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ISO 10993-18 Expands to Account for Variability

Over the past 15 years, ISO 10993-18 has become a veritable beacon that has guided medical device companies through the process of assessing the chemical risk associated with their products. Therefore, whenever the document is revised the impact of the changes made is widespread. The modifications not only affect all associated medical device sponsors and contract laboratories, but also the overall safety of medical devices for the general public. One of these guidance changes occurred in January 2020, when an updated revision of ISO 10993-18 was released to the public. A few of the major changes from this revision compared to the previous version are:

1. Greater harmonization of ISO 10993-18 with ISO 10993-1, 10993-12, and 10993-17.
2. A revision and expansion of the general chemical characterization process
3. Added definitions and a slight change in terminology
4. A new breakdown of quantitation practices
5. A new discussion of considerations for analytical method qualification
6. New detail in the Analytical Evaluation Threshold (AET) and Uncertainty Factor (UF) annexes

The goal of this whitepaper will be to aid in understanding the most current version of ISO 10993-18.

New Considerations Prior to Submitting a Device for Testing

The new ISO 10993-18 revision emphasizes the importance of information gathering prior to submission for analysis. This is emphasized in the expanded general chemical characterization process which outlines the steps that should be followed when performing chemical characterization. The information needed may be acquired from the raw material supplier, the manufacturer, or through chemical testing.

In the information gathering step, it is important to determine the presence of possible cohorts of concern compounds. The cohort of concern was defined by ICH in M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk. Application of a threshold of toxicological concern (TTC) approach requires the absence of these compounds as is referenced in ISO/TS 21726 in the newest revision of ISO 10993-18. The reference to other documentation is one instance of the increased harmonization of ISO 10993-18 with other standard procedures such as ISO 10993-1, ISO 10993-12, and ISO 10993-17. Similar incorporation of other chapters of ISO 10993 can be observed in the flowcharts of the recent ISO 10993-18 revision.

Another noteworthy change in the revised documentation is the addition and modification of definitions surrounding analytical practices. The changes are slight; however, they do still impact parameters in the study such as extraction conditions. For instance, the definition of ‘leachables’ now adds ‘simulated use conditions’ as being applicable for leachables extraction. This is a case of a definition broadening to account for circumstances when a medical device’s

conditions of exact use cannot be replicated in an analytical lab. Furthermore, definitions for qualification, qualitative analysis, quantification, estimated quantitative analysis, semi-quantitative analysis, and quantitative analysis were added to the revised version of the document. It is of particular importance that semi-quantitative analysis is defined in the document, as this addresses large scale changes in ISO 10993-18 to account for response factor variation. When considering the implications of the definition changes, it is possible that they have an impact on any protocols and procedures already in place that follow ISO 10993-18.

Changes to the Chemical Characterization Process

In addition to the closing annex, the latest revision of ISO 10993-18 provides a new table of recommended extraction conditions in the body of the document. The recommendations are primarily based upon the nature and duration of patient-to-device contact. Furthermore, the newly edited document expands on the necessity of triplicate extractions. From the text, if there is enough evidence to establish that test article and extraction variability is, in fact, low, then one extraction replicate for each extraction vehicle is deemed sufficient. However, if the variability is unknown, then multiple extractions (i.e. triplicate) are recommended for each extraction vehicle. This change is likely a direct response to regulatory agencies such as the U.S. FDA frequently requiring triplicate analysis for extractables and leachables studies.

A small change to the section of the document outlining the procedure for qualification of analytical methods is that dynamic range is now specified as a necessary parameter to report. Dynamic range is defined in ISO 10993-18 as ‘the concentration range over which the response and the analyte concentration producing that response are relatable by a simple mathematical function.’ In simpler terms, dynamic range is the concentration range over which a calibration curve can be used accurately.

Revisions to the Reporting of Compounds

Clearly, a point of interest, the sections of ISO 10993-18 pertaining to the AET and its determination were heavily targeted in the new revision. A revised equation for the AET was provided which includes an uncertainty factor (UF) to account for response factor variation. In the new document, there is now a section detailing examples of calculating the AET for the reader’s reference. Previously this was not the case. There is also now language in the document that advises that the AET only be applied to organic extractables and leachables. The statement is a result of the lack of an applicable Dose Base Threshold (DBT) for all metals.

Another significant change to the revised document is an extensive section that provides guidance on how to appropriately determine an uncertainty factor (UF). The basis of including such a section is to prevent underreporting due to response factor (RF) variation. Response factor variation can be colloquially defined as the difference in responses between analytes when analyzed on the same instrument, at the same concentration. Underreporting can occur when compounds that are at equal concentration do not give equal responses. Compounds which respond weaker than the corresponding standard can be excluded even though their concentration is at the toxicologically relevant level. Subsequently, this section outlines the

dilemma of response factor variation in chemical analysis, as well as how an uncertainty factor attempts to address it. As previously mentioned, terms such as semi-quantitation were newly defined in the document revision for the very purpose of addressing how response factor variation can change depending upon the method of quantitation utilized. Additionally, justification is required for the use of both surrogate and internal standards.

ISO Testing in Practice

These wholesale revisions to ISO 10993-18 enable contract testing laboratories and in-house quality assurance and control (QA/QC) teams to account for variability in fully qualitative and quantitative analysis, estimated quantitative analysis, and semi-quantitative analysis. With greater alignment between peripheral ISO regulations that pertain to medical device safety and previously unattainable detail for AET and UF annexes, the revised ISO 10993-18 provides greater clarity and empowers all businesses throughout the medical device production chain to deliver a higher quality product.

If you need more information about the latest ISO 10993-18 revisions, simply contact a member of the Jordi Labs team today. Our team has significant experience of working within ISO regulatory testing parameters and would be happy to answer your questions.