

EXTRACTABLES AND LEACHABLES - PHARMACEUTICAL REVIEW**Rajendra Phadke^{1*}, Rupali Mali² and Dr. Amit Gosar²**¹Research Scholar, J.J.T University, Churu, Jhunjhunu Road, Rajasthan -333001.²Indoco Remedies Limited, Analytical Research & Development Department, Navi Mumbai, 400701, Maharashtra, India.***Corresponding Author: Rajendra Phadke**

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ABSTRACT

Establishing a link between extractables and leachables must necessary to understand, interpret, assess, quantify, or control the interaction between a drug product and its container/closure system. Extractables and Leachables (E/L) studies help to identify, quantify and minimize harmful impurities which could leach from pharmaceutical container closure systems and packaging into pharmaceutical products. To incorporate quality by design concepts into the management of leachable, an emphasis is often put on understanding the extractable profile for the materials of construction for manufacturing disposables, container-closure, or delivery systems. Component manufacturing processes may also impact the extractable profile. Since the FDA released their Container Closure Systems for Packaging Human Drugs and Biologics guidance in 1999, evaluation of final packaging components for extractables and leachables has become the expectation within the industry. Additionally, the increase in the use of single-use systems in manufacturing has drawn scrutiny as another potential source of extractables and leachables. These single-use systems include bioprocess bags, filters, tubing, fittings, connectors, bioreactors, etc. Many of these single-use systems are constructed from polymeric materials, increasing the concern of the introduction of leachable compounds to product. This paper considers the applied to evaluate the impact of material composition and processing parameters on extractable profiles and utilized to manage product leachable early in the development process and throughout the product lifecycle hence need to control impurities in drug product.

KEYWORDS: Extractables and Leachables, Container closer, Analytical method development, Isolation and Characterization.

INTRODUCTION AND BACKGROUND

A crucial undertaking when releasing pharmaceutical products for the market, is to determine the purity of the final product, necessitating the need to determine its impurity profile. Traditionally, this was concerned only with those impurities arising from the manufacture and degradation of the pharmaceutical product. Nowadays, migration of mobile chemical species from components used in the manufacture and storage of pharmaceutical products must be assessed. Regulatory bodies such as the US Food and Drug Administration (FDA) and The European Medicines Agency (EMA) are increasingly focusing on the interactions between various manufacturing components, drug delivery devices and container-closure systems (CCS), and the final pharmaceutical product. The aim is to identify and assess any toxicological risks which could arise via such interactions.

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.” Consequently, extractables and leachables (E&L) studies are now a crucial component of product release. Extractables and leachables (E/L) studies are critical to the identification and quantification of harmful leachable impurities which could migrate from pharmaceutical container closure systems, process equipment and packaging to contaminate pharmaceutical products.

The type of extractables and potential leachables vary based on the material type. Certain types of these compounds are introduced from the polymer material synthetic process, such as residual monomers, oligomers, polymerization reaction initiators and their degradants, catalysts and polymerization media residuals, curing agents and their degradants for rubber materials, etc. Residual monomers and oligomers are inherent to the polymer materials and are material specific, such as caprolactam monomer for polyamide 6, and cyclic polybutylene terephthalate (PBT) dimer and cyclic PBT trimer for PBT material. Many extractables and leachables (E&L) are additives to the polymer materials or their degradants. The most common polymer additives

are antioxidants such as butylated hydroxytoluene (BHT), Irganox 1010, Irganox 1076 and Irgafos 168. Also, certain polymers include plasticizer additives such as diethylhexyl phthalate (DEHP), epoxidized soybean oil and antistatic agents, colorants and stabilizers, among others.

There are also extractables and leachables that are introduced from the component molding process, and although they are not intentionally added to the material, they can end up being introduced to the product as a leachable. Examples of this are mold release agents and lubricants used in the molding process. Since leachables may affect drug product safety, efficacy and quality, regulatory guidance's have provided recommendations regarding their analysis and toxicological safety assessment, i.e., qualification. Extractables studies are necessary to facilitate the leachables' analysis, providing predictive information of potential leachables and in certain cases controlling leachable amounts in the final drug products through the control of extractable amounts of the container/closure components.

