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AMENDMENT 1
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Biological evaluation of medical devices —

Part 18: Chemical characterization of medical device materials within a risk management process

AMENDMENT 1: Determination of the uncertainty factor

Évaluation biologique des dispositifs médicaux —

Partie 18: Caractérisation chimique des matériaux des dispositifs médicaux au sein d'un processus de gestion du risque

AMENDEMENT 1: Détermination du coefficient d'incertitude

Reference number
ISO 10993-18:2020/Amd.1:2022(E)

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Biological evaluation of medical devices —

Part 18:
Chemical characterization of medical device materials within a risk management process

AMENDMENT 1: Determination of the uncertainty factor

5.6, paragraph below Figure 3

In the last sentence of the paragraph below Figure 3, replace "Table 3" by "Table 4".

6.2, Table 3

In the column “Qualitative” for the example method “Gravimetric”, insert “—”.

6.3, Table 4

In the columns “Qualitative” and “Quantitative” for the example methods “HPLC, with UV, CAD, ELSD and/or MS*” insert “X” in both columns.

Clause D.1, last paragraph

Replace the "where" list for Formula (D.1) with:

Φ_A is the mole fraction of solvent A;

P_A is the polarity of solvent A;

Φ_B is the mole fraction of solvent B;

P_B is the polarity of solvent B.

Table D.2, footnote a

Replace the text of footnote a with the following:

[a] Abbreviations include:

ABS poly(acrylonitrile-butadiene-styrene);

ACN acetonitrile;

EA ethyl acetate;

DCM dichloromethane;

DMF dimethylformamide;

HFIP hexafluoroisopropanol;

PET poly(ethylene terephthalate);

TCB trichlorobenzene;

THF tetrahydrofuran;

MeOH methanol;

EtOH ethanol;

iPrOH isopropyl alcohol.

Table D.2

In the column “Anti-solvents” for “Polymer” Polystyrene and Styrenics (ABS), replace “can” by “ACN”.

Clause E.3

Replace Clause E.3 with the following:

Quantification in extractables profiling is accomplished by various means which differ with respect to the accuracy of the estimated and reported concentration, where the accuracy can vary significantly depending on the quantification means employed. For example, quantification can involve the use of a surrogate standard to normalize the responses obtained for all relevant analytes. In such an approach, one estimates the concentration of each analyte based on the simplifying assumption that all analytes respond similarly, among themselves and with respect to the surrogate standard (i.e. all substances have the same response factor). Depending on the validity of this simplifying assumption, the concentration estimates thus obtained can have widely differing uncertainties and degrees of accuracy. If the simplifying assumption is true and response factors are constant, then the resulting concentration estimates for all analytes is highly accurate. If the simplifying assumption is false and the response factors vary widely, then the resulting concentration estimates for the analytes will have widely varying accuracies and the accuracy of the concentration estimate for each analyte will vary in proportion to the difference between the analyte’s response factor and the surrogate standard’s response factor.

Other quantitation means can produce highly accurate concentration estimates. For example, if quantification is achieved via the use of calibration curves generated via the analysis of authentic standards employed in qualified analytical methods, the concentration estimates obtained for the qualified analytes will be highly accurate. As noted above, if response factors are constant, then quantitation with a surrogate standard will also be highly accurate.

Other quantification strategies can produce concentration estimates whose accuracy is somewhere between these two extremes; greater accuracy than use of a surrogate standard’s response factor but lesser accuracy than use of a calibration curve generated with an authentic reference standard. For example, relative response factors can be obtained for extractables, where the relative response factor is the ratio of the response of the extractable versus that of a surrogate standard at equal concentrations of extractable and surrogate standard. Use of relative response factors in quantification accounts and adjusts for differences in response factors, extractable versus surrogate standard.

Recognizing that response factors for extractables and surrogate standards can vary, the AET is adjusted to account for more poorly responding analytes. Such an adjustment increases the likelihood that even a poorly responding analyte can be recognized as being above the AET when it is present in a sample at levels greater than or equal to the AET. The adjustment is accomplished by adding an uncertainty factor (UF) to the calculation of the AET to account for response factor variation. Use of a UF is the same principle as calculation of a final AET from an estimated AET (e.g. see Reference [45]). In essence, use of the UF adjusts the AET down to a lower value, ensuring that poorly responding compounds are properly flagged as being at or above the AET and therefore being reportable.

