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Biological evaluation of medical devices —

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

Évaluation biologique des dispositifs médicaux —

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

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Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

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For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 194, *Biological and clinical evaluation of medical devices.*

This second edition cancels and replaces the first edition (ISO 10993-18:2005), which has been technically revised. The main changes compared to the previous edition are as follows:

— greater integration and harmonization with ISO 10993-1, ISO 10993-12, and ISO 10993-17;

— a revised and expanded chemical characterization process flowchart;

— a strengthened explanation that analytical testing is not necessarily required;

— added a number of definitions (e.g. medical device configuration, materials of construction, and material composition);

— clarified testing approaches unique to chemical characterization (i.e. digestion and dissolution for hazard identification);

— added discussion of considerations related to analytical method qualification;

— added informative annexes on general principles, vehicle extraction considerations, and the analytical evaluation threshold (AET; concentration threshold below which extractables or leachables identification is unneeded).

A list of all parts in the ISO 10993 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

ISO 10993-1 serves as a framework in which to plan a biological evaluation which, as scientific knowledge advances our understanding of the basic mechanisms of tissue responses, minimizes the number and exposure of test animals. Preference is given to the assessment of chemical/physical properties and testing with *in vitro* models in situations within a risk assessment process. These methods are used when the results yield equally relevant information to that obtained from *in vivo* models.

The characterization procedure and its associated flowchart is based on the principles in ISO 10993-1; specifically, that the biological evaluation and risk assessment process is most efficient and effective if it is based on the minimum amount of acceptable and necessary chemical information that can establish that a medical device presents an acceptable health risk.

ISO 10993-1:2018, 4.2 states that in the selection of materials to be used in medical device manufacture, the first consideration shall be fitness for purpose with regard to characteristics and properties of the material, which can include chemical, toxicological, physical, electrical, morphological and mechanical properties. Furthermore, ISO 10993-1:2018, 6.1 states that gathering physical and chemical information on the medical device or component is a crucial first step in the biological evaluation process and its associated process of material characterization.

Lastly, ISO 10993-1:2018, and by reference ISO 14971, points out that a biological risk analysis depends on what is known about the material formulation, what nonclinical and clinical safety and toxicological data exist, and on the nature and duration of body contact with the medical device.

The requirements specified in this document are intended to yield the following information, which will be of value in assessing the biological response to the materials as represented in the final product.

— The identities and quantities, as appropriate, of the materials of construction of the medical device (device configuration).

— The identities and quantities, as appropriate, of the chemical constituents in each material of construction (material composition).

— The identities and quantities, as appropriate, of chemical substances used in the medical device's manufacturing process, including processing aids and residues.

— The potential of the medical device and/or its materials of construction to release chemical substances to which a potentially affected individual could be exposed to during clinical conditions of use.

The composition of the materials of construction is mainly established by the suppliers of these materials. The composition can change during manufacture of a medical device. Other medical device characteristics are chiefly established by component suppliers or device manufacturers to address the performance and quality requirements to be met by the finished medical device as well as the production, storage and distribution processes experienced by the medical device.

Biological evaluation of medical devices —

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

1 Scope

This document specifies a framework for the identification, and if necessary, quantification of constituents of a medical device, allowing the identification of biological hazards and the estimation and control of biological risks from material constituents, using a generally stepwise approach to the chemical characterization which can include one or more of the following:

— the identification of its materials of construction (medical device configuration);

— the characterization of the materials of construction via the identification and quantification of their chemical constituents (material composition);

— the characterization of the medical device for chemical substances that were introduced during manufacturing (e.g. mould release agents, process contaminants, sterilization residues);

— the estimation (using laboratory extraction conditions) of the potential of the medical device, or its materials of construction, to release chemical substances under clinical use conditions (extractables);

— the measurement of chemical substances released from a medical device under its clinical conditions of use (leachables).

This document can also be used for chemical characterization (e.g. the identification and/or quantification) of degradation products. Information on other aspects of degradation assessment are covered in ISO 10993-9, ISO 10993-13, ISO 10993-14 and ISO 10993-15.

The ISO 10993 series is applicable when the material or medical device has direct or indirect body contact (see ISO 10993-1 for categorization by nature of body contact).

This document is intended for suppliers of materials and manufacturers of medical devices, to support a biological evaluation.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-17, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances*

ISO 14971, *Medical devices — Application of risk management to medical devices*

Note 2 to entry: For some medical devices (e.g. infusion systems) that are labelled for use with a drug, the most appropriate extraction medium may be the drug product or drug product vehicle.

3.19
identification
process of assigning a molecular structure and chemical name to an organic compound or assigning constituent elements or molecular structure as appropriate, and a chemical name to an inorganic compound

3.20
information gathering
process of collecting existing chemical information, including available test results, that is relevant to chemical characterization

3.21
information generation
process of producing chemical information via laboratory testing

3.22
leachable
substance that is released from a medical device or material during its clinical use

Note 1 to entry: For many medical devices, a leachables study is not practical due to challenges with reproducing actual clinical conditions, so simulated-use extraction studies are often performed instead. See definition for simulated-use extraction.

3.23
manufacturer
natural or legal person who manufactures or fully refurbishes a medical device, or has a device designed, manufactured, or fully refurbished, and markets that medical device under its name or trademark

3.24
material composition
listing of the constituents that are contained in a material (qualitative) and the amount of each substance in the material (quantitative)

Note 1 to entry: A material's composition establishes the hypothetical situation in which the total amount of all substances present in a medical device are released during clinical use. These amounts can be derived directly from known composition; experimentally, they can be derived from digestion, dissolution, and, in many cases, exhaustive extraction studies.

3.25
material of construction
individual raw material that is used to produce a component

EXAMPLE Polymer resins.

3.26
medical device configuration
listing of a medical device's components (qualitative), including a listing of the component's materials of construction (qualitative) and the proportion of each material in each component (quantitative)

Note 1 to entry: Device configuration should also take into account the shape and relative arrangement of the parts in the medical device and surface properties (topography and chemistry).

3.27
potentially affected individual
person having direct or indirect body contact with the medical device

Note 1 to entry: See ISO 10993-1 for categorization by nature of body contact.

3.28
qualification
process of establishing that an analytical method is suitable for its intended use

3.29
qualitative analysis
analytical approach which estimates an analyte's concentration by using the response from a surrogate substance (or substances) chosen without specifically addressing or considering the relative responses of the analyte and the surrogate(s)

3.30
quantification
process of assigning a concentration to an analyte present in a sample

Note 1 to entry: There are several possible levels as shown in 3.31, 3.32 and 3.33.

3.31
estimated quantitative analysis
analytical approach which estimates an analyte's concentration by using the response from a surrogate substance chosen without specifically addressing or considering the relative responses of the analyte and the surrogate

3.32
semi-quantitative analysis
analytical approach which provides an analyte's concentration by using the response from a surrogate substance (or substances), specifically accounting for the relative responses of the analyte and the surrogate

3.33
quantitative analysis
analytical approach which establishes the most accurate estimate of an analyte's concentration by using a response function (calibration curve) generated specifically for the analyte via the use of a reference standard

Note 1 to entry: Estimated quantitative analysis is generally less accurate than semi-quantitative analysis, which is generally less accurate than quantitative analysis.

3.34
safety concern threshold
SCT
threshold below which a leachable (or an extractable as a probable leachable) has a dose so low that it presents a negligible safety concern from carcinogenic and non-carcinogenic toxic effects

Note 1 to entry: See Reference [27].

3.35
simulated-use extraction
extraction using a method that simulates clinical use

Note 1 to entry: A simulated-use extraction is performed to estimate the type and amount of substances that are expected to be released from a medical device during its clinical use. A simulated-use extraction is designed to produce an extractables profile that represents the worst-case leachables profile, meaning that all leachables are also extractables and the levels of all individual extractables are at least equal to the level of all individual leachables.

3.36
solubilisation
action or process of using a vehicle to dissolve part or all of a test article

Note 1 to entry: Leaching, extraction, dissolution, and digestion are (progressively more complete) sub-categories of solubilisation.

NOTE 2 It can be possible to evaluate biological safety of devices with low risk exposure (e.g. intact skin) based on qualitative information on material composition, if the device is made of widely used materials having extensive history of clinical use and manufactured using the same methods (e.g. ISO implant grade stainless steel and common passivation and post passivation processing). In these cases, chemical analysis and toxicological risk assessment might not be necessary.

5.5 Establish an analytical evaluation threshold

An AET shall be determined and justified (see Annex E). The AET should preferably be derived from a safety-based threshold (such as the TTC) but if this is not practically achievable, an analytical threshold, such as the Limit of Quantification (LOQ) can be used as the reporting threshold. However, the difference between the AET and the LOQ shall be considered in the toxicological risk assessment and the difference shall be justified.

