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Extractable and Leachables Studies: designed and performed to meet all intended needs

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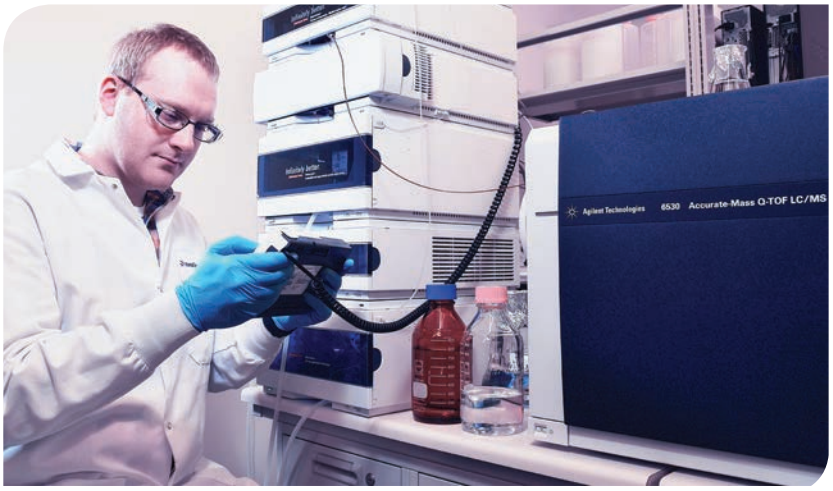
Since the FDA released their Container Closure Systems for Packaging Human Drugs and Biologics guidance in 1999, evaluation of final packaging components for extractables and leachables has become the expectation within the industry. Additionally, the increase in the use of single-use systems in manufacturing 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. And with the tremendous growth of the implantable device market and continuous emergence of new medical device technologies, there is a greater potential for extractables and leachables to negatively impact a device's biocompatibility.

Extractables are compounds that can be extracted from a product contact material under exaggerated conditions such as elevated temperatures, extended storage times, or exposure to harsh extraction solutions. Leachables, which are typically a subset of extractables, are compounds that leach from product contact materials into the drug product under normal conditions of use. Sources of extractables and leachables



compounds include antioxidants, antiozonants, UV stabilizers, plasticizers, processing aids, accelerants, coatings, elastomers, inks and vulcanizing agents, to name a few. Both extractables and leachables represent potential contaminants to a final product and may affect the pH or color of the product, impact the efficacy of the product, or alter the active ingredient. In addition, extractables and leachables compounds may be toxic.

There are no definitive requirements on how to perform extractables and leachables studies; however, the USP recently released two chapters to provide guidance on performing E&L studies. Chapters <1663> and <1664> discuss options and considerations in performing both an extractables study and a leachables study. Additionally, USP <665>, currently in the draft stage, presents recommendations for evaluating single-use and multiple-use systems for extractables and leachables. There are also various workgroups that have published guidance documents to assist the industry in designing and performing these studies. The Product Quality Research Institute (PQRI), the Bio-Process Systems Alliance (BPSA), and the Bio-Phorum Operations Group (BPOG) have all released publications defining a best practices approach to performing the testing. The PQRI guidance document focuses primarily on performing studies on Orally Inhaled and Nasal Drug Products. Both BPSA and BPOG focus on the evaluation of single-use technology. While the general approach to generating an extractables profile of a contact material is similar, the details in performing the studies differ between the guidances. In addition, ISO-10993 provides guidance specifically for the chemical characterization of medical

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devices for extractables and leachables. Eurofins BioPharma Product Testing has experience in performing studies following any of these workgroup and/or industry guidances, as well as establishing custom study designs.

Typically, an extractables study involves exposure of components to solvents of varying polarity at elevated temperatures. The extraction may involve incubating components at elevated temperatures, or using sonication, accelerated solvent extraction (ACE), soxhlet or reflux to extract the component. The resulting extracts are then tested by a variety of different analytical techniques to generate a broad extractables profile that can then be used to perform a safety assessment. Typically, these analytical techniques utilize mass spectrometry to allow for identification of the observed extractable compounds.

Liquid chromatography-mass spectrometry is utilized to evaluate the presence of non-volatile organic compounds. Both electrospray and atmospheric pressure chemical ionization techniques are used to generate the data. These ionization techniques are considered soft ionization and typically result in the mass spectrum displaying the molecular mass. The resulting mass spectra must then be evaluated to determine identifications so the safety assessment can be performed. However, there are a limited number of choices of commercially available databases that allow for rapid identification of the observed peaks. Therefore, Eurofins BioPharma Product Testing has generated its own in-house, proprietary database. The Eurofins Extractables Index (EEI) contains over 1,500 non-volatile compounds that are commonly used in the production of plastics and polymers. This database is integrated directly into the processing software, allowing for automated searching and comparison of spectra.

Gas chromatography-mass spectrometry (both headspace and direct injection sample introduction) is used to evaluate the presence of both volatile and semi-volatile compounds. Eurofins BioPharma Product Testing utilizes the NIST and Wiley databases to assist in the identification of observed extractables compounds.

In addition, inductively coupled plasma with either mass spectrometry or optical emission spectroscopy detection is used to monitor the presence of metals. Eurofins BioPharma Product Testing evaluates metals listed in USP <232> and ICH Q3D and has the ability to evaluate additional metals.

Eurofins BioPharma Product Testing performs more than 250 controlled extraction studies per year and designs extractables studies to meet clients' project objectives. Whether the study will be performed on a container-closure system, drug-delivery device, single-use system or a medical device, Eurofins BioPharma Product Testing has the experience and expertise in designing and performing studies to surpass expectations.