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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*

3 Terms and definitions

For the purposes of this document, the definitions in ISO 10993-1 and the following apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available from https://www.iso.org/obp

— IEC Electropedia: available from http://www.electropedia.org/

3.1
accelerated extraction
extraction whose duration is shorter than the duration of clinical use but whose conditions do not result in a chemical change to the substances being extracted

Note 1 to entry: See also Annex D.

3.2
analytical evaluation threshold
AET
threshold below which the analyst need not identify or quantify leachables or extractables or report them for potential toxicological assessment

Note 1 to entry: See Annex E.

3.3
analytically expedient
situation where an extraction vehicle can be directly evaluated with generally available analytical methods with the sensitivity and selectivity necessary to achieve a designated reporting threshold such as the AET

3.4
analytical screening method
method whose purpose is to discover, identify and semi-quantitatively estimate the concentration of all relevant analytes in a test sample above an established reporting threshold (such as the AET)

3.5
analytical targeting method
method whose purpose is to quantify, with an appropriately high degree of accuracy and precision, specified analytes in a specified test sample over a specified concentration range

3.6
chemical characterization
process of obtaining chemical information, accomplished either by information gathering or by information generation, for example, by literature review or chemical testing

3.7
chemical information
qualitative and quantitative, if applicable, knowledge related to the configuration, composition and production of the medical device and/or its materials of construction, thereby establishing the identities and amounts of constituents present in the materials and device

Note 1 to entry: See also 5.2.1, 5.2.2, 5.2.3, and Annex B.

Note 2 to entry: Chemical information can be used to establish the hypothetical worst-case release of chemicals from a medical device, predicated on the circumstance that all chemicals present in the device are released from the device under its clinical conditions of use.

3.8
clinically established
medical device, component, or material of construction which has been used extensively for specified and established clinical uses for which biocompatibility has been established

3.9
component
item which forms one part of a medical device, but is not itself a medical device

3.10
constituent
chemical that is present in a finished medical device or its materials of construction

Note 1 to entry: Constituents may be intentionally present (e.g. an additive such as an antioxidant) or unintentionally present (e.g. an impurity or degradant).

3.11
convertor
person or company who converts or fabricates a basic raw material into a semi-finished product (e.g. a former of lengths of rod, tubing, or plastic components)

3.12
digestion
process of completely solubilizing a medical device, one or more of its components or one or more of its materials of construction by breaking it down into its fundamental structural units, including its elemental constituents or monomeric units

3.13
dissolution
process of completely solubilizing a medical device, one or more of its components or one or more of its materials of construction, generally preserving the molecular structures of its constituents

3.14
exaggerated extraction
extraction that is intended to result in a greater number or amount of chemical constituents being released as compared to the amount generated under the clinical conditions of use

Note 1 to entry: It is important to ensure that the exaggerated extraction does not result in a chemical change of the material or the substances being extracted.

3.15
exhaustive extraction
multi-step extraction conducted until the amount of material extracted in a subsequent extraction step is less than 10 % by gravimetric analysis (or achieved by other means) of that determined in the initial extraction step

3.16
extractable
substance that is released from a medical device or material of construction when the medical device or material is extracted using laboratory extraction conditions and vehicles

3.17
extraction power
ability of an extraction vehicle to extract (or leach) substances from a medical device, component or material of construction

Note 1 to entry: The extraction power of an extraction vehicle is impacted by its physicochemical properties, including, but not limited to, its polarity, pH and dielectric constant.

3.18
extraction vehicle
medium (solution or solvent) which is used to extract (or leach) a test article for the purpose of establishing the test article's extractables or leachables profile

Note 1 to entry: It is preferred that extraction vehicles be analytically expedient.

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.

3.37
sponsor
individual or organization that plans, commissions, and takes responsibility for testing of a medical device

3.38
supplier
person or company who manufactures or provides the materials of construction or components to be used in the manufacture of a medical device

3.39
threshold of toxicological concern
TTC
level of exposure for constituents, below which there would be no appreciable risk to human health

Note 1 to entry: See ISO/TS 21726 for full context.

3.40
toxicological risk assessment
act of determining the potential of a chemical to elicit an adverse effect based on a specified level of exposure

4 Symbols and abbreviated terms

The abbreviated terms given in Table 1 are used in this document.