5.6 Estimate the chemical release; perform extraction study

An extraction study can be performed to identify and quantify extractables for toxicological risk assessment per ISO 10993-17. In some cases (e.g. with exhaustive extractions), information on the release kinetics of extracted chemicals can be helpful. The extraction conditions used; exhaustive, exaggerated or simulated use shall be documented and justified. Annex D provides guidance on principles of extractions.

The nature of use for some medical devices (e.g. indirect contact devices such as saline infusion bags) can obviate the need for extractables testing, as the conditions of use associated with the maximum human exposure to leachables can be replicated and the clinical use solutions can be analysed in a straightforward manner. In such cases, extractables testing could reasonably be replaced by leachables testing.

NOTE 1 Extractables can, in some cases (e.g. for well understood materials), be forecasted through sound scientific and computational methods, as well as determined empirically.

NOTE 2 As indicated in ISO 10993-1, biological testing or additional analytical testing can be used to mitigate any potential concerns raised by chemical characterization.

The design of the extraction study should take into account the nature of contact (of the device) with the potentially affected user; the influence of (or interaction with) other substances such as drugs in an administration device may also need to be considered.

Table 2 — Recommended extraction conditions

Contact category	Recommended extraction conditions	Credible alternatives
Limited contact devices	Simulated use conditions[a]	Exaggerated conditions
Prolonged contact devices	Exhaustive conditions	Exaggerated conditions[b,c]
Long-term contact devices	Exhaustive conditions	Exaggerated conditions[b,c,d]

[a] Note that some legal authorities (e.g., U.S. FDA) can request exaggerated extraction, unless otherwise justified.

[b] Examples of instances where exhaustive extraction would not typically be required include:

— single use devices used for less than 24 h, where repeat use of a new device each day would result in categorization as prolonged or long-term contact;

— single use devices used for several days, where repeat use of new devices would result in categorization as prolonged or long-term contact;

— reusable devices, where a patient may be exposed to repeated use of the same device, resulting in categorization as prolonged or long-term contact; when an exaggerated extraction is used for a reusable device, the extraction should properly account for the duration of each individual use.

[c] Exaggerated conditions can be appropriate for external communicating or non-absorbable surface contact devices, with justification.

[d] An example is a device comprised entirely of non-absorbable metal (e.g. a vascular stent), because migration of constituents from within the material is not possible, and the constituents of interest are related to the surface only and exaggerated extraction can be adequate to generate a complete extractables profile.

5.9 Assess the actual chemical release (leachables profile)

Results of leachables studies, including both targeted leachables and leachables revealed by screening at levels above the AET, shall be reported so that the potential risks attributable to each constituent released can be assessed according to ISO 10993-17, ISO 10993-1 and ISO 14971.

5.10 Exiting the chemical characterization process

If the chemical characterization supports equivalence, or a toxicological risk assessment conclusion (per ISO 10993-17) that constituents, extractables, or leachables present an acceptable health risk, then the chemical characterization process has been completed and this outcome can be used to support biological evaluation under ISO 10993-1.

If the chemical characterization does not support a toxicological risk assessment conclusion (per ISO 10993-17) that constituents, extractables, or leachables present an acceptable health risk, the chemical characterization process has been completed but cannot be used to support biological evaluation. The need for further assessment (e.g. biological testing) or other mitigation activity should be evaluated per ISO 10993-1 and ISO 10993-17.

6 Chemical characterization parameters and methods

6.1 General

Clause 5 describes the stepwise generation of qualitative and quantitative chemical characterization data for use in the risk assessment. The characterization parameters to be used should be appropriate to the material or finished medical device. Due to the diversity of medical devices, it is recognized that not all of the parameters identified for a material will be required for all/some medical device uses. As noted previously, the extent of characterization required is determined by the invasiveness and duration of clinical exposure in the intended use (see ISO 10993-1:2018, 6.1). The type and amount of characterization data should be consistent with all of the parameters considered relevant to the risk assessment of the medical device and should consider the clinical application.

Chemical characterization data can be collected by information gathering from supplier information or literature review, or produced by information generation through testing a medical device or material directly in its natural state (e.g. IR analysis of a film). However, it is often necessary to solubilize all or part of the test article prior to analysis. The type and extent of solubilization employed shall match the intent and purpose of the testing. For example, if the purpose is to:

— generate information on the composition of a material (e.g. additives, residuals), then the appropriate solubilisation could involve complete dissolution or exhaustive extraction of the test article;

— establish the presence of elemental impurities in the material, then digestion of the material could be appropriate;

— establish the test article's extractables profile, then complete dissolution is inappropriate, and exhaustive, exaggerated, accelerated or simulated-use extraction, is appropriate.

Additionally, the vehicles/media used for solubilisation should be considered in the context of the methods chosen for testing those extracts, as the vehicles should be compatible with the test methods employed to analyse the extracts. If visible particles or precipitates occur during extraction, and are not solubilized, these should be analysed as well, using applicable methods.

Due to the diversity of medical devices, their materials of construction and the conditions of their clinical use, it is recognized that extraction conditions suitable for simulating, accelerating or exaggerating clinical use will vary greatly. Nevertheless, Annex D provides considerations in determining extraction parameters for typical medical devices, including the choice of extraction vehicle, based on type of contact and duration of exposure.

Table 5 *(continued)*

Material type	Characteristic	Example methods[a]	Qualitative	Quantitative
Metals and alloys	Crystallographic phases	X-ray diffraction	X	—
		Electron diffraction	X	—
	Micro/Macro structure	Metallography	X	X
Ceramics	Valency	Colourimetric analysis	X	—
	Phases	X-ray diffraction	X	X
	Microstructure	Microscopy	—	X
Natural macromolecules (see NOTES)	Configuration, pendant group analysis	Titration	—	X
		Spectroscopy	X	X
	Chain configuration, tacticity	Spectroscopy (^{13}C NMR)	X	X
		DSC	X	—
	Chain configuration, presence of crosslinks	Sol-gel extraction	X	—
		Di-sulphide link analysis	—	X
	Chain configuration, branching	DMTA	—	X
		Spectroscopy	X	X

[a] Not comprehensive or exclusive.

NOTE 1 Natural macromolecules utilized in medical devices include but are not limited to proteins, glycoproteins, polysaccharides and ceramics. Examples include gelatin, collagen, elastin, fibrin, albumin, alginate, cellulose, fatty acids (such as stearic acid), heparin, chitosan, processed bone, coral and natural rubber. These materials could have been processed, purified and modified to different extents.

NOTE 2 For natural macromolecules, it is essential that the source organism (species) and breed/strain be clearly identified as a first step.

NOTE 3 The ISO 22442 series covers the safe utilization of animal tissues and derivatives in the manufacture of medical devices. EN 455-3 covers the assessment of risks associated with protein residues in natural rubber latex.

NOTE 4 Pharmacopoeial monographs (e.g. Ph. Eur./USP/JP) exist for many of these materials, and several ASTM F04 standards also cover the characterization of these materials (see Bibliography).

NOTE 5 For characterization of nanomaterials, see ISO/TR 10993-22.

6.5 Analytical methods

Analytical methods used in chemical characterization generally serve one of two purposes: screening samples for unspecified analytes and testing samples for specified (targeted) analytes. The purpose of a screening analysis is to reveal analytes present in the sample above a relevant reporting threshold (e.g. AET), to estimate the concentration of such analytes, and to secure the identities of such analytes. The purpose of a targeting analysis is to accurately and precisely establish the concentration of the specified (targeted) and identified analytes in the sample.

Appropriate analytical methods shall be developed and qualified for these purposes, where qualification is defined as the process by which a method is established to be suited for its intended use. Prior to new method development, existing standards, monographs, scientific articles or other relevant scientific documents should be consulted to check for existing appropriate test methods. Methods from the literature could potentially need to be adapted and qualified before use. If suitable methods cannot be identified, appropriate new methods shall be developed.

As it is generally the case that the potential population of analytes which is addressed by analytical screening methods is large and diverse, a single method cannot be qualified for all potential analytes and it is not possible that a single method produces highly accurate and precise concentration estimates for all potential analytes. Thus, analytical methods used for screening should be qualified, whenever possible, using a set of surrogate analytes representative of the entire population of possible analytes. For example, when an analytical method is employed to screen an extract for extractables above the AET, the method shall be qualified using a set of potential extractables as surrogate analytes. The rationale for selecting surrogate analytes shall be documented. Potential factors in such a rationale could include

Table D.1 *(continued)*

	Solvent[a]	Polarity index[50]	Boiling point (°C)[b]
	i-Propyl alcohol	3,9	82
	Dichloromethane	3,1	41
Non-Polar	Toluene	2,4	111
	Cyclohexane	0,2	81
	Heptane	0,1[e]	98
	n-Hexane	0,1	69

[a] These solvents serve only as a starting point for solvent vehicle selection, and their inclusion here does not constitute a complete justification for their use.

