westpharma.com](mailto:laura.stubbs@westpharma.com)

### Heike Kofler,

Manager Technical Customer Service Europe, West Pharmaceutical Services.



Dr. Heike Kofler holds a PhD in Life Sciences from the University of Cologne, Germany. She joined West in 2008 as Manager Biotechnology Services in Europe. Since 2011 she is Manager Technical Customer Service Europe and also dedicated to strategic coordination of technical assistance for European start-up companies and universities.

Email: [heike.kofler@westpharma.com](mailto:heike.kofler@westpharma.com)