Drug manufacturers invest a tremendous amount of time and money to identify, quantify, and minimize impurities related to their drug products so that the US Food and Drug Administration can make informed decisions regarding drug product purity and safety. An area of increasing concern and scrutiny for FDA’s Center for Drug Evaluation and Research (CDER) is the potential adulteration of drug products by extractable and leachable compounds that enter a drug from a container, closure system, disposable, or device.

Addressing this concern, 21 CFR 211.94 a) states 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).

FDA provides guidance for protection against extractables and leachables in various documents (2, 3).

Therefore, the qualification and quality control of all components...
coming into contact with the drug formulation is an integral part of any FDA application process.

Extractables and leachables issues often are not addressed up front and ultimately can cause regulatory delays for the drug manufacturer. The development of unique packaging, novel formulations and delivery systems, and drug-coated medical devices has exacerbated this issue because of the increasing opportunities for foreign materials to come into contact with drug products. In addition, the increasing popularity of single-use disposables such as filters, tubing, and bags for biopharmaceuticals can introduce unwanted extractables into the final product. (For the rest of the article, the word components will refer to container closures, labels, drug delivery systems, packaging materials, devices, disposables, and so forth).

The development, validation, and testing of these components must be carried out under International Conference on Harmonization and United States Pharmacopeia guidelines in a laboratory that complies with current good manufacturing practices. These activities may be time consuming and require expertise and a wide array of analytical techniques. Drug manufacturers may not have the resources available or may want to keep these resources focused on development of new products. Therefore, it is common for drug manufacturers to outsource these activities to contract laboratories.

What are extractables and leachables?

Extractables are compounds that can be extracted from a component under extreme conditions such as the presence of harsh solvents or elevated temperatures. These compounds can contaminate the drug product. Leachables are compounds that leach into the drug product formulation from the component as a result of direct contact with the formulation under normal conditions. Leachables are typically a subset of extractables. Sources of these compounds include plastic components, elastomers, coatings, accelerants, antioxidants, inks, and vulcanizing agents. Phthalates are one specific example. These carcinogens are

![Collaborative approach](image-url)
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added to plastics to make them more flexible and can be found throughout the manufacturing process and in packaging materials. Other examples are nitrosamines and polynuclear aromatic hydrocarbons (PAHs), which are classes of carcinogenic compounds found in rubber. Many drug products are distributed or administered in packages made of plastic and rubber components, and, therefore, phthalates, PAHs, or nitrosamines could potentially come into contact with the drug product and be passed on to the patient. Metered-dose inhalers (MDIs), dry-powder inhalers (DPIs), and nebulizers can be complex because they may be constructed from a myriad of plastic, rubber, and stainless steel components. Nevertheless, these devices have many advantages (e.g., rapid absorption and onset of activity and reduced dosing) for effective drug delivery.

In summary, extractables must be controlled to the extent that components used are appropriate. Leachables must be controlled so that the drug products are not adulterated.

Team approach
For an extractables and leachables evaluation to be meaningful and successful, it must be a collaborative approach on the part of the drug manufacturer, component vendor, analytical laboratory, toxicologist, and regulatory agency. Each party has critical input and is a significant contributor to the overall process (see Figure 1). The laboratory can only perform appropriate testing if all relevant information is provided. It is critical that vendors provide data on their potential extractables so that the manufacturer can choose the appropriate components early in the process. Vendors often do not make extraction data available to drug manufacturers, however. Ideally, after the extractables study, a toxicologist reviews the data to assess risk and set maximum levels based on total daily intake, as defined by the product dosing. This part of the process is typically beyond the scope of the analytical laboratory. Specific extractables are chosen to be monitored in the components and as leachables in the drug product. At this point, the laboratory can proceed to the other phases of the study.

Design of study
Single-standard, regulatory-accepted procedures are not available. Each project is unique. Designing a study for a vial is much different than one for an MDI composed of many parts. In addition, the formulation must be considered. Injection products pose a greater safety risk than topical products. Studies are carried out in phases (see sidebar, “Various phases of study”) that may be separated by long periods of time, during which analysis, data reduction, and risk assessment are performed. Each phase typically is described in a protocol.

Extractable characterization is carried out first and is probably the most critical because all other decisions and testing are based upon it. Lancaster Laboratories (Lancaster, PA) has attempted to formalize a consistent approach, which is de-
scribed in more detail later in this article. The process starts with gathering information and continues with the profiling and characterizing the extractables. In general, preparation requires both nonpolar and polar solvents. The instrumentation used includes high-performance liquid chromatography–photo-diode array detection–mass spectrometry (HPLC–PDA–MS) for organics analysis; gas chromatography–mass spectrometry (GC–MS) for organics analysis; inductively coupled plasma–optical emission spectroscopy or mass spectrometry (ICP–OES or ICP–MS) for metals analysis; and sometimes ion chromatography (IC) for inorganics and ion analysis. These techniques are complementary and provide a wealth of information needed to profile the extractables and leachables that may come from the component. Mass spectrometry is used because it is a powerful tool that elucidates structure. Sometimes more advanced MS detectors such as time-of-flight (TOF) are used to obtain accurate mass information. It should be noted, however, that unambiguous identification is not always possible. This issue will be discussed later in the article. Once the extraction profile is established, it is crucial that the toxicologists review the data, perform risk assessment, and propose maximum levels based on the total daily intake defined by the product dosing.

After extractables have been characterized and qualified, the analytical methods are optimized and validated for the compounds of concern. Then, these methods are used for analysis of the components. Typically, several batches of components are tested, and suitable specifications are proposed for controlling consistency in the quality of these materials.