[b] Not consistently related to solvent polarity (e.g. Reference [49]), but of practical value when solvent is evaporated from an extract (e.g. in common approaches to NVR in exhaustive extraction).

[c] Physiological saline and aqueous buffer systems such as phosphate buffered saline (PBS) are also considered polar solvents. Although specific values for their polarity index have not been developed, the presence of relatively small amounts of dissolved salts is not expected to markedly change their extracting power.

[d] Aqueous solutions of ethanol will have polarities between those of pure ethanol and water; their polarity indexes may be estimated according to Formula (D.1). For example, a 20 % ethanol$_{aq}$ solution will have an estimated polarity index of 9.0.

[e] See Reference [32].

The polarity index developed by Snyder was derived empirically from data on mixtures of solvents commonly used in chromatography (GC stationary phases and LC mobile phases)[49]. Other categorization schemes have been proposed for categorizing solvent extraction power. For example, Hansen[35] has expanded the Hildebrand solubility parameter 'δ'[36], attempting to account for the effects of dispersion forces, dipole moments, and hydrogen bonding. When Hansen solubility parameters are available for both material and solvents, they can provide an estimation of the degree of interaction between materials and solvents; materials with similar solubility parameters can interact with each other, resulting in solvation, miscibility or swelling. Either of these scales can contribute to the rationale for selection of vehicles for extraction in chemical characterization. Stults, et al.[52] have compiled some information on plastic and elastomer compatibility with several common solvents.

The polarity of binary mixtures can be estimated by taking into consideration the polarity (P) and the mole fraction (Φ) of each solvent of the mixture[49] and is calculated as in Formula (D.1):

$$P_{\text{mix}} = \left(\Phi_{\text{A}} \times P_{\text{A}}\right) + \left(\Phi_{\text{B}} \times P_{\text{B}}\right) \tag{D.1}$$

where

Φ_{A} is the volume fraction of solvent A;

P_{A} is the polarity of solvent A;

Φ_{B} is the volume fraction of solvent B;

P_{B} is the polarity of solvent B.

D.2 Approaches to establishing the compositional aspects of the configuration of a medical device or the composition of a material of construction

The terms composition applied to a material and configuration applied to a medical device address the same concept in that they both establish what chemical entities are present in the test article and at what amounts they are present. Although certain non-destructive test methods exist for establishing composition and configuration, it is typically the case that both require test article solubilisation followed by chemical testing of the resulting solution. When solubilisation is used, it can be accomplished in several different manners including digestion or dissolution.

If an exaggerated extraction cannot be justified or experimentally verified, then its use for producing chemical information that is the basis of a toxicological risk assessment is not recommended.

When an exaggerated extraction is employed, it is necessary to account for the exaggeration both in designing the extraction and in interpreting the result of the extraction study. One means of accounting for the exaggeration is via an exaggeration factor (a numerical factor that estimates the degree to which an exaggerated extraction amplifies the clinical conditions of use), although other means can be envisioned and employed. Regardless of the means, the degree of exaggeration is established by a rigorous assessment of the extraction and clinical use conditions and knowledge of the degree of exaggeration may be used to adjust the results of the exaggerated extraction to allow for the toxicological risk assessment of the extractables. Thus, for example, if quantity of extracted medical devices is doubled over that used clinically, or the device contact surface area to contact solution volume ratio of the extraction is doubled this degree of exaggeration should be taken into account when the extractables data are reported for toxicological risk assessment. It should be noted that greatly exaggerated surface area/solution volume ratios may not produce proportionally exaggerated extractables profiles, making an accounting of the degree of exaggeration more challenging. Furthermore, any quantification of degree of extraction exaggeration should address whether the extractables' concentrations have reached an equilibrium-based plateau (i.e. that sink conditions have been maintained).

Due to the vast number of various medical devices and usage conditions within the scope of this document, it is unrealistic to provide specific guidance here. However, points to consider in establishing exaggerated conditions are outlined as follows.

Dimensions to consider when establishing and justifying an exaggerating extraction vehicle include pH (for aqueous vehicles) and polarity (for organic or "organic-like" vehicles). Considering extraction vehicle pH, it is noted that pH is an exaggerating dimension only for acidic or basic extractables (that is, the extraction of neutral or un-ionisable extractables is largely unaffected by the pH of the extraction vehicle). For acidic extractables (e.g. stearic acid), it is generally the case that an extraction vehicle with a pH higher than that of the clinical contact solution will exaggerate extraction. For a basic extractable (e.g. dibenzylamine), it is generally the case that an extraction vehicle with a pH lower than that of the clinical contact solution will exaggerate extraction. A neutral extractable's accumulation level will be unaffected by pH unless that neutral compound is reactive as a function of pH.

For neutral extractables, extraction vehicle polarity can be an exaggerating dimension. For example, increasing the alcohol content of an extraction vehicle versus the clinical contact solution will typically result in an exaggerated extraction.

The use of temperature as an exaggerating dimension is addressed in D.4.

Exaggerated extraction conditions should not alter the extractables profile. For example, the use of extreme temperatures as a means of accomplishing the exaggeration might result in either the decomposition of the extractables or the alteration of the medical device materials (e.g. curing, cross-linking, or degradation of the device's polymeric materials of construction, physical state change over the glass transition temperature), any of which could result in an altered extractables profile.

When extraction is exaggerated using multiple dimensions (e.g. both temperature and surface area), the combined effect of the multiple dimensions should be considered and justified, although doing so can be scientifically challenging.

As altered extractables profiles can be obtained when greatly exaggerated extraction conditions are employed, it is recommended that exaggerations be kept as small as is necessary, minimizing potential complicating effects such as degradation. As exaggeration is justified in the context of the circumstances in which it is employed, determining whether an exaggeration is appropriate or excessive is done on a case by case basis and it is difficult to provide general guidelines in terms of when an exaggeration is no longer appropriate and becomes excessive. Nevertheless, highly exaggerated conditions can be sufficiently extreme that the exaggerated extractables profile becomes poorly correlated with the clinical use extractables profile. The justification of any exaggeration, but especially a significant exaggeration should consider the exaggerated extraction's propensity to chemically or physically alter the test article and/or the extracted substances, as extractions that alter either the test article or the extracted substances are not permitted.

Regardless of the means by which an exaggeration is accounted for, the use of exaggeration in toxicological risk assessment should be rigorously justified and documented. While such a justification could be derived from scientific first principles, it is always the case that the most definitive means of justifying an exaggeration is to verify the exaggeration with experimental data.

Any exaggeration resulting from the extraction process or the testing of the extracts should be clearly described to facilitate a proper and accurate safety risk assessment and to ensure that the exaggeration is properly accounted for in the safety risk assessment.

D.4 Simulated or accelerated extractions to establish clinical use extractables profiles

The exaggerated extraction produces a practical worst-case assessment of the leaching of a medical device. As discussed in Clause 5, should a toxicological risk assessment of this practical worst-case establish that the risk related to the extractables be acceptable, then the risk assessment is essentially complete and the medical device is accepted as being chemically suitable for its intended use with no further chemical testing.

However, if the toxicological risk assessment establishes that the practical worst-case could represent a risk, then a more realistic estimate of the medical device's leaching characteristics is necessary and appropriate. This more realistic estimate is obtained by using either simulated extraction conditions that very closely reflect the clinical conditions of use or accelerated extraction conditions which use durations that are shorter than clinical use.

The purpose of a simulated extraction is to produce an extractables profile which closely matches the clinical case leachables profile. A simulated-use extraction establishes the actual amount of extractables that will be released as leachables by the medical device or material during clinical use/lifetime. The simulated extraction is performed in those circumstances where either the clinical conditions of use cannot be achieved in the laboratory or when use of the clinical conditions produces a solution for testing which cannot be analytically profiled for leached substances. If the clinical conditions of use can be replicated in the laboratory and if the resulting solution can be analytically profiled for leachables, then the value of performing a simulated extraction is lessened and it is reasonable to suggest that the simulated extraction be replaced with an actual leachables study.