EXTRACTABLES AND LEACHABLES: DEFINITIONS AND SOURCES

The FDA defines extractables and leachables as follows

Extractables: Organic and inorganic chemical species that can be released from the surfaces of components used in the manufacture and storage of drug products under laboratory conditions (accelerated or exaggerated

temperatures, solvents or surface exposure). Extractables represent the worst-case scenario regarding release of mobile chemical species from manufacturing and packaging components during forced extraction.

Leachables: Organic and inorganic chemical species that can be released from the surfaces of components used in the manufacture and storage of drug products under conditions of normal use. Leachables should then comprise a sub-set within this pool of mobile chemical species, released under the gentler conditions of on-shelf storage.

A profile of extractable components must be obtained, via controlled extractables studies (CES), in order to identify potential sources of leachables such as antioxidants, plasticizers, dyes and metal catalysts. As pharmaceutical packaging, drug delivery systems and implantable medical devices can be extremely complex, with mixtures of plastic, polymer, rubber or glass materials, printed surfaces and coatings all utilized, it is critical that E/L studies are designed specifically for your drug product and the container materials so that the risks associated with leachable impurities can be assessed. In practice, however, the leachables study identifies species that were not all observed during the preceding extractables study. Thus, the set of leachable species is not wholly included within the set of extractables, but there is strong overlap between both sets.

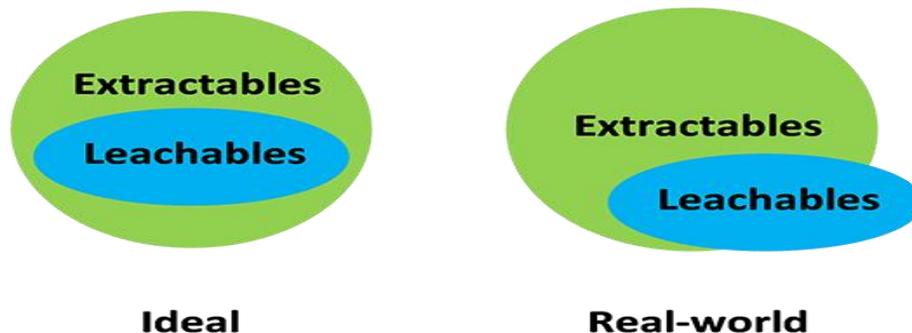


Fig 01: Relationships between extractables and leachables.

There are multiple sources which can contain leachable species, and some common examples are detailed below.

- Manufacturing
 - Filters
 - Single-use bags
 - Tubing
- Primary packaging - External components
 - Container-closure system (vials, caps, lids and foils)
 - Single-use systems (syringes and intravenous bags)
- Primary packaging - Internal components
 - Gaskets and O-rings
 - Valves
 - Springs
- Secondary and tertiary packaging
 - Labels and adhesives
 - Inks and colourings

Leachable species to consider as part of an E&L study include

- Antioxidants and stabilisers
- Anti-static coatings
- Lubricants, slip agents and emulsifiers
- Dyes and colourants
- Vulcanising agents
- Residual monomer, polymer and oligomer species
- Phthalates, nitrosamines and polyaromatic hydrocarbons (PAHs)
- Toxic elements – e.g. mercury, lead, arsenic, cadmium

Pharmaceutical packaging performs several vital functions in assuring the drug product quality and safety. First and foremost, packaging must be a barrier to the

external environment and maintain the sterility of its contents. Depending upon the contents, packaging may also use to prevent the drug product from many chemical reaction like oxidation, light degradation, and moisture permeation. A package may help to ensure accurate dosage of a drug product, in an easy and foolproof way. Satisfying all of these functional requirements includes testing of components and materials: plastic containers, metal springs, elastomeric valves and gaskets, adhesives, and coatings. While these materials may meet the functional goals of the container closure, if quality is considered at the beginning of the process, harmful contaminants may inadvertently be introduced into the drug product.

