Chemical Characterization (E&L) of Medical Devices: Seismic Shifts in ISO 10993-18:2020

It is a time of great change in medical device chemical risk assessments, as manufacturers who have gone through the process have undoubtedly experienced in recent years. January 2020 brought a new and transformative revision of ISO 10993-18, the principle standard governing chemical characterization of medical devices. Coming 15 years since the last published revision, the standard dramatically transforms the scope of the chemical characterization workflow.

Medical device companies may understandably consider the chemical characterization process with skepticism and distrust. Testing by aggressive organic solvent extraction certainly seems distantly removed from end use clinical conditions and of questionable relevance. And combined with complex chromatographic/mass spectral tests that can seemingly yield every compound under the sun? No thank you, they may be tempted to say. Properly conducted, however, the chemical risk assessment process yields a wealth of information that may be leveraged not just for the purposes of a regulatory submission, but for better understanding and control of the device materials and manufacturing.

While an exhaustive description of changes in 10993-18:2020 is beyond the scope of this document, some of the most substantial ones are highlighted.

Chemical Characterization: What it is (and isn't)

Chemical characterization is fundamentally a process of information gathering—the goal is to establish the chemicals present in a medical device—in some cases down to sub-microgram levels. This information is then inputted to a toxicological analysis (generally per ISO 10993-17) in order to determine the risk associated with potential patient exposure to the medical device's constituents.

Chemical characterization is a **required** part of a broader biocompatibility risk assessment of a medical device, as one of the first steps in the process. Per ISO 10993-1, some form of chemical characterization is required for all medical devices irrespective of nature of body contact. In some cases, the results of a chemical characterization may be justified as sufficient in lieu of certain animal testing. However chemical characterization should not be considered as demonstrating biocompatibility on its own.

In broad brushstrokes, the chemical risk assessment workflow may be viewed as a potential three-tiered structure composed of 1) information gathering 2) extractables analysis, and 3) leachables analysis. The need to perform each successive tier of characterization depends on the nature of the device and the results of the previous stage.

In some cases, chemical risk assessment can be performed as purely a "paper exercise" on the basis of material composition information obtained from material suppliers and contract manufacturers. An example of such a situation may be a device with low risk, e.g. contacting intact skin, and if the device is made of common materials with an extensive history of clinical use, and manufactured using the same methods as established devices. No further testing may be needed in devices meeting these criterion.

For devices of greater risk or more uncertainty in materials/manufacturing, an extractable study is likely to be required, at minimum. Such extractable studies generally aim to remove either more chemical species than would be expected to leave the device under anticipated clinical conditions (exaggerated extraction), or aim to remove all chemical species that could conceivably be removed from the device (exhaustive extraction). For permanent implant devices, exhaustive extraction is generally performed. Compounds identified through these extractions are first considered through a 'worst case' lens—e.g. the device suddenly dissolving and all potential extractables are released in a single bolus. If the results of this extractable study and conservative risk assessment flag compounds at concentrations that present a potential toxicological concern, leachable studies may be necessary to more accurately estimate the actual patient exposure to these species under simulated clinical use conditions.

Information Gathering

Made explicit in ISO 10993-18:2020, the critical first step of the chemical risk assessment is information gathering. This involves collecting all available data on the medical device materials of construction, additive packages, surface treatments/coatings, etc. In addition to information on the compositional level, the information gathering step also includes collection of the manufacturing processing aids and processing conditions: e.g. machine oils, spin finishes, polishing compounds, sterilization modes, etc. Essentially, the practitioner should consider anything that may be left behind on the device as a residue and result in subsequent patient exposure. In practice, the information gathering step is often challenging to thoroughly complete due to the use of proprietary mixtures/formulations in the device or its manufacturing process.

Such information gathering efforts provide a baseline level of information that may be able to justify whether additional chemical characterization testing (extractables) is necessary. Furthermore, the information provides critical context for guiding analytical method selection, reference/surrogate standards employment, and is an invaluable aid in compound identification.