The simulated extraction is accomplished by using extraction conditions (i.e. temperature and duration) that mimic the conditions of clinical use. Additionally and as appropriate, the simulated extraction can be performed with a vehicle whose extraction power equals that of the solution that mediates the clinical contact between the medical device and potentially affected individual. The aspect of specifying a simulating extraction vehicle has been discussed previously in considering exaggerated extractions (see D.3). Considering this aspect more specifically for simulating extractions, guidance can be provided for certain medical device categories considering the nature of body contact and the application site. For example, if the clinical application of the device:

— involves contact with blood, then a mixture of ethanol in water could be an appropriate simulating vehicle. If an ethanol/water mixture is used, it should be demonstrated to extract comparable levels of the target leachables with respect to blood (e.g. Reference [38]). Other simulating vehicles can be used if justified;

— is such that the medical device communicates with the potentially affected individual via an aqueous solution, then the appropriate simulating vehicle is either physiological saline, adjusted and buffered to a relevant pH, or an appropriate pH adjusted salt solution whose composition is justified. If the clinical application of the medical device involves contact with numerous solutions with varying pH (e.g. solution administration sets), then the pH range should be properly bracketed by two simulating vehicles, one adjusted to a pH of 2 and the other adjusted and buffered to a pH of 10 (see Reference [40]). If the pH range of solutions encountered in clinical use is smaller than this range, simulating extraction solutions bracketing the smaller range can be used;

— is such that the medical device communicates with the potentially affected individual via a solution with lipophilic properties (e.g. lipid emulsions, drug products containing solubilizing agents such

as polysorbate 80) then an appropriate simulating vehicle should be identified and scientifically justified. In many situations, an alcohol/water mixture whose proportion of alcohol to water is justified, can serve as a suitable simulating vehicle. Reference [38] contains information which could facilitate the identification and justification of such proportions for certain "organic-like" solutions.

Information on solvents that may be used to simulate body fluids has been published[24][44][47]. Simulating extraction vehicles relevant to either surface-contacting medical devices or devices which contact tissue/bone/dentin are not specified in this document. Any simulating solvent use should be established and justified on a case-by-case basis.

Other design parameters are typically matched between the simulated extraction and the clinical conditions of use. Thus, in a simulated extraction, the surface area/volume ratio that is used is the same ratio that is experienced during clinical use, where possible. For example, for infusion systems, the device surface area and infusate volume could be used. In contrast, it will often be difficult to justify a surface area/volume ratio for implanted devices, as it can be difficult to establish the volume of physiologic fluid that contacts the device over its implantation time. Moreover, sequential extraction is generally not appropriate for simulated extractions, with the exception of reusable or multi-use medical devices.

In certain circumstances (such as for medical devices with long term contact duration), a simulated extraction might be performed under accelerated conditions. For example, an accelerated extraction might be performed at a temperature that exceeds the clinical use temperature and a duration that is shorter than clinical use. However, the accelerated extraction should be performed in such a manner that the accelerated conditions and the clinical use conditions subject the device to the same heat exposure (i.e. the same transfer of thermal energy). Additionally, acceleration can be accomplished by agitation during extraction or use of recirculating or flowing extraction vehicles. However, the extent of acceleration by these approaches can be challenging to quantify.

In certain circumstances, such as when an accelerated extraction can be appropriate to simulate longer duration and greater invasiveness of contact, an analysis that provides information on the kinetics of extraction might be necessary to establish and justify the proper extraction procedure.

Considering the acceleration of extraction conditions, it makes little sense to accelerate limited contact durations of less than 24 h and in such cases the actual clinical conditions of use are used in the simulated extraction. A similar logic applies to prolonged contact durations of 3 d or less. However, for contact durations longer than 3 d and for all long-term contact durations, acceleration could be desirable to facilitate appropriate extraction.

As was the case with exaggerated extraction discussed previously, accelerated extraction conditions should be fully and rigorously justified. Although certain accelerated conditions might be justifiable in certain circumstances, the same accelerated conditions or the same justification might not be applicable to other situations.

It is beyond the scope of this document and the current state of good science to provide specific guidance on how to devise and justify accelerated extractions and how to calculate appropriate and justifiable acceleration factors for all medical devices and their clinical conditions of use. Nevertheless, careful review of the chemical literature may suggest means for performing such calculations and justifications.

Care should be exercised in the selection of accelerating conditions and the effects of higher temperatures or other accelerating conditions on extraction kinetics and the identity of the extractables should be considered carefully if accelerated extraction is used. Proper accelerating conditions are those which reduce the extraction duration to a value shorter than the duration of clinical use but which do not result in a chemical modification of the device itself or to the type and amount of extracted substances. Any model or concept used to establish acceleration or exaggeration factors shall be justified and documented.

D.5 Extractions performed for correlating chemical characterization with biological testing

Generally, there are two reasons for correlating chemical characterization with biological testing:

— to elucidate the chemical cause of a particular biological test result;

— to establish the biological test outcome of a chemical or set of chemicals.

When correlating chemical characterization, most likely extractables profiling, with biological testing, it is clear that the best case is when the chemical testing and the biological testing occurs on the same extract, as so doing will produce the closest and most rigorous correlation. The proper extraction methods for correlating chemical and biological testing are documented in ISO 10993-12:2012, specifically in Clause 10 and Annex C. Whenever possible, the exact conditions used to generate an extract for biological testing should also be used for generating the extract for chemical characterization. This recommendation is typically easier to achieve for extraction parameters such as surface area to volume, extraction time and extraction duration. However, it can be more difficult to follow this recommendation when considering the extraction vehicle. As is noted in ISO 10993-12:2012, C.7, "the vehicles selected as the extraction vehicle (for biological testing) should be suitable for use in the specific biological test systems". While such a recommendation most certainly facilitates biological testing, in certain circumstances it confounds chemical testing, as an extraction vehicle that is appropriate for biological testing might not be amenable to chemical testing. In such circumstances, either a surrogate extraction vehicle should be found to facilitate the chemical testing or the extract for biological testing should be manipulated to make it analytically viable. If a surrogate extraction vehicle is used, such a surrogate extraction vehicle should, in addition to being analytically viable, ideally have similar extracting properties as the extraction vehicle used for biological testing. If a chemical manipulation (e.g. derivatization) of the extract is used, care should be taken to avoid a chemical change of one or more extractables.

ISO 10993-12:2012, 10.3.5, establishes extraction vehicles appropriate for biological testing, including:

— polar extraction vehicles such as water, physiological saline, culture media without serum;

— non-polar extraction vehicles such as freshly refined vegetable oil;

— additional extraction vehicles such as ethanol/water, ethanol/saline, polyethylene glycol 400 (diluted to a physiological osmotic pressure), dimethylsulphoxide and culture media with serum.

Several of these extraction media are readily amenable to chemical testing and thus should be used for both biological and chemical testing when a correlation between the two is desired. Such extraction media can include water, physiological saline, ethanol/water, ethanol/saline and dimethylsulphoxide.

The other extraction vehicles listed previously might or might not be analytically viable from a chemical characterization perspective. If it can be established that such an extraction vehicle is analytically viable from a chemical perspective, then the same vehicle should be used for both biological and chemical testing. If the vehicle is not analytically viable, then a surrogate vehicle should be used for chemical testing.

As the purpose of using the surrogate vehicle is to facilitate the discovery of the chemical agents responsible for a biological test result, any surrogate vehicle that accomplishes this objective is an appropriate surrogate solvent. Potential surrogate extraction vehicles that can be employed for chemical testing and which meet the dual requirements of approximating extracting power and facilitating analytical testing are given in Table D.3. Although use of these surrogate vehicles does not ensure that the chemical investigation will be successful, they represent a good starting point for such an investigation and their use will typically lead to the desired positive outcome. Justification for a chosen surrogate extraction vehicles should be provided. Justification should include biological testing that confirms the indicted chemicals are actually causing the biological test failure. It can also be possible to confirm causality with information from the literature.

It is noted that these surrogate vehicle recommendations are relevant solely for the purpose of correlating biological and chemical test results and are not necessarily specified for the broader

purpose of generating an extractables profile for the purpose of toxicological risk assessment. As the appropriateness of surrogate vehicles can vary somewhat from situation to situation, surrogate vehicles other than those proposed above may be used if they meet the two criteria noted previously, that they are amenable to the anticipated chemical testing and that their solvating properties have been established to be similar to those properties of the extraction vehicles that the surrogates would replace.

Table D.3 — Potential surrogate extraction vehicles for correlating chemical to biological testing

Extraction vehicle for biological testing	Potential surrogate extraction vehicle for chemical testing
Water[f]	Water
Physiological saline[f]	Physiological saline
Ethanol/water[f]	Ethanol/water
Ethanol/saline[f]	Ethanol/saline
Dimethylsulphoxide[f]	Dimethylsulphoxide
Culture medium without serum	1/9 (v/v) ethanol/saline[a]
Vegetable oil	1/1 (v/v) ethanol/water[b] (Reference [25])
Polyethylene glycol 400[e]	1/3 (v/v) ethanol/water[c] (Reference [38])
Culture medium with serum	2/3 (v/v) ethanol/saline[d] (Reference [38])

[a] In general, culture media contain all the elements that most bacteria need for growth, including: a carbon source (such as glucose), water, various salts, and a source of amino acids and nitrogen (e.g. beef, yeast extract). To account for the salt content of the culture medium, saline is used in the surrogate vehicle. To account for the organic character of the culture medium, a 10 % (by volume) portion of ethanol is used in the surrogate vehicle.