As there is wide history of harmful packaging additives leaching to store contents. Up until the 1980s, carbon black was added to rubber to make it suppler. It was also added to elastomers used in everything from asthma inhalers to baby bottle nipples, until it was shown that cancer causing polyaromatic hydrocarbons leached from rubber made with carbon black. Bisphenol A is used as a building block in polycarbonate bottles and as a liner in metal cans, and was common in baby bottles, but is now known to be an endocrine disruptor and is a banned plastic additive in several states.

Difficulty in packaging means that a wide range of materials are involved. Therefore, potentially harmful leachables, including metals, catalysts, antioxidants, curing agents, activators, accelerators, pigments, stabilizers, plasticizers, and lubricants may be introduced.

A standard extractable and leachable program begins by leachables from packaging or processing materials in an overstated extraction study. Components are shredded and placed in solvents of varying polarity, regardless of final drug product solvent. This solvent component mixture is heated at elevated temperatures to extract all potential impurities out in a short period of time. These extracted chemicals are then identified by various analytical techniques, typically inductively coupled plasma mass spectrometry (ICP-MS), liquid chromatography-mass spectrometry (HPLC-MS), and gas chromatography-mass spectrometry (GC-MS).

Extractables of concern are highlighted and targeted in the leachable study. Not all extractables are leachables, but because it is not always clear which components could leach out under storage conditions likely to be encountered, methods are developed to detect the extractables in the product matrix. During finished product testing, it will be useful to quantify the leachable impurity in the presence of the drug product. These impurity methods are validated for accuracy, precision, specificity, linearity, range, and limit of quantitation.

These validated impurity tests are then added to the suite of tests run during the product stability study.

CURRENT REGULATORY AND INDUSTRIAL GUIDANCE

Many regulatory guidance documents have been established to define the requirements of E&L assessment, including the documents listed below:

- 21 CFR Part 211.94: Drug product containers and closures should not be reactive, additive or absorptive so as to alter the safety, identity, strength, quality or purity beyond the official or established requirements
- Container Closure Systems for Packaging Human Drugs and Biologics Chemistry, Manufacturing and Controls Documentation (FDA, May 1999)
- Metered Dose Inhaler and Dry Powder Inhaler Drug Products Chemistry, Manufacturing and Controls Documentation (FDA, Oct 1998)
- Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing and Controls Documentation (FDA, July 2002)
- Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products (EMA, June 2006)
- Guideline on Plastic Immediate Packaging Materials (EMA, May 2005)
- Specific to medical devices, ISO 10993-12 and ISO 10993-17 describe in detail the E&L sample extraction procedures and the allowable limit for leachables for the biological evaluation of medical devices.

OTHER RELATED GUIDANCE DOCUMENTS INCLUDE.

- USP(659) for packaging requirements, USP(660) for glass and USP(381) for elastomeric closures for injections, which describes the general testing requirements for the container/ closure components;
- USP(232) and ICH Q3D for elemental impurities; and
- ICH M7 guidance, and FDA guidance for Genotoxic and Carcinogenic Impurities in Drug Substances and Products, which describe the limits of impurities in the drug substance or drug product.
- FDA Guidance for Industry, Q8 (R2) Pharmaceutical Development describes the Pharmaceutical Development section establishes that the type of dosage form selected and the formulation proposed are suitable for the intended use. This section should include sufficient information in each part to provide an understanding of the development of the drug product and its manufacturing process. The guidance outlines a series of proactive steps used to introduce quality into the final product.