Question: *"But my device is made up of biomedical grade materials. Do I really have to do a chemical risk assessment?"*

Indeed, the use of USP Class VI, ISO 5832, or FDA Master File materials can reduce the risk of potentially toxic extractables. However, such designations are generally associated with the raw material, which may be transformed or change in composition during the process of converting it to the final finished form. Therefore, the use of a "biomedical" grade material is generally not sufficient justification to avoid chemical characterization or extractable testing.

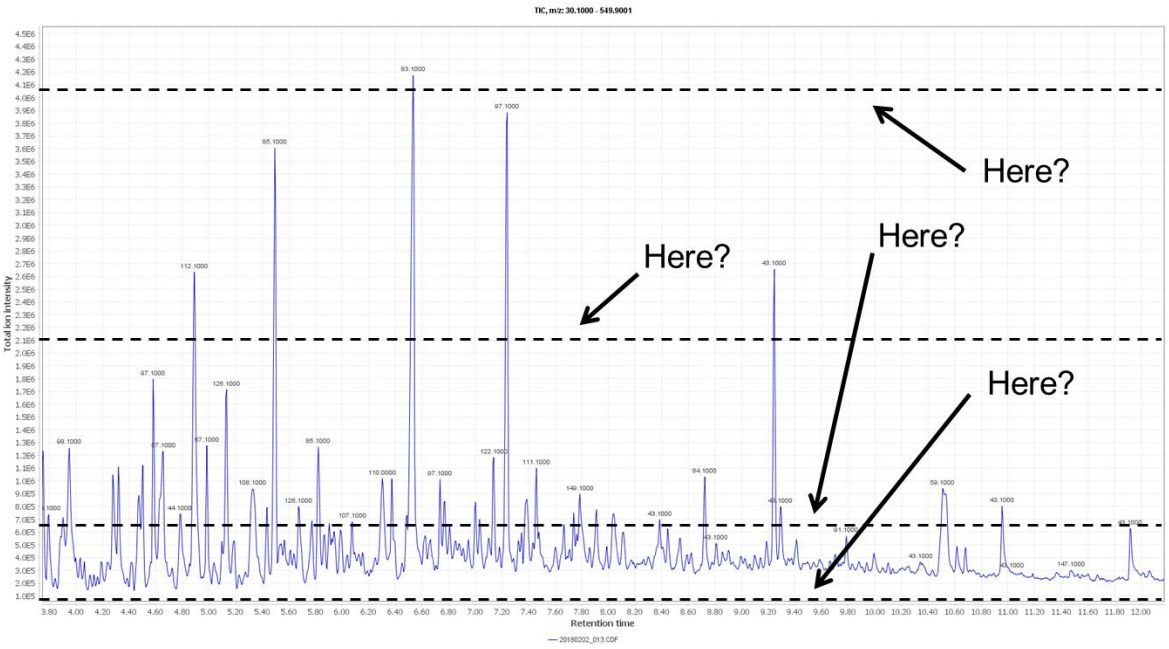

Figure 1: Model LC-MS total ion chromatogram. Which peaks should be identified and evaluated for potential toxicological risks? Where do we draw the line? Note the line below the instrument baseline – is the method even suitable for the level of toxicological risk we are trying to evaluate?

The analytical evaluation threshold (AET) – "How low do you go?"

A key concept formalized in ISO 10993-18:2020 is that of the analytical evaluation threshold (AET). The AET answers the critical questions of:

1. How sensitive does the analytical method have to be?
2. Of all the peaks detected in a sample extract, which must be identified and undergo toxicological risk assessment?