[b] This recommendation is based on surrogate extraction vehicles specified for, and widely used, with food packaging. This surrogate extraction vehicle (1/1 ethanol/water) is acceptable for most polymers; however, for polyolefins complying with 21 CFR 177.1520 and ethylene - vinyl acetate copolymers complying with 21 CFR 177.1350, a surrogate extraction vehicle of 95 % or absolute ethanol should be considered.

[c] Published research has noted that "glycols (such as polyethylene glycol and propylene glycol) are weak solubilizing agents and can be simulated by ethanol/water mixtures containing 25 % ethanol or less". Thus, a 1/3 mixture of ethanol/water is recommended as the appropriate simulating vehicle for polyethylene glycol 400.

[d] Based on published research, 40 % (by volume) mixture of ethanol/water is considered an appropriate surrogate for blood and blood related substances, which would include serum. Thus the 40 % (by volume) portion of the surrogate vehicle (ethanol) is used to account for the serum.

[e] And its associated aqueous mixtures.

[f] These vehicles are analytically expedient and can readily be screened for extractables. Thus, surrogate vehicles are not warranted.

NOTE 1 It cannot be emphasized more strongly that the extraction vehicle examples provided in Table D.3 are solely for the purpose of correlating the results of biological and chemical testing. These examples are not meant to be applied to the selection and justification of extraction vehicles used for the purpose of extractables or leachables profiling, although in certain situations these vehicles can be suitable for those purposes. Furthermore, it is noted that while these vehicles can be applicable for a large population of medical devices, no leaching vehicle is applicable to every medical device and every clinical use circumstance. Thus, use of these or any other vehicles should be evaluated and justified on a case by case basis.

NOTE 2 Inclusion of vehicles here does not fully justify their use in chemical-biological comparisons.

ISO 10993-12:2012, 10.3.5, Note 1, states that "other extraction vehicles appropriate to the nature and use of the medical device or to the methods for hazard identification can also be used (for biological testing) if their effects on the material and the biological system are known". If these other extraction vehicles are amenable to both biological and chemical testing then the vehicles should be used for both biological and chemical testing. If these other extraction vehicles are not amenable to chemical testing, then a surrogate vehicle should be identified and justified.

Given a potentially differing level of sensitivity for biological versus chemical testing, other extraction conditions, such as the extracted surface area to extraction solution volume ratio, might need to be adjusted to facilitate the generation of a useful correlation.

Annex E
(informative)

Calculation and application of the analytical evaluation threshold (AET)

E.1 Discussion

Analytical methods used to screen an extract for extracted substances should perform four functions:

a) they should detect the extractables;

b) they should distinguish between the extractables so that each extractable provides a unique response;

c) they should provide information with which the extractable's identity can be elucidated;

d) they should provide information with which the extractable's concentration can be established.

Considering chromatographic methods used to screen extracts for organic extractables, the methods could be more capable of detecting extractables than they are at correctly identifying or accurately quantifying extractables.

When an extractable has been detected, it is necessary to consider the safety impact that extractable might have as a leachable. However, if the extractable's identity cannot be established, a toxicological risk assessment of this extractable, as described in ISO 10993-17, cannot be performed. Furthermore, if the extractable is inaccurately quantified, the outcome of any toxicological risk assessment can be incorrect.

The purpose of this annex is to address the quantitative aspect of extractables screening, specifically considering the issue of an AET.

Thresholds such as a TTC establish a dose of leachables (and other potentially toxic impurities) below which there is insufficient quantity present to elicit toxicity, irrespective of the substance's identity. It is important to note that some highly toxic substances (i.e. cohorts of concern) are excluded from a TTC approach and their presence should be ruled out (see ISO 10993-17) before the AET is applied. Any specifically targeted analytes of concern for the specific medical device should also be assessed individually, independent of the AET.

Leachables present at levels below the TTC are deemed to be appropriately safe and not to require additional assessment (identification and quantification). In essence, these thresholds (e.g. TTC) in combination with an appropriate factor that addresses the uncertainty of the analytical method, become identification thresholds, as substances dosed at and above the threshold should be identified to allow for their safety assessment — while substances dosed below the threshold are deemed to present an acceptably low toxicological safety risk without identification.

The threshold concept can be applied to extractables in the circumstance that extractables are used to project the worst-case release of leachables from medical devices.

The application of the threshold concept requires that a dose-based threshold (TTC) be converted to a concentration-based threshold (AET), as such a conversion would facilitate extractables assessment decisions based on the concentration of the extractable in an extract.

Such an analytical threshold has been termed the AET. By definition, the AET establishes a threshold for the toxicological risk assessment of extractables or leachables. Extractables whose concentrations are above the AET should be identified and quantified as a prerequisite for their toxicological risk

assessment, as there is a sufficient possibility that the extractables could be toxic. On the other hand, extractables whose concentrations are below the AET do not need to be identified or quantified for toxicological risk assessment.

Although PDEs for individual metals have been established[19], a dose based threshold (DBT) applicable to all metals has not been established. Thus, practically speaking, the AET is only applied to organic extractables or leachables.

The relationship between the AET and frequently encountered analytical limits, such as the limit of detection (LOD) and LOQ, is as follows. As the AET is a threshold that requires the compound responsible for an analytical response to be identified and quantified, it is clear that the analytical response should be discernible above the analytical noise (detected) before its source compound can be identified. Thus, the AET should be greater than or equal to the LOD as an AET lower than the LOD would indicate that the analytical method is incapable of producing analytical responses at the necessary concentration levels for relevant compounds. Although the LOD might not be determinable for compounds detected during the screening process, the LODs of one or more relevant surrogates or internal standards can be used to represent the method's LOD for all compounds that the method is suited for. It is also clear that if one purpose of the analytical testing is quantification, the AET should be higher than or equal to the LOQ. However, it is understood that semi-quantitative concentration estimates obtained in screening cannot meet the rigorous accuracy and precision expectations inherent in an LOQ and thus that there can be cases where screening studies provide concentration estimates when the AET is lower than the rigorously determined LOQ. Concentration estimates below a method's established LOQ might not be sufficiently accurate to support a valid toxicological risk assessment. Lastly, it is observed that the AET is also an identification threshold and that the process of identification requires that the response contain more complex and/or advanced information than does the process of quantification (i.e. quantification can typically be accomplished at concentrations lower than those required for identification). This being the case, it is possible that the AET could be above the LOQ but it would still not be possible to secure an identification for an analyte present in the sample at the AET.

E.2 Calculation of the AET

The conversion from a dose-based threshold (e.g. TTC) to a concentration-based threshold (AET) requires inputs including:

— the frequency and duration of the medical device's clinical use;

— the various extraction conditions used to produce the extractables profile;

— the uncertainty of the analytical method.

The duration of the medical device's clinical use could dictate the actual value used for the dose-based threshold (e.g. a staged TTC based on duration)[18] while the frequency of clinical use establishes the magnitude of clinical exposure. The AET in µg/ml can be calculated as given in Formula (E.1):

$$AET = \frac{DBT \times \frac{A}{BC}}{UF} \tag{E.1}$$

where

A is the number of medical devices that were extracted to generate the extract;

B is the volume of the extract (measured in ml);

C is the clinical exposure to the medical device (number of devices a user would be exposed to in a day under normal clinical practice);

DBT is the dose-based threshold (e.g. TTC or SCT) in µg/d (a toxicologist should be consulted in selecting a specific threshold that can support risk assessment);

UF is an uncertainty factor that could be applied to account for the analytical uncertainty of the screening methods used to estimate extractables' concentrations in an extract (see E.3 for a discussion on how to determine the proper value to assign to UF).

The extract processing (e.g. any dilution or concentration steps) should be considered during analytical concentration calculations and the calculation of the AET value adjusted accordingly.

Several examples of AET determination are provided in E.4 to illustrate the process in various settings. These examples use values for various inputs (e.g. UF) that were chosen for illustrative purposes and the choice is not meant to imply that the exact value used should be unilaterally applied in all circumstances.

NOTE The application of Formula (E.1) to long term implants could require knowledge and consideration of the release kinetics of the constituents of interest.