A CONTAINER/CLOSURE SYSTEM DEVELOPMENT BY QUALITY BY DESIGN (QBD) APPROACH TO MINIMIZE THE IMPACT OF LEACHABLES

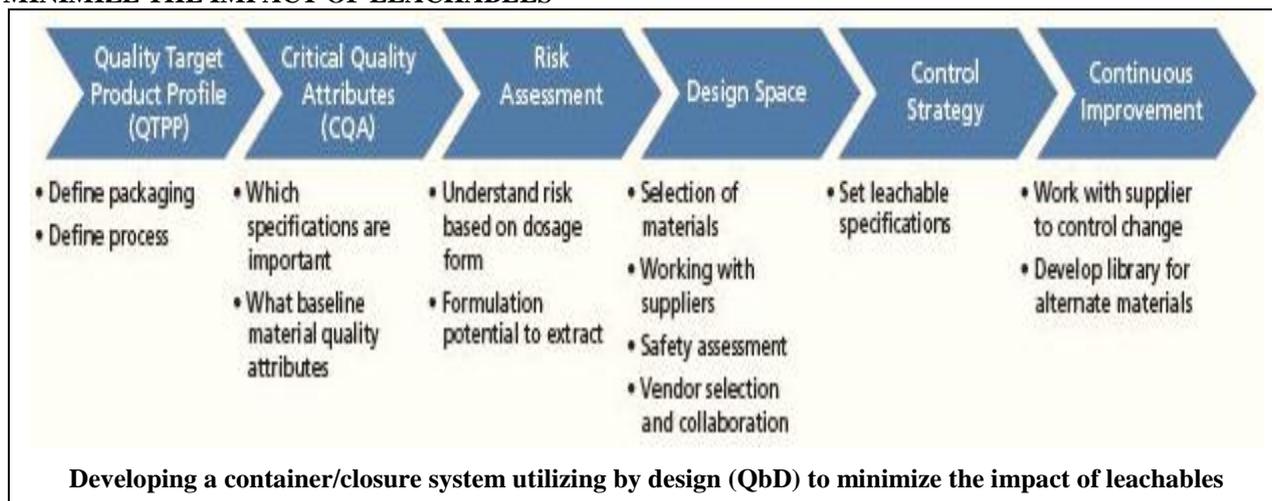


Fig 02.

The quality target product profile (QTPP) is the basis for the design of the drug product and its packaging. It is at this stage that the team will describe intended use, route of administration, dosage form, patient population, chronic- versus short-term use, etc. QTPP information informs the second element of QBD, the critical quality attributes (CQA). CQA is defined as a physical, biological, or microbiological property or characteristic that should be within an acceptable range to ensure the desired product quality. The FDA guideline states that CQAs are generally associated with drug substances, excipients, intermediates, and drug product, but the concept can also be applied to container closure systems.

QAs for specific leachables are added after conducting extractable risk assessment. The relative risk to patient health of design parameters outlined during the QTPP is evaluated and informs CQAs. Consider, for example, the analysis of risk posed by dosage form.

Risk associated with route of administration:

A leached impurity in an inhalation or parenteral product poses a higher risk than the same impurity in an oral or topical product. Similarly, aqueous drug products pose a higher likelihood of drug product interactions than solid oral dosage forms. Therefore, a broader range of leachables at lower detection levels is suggested by liquid parenteral or solvent propelled inhalant drug packaging.

Route of administration and potential harm from leachables, compiled from FDA guidelines for industry, container closure system for packaging of drugs and biologics.

Degree of concern associated with the route of administration	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.

FDA guidance of industry for safety of potential leachables

Route of administration and tests to assess safety of potential leachables, compiled from FDA guidance for industry, containers closers systems for packaging drugs and biologics.

Route of administration	Safety
Inhalation aerosols and solutions	1S: Typically provided are USP biological reactivity test data, extraction/toxicological evaluation, limit on extractables, and batch-to-batch monitoring of extractables.
Injections, injectable suspensions, sterile powders for injections, ophthalmic solutions.	2S: Typically provided are USP biological reactivity test data and possibly extraction/toxicological evaluations.
Topical solutions, suspensions, delivery systems, oral solutions and suspensions.	3S: Typically an appropriate reference to indirect food additive regulations for aqueous drug products; non aqueous solvents require additional suitability information.
Topical powders, Oral Powders	4S: An appropriate reference to indirect food additive regulations
Oral tablets and oral (hard and soft gelatin) capsules.	5S: An appropriate reference to indirect food additive regulations

Assessing Leachable Risk

An Ishikawa diagram can be made by the design and quality team to assess potential risks leading to a reasonable extractable and leachables assessment.