The AET is not a single value for a compound—it is calculated (see Annex E of ISO 10993-18:2020) on the basis of a toxicological threshold and depends on the nature of the patient contact, the frequency and duration of the device's use, the number of devices that may be simultaneously implanted, and the specific extraction conditions employed in the chemical characterization study (accounting for dilutions etc.). As discussed later in this document, the AET is also modified by an analytical uncertainty factor (UF).

Once calculated, the AET immediately imposes a requirement on the analytical methods, namely that the method's limit of quantitation (LOQ) is less than the AET. Furthermore once data is collected, only peaks greater than the AET are identified, quantified, and reported for toxicological assessment.

The concept of the AET is an invaluable reference point to keep in mind throughout the chemical characterization process. It prevents analysts from getting "buried in the weeds," identifying and assessing compounds that could not pose a toxicological risk. It also ensures that the practitioner has confidence in the suitability of the analytical method sensitivity at the outset—mitigating the possibility of finding out months later that potentially hazardous constituents were buried in the baseline noise, requiring costly retests and delays.

Given the dependence on toxicological thresholds (e.g. TTC) and the wide ranging impact of the AET on subsequent testing, it is generally recommended to consult with a toxicologist when defining an AET value.

Exceptions to the AET

Note that the AET cannot be used indiscriminately against all possible chemical classes. Specifically, the limitations of the AET approach are generally bounded by the set of chemicals originally used to derive threshold of toxicological concern (TTC) values. Compounds that were not considered in this derivation are considered as part of the cohort of concern (CoC). As described in ISO 21726:2019, examples of CoC include chemical classes listed in Table 1.

Table 1: Examples of chemical classes known to contain cohorts of concern (not exhaustive)

Aflatoxin-like compounds	Azo compounds
N-Nitroso compounds	Heavy metals
Strained heteronuclear rings	Steroids
Alpha-nitro furyl compounds	Particles/Nanoparticles
Polycyclic amines	Ceramics
Radioactive Constituents	Proteins
Organophosphorous compounds	
Hydrazines/triazenes/azides/azoxy compounds	
Polyhalogenated –dibenzodioxins, -dibenzofurans, and –biphenyls	
High molecular weight polymeric constituents	

Exhaustive Extractions – did we get it all?

A key underpinning of the toxicological risk assessment process, especially for permanent implants, is that the compounds identified represent **all** possible extractables from within the medical device. This assumption is justified by the use and demonstration of exhaustive extraction conditions. Generally, an extraction is shown to be exhaustive by performing repeated extractions and demonstrating that the N^{th} extract generates <10% residue as compared to the 1^{st} extraction. Previous standards have indicated that these criteria be demonstrated by gravimetric means, however in ISO 10993-18:2020 the standard offers the flexibility of demonstrating this by other more sensitive and relevant means. Regardless, performing a single extraction pass is generally not recommended (without clear justification) due to the risk of underestimating compound concentrations and by extension, the potential toxicological risk. Exhaustive conditions should be demonstrated on final finished device forms and for all solvent conditions employed: generally using polar, semi-polar, and non-polar vehicles.

Analytical Testing

The most commonly analytical tests performed on device extracts consists of GC-MS, LC-MS, and ICP-MS techniques for volatile, non-volatile, and elemental/inorganic extractables respectively. However, based on the nature of the device and on information gathered at the start of chemical characterization, additional analytical techniques may be necessary to capture all potential extractables. For example, HS-GC-MS may be necessary for solvents and highly volatile species, while ion chromatography may be necessary for inorganic ions or residual passivation agents.

Some historically employed analytical methods like FTIR, TOC or THC/HOI remain useful as screening tools and for the purpose of process characterization/QC, but are now regarded as generally insufficient to generate the required information for a chemical risk assessment.

In selecting analytical conditions, it is important to keep in mind that no analytical technique can see "everything." Selected test conditions should be guided by known compounds, but sufficiently flexible to reasonably account for unknown chemical species. A review of the materials obtained during information gathering may indicate the need for specialized or modified analytical methods (e.g. derivatization workups to make certain classes of compounds amenable for GC-MS or LC-MS detection).