E.3 Determination of the uncertainty factor

Quantification in extractables profiling is achieved by various means which differ in the degree of certainty in the estimated and reported concentration. The degree of uncertainty can vary significantly depending on the quantification strategy employed. For example, quantification in some cases could involve the use of an internal standard to normalize the responses obtained for all relevant analytes and estimates the concentration of each analyte based on the simplifying assumption that all analytes respond similarly, among themselves and with respect to the internal standard. 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 will be 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.

In other cases, the degree of uncertainty can be low. For example, if quantification is achieved through the use of authentic standards employed in qualified analytical methods, the concentration estimates obtained for the qualified analytes will be highly accurate. Considering quantification via an internal standard, if the simplifying assumption noted previously is true and response factors are constant, then the resulting concentration estimates for all analytes will also be sufficiently accurate for toxicological risk assessment.

Other quantification strategies could produce concentration estimates whose uncertainty is somewhere between these two extremes; lower uncertainty than use of an internal standard's response factor but higher uncertainty then use of a calibration curve generated with an authentic reference standard. For example, relative response factors can be obtained for extractables, were the relative response factor is the ratio of the response of the extractable versus that of an internal standard at equal concentrations of extractable and internal standard. Use of relative response factors in quantification essentially accounts for differences in response factors, extractable versus internal standard.

Recognizing that the accuracy of and uncertainty in concentration estimates obtained in extractables studies can vary, an UF is added to the calculation of the AET to account for the analytical uncertainty that arises due to the variable accuracy. Use of a UF is the same principle as calculation of a final AET from an estimated AET (e.g. see Reference [45]).

In cases where the analytical uncertainty 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 internal standards in qualified methods for targeted extractables. 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 semi-volatile extractables via GC-FID or GC-MS, as analytical FID or MS response factors for extractables are somewhat consistent, extractable to extractable. Alternatively, response factors for other analytical methods used for extractables screening, such as HPLC-UV and HPLC-MS (which are typically applied to non-volatile extractables), may 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.

A statistical 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 one possible approach, the value of the UF would be linked to the relative standard deviation of the response factors according to Formula (E.2):

$$\text{mean} / \left[1 - (t \times \text{std})\right] \tag{E.2}$$

where

mean is the mean response factor from the reference database;

t is the desired degree of confidence;

std is the standard deviation in the response factor database.

Applying commonly used statistics for normally distributed data, $t = 1$ would provide 68 % confidence, $t = 1{,}65$ would provide 90 % confidence, $t = 2$ would provide 95 % confidence, and $t = 3$ would provide 99,7 % confidence. Note that when the mean response factor is 1 and $t = 1$, Formula (E.2) simplifies to that proposed by PQRI and Jordi (see References [41] and [46]). There are two implications of these points. First, if the mean response factor is not 1, best practice would be to pick an internal standard that makes it 1. This approach minimizes potential bias in this part of the analytical process. Second, use of $t = 1$ is a reasonable option as it: 1) is consistent with previously published approaches[41][46]; 2) actually provides a 95 % level of confidence, because the distribution of interest is single tailed (i.e. of the population outside of the confidence interval, only the half that would fall below the AET is a safety concern).

When the variation in responses factors is large relative to the mean response factor (e.g. std = 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, while a UF > 10 can be calculated, the fact that the UF is as large as 10 (or larger) suggests that the quantification method being used is inherently inaccurate and thus might not be appropriate for the purpose of toxicological safety risk assessment. In this case, an adjusted AET should not be established and the concept of an AET should not be applied to the method.

In cases where $t \times \text{std} > 1$, a UF cannot be calculated, as the result is either infinity or a negative number. Clearly an analytical method with this much variation in response factors is not suitable for the purpose of toxicological safety risk assessment.

In any event, the use of the uncertainty factor, and the value of the uncertainty factor that is used, should always be justified. In some 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 AET becomes 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 circumstances, use of the AET cannot be justified and thus the AET should not be applied. In such cases, it can be necessary to identify and quantify all the compounds associated all observed analytical responses obtained by the screening analyses.

E.4 AET determination examples

EXAMPLE A

Consider a limited contact medical device (e.g. a balloon catheter) in which a single device is used clinically and therapy is completed in less than 1 day. In the extraction study, a single device was extracted in 9,0 ml of extracting vehicle. The resulting extract was neither diluted nor concentrated. GC-FID was used as the analytical method; therefore, an uncertainty factor of 2 was considered appropriate. In this case, the value of the DBT was set to the ICH M7 TTC for potentially mutagenic impurities[18], and DBT = TTC = 120 µg/d (duration of treatment 24 h).

— A = 1 device

— B = 9,0 ml

— C = 1 device/d

— UF = 2

and the AET is calculated as given by application of Formula (E.1):

$$\text{AET (µg/mL)} = \{120\ \text{µg/d} \times [1\ \text{device}/(1\ \text{device/d} \times 9{,}0\ \text{ml})]\} \div 2$$

$$\text{AET (µg/mL)} = 6{,}6\ \text{µg/ml}$$

EXAMPLE B

Consider a medical device that is used in a therapy which is completed in 7 d. On each day of therapy, 2 devices are required. In the extraction study, 4 devices were extracted in 100 ml of extracting vehicle. The resulting extract was neither diluted nor concentrated. The analytical method was supported by a response factor database which established that the response factors were acceptably consistent between extractables. In this case,

— DBT = TTC = 120 µg/d (M7 assessment for potentially mutagenic impurities, duration of treatment ≤ 1 month),

— A = 4 medical devices,

— B = 100 ml,

— C = 2 medical devices/d,

— UF = 1.

and the AET is calculated as given by application of Formula (E.1):

$$\text{AET (µg/ml)} = \{120\ \text{µg/d} \times [4\ \text{devices}/(2\ \text{devices/d} \times 100\ \text{ml})]\} \div 1$$

$$\text{AET (µg/ml)} = 2{,}4\ \text{µg/ml}$$

EXAMPLE C.1

Consider a medical device that is permanently implanted (e.g. a cardiovascular stent), and a single device is used. The circumstance that this is a permanent implant requires that the extraction study be exhaustive. In the extraction study, 20 devices were extracted in 33,3 ml of extracting vehicle. The exhaustive extraction was accomplished in 2 sequential extracts, meaning that the levels of extractables present in the second extract was less than 10 % of the levels present in the first extract. The resulting extract was neither diluted nor concentrated. The analytical method had a response factor database which established that the %RSD of response factors was 25 %, suggesting that a UF value of 2 is appropriate.

EXAMPLE C.2

In this case, the critical issue is establishing the proper DBT. Because the device is a permanent implant, the most likely leaching scenario is that all extractables present in the medical device will leach out of the device during the device/patient contact. This is why the proper extraction study for a permanent implant is an exhaustive extraction. Considering potentially mutagenic extractables, a DBT of 120 µg/d is appropriate, regardless of leaching kinetics, as illustrated below.

Consider a mutagenic substance, revealed after exhaustive extraction with a level of 120 µg/d, which corresponds to 120 µg/device in the example above based on a single device.

— If the 120 µg/device is leached in 1 d, the amount leached is equal to 120 µg/day, which is the TTC for this duration category per ICH M7.

— If the 120 µg/device is leached in 31 d (1 month), the amount leached is 120/31 = 3,9 µg/d, which is lower than 20 µg/d, the TTC for this duration category per ICH M7.

— If the 120 µg/device is leached in 365 d (1 year), the amount leached is 120/365 = 0,33 µg/d, which is lower than 10 µg/d, the TTC for this duration category per ICH M7.

— If the 120 µg/device is leached in 3 650 d (10 years), the amount leached is 120/3 650 = 0,033 µg/day, which is lower than 1,5 µg/d, the TTC for this duration category per ICH M7.

Note that 20 µg/d for 31 ds would be an exposure of 620 µg, 10 µg/d for 365 d would be an exposure of 3,650 µg, and 1,5 µg/d for 3 650 d would be an exposure of 5,475 µg. Each of these theoretical extreme approaches would therefore be less conservative.