In cases where the response factor variation is known to be acceptably low, a UF value of 1 can be justified. Examples of these cases are methods with comparable response factors between expected extractables and applied surrogate standards, qualified methods for targeted extractables and use of a poorly responding compound as a surrogate standard. Otherwise, the value of the uncertainty factor is based on an assessment of the analytical methodology to which the AET is applied. For example, a UF value of 2 has been proposed[39],[45] as being appropriate, in certain situations, to the screening of extracts for organic extractables via GC-FID or GC-MS, as analytical FID or MS response factors for extractables are somewhat consistent, extractable to extractable. Alternatively, the UF for other analytical methods used for extractables screening, such as HPLC-MS, can be higher, given the frequently wide variation in response factors among extractables by this methodology. At the current time, there is no available general guidance which recommends a specific value for the UF for these methods; however, the user should justify the UF values selected.

One approach to establishing and justifying a particular UF is statistical analysis of a database of response factors specific to the analytical method being considered and the population of extractables for which that method is applicable. In this approach, the value of the UF is linked to the relative standard deviation of the response factors according to Formula (E.2):

$$UF = \frac{1}{(1 - RSD)} \tag{E.2}$$

where RSD is the relative standard deviation of the response factors from the reference database.

Formula (E.2) presumes a more or less normal distribution of response factors, which is not exhibited for all chromatographic detection methods. The database of response factors used to calculate a UF according to this formula should be described and reviewed to establish whether the resulting UF is sufficiently conservative to properly account for low response factor analytes. In certain circumstances, alternate means of establishing the UF can be considered and justified if adopted.

Formula (E.2) is equivalent to formulae proposed by PQRI and Jordi (see References [41] and [46]).

When the variation in responses factors is large relative to the mean response factor (e.g. standard deviation = 0,9 X mean), the variation in response factors is so large that although a UF can be calculated, its scientific validity becomes questionable. For example, although a UF > 10 can be calculated, the reality of a UF as large as 10 (or larger) is that the quantification method being used is inherently inaccurate and thus can be inappropriate for the purpose of producing the data that is the foundation of a toxicological risk assessment. Additionally, the use of a large value for UF can produce an adjusted AET that is so small that it cannot be achieved by the specified analytical method; that is, the method's limit of detection (LoD) is greater than the AET. In these cases, while it is possible to establish an adjusted AET, it is inappropriate to do so. The AET concept should not be applied in these cases and consideration should be given to further improvement of the method before it is used for the purpose of quantification of the supporting toxicological risk assessment.

In cases where the standard deviation is greater than or equal to the mean (i.e. $RSD \geq 1$), a UF cannot be calculated via Formula (E.2), as the result is either infinity or a negative number. Clearly an analytical method with this much variation in response factors is not optimal for the purpose of reporting data that is the foundation of a toxicological risk assessment. Optimization of the method to reduce response factor variation should be considered.

In cases where the variation in response factors among extractables cannot be established or where the variation is established to be large, the value of UF can be so large (e.g. UF values of 10 or greater) that the adjusted AET is so low that the AET concept has little practical value (e.g. the analytical method's LoD or LoQ are greater than the AET). In such cases, it is necessary that all the compounds associated with all observed analytical responses obtained by the screening analyses be identified and quantified, as all the observed analytical responses can be greater than the AET. Optimization of the method to reduce response factor variation should be considered in such cases.

It is noted that screening for extractables is typically accomplished via the use of orthogonal and complementary analytical methods, for example, GC-MS and LC-MS. The use of multiple analytical methods can reduce response factor variation and can be considered in the determination of the necessary UF that is then applied to all the complementary methods. See References [56] and [57].

In any event and in all circumstances, the use of the uncertainty factor, the value of the uncertainty factor that is used and the means by which the uncertainty factor is established should always be justified.

Clause E.4, Example C.2, paragraph after fourth indent

Replace the paragraph with the following:

Note that 20 µg/d for 31 d means an exposure of 620 µg, 10 µg/d for 365 d which means an exposure of 3 650 µg, and 1,5 µg/d for 3 650 d which in turn means an exposure of 5 475 µg. Each of these theoretical extreme approaches are therefore less conservative.

Bibliography

Add the following references:

[56] Jenke D., Christiaens P., Beusen J.M., Verlinde P., Baeten J., A practical derivation of the uncertainty factor applied to adjust the extractables/leachables analytical evaluation threshold (AET) for response factor variation. *PDA J Pharm Sci Technol.* 2021 [Online ahead of print] Available from https://journal.pda.org/content/early/2021/11/15/pdajpst.2021.012692

[57] Jordi M.A., Rowland K., Liu W., Cao X., Zong J., Ren Y., Liang Z., Zhou X., Louis M., Lerner K., Reducing relative response factor variation using a multidetector system forextractables and leachables (E&L) analysis to mitigate the need for uncertainty factors. *J. Pharm. Biomed. Anal.* 2020; **186**:1-14 Available from https://www.sciencedirect.com/science/article/pii/S073170 8520304283?via%3Dihub

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