Table 1 — Methodology abbreviations

Abbreviated term	Analytical method
2D PAGE	Two-dimensional polyacrylamide gel electrophoresis
AES	Atomic emission spectroscopy
AET	Analytical evaluation threshold
DMTA	Dynamic mechanical thermal analysis
DSC	Differential scanning calorimetry
FID	Flame ionization detection
FTIR	Fourier transform infrared spectroscopy
GC	Gas chromatography
GPC/SEC	Gel permeation chromatography/size exclusion chromatography
HPLC (or LC)	High performance liquid chromatography (or liquid chromatography)
HS	Headspace sampling
IC	Ion chromatography
ICP	Inductively coupled plasma
IR	Infrared spectroscopy
MS[a]	Mass spectrometry
NMR	Nuclear magnetic resonance spectroscopy
NVOC	Non-volatile organic compound
NVR	Non-volatile residue
SEM-EDS (or SEM-EDX)	Scanning electron microscopy-energy dispersive X-ray spectroscopy
SVOC	Semi-volatile organic compound
TOC	Total organic carbon
UV	Ultraviolet spectroscopy

[a] Mass spectrometry is frequently combined with other techniques (especially chromatographic) in coupled methods such as GC-MS, LC-MS and MS-MS.

Table 1 *(continued)*

Abbreviated term	Analytical method
VOC	Volatile organic compound
XPS	X-ray photoelectron spectroscopy
XRF	X-ray fluorescence

[a] Mass spectrometry is frequently combined with other techniques (especially chromatographic) in coupled methods such as GC-MS, LC-MS and MS-MS.

5 Characterization procedure

5.1 General

The chemical characterization information, either collected or generated, and augmented with additional supporting information as appropriate, can be used for a range of important applications, for example:

— supporting the overall biological safety of a medical device (ISO 10993-1 and ISO 14971);

— supporting the biological safety of a reprocessed medical device;

— determining the amount of chemical substances that might be leached from a medical device under the conditions of its clinical use, to support performing a toxicological risk assessment (ISO 10993-17);

— supporting equivalence of a proposed medical device to a clinically established device, used for the same type of clinical exposure, with regards to either the device's configuration or its extractables/leachables profiles and any subsequent relevant evaluations;

— supporting equivalence of a clinically established medical device, used for the same type of clinical exposure, after changes in the manufacturing process, (including, but not limited, to changes in the sterilization process), manufacturing sites, suppliers of materials or components, etc.;

— supporting equivalence of a proposed material of construction to a clinically established material of construction with regards to either the material's composition or its extractables profiles and any subsequent relevant evaluations;

— supporting equivalence of a final medical device to a prototype device with regards to the use of data secured on the prototype to support the assessment of the final device, specifically considering relevant information such as composition, device configuration and extractable profile obtained for either the device or its materials of construction; or

— screening of potential new materials for chemical suitability in a medical device for a proposed clinical application.

These important applications notwithstanding, chemical characterization alone can be insufficient to establish the equivalence or biocompatibility of materials and medical devices, and cannot unilaterally substitute for biological testing. However, chemical characterization in combination with risk assessment can be a necessary part of judging chemical equivalence and assessing biocompatibility, and if appropriately conducted can be used in lieu of certain biological tests.

Chemical characterization of a medical device provides the necessary input into the device's biological evaluation and toxicological risk assessment (see ISO 10993-1 and ISO 10993-17). A flowchart describing the general chemical characterization process is given in Figure 1. This flowchart represents the chemical characterization portion of the overall biological evaluation flow as discussed in ISO 10993-1 and is meant to illustrate the characterization process that is described in this clause. This general flowchart is supplemented with additional flowcharts (see Figures 2 to 4) that provide greater detail to specific steps in the general process.

The requirements and guidance for each step of the chemical characterization process are specified in 5.2 to 5.10. When specified in the applicable flowchart, knowledgeable and experienced individuals shall compile existing information relevant to the chemical characterization (information gathering) and assess its adequacy as the basis for a toxicological risk assessment of the material/medical device. If the existing information is insufficient to complete the assessment, additional information shall be gathered or produced by testing (information generation) to enable the toxicological risk assessment.