Once appropriate components are chosen, analytical methods for leachables in the drug product are developed and validated. Samples of the drug products, which have been in contact with the components for an extended length of time, are tested. In case such samples are not available, the drug product and component are stressed under appropriate conditions to generate the leachables. Note that the leachables may be the same compounds as those identified during extractable studies or their chemical identity may be different from the extractables because of drug product interaction. All major compounds and target compounds that do not have origins in the drug substance or excipients are identified and quantified. These goals can be accomplished by making a formulation in an inert glass container to exclude the leachables originating from the components.
The remainder of the article will discuss this critical first phase.

Protocol for extractable characterization

To develop an accurate risk assessment of compounds that can be extracted or leached from a given component, the component must first be exposed to extreme solvents and conditions to generate every potential extractable. The goal is to quantify and qualify these compounds if it is analytically possible. Lancaster Laboratories has been following a consistent protocol when applicable. The general protocol is described below and is modified based on the component and drug product to be investigated.

For organics analyses, each component is prepared so that the maximum exposure of the component to the extraction solvent can be attained. United States Pharmacopeia General Chapter (88) Biological Reactivity Tests recommends that the total surface area (both sides combined) to volume of solvent ratio be 60 cm²:20 mL (4). The components often are cut or crushed to maximize surface area. They undergo a variety of solvent extractions, typically employing either a Soxhlet extractor or sonication. For example, components may be exposed to hexane (i.e., nonpolar, organic), alcohol (i.e., polar, organic) and water (i.e., aqueous) and heated for a specified amount of time. After extraction, internal standards are added to monitor system performance and to define lower detection limits for the analyses.

For metals analysis, samples are prepared for ICP by placing a known amount of the component in a beaker and then adding deionized water and concentrated nitric acid. The sample is covered and heated at specified temperatures for a specified amount of time. Then, the samples are diluted into deionized water and analyzed by ICP–OES or ICP–MS.

For each set of preparations, blank solutions containing the solvents without the component are prepared and analyzed in the same manner as the test samples. This process ensures that no contamination from the labware or reagents is present that could be interpreted as an extractable. Postextraction steps may include filtration, concentration, and exchange of solvent to improve detection.

Hexane and alcohol extractions are analyzed by GC–MS. Blanks spiked with internal standard are first injected five times, and the percent relative standard deviation (%RSD) is determined to ensure the system is operating properly. In addition, the response is used to establish the detection limit. The mass spectra of detected extractable compounds are compared with the NIST98K database for identification. Although the database is used to assist in identifying the extractable components, the identification of each component cannot be guaranteed. All extractable peaks are quantitated on the basis of the average area response for the internal standard, assuming equivalent response factors.
Water and alcohol extractions are analyzed by HPLC. The HPLC system is configured with PDA and MS detection and the mobile phase is water–acetonitrile or methanol. The PDA is used to screen the samples. Again, blanks spiked with internal standard are first injected five times and the % RSD is determined to ensure the system is operating properly. The response is used to establish the detection limit. The MS is set first in the electrospray positive mode, then the negative mode, and finally chemical ionization in the positive mode.

The identification of the extractable compounds is attempted based on the molecular weight of the compound and compared to the molecular weight of known chemical compounds. The industry currently has no comprehensive databases for assistance in identifying liquid chromatography (LC)–MS-generated mass spectra. If a compound cannot be identified, an attempt is made to identify a class of compound for the extractable. Sometimes an accurate mass determination can be made using an LC–MS TOF. All extractable peaks are quantitated based on the average area response for the internal standard, assuming equivalent response factors.

The acid-digested sample is analyzed by ICP–MS. Once digested, the sample can be analyzed for more than 25 elements simultaneously with detection limits in the part-per-trillion to part-per-billion range.

**Mass spectroscopic identification**

As mentioned previously, mass spectrometry is a powerful tool for structural elucidation. Still, it is not always possible to make an indisputable identification of every peak (or compound) detected. Each of the different mass spectrometry techniques has its advantages and disadvantages. GC–MS data consist of fingerprint patterns that can be compared with large databases of organic compounds. Identification often can be performed with a high degree of confidence, and certified standards can be purchased for con-
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firmation. The compounds amenable to GC, however, only make up a minority of the possible organic compounds that may be present in a component. Furthermore, some classes of compounds such as alkanes yield very similar fingerprint patterns or fragments, and thus a specific molecular entity cannot be identified.

LC–MS data typically only provide a few ions, not a fingerprint pattern as those observed with GC–MS. Other advanced techniques such as tandem mass spectrometry (MS–MS) and TOF can provide more information such as molecular fragments and accurate mass. Database matching, however, is not achievable as it is with GC–MS. Orthogonal approaches such as nuclear magnetic resonance (NMR) and Fourier transform infrared (FTIR) spectroscopy also can be used to try to solve this sometimes complex puzzle.

At some point, the toxicologist should perform a risk assessment. These other analytical techniques can be time-consuming and expensive and do not always yield answers. Sometimes the data must be looked at from a different perspective. For example, an extractable is detected at 50 ppb from a component sample exposed to a strong solvent at high temperature for an extended period of time. The drug product is formulated in an aqueous buffer, exposed to this component for a relatively short amount of time, and must be kept refrigerated. Therefore, the extractable would probably not leach into the final product. The effort put into method development, analytical testing and identification must be weighed against the risk.

Conclusion

Qualification and quality control of components that come into contact with the drug formulation is an integral part of any US Food and Drug Administration application. Therefore, extractable and leachable issues should be investigated and resolved early in the process. For a successful study, it is imperative that the component vendors, laboratories, toxicologists, and the regulatory agency have open, effective, and timely communication. As new delivery devices, disposables, and medical devices are developed, it is certain that FDA will continue to demand information about these components so that the agency can make informed decisions on risk and safety.

References