Consideration should be given to materials sourced, formulation, storage conditions, and sterilization techniques.

Ishikawa diagram to assess leachable risk associated with drug design

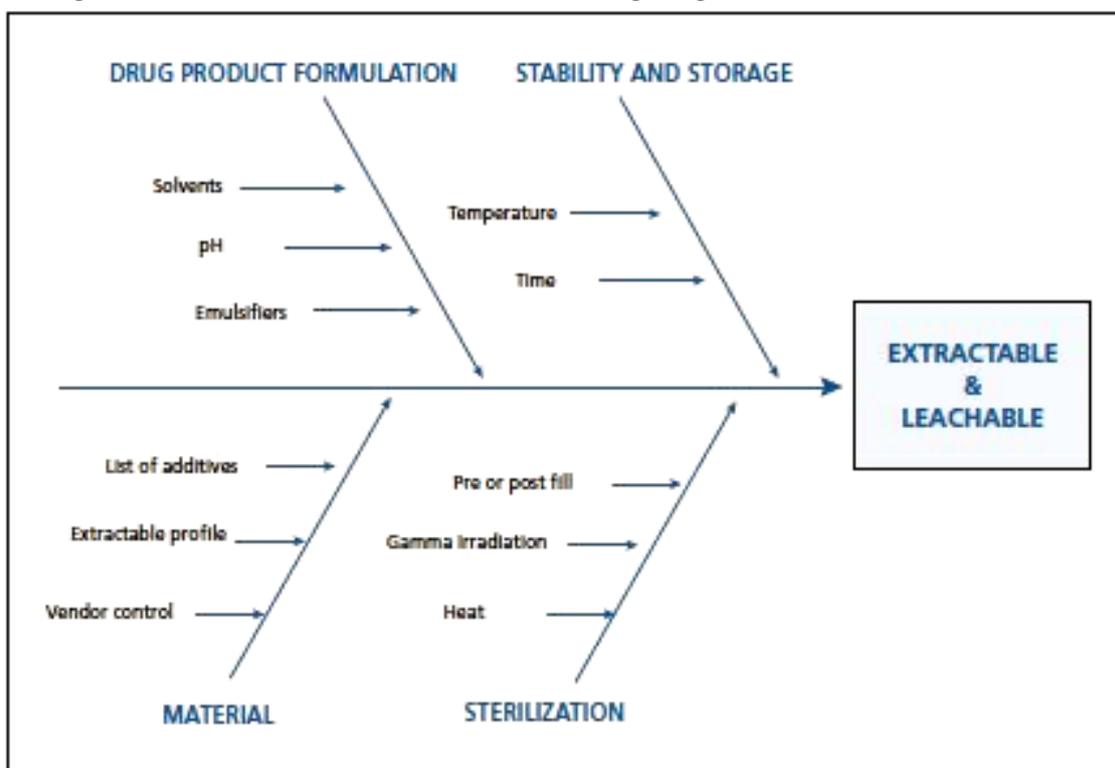


Fig 03.

Designing an E&L Study

An E&L study is composed of two individual. The extractables study identifies species from manufacturing components and the packaging system that could migrate into the pharmaceutical product upon storage under normal conditions. This establishes a baseline for the following leachables study, a series of tests carried out at predefined time-points on the pharmaceutical product for the duration of its shelf-life. Pharmaceutical products may incorporate the use of or interaction with a wide

variety of polymer materials, numerous sources for possible E&L compounds and a diversity of different dosage forms, manufacturing processes and drug product delivery mechanisms. It is not possible, therefore, to present a universal test condition that applies to all E&L testing. However, the study design should harmonize with regulatory expectations and be based on sound scientific principles that are appropriate for the type of dosage form(s) and route of administration.