This procedure should consider each of the direct and indirect contact materials of construction used in a medical device in addition to the requirement for chemical characterization of the finished medical device. Since the chemical nature of a medical device can be affected by its processing during its construction (e.g. sterilization), the effect of this processing on the device shall be taken into account in the design and interpretation of the chemical characterization.

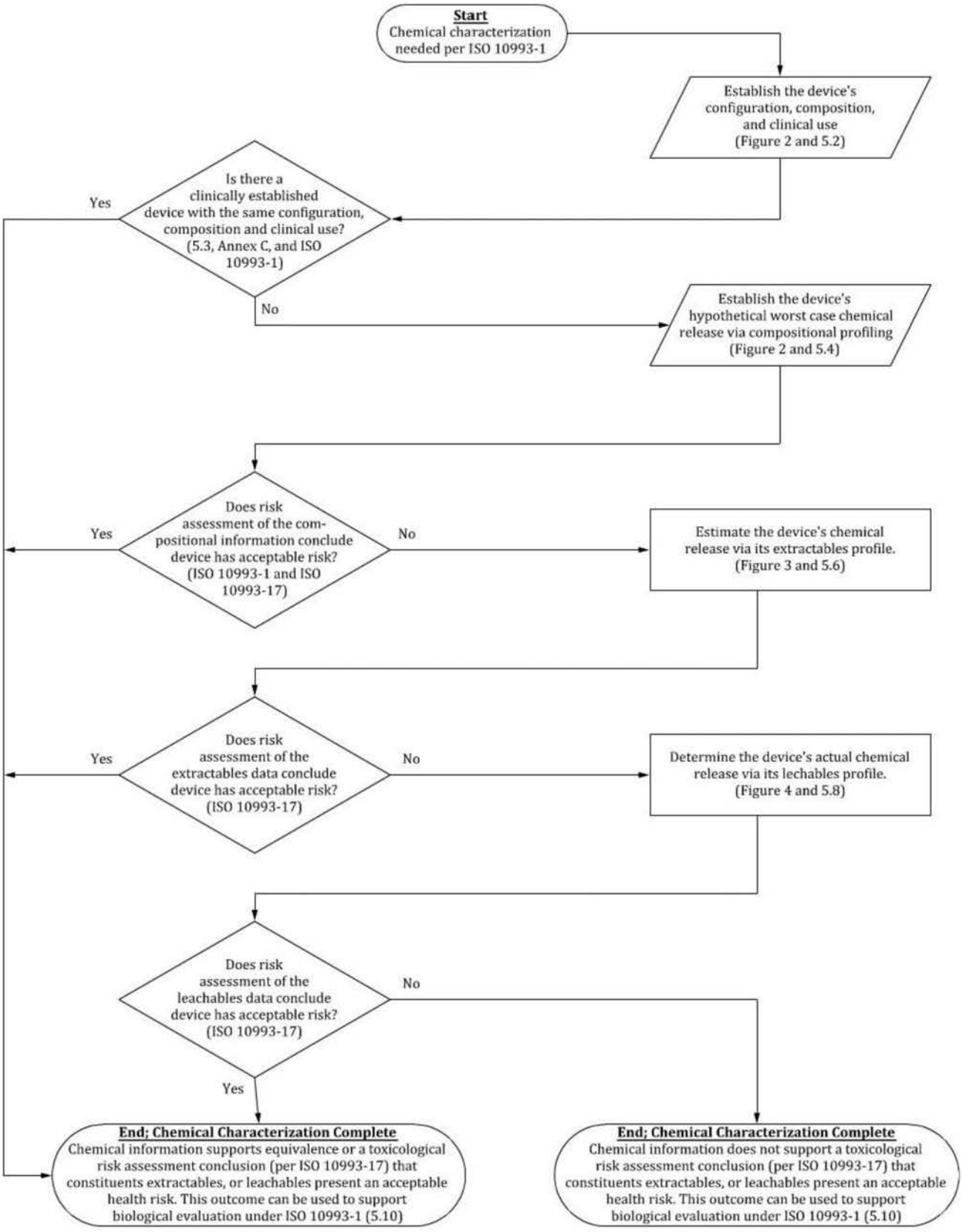
At each step of the characterization procedure, the adequacy of the available data as the basis for performing the risk assessment shall be established. The available data can be considered adequate if it reflects or exceeds the conditions of clinical use and a risk assessment based on the available data can be completed. Inadequacies in the data can be addressed by filling gaps in such data (e.g. literature review) and/or supplementing the data via analytical testing.