As compared to previous standards, ISO 10993-18:2020 provides additional guidance on the selection, qualification, and implementation of analytical methods. However, one should not expect to find detailed protocols, instrument configurations, or test conditions. On these topics, the standard provides high level guidance and leaves it to the practitioner to justify their analytical techniques are fit to purpose.

Addressing Analytical Method Uncertainty

A major change in ISO 10993-18:2020 is the explicit requirement to address analytical method uncertainty. This requirement stems from an inherent constraint of "broad screen" methods that aim to identify a multitude of possible chemical species on a medical device.

Analytical methods such as GC-MS and LC-MS generate quantitative information when they are calibrated to a chemical at multiple concentrations. However, different chemicals will elicit different detector response factors. Because of the dozens of compounds that may be detected in the course of an extractable study (some of which may not be commercially available), it is not analytically expedient to individually calibrate an instrument to every chemical present in a medical device extract. Instead, instruments are calibrated to so-called surrogate standards, whose calibration is used to assign a concentration for compounds detected in sample extracts. Where the structure or chemical properties of an extractable differ from the surrogate standard, a potential error (inaccuracy) in quantitation may occur.

This fundamental method uncertainty has two principle implications: in the determination of the AET, and in the determination of compound-specific concentrations for toxicological risk assessment.

The Response Factor Database –Impact on AET

ISO 10993-18:2020 requires that the AET be divided by an uncertainty factor (UF) appropriate and justifiable for the specific analytical technique employed. The standard offers the concept of a response factor database as a method for calculating the uncertainty factor. Specifically, the workflow entails analyzing a database of compounds that are specific to the analytical method and expected population of extractables and determining the relative standard deviation (RSD) of this response factor database. The uncertainty factor is then calculated from the RSD value. General guidance is that a UF of 2 may be appropriate for GC-MS, with limited guidance for other analytical methods.

Quantitation: Multiple surrogate standards

In assigning concentrations to individual compounds after detection and identification, ISO 10993-18:2020 generally indicates that potential uncertainty in quantitation should be considered and mitigating factors justified. Although the standard does not indicate an explicit number of surrogate standards, the implication is for multiple surrogate standards to be employed where there is potential variance in response factor between a single surrogate standard and the range of observed extractables. For each extractable, the structurally closest surrogate standard should be used for the quantitation calculations—the range of surrogate standards selected

should therefore represent a diversity of compounds similar in nature to the range of possible extractables. The medical device composition and manufacturing context obtained during the information gathering step is here valuable in selecting surrogate standards *a priori*.

Now what? Also, what about leachables?

After the extractable testing is complete, identified compounds and their concentrations are submitted for a toxicological risk assessment, generally by ISO 10993-17 (this process should be performed by a certified toxicologist). A key output of this assessment includes margin of safety (MoS) values for each chemical, however the process of evaluating the results should also consider if individual chemicals are "expected" or "unexpected" based on the device materials and manufacturing process, as well as evaluating variability between samples or manufacturing lots.

If some chemicals are found to present a potential toxicological risk (i.e. MoS near or less than 1), a targeted leachable study may be necessary in order to evaluate the actual concentration of the compound when the device is subjected to simulated end use conditions. Only compounds flagged as potentially above toxicological threshold need be evaluated in the leachable study.

Final Thoughts

Given the dramatic changes and changing regulatory landscape, medical device manufacturers are encouraged to review the standards carefully, consult with expert practitioners, and where possible, present a detailed experimental protocol to the FDA ahead of time.

CPG is experienced in designing chemical risk assessment studies and has a full analytical chemistry laboratory in-house and under our ISO 9001/17025 quality management systems. We have a successful track record in helping our clients perform chemical characterizations as part of their broader biocompatibility risk assessments. Please contact us for more information on how we can assist in evaluating your devices to these new standards and workflows.