Extractables and leachables testing studies are recommended even if containers or closures meet compendial suitability tests. Testing should demonstrate that the extractable and leachable profile is acceptable for the specific dosage form and that levels observed will not be approached or exceeded during the drug's shelf life. Test methods must be specific to the drug product and placebo in order to evaluate interferences, linearity and other critical factors. In addition, evaluators must test the final drug/packaging combination for leachables during stability studies.

Prescreening procedures should begin with a basic evaluation of container and closure options. The process can involve multiple temperatures and conditions for acceleration. Extractables can be identified through analytical testing, such as liquid chromatography/mass spectrophotometry (LC/MS), gas chromatography/mass spectrophotometry (GC/MS), inductively coupled plasma (ICP) and infrared (IR). Suppliers of these systems may be able to provide information on testing procedures.

Extractables Study

The components under investigation are extracted in isolation of the pharmaceutical product. Key points to consider are the number of components and material types that are to be tested, and the solvents with which to perform the extractions.

Simple storage systems, e.g. glass ampoules or plastic bottles with screw caps, will have a limited number of components. However, more intricate units, e.g. pump dispensers containing O-rings and springs, will contain multiple components which all require investigation. Secondary and tertiary packaging also needs to be considered at this stage.

Extractions should be performed with a range of solvents of varying solvating power, to ensure a representative pool of organic and inorganic extractable species are generated. In the case of liquid formulations, those chosen should best mimic the composition of the pharmaceutical product to provide a worst-case extractables profile. The use of overly-powerful solvents is discouraged. This could destroy component materials, creating an unrealistically large set of extractables.

Two or three solvents are typically chosen, but more can be used if considered appropriate. Common examples include.

- Water (neutral, and acidic or basic if pH \neq 7)
- Organic solvent (ethanol, isopropanol or n-hexane)

One final aspect to consider is the material type under investigation. Plastics and rubbers should be extracted by all solvents chosen. However, there is little value in performing organic solvent extraction of metal springs, which would only yield inorganic impurities. Such

considerations should be made between the solvents used and the components under investigation.

Extraction Study

The basic purpose of the controlled extraction study is to generate a complete profile of the extractables of the components evaluated, which may be potential leachables in the drug product. The controlled extraction study typically is guided by the Analytical Evaluation Threshold (AET) for selecting the appropriate sample preparation procedures and analytical methods. Following are major points for the design of the controlled extraction study.

- Material preparation
- Extraction solvent
- Extraction ratio
- Extraction techniques, extraction temperature and extraction time
- Analytical methodology

Material Preparation

Controlled extraction studies are performed on individual components whenever possible to trace back the source of leachables, if leachables are detected in the drug product samples. However, components made of the same material type may be combined for the extraction study since this will not affect the leachables' traceability. Sometimes components of different materials are combined in the controlled extraction study. The potential disadvantage of combining components is that it removes the possibility of tracking the extractables from specific components. Components may be extracted whole or reduced to a smaller, possibly more appropriate size for extraction.

Extraction solvent

Extraction solvents should be appropriate for the dosage forms and materials being evaluated, and should provide the worst case possible leachables profile for the drug product formulation without degrading the material. Typically, multiple solvents are used with one solvent being the same or similar to the drug product formulation. Considerations for selecting the appropriate extraction solvent include both solvent extraction capability and the ease of detecting extractables from the extraction solvents.

Extraction solvents with complex composition may interfere with the chromatographic detection of extractables, so, in this regard, simple and high purity solvents are preferred. In addition, solvent selection should consider possible side reactions between the extraction solvents and possible extractables in the materials.

Extraction techniques, extraction temperature and extraction time

The common extraction techniques are still reflux, Soxhlet extraction, sealed vessel extraction and solvent soaking, but other techniques are used, including

sonication, microwave extraction, pressurized solvent extraction with Accelerated Solvent Extractor (ASE) and supercritical fluid solvent extraction. For volatile extractables analysis, a sealed vessel extraction is preferred to prevent the loss of volatile extractables during the extraction process.