In this case, the calculation of the AET proceeds as follows:

— DBT = TTC = 120 µg/day (Note, however, that this DBT is "distributed" over both extraction steps; thus, the DBT for each extraction step is 120 µg/d ÷ 2 extracts = 60 µg/d) A = 20 medical devices,

— B = 33,3 ml,

— C = 1 medical devices/d,

— UF = 2.

and the AET is calculated as given by application of Formula (E.1):

$$\text{AET (µg/ml)} = \{60\ \text{µg/d} \times [20\ \text{devices}/(1\ \text{device/d} \times 33{,}3\ \text{ml})]\} \div 2$$

$$\text{AET (µg/ml)} = 18\ \text{µg/ml}$$

EXAMPLE C.3

Because the device was exhaustively extracted to screen for toxic chemicals to which the patient could be exposed, application of 1,5 µg/d without modification is the most conservative approach that can be applied so that all toxic chemicals present in/on the device will be identified/quantified and toxicological risk assessed. In this highly conservative approach, the expected DBT becomes the TTC of 1,5 µg/d and the calculation of the AET proceeds as follows:

— DBT = TTC = 1,5 µg/d (Note, however, that this DBT is "distributed" over both extraction steps. Thus, the DBT for each extraction step is 1,5 µg/d ÷ 2 extracts = 0,75 µg/d),

— A = 20 medical devices,

— B = 33,3 ml,

— C = 1 medical devices/d,

— UF = 2.

and the AET is calculated as given by application of Formula (E.1):

$$\text{AET (µg/ml)} = \{0{,}75\ \text{µg/d} \times [20\ \text{devices}/(1\ \text{device/d} \times 33{,}3\ \text{ml})]\} \div 2$$

$$\text{AET (µg/ml)} = 0{,}23\ \text{µg/ml}$$

NOTE Data establishing the actual release kinetics of leachables can be an essential input for establishing an appropriately conservative DBT. If the actual release kinetics of leachables establishes that the exposure to extractables is less than 10 years, then the kinetic data can potentially support a higher DBT value (see ISO/TS 21726).

E.5 Use of the AET

The conversion of the DBT to an AET enables an analytical chemist to address the question of whether a specific extractable need be identified and quantified. However, analytical methods do not produce concentrations directly but a response in units that should be converted to concentrations. For example, the output of chromatographic analysis of a sample is a chromatogram in which extractables appear as peaks in the chromatogram (see Figure E.1). In this case, peak A corresponds to an analyte present in the test sample at a concentration equal to the AET. Thus, a horizontal AET line can be drawn across the chromatogram using the apex of A as the reference point. Peaks whose responses fall above such a line (e.g. peak B) are present in the sample at levels above the AET and the substance responsible for peak B should be identified and reported for toxicological risk assessment. Peaks whose response fall below the line (e.g. peak C) are present in the sample at levels below the AET and do not need to be identified for toxicological risk assessment.

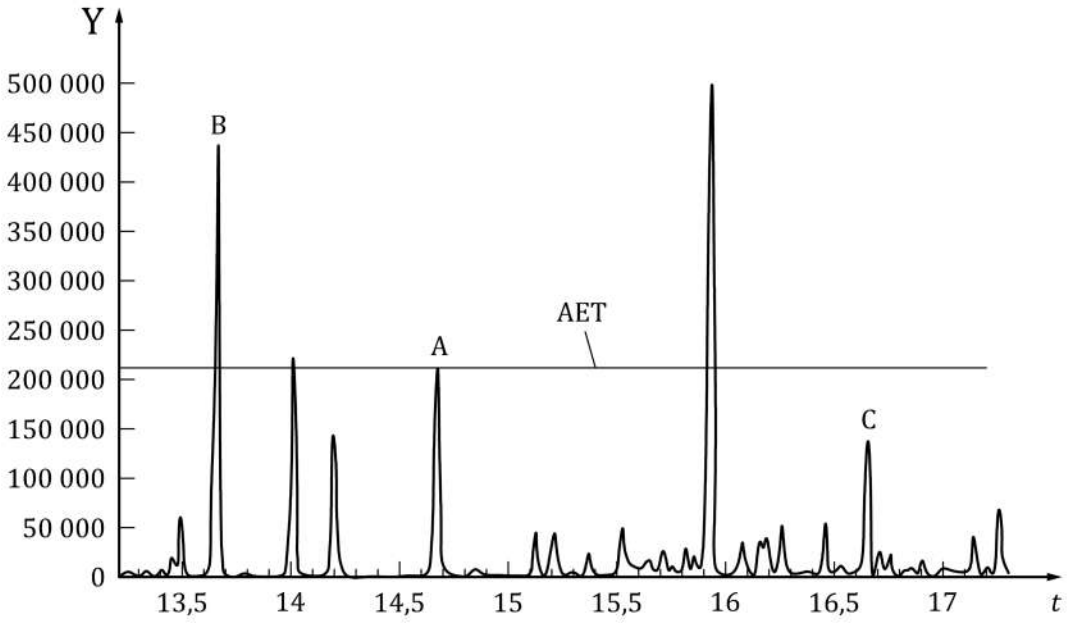

Figure E.1 — Application of the AET in chromatographic analysis

Although Figure E.1 illustrates the application of the AET in terms of peak height, peak area may also be used to compare individual extractables peaks with the AET and can be more appropriate. Furthermore, while this example and illustration specifically relates to chromatographic analysis, the concept of the AET is widely applicable to many analytical techniques.

E.6 Exclusions to the AET; cohorts of concern

The term "cohorts of concern" has been applied to those sets of compounds that possess structural groups of such high potency that intakes even below the TTC would be associated with a potential for

significant patient safety risk, including, but not necessarily limited to, carcinogenic risk. Compound classes that comprise the cohorts of concern are described in ISO/TS 21726. Some colorants can also have the potential to raise concern and should be considered for exclusion from the AET. See also Reference [42] and ISO 10993-17.

The previously established convention that extractables below the AET are taken to be toxicologically safe regardless of their identities is clearly not applicable for a cohort of concern, as by definition the cohort could pose a risk even at concentrations below the AET. Since the AET is both an identification and quantification threshold, the cohorts of concern present an analytical dilemma in the sense that it is impossible to know whether a compound whose concentration is less than the AET is from a cohort of concern unless the compound is identified at the extent that its molecular structure can be established in sufficient detail to allow for a toxicological risk assessment. Although there are several options for reconciling the AET with potential cohorts of concern, some are not practical. For example, rejecting the AET concept based on the possibility that there might be an extractable that is a cohort of concern is likely an excessively conservative response to a relatively low probability circumstance. Rather, the decision is whether to accept the low risk of a cohort of concern and apply the AET to all the analytical responses or to perform testing whose purpose is to establish whether one or more substances from a cohort of concern could be present. To facilitate the decision-making process, the following approach is recommended.

— When there is experimental evidence or a compositional reason to suspect that a cohort of concern could be present, then either the general absence of cohorts of concern should be established by information gathering and proper documentation, or the extracts should be screened for targeted potential substances from cohorts of concern. In the absence of cohorts of concern, the AET can be applied to all analytical responses. If cohorts of concern are present, then the AET can only be applied to those analytical responses that are not attributable to cohorts of concern. Analytical responses attributable to a cohort substance should be safety assessed based on the concentration of the cohort substance and its toxicological safety data.

— When there is no experimental evidence or a compositional reason that suggests that a cohort substance could be present, it can be concluded that it is unlikely that a cohort of concern is present and the AET can be applied to all analytical responses.

Annex F
(informative)

Qualification of analytical methods used for extractables/ leachables

An analytical method is qualified to establish that it is suited for its intended purpose. In extractables/ leachables studies, analytical methods serve one of two purposes; screening samples for unspecified analytes and testing samples for specified (targeted) analytes. As these purposes are quite different, it is reasonable to suspect that their qualification would differ.

The qualification of an analytical method is documented in a qualification protocol, which establishes the:

— relevant qualification parameters;

— experimental means by which the qualification parameters will be assessed;

— performance expectations for each parameter.

Qualification parameters that are specifically relevant to screening methods include:

— sensitivity, as it is expected that the method's LOQ be less than or equal to the reporting threshold (note that this expectation is discussed in greater detail in Annex E);

NOTE 1 In cases of very low reporting thresholds, it might not be possible to achieve an LOQ which is less than or equal to the reporting threshold. In such cases, the lowest reasonably attainable LOQ should be used, and all analytes above this LOQ should be reported. If the LOQ is higher than the AET, this should be explained and justified.

— specificity, which is ability to assess unequivocally the analyte in the presence of other constituents that can be expected in the sample;

— accuracy, taken as the ability to produce a response that is comparable to the true value (e.g. a measured concentration in a spiked extract that is comparable to the spiked amount). Accuracy for screening tests is typically accomplished using surrogate substances that are representative of extractables;

— precision, taken as the variation in replicate analyses of either the same extract or a standard solution containing extractables or leachables;

— dynamic range, taken as the concentration range over which the response and the analyte concentration producing that response are relatable by a simple mathematical function. Dynamic range can be established by analysis of surrogate or standard solutions at various concentrations.

NOTE 2 The objectives of this parameter can be achieved within establishment of the LOQ along with system suitability results.

NOTE 3 Dilution might be needed if analytes of interest are clearly out of range.

Qualification parameters that are specifically relevant to targeting methods include:

— sensitivity, relevant in the circumstance that the method's range includes, or is near to, the LOQ;

— specificity, as described for screening methods;

— accuracy, as described for screening methods; however, as opposed to screening tests, accuracy in targeting is accomplished with the actual substances being targeted;

NOTE 4 Spiking samples can help to determine the recovery.

