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Chemical Characterization of Medical Devices

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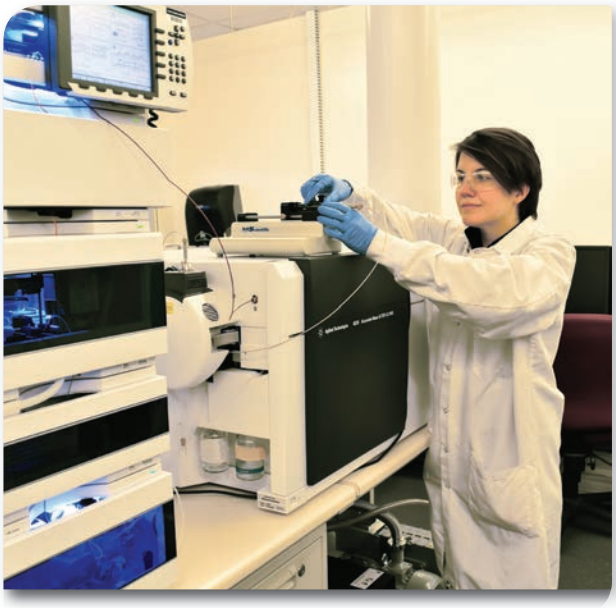
Chemical characterization, commonly known as extractables and leachables testing, is a key step in evaluating a medical device's biocompatibility. According to ISO 10993, the international standard for establishing a device's biocompatability, extractables are "substances that can be released from a medical device or material using extraction solvents and/or extraction conditions that are expected to be at least as aggressive as the conditions of clinical use."[1] Leachables, which are typically a subset of extractables, are "substances that can be released from a medical device or material during clinical use."[1] Most extractables and leachables are a result of material additives – such as antioxidants, plasticizers, heat and UV light stabilizers, and colorants – used to improve the functionality and performance of the device's materials of construction. In addition, extractables and leachables may be due to surface residues or physical degradation of the device.

Since extractable and leachable compounds may be toxic, they pose a potential risk to patient safety. Historically, extensive animal testing was required for each medical device in order to establish its biocompatibility. But, by identifying the potential leachables via chemical analysis, their impact to patient safety can typically be assessed by researching the available toxicological literature.



The first step in a chemical characterization study is sample preparation, which involves extracting chemical compounds out of the medical devices into extraction solvents. The extraction conditions used to prepare the device for subsequent chemical characterization should be based on how the device will be used by the patient. Although there is no "one-size-fits-all" set of extraction conditions, ISO 10993-12 does provide some guidance. Typically the intact device is incubated in several extraction solvents of varying polarity – such as water, ethanol, and hexanes – under one of the conditions listed in the standard (i.e., 37 °C or 50 °C for 72 hours, 70 °C for 24 hours, or 121 °C for 1 hour).

However, the extraction conditions listed in the standard may not always be suitable. For long-term implantable devices, an exhaustive extraction is the regulatory expectation. An exhaustive extraction is "conducted until the amount of extractable material in a subsequent extraction is less than 10% by gravimetric analysis of that detected in the initial extraction."[1] If, for example, the targeted extraction conditions are 50 °C for 72 hours, then the first step is to determine if those extraction conditions are actually exhaustive for the device under test. To do so, the device would be exposed to each of the extraction solvents at 50 °C for 24 hours. After the 24 hours, the solvent would be removed and its nonvolatile residue determined gravimetrically. The same device would then be exposed to fresh extraction solvent at 50 °C for an additional 24 hours, followed by another determination of the nonvolatile residue. This process

would continue for each solvent until the weight of the nonvolatile residue was less than 10% of the weight of the original nonvolatile residue, at which point the extraction would be deemed exhaustive.

Once the samples are prepared the extracts are tested by several orthogonal analytical techniques in order to generate a broad extractables profile in accordance with ISO 10993-18. Liquid chromatography mass spectrometry is used to detect nonvolatile organic extractable compounds. Eurofins Medical Device Testing utilizes accurate mass time-of-flight (TOF) mass spectrometers and quadrupole time-of-flight (QTOF) mass spectrometers for this analysis. "Soft" ionization techniques, such as electrospray ionization (ESI), atmospheric chemical ionization (APCI), or a multimode source that combines the two types of ionization, are used often resulting in the mass spectrum displaying the molecular mass. The resulting mass spectra for each observed extractable compound must then be evaluated to determine identifications so that an accurate toxicological safety assessment can be performed. However, there are a limited number of choices of commercially available databases that are suitable for rapid identification of the observed peaks. Therefore, Eurofins Medical Device Testing has developed its own in-house proprietary database to aid in identification. The Eurofins Extractables Index (EEI) contains over 1,500 nonvolatile organic compounds that are commonly used in the production of medical devices and their materials of construction, such as plastics, polymers, elastomers, inks, and adhesives.

Gas chromatography-mass spectrometry (both headspace and direct injection sample introduction) is also used to evaluate the presence of both volatile and semi-volatile organic compounds. Eurofins Medical Device Testing utilizes the NIST and Wiley databases to assist in the identification of observed extractable compounds. Finally, Inductively Coupled Plasma (ICP) with either mass spectrometry or optical emission spectroscopy detection is used to monitor the presence of metals. Eurofins Medical Device Testing typically evaluates the metals listed in USP <232> and ICH Q3D and has the ability to evaluate additional metals.

When seeking approval for a device for which a previously approved predicate exists, a fingerprint study to compare the extractables profile of the new device to that of the predicate may be appropriate in lieu of a full chemical characterization study. This fingerprint analysis consists of conducting chemical characterization of both the new and predicate devices and comparing the results. Only those compounds detected at higher concentrations in the analysis of the new device would require further toxicological evaluation to establish patient safety. Ideally this comparison study, included in the 510(k) submission to the FDA, would support the substantial equivalency of the device to the predicate. Using the fingerprint analysis is also an option when making minor changes to the material supply chain for a given device in order to show that the device is equivalent following the material change.

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With the increasing concern for animal welfare, there is a push to reduce the burden of *in vivo* animal studies, which may be achieved by relying on chemical characterization data and the corresponding toxicological safety assessment. Eurofins Medical Device Testing performs more than 400 extractables and chemical characterization studies per year, designing each study to meet the client's project objectives. Eurofins Medical Device Testing has the experience and expertise in designing and performing these studies to surpass expectations.

References:

[1]Use of International Standard ISO 10993 -1, Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing within a Risk Management Process. N.p.: Food and Drug Administration, 16 June 2016. PDF.