Extraction temperature and extraction time selection should be based on achieving an extraction amount. A balanced consideration and approach should be applied, with the goal to achieve optimal extractables amount under practical lab conditions without causing degradation of the material. For medical devices, the extraction temperature and extraction time are defined in ISO 10993-12.

Leachables Study

Samples are screened for leachables, including those identified during the extractables study and any new species found during the leachables study. Those found

Validated analytical methods are required to analyse all samples, and can be used across both studies. Below Figure exemplifies the typical analytical strategy employed.



Fig 04.

ANALYTICAL METHODOLOGY

The diversity of materials and possible compounds and elements present in the materials require a methodology that is able to detect, identify and quantify a wide range of possible extractables.

Methods including headspace GC/MS, direct injection GC/MS, LC/MS (With UV or CAD detection), and ICP/MS is used to screen all known and unknown, expected and unexpected extractables, targeting but not limited to, volatile, semi-volatile, nonvolatile extractables and extractable inorganic elements, respectively.

These MS methods are run in scan mode across a wide mass range, with appropriate gradients, column and

to exceed the SCT are identified and assessed for toxicity.

The control sample should be stored in such a fashion that there is minimal risk of leachable ingress, and carefully labelled avoiding the use of inks and adhesives directly on the container. For the leachables samples, whether they should be stored inverted as well as upright (e.g. bottles fitted with caps or lids), and storage conditions (e.g. 4°C, 25°C/60% RH, 40°C/75% RH) should be considered.

ANALYZING EXTRACTABLES AND LEACHABLES

In general, extractables and leachables can be divided into three broad groups:

- Non-volatile leachables
- Volatile and semi-volatile leachables
- Inorganic / elemental leachables.

mobile phases to elute, separate and detect any known, expected or unknown, unexpected extractables. The method sensitivity should be guided by the AET. There are also other methodologies with targeted extractables analysis for special case compounds, or compounds that may not be detected with the methodology discussed above, such as.

- Nitrosamines analysis with GC/TEA, LC/MS/MS, GC/NCD.
- PAH analysis with GC/MS/MS or GC/MS in SIM mode.
- Silicone oil analysis with AA, ICP/OES, ICP/MS, HPLC (including GPC) with RI, CAD or ELSD detectors.
- Ionic extractables analysis with IC.

CHARACTERIZING THE EXTRACT

Once an extract has been generated, the next objective is to perform a thorough chemical characterization of the extract. Setting a threshold, which is a specified level of an individual extracted chemical entity which requires characterization, can be based on safety considerations. The extract characterization phase of the extraction study must enable the realization of the overall goals of the extractables assessment.

It is a reality that there is no analytical technique or combination of analytical techniques that is capable of the discovery, identification, and quantitation of any and all organic and inorganic extractable chemical entities known to science. In some cases, authentic reference compounds for organic extractables may not be available for confirmation of identifications, or for quantitative instrument calibration. Thus, the objective of extract characterization must therefore be discovery, identification, and quantitation to a reasonable degree of scientific certainty of all individual extractable chemical entities present in an extract above a specified level or threshold.

Processes Involved in Extract Characterization

- Scouting,
- Discovery,
- Identification,
- Quantitation.

SCOUTING

The most useful analytical techniques in a scouting exercise are not compound specific, as they do not provide chemical information specific to the molecular structure of any particular extractable or chemical class of extractables. These analytical techniques provide information regarding bulk chemical properties of organic and/or inorganic chemical entities present in an extract, which can be used to guide extractables discovery, identification, and quantitation.

DISCOVERY

Discovery is the process of searching for, and ultimately finding, individual organic and inorganic chemical entities present in an extract. The process of discovery involves testing an extract and thereby producing one or more analytical results that are attributable to individual extractables. The process of discovery is accomplished by detecting instrumental responses from the individual organic and inorganic extractables that are proportional to the levels of these individual extractables within the extract. It is in the discovery process that analytical techniques typically associated with trace organic and inorganic analysis are first required for extract characterization.

