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 biocompatibility, 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.” Leachables, which are typically a subset of extractables, are “substances that can be released from a medical device or material during clinical use.”

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.” 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
demed 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.

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:

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