— precision, as described for screening methods;

— dynamic range, taken as the concentration range over which the response and the analyte concentration producing that response are relatable by a simple mathematical function. Dynamic range can be established by analysis of standard solutions at various concentrations;

— goodness of fit, taken as the degree to which a simple mathematical function can express the relationship between an analyte's concentration in a standard and the method response obtained when the standard is analysed. Although the desired mathematical function is generally a linear function, simple, non-linear functions can be used if they are able to meet the acceptance criteria for goodness of fit.

Qualifying that a method is rugged is relevant for both screening and targeting methods.

Additional performance parameters can be included in a qualification at the discretion of the method's user and with appropriate justification. These additional parameters could include: robustness, efficiency (for a chromatographic separation this might include resolution), matrix effects, sample and standard stability.

Given their different purpose and function, the processes of qualifying a screening or targeting method will be different, even if the qualifying criteria are generally the same. For example, while both screening and targeted methods are qualified for accuracy, the nature of the qualification activity is different. While accuracy is established in a targeting method specifically for the analyte(s) of interest, in a screening method accuracy is established more generally by considering a group of surrogate analytes. Additionally, as screening methods provide concentration estimates, the acceptance criterion for accuracy is less rigorous than the acceptance criterion for accuracy in targeted analysis, where the calculated concentration is expected to be highly quantitative.

The same concept is applicable to precision, as it is generally accepted that the precision expectations for a targeting method are more rigorous than are the precision expectations for a screening method.

Specificity is important in a screening method as the identification of individual extractables is facilitated if the chromatographic peak associated with an extractable is produced by only that extractable. In a targeting method, specificity for the targeted compound, meaning that the target compound's chromatographic peak is pure, is necessary to provide the required degree of accuracy and precision. Because a targeted substance is established in advance of implementing the method, specificity can be established up-front. However, since it is not possible to establish up-front what analytes might be discovered in screening, specificity in screening methods is typically established at time of use. Thus, specificity could be measured and judged quite differently in screening versus targeting.

A method is considered to be qualified (that is, suited for its intended use) when

— it has been established that the method is able to routinely meet the performance expectations contained in the qualification protocol, and

— appropriate system suitability has been established.

In addition to having documented performance capabilities, qualified analytical methods should have additional controls that may include, but are not limited to:

— documentation of the method in the form of a standard operating procedure (SOP) which is controlled in a document change system;

— an approved and specified Scope, captured in the method's SOP;

— a detailed scientific description and justification of the method, establishing its suitability for the intended use;

— a requirement that the qualified method is implemented by an appropriately qualified and trained staff;

— a requirement that the qualified method is implemented on calibrated/qualified instrumentation.

Considering system suitability specifically, establishing system suitability is a time of use assessment that addresses three performance aspects of the method:

a) the method has been set up and implemented properly;

b) the method as set up is capable of performing at the same level it performed at during its qualification;

c) that the method has performed acceptably throughout its use.

System suitability assessment should focus on that minimum number of performance characteristics which individually and in aggregate demonstrate that these three performance criteria were achieved. The system suitability parameters to be assessed and their associated acceptance criteria should be rigorous enough to ensure that the method produces data of acceptable quality but not so rigorous that potentially acceptable analytical runs are rejected on a frequent basis. Properly collected and statistically evaluated system suitability data can provide diagnostic evidence of imminent method failure.

Reference [23] can provide helpful information when devising and implementing a method qualification process. The reporting of method qualification information is addressed, to a certain extent, in Annex G.

Annex G
(informative)

Reporting details for analytical methods and chemical data

G.1 General

Clause 7 provided general guidelines in terms of the type of chemical and compositional information that should be reported, facilitating the information's use in a toxicological risk assessment. Users should recognize that additional details can be necessary for regulatory review of the analytical methods and chemical data. Such information includes:

G.2 Reporting of analytical data to facilitate toxicological risk assessment

— Accounting of qualitative data generated (e.g. extractable's identities).

— Accounting of quantitative data generated (e.g. extractable's concentrations, including a discussion of the quantification approach and providing the classification of the quantitative data as estimated quantitative analysis, semi-quantitative analysis or quantitative analysis).

— A discussion and justification of the reporting threshold and its relevance to toxicological risk assessment (e.g. safety thresholds).

— List of chemical compounds above the reporting threshold. Such a list can be provided in a tabular format and the table should contain the chemical compounds including their mass, proposed structure, chemical formula, IUPAC chemical name, common chemical name(s) and abbreviation(s), CAS registry number, their identification status (e.g. confirmed, confident, tentative, speculative) and their measured levels in the relevant samples. Additional information, such as chemical structure, may be provided in the document. When multiple candidate identifications are found (e.g. a class of compounds such as is often reported in tentative identifications), all should be reported.

— Information about the device's clinical use which, when combined with the chemical data, allows for the calculation of the worst-case amount of the chemical in appropriate units (e.g. µg/medical device) that can be readily used in toxicological risk assessment (establishing human daily exposure).

— Appropriate figures, diagrams, etc. that illustrate the analytical data and/or facilitates data review and/or interpretation (e.g. labelled chromatograms, migration curves).

— Approach and rationale addressing cohorts of concern substances (see E.5).

Note that the reporting of analytical data should facilitate the calculation of estimated clinical exposure to the reported chemicals, as this is an essential aspect of the toxicological risk assessment. It is not necessary that the analytical reports themselves contain these estimated exposures.

While the information outlined above is sufficient to enable toxicological risk assessment, it typically is not sufficient to fully specify and justify the experimental and analytical approaches that were used to perform a specific study to produce specific data and information. This critical information is used to establish the validity of the experimental design, the applicability of the analytical approach and the suitability of the specific analytical methods employed for their intended purpose, during, for example, regulatory review. Thus, a report should include some of the following information to provide the proper context with respect to the experimental design, the experimental approach and the experimental methods.

G.3 Details of test article preparation (extraction)

— Appropriate and complete description of the test article, including relevant processing details (e.g. sterilization, rinsing), and parts removed, if applicable;

— Extraction method with justification (e.g. refluxing, sealed vessel);

— List of extraction vehicles with justification;

— Extraction vehicle/ sample ratio (e.g. extracted surface area to extraction solution volume ratio);

— Extraction time and temperature;

— Number of extraction cycles (e.g. single vs. exhaustive);

— Methods for determining when exhaustive extraction endpoints are reached (as appropriate);

— Description of changes to the vehicle or test article (e.g. medical device) post-extraction, to include physical state, appearance, colour, clarity, or presence of particles;

— If particles are present in the extract, a description of how they were addressed, including, if performed, the means by which they were separated from the extract prior to analysis and the means by which they were chemically characterized.

G.4 Extract preparation for analysis

— Description of any dilution, concentration and other significant processing steps (e.g. vehicle exchange).

— Justification for all significant processing steps.

— Description of any sample filtering/particle separation that was performed.

— Description of the storage conditions and duration of extracts, if stored prior to analysis.

G.5 Description of the analytical methods for testing prepared extracts (include all that apply)

— Justification for choice.

— Relevant operating conditions (e.g. chromatographic mobile phase, methods, flow rates, gradient run time, column temperature).

— Analytical column; Dimensions and stationary phase used.

— Analytical instrumentation manufacturer, model, principal components.

— For methods using mass spectrometric detection:

  — ionization technique (APCI, ESI),

  — polarity mode (positive, negative),

  — mass range (or specific masses analysed for ICP-MS data),

  — nominal mass resolution.

— For methods using UV detection, detection wavelength.

— For other detection methods, key operational parameters.

— Surrogate standard(s) used, with justification, and resulting response factor to be applied in semi-quantitative analysis.

— Quantification approach applied, with justification:

  — which analytical endpoint is used for quantification (e.g. MS signal or UV response);

  — description of how any surrogate and internal standards are applied for quantification of specific analytes (e.g. closest retention time, similarity in chemistry between the reference standard and the analyte, or use of "worst case," meaning lowest response factor, or use of an averaged response factor).

— A description of how confidence in identifications was determined and assigned (e.g. definitions of categorization terms or match scores), with justification;

— Means used to address unknowns (e.g. additional analytical testing to identify or risk mitigation per ISO 10993-1);

— Determination, justification and application of reporting thresholds (such as the AET).

G.6 Qualification metrics for the analytical methods:

System suitability (per qualification protocol in Annex F) to include:

— LOD and LOQ (including how LOQ was established);

— Linearity [calibration curve(s)];

— Specificity;

— System suitability;

— Recovery (accuracy);

— Precision;

— Dynamic range;

— Other relevant parameters as appropriate.

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