IDENTIFICATION

Identification is the process of assigning a molecular structure to an organic extractable, or assigning constituent elements in the case of an inorganic extractable. Identification of an extractable can be accomplished either by structural analysis or qualitative analysis. Structural analysis is the process by which the molecular structure of an unknown analyte is elucidated from compound-specific data, and therefore requires compound-specific detection of the unknown analyte. A compound-specific detector is one that provides information specific to the molecular structure of the individual unknown analyte.

QUANTITATION

Quantitation is the process of measuring the level, or concentration, of an individual organic or inorganic chemical entity contained in an extract. Quantitation is typically based on the instrumental response of an individual extractable relative to an authentic reference compound, and therefore requires that individual extractables be separated and produce detector responses that are directly proportional to the level of the extractable in a given extract. Calibration of an analytical system is accomplished by analysis of authentic reference compounds.

Analytical techniques which can be employed for scouting are listed in below Table, along with the particular bulk chemical property available from each technique. Some examples of the utility of scouting include the following.

Analytical Technique	Analytical Method	Application				Information/ Utility
		Scouting	Discovery	Identification	Quantitation	
Spectroscopy	UV	X		X		Bulk property of UV absorbing organic extractables; semi-quantitative with limited identification ability
	FTIR	X		X		Bulk property of IR absorbing organic extractables, moderate identification ability
Wet Chemical	NVR	X				Bulk property reflecting total amount of nonvolatile organic and/or inorganic extractables
	pH	X				Bulk property of acidic or basic extractables
	TOC	X				Quantitative measure of organic extractables
Gas	FID		X	X	X	Discovery and quantitative assessment of

Chromatography						individual organic extractables; note that qualitative identification is possible
	MS		X	X	X	Discovery, identification, and quantitation of individual organic extractables; note that identification can be either qualitative or structural
	FTIR		X	X		Discovery and identification of individual organic extractables; note that FTIR has limitations relative to structural analysis (however identification via qualitative analysis is possible)
Liquid Chromatography	UV,CAD & ELSD		X		X	Discovery and quantitative assessment of individual organic extractables; note that identification via qualitative analysis is possible and that Diode Array UV detectors can assist with structural analysis
	MS		X	X	X	Discovery, identification, and quantitation of individual organic extractables; note that identification can be by either qualitative or structural and that ionization sources with different selectivities are available
	FTIR		X	X		Discovery and identification of individual organic extractables; note that FTIR has limitations relative to structural analysis (however identification via qualitative analysis is possible)
	NMR		X	X		Identification of individual organic extractables; note that identification can be by either qualitative or structural

Analytical Technique	Analytical Method	Application				Application
		Scouting	Discovery	Identification	Quantitation	
Ion Chromatography	Conductivity		X		X	Discovery and quantitation typically of individual ionic species
	MS		X	X	X	Discovery, identification, and quantitation of individual ionic extractables; note that identification can be by either qualitative or structural and that ionization sources with different selectivities are available
Spectrometry	MS			X		Identification of individual organic extractables
	NMR			X		Identification of individual organic extractables
	IMS		X	X	X	Discovery and quantitative assessment of individual organic extractables; note that various ionization sources are available and that qualitative identification is possible
Atomic Spectroscopy	AAS		X	X	X	Discovery, identification, and quantitation of individual extracted elements (trace elements, metals); note that AAS can be applied to only one element at a time. Identification of the chemical form or speciation of the extracted element may require additional testing
	ICP-AES		X	X	X	
	ICP/MS		X	X	X	

CONCLUSION

The completeness of an extractables determination can only be judged against the overall goals of the

assessment. The investigative nature of the work demands a team of analysts with capabilities across method validation, molecular identification and

toxicological evaluation, to ensure that the study is run smoothly and data is interpreted correctly.

E&L testing also is expanding in the extent and complexity of testing, which requires comprehensive design of the E&L program based on sound scientific principles. The complexity of the E&L study program poses significant challenges for pharmaceutical product development, and requires significant expertise for the successful design and execution of an E&L program.

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