The flowcharts have the following types of process steps; start/stop, decision points, information gathering and evaluation, and analytical testing. Each type of step is represented by a geometric shape. Start/stop steps are identified as ovals, a decision step is identified as a diamond, an information gathering/evaluation step is represented as a parallelogram, and a step that involves analytical testing is represented as a rectangle.

The steps and actions defined in 5.4.2, 5.7 and 5.9 are part of the risk assessment process and represent the points at which chemical information is provided for assessment. As such, they are for the most part, outside the scope of chemical characterization, which is the focus of this document. These steps are included to indicate the important link between chemical characterization and risk assessment (see ISO 10993-1, ISO 10993-17, and ISO 14971).

The characterization procedure and its associated flowchart system is based on the principles in ISO 10993-1; specifically, that the biological evaluation and toxicological risk assessment process is most efficient and effective if it is based on the appropriate (minimum) amount of acceptable and necessary chemical information that can establish that a medical device presents an acceptable health risk. Thus, the first step of the procedure is to establish the configuration of the medical device and the composition of the device's materials of construction so that it can be compared to a clinically established device or assessed based on hypothetical worst-case chemical release (i.e. "it all comes out"). This assessment should include potential contaminants, degradants, processing aids and additives which could be introduced by the manufacturing process. If an assessment based on the hypothetical worst-case chemical release leads to the conclusion that there is an acceptable risk, then the process can be completed with the collection or generation of a minimum amount of information. On the other hand, if the conclusion of acceptable health risk cannot be supported, then additional data shall be collected, following a step-wise process from determining and evaluating the medical device's hypothetical worst-case chemical release to the actual chemical release under clinical conditions of use. In any and all cases, the information collected shall reflect (or exceed) and be assessed according to the clinical conditions of use.

In using the flowcharts, it is not always necessary to complete all steps in the entire sequence; thus, the flowchart system has multiple points of exit. For example, if one can demonstrate that a hypothetical exposure to all of the chemical constituents of a medical device presents an acceptable health risk, additional chemical testing is not necessary, the characterization is complete and the flowcharts are exited and biological evaluation continued according to ISO 10993-1.



NOTE The flowchart can be entered and exited at multiple points.

Figure 1 — General chemical characterization process

In addition to multiple possible exit points, the flowchart system also has multiple points of entry. While the first actions taken in the flowcharts can facilitate the later actions in the flowcharts, they are not necessarily prerequisites for those further actions. For example, although knowing a device's configuration and material composition (including potential impurities) might facilitate establishing its leachables profile, the leachables profile can be delineated without configuration and composition information. Thus, if a sponsor has reason to believe that a leachables assessment will be necessary or most relevant (e.g. for certain indirect contact medical devices) to properly and completely establish the medical device's toxicological risk, then compositional profiling and extractables studies need not be conducted. Likewise, available knowledge of the medical device's composition can make it clear that an extractables study is likely to produce an extracted substance above an acceptable threshold; in this case, it can be appropriate to skip the extractables study and proceed directly to a leachables study.

This multiple entry and exit approach is proper and justifiable as the flowchart system is constructed such that each successive step gets closer to establishing the actual clinical exposure to leachables and thus gets closer to establishing the actual risk. Entering the process at an intermediate point can still assure that the most accurate estimate of exposure is produced for toxicological risk assessment. If an alternative entry to the flow chart (i.e. other than "start at the beginning") is taken, it shall be justified.

Additional general guidance on chemical characterization is provided in Annex A.

5.2 Establish medical device configuration and material composition

5.2.1 General

A medical device's ability to interact with a potentially affected individual requires contact, as established in ISO 10993-1. For medical devices (or components) that do not have direct or indirect contact with the body, chemical characterization is not necessary. The hypothetical worst-case chemical release is established by the configuration and composition of the medical device. Thus, the first step is to compile all required chemical information related to the configuration and composition of the medical device and its materials of construction. This information is secured either from an appropriate source (e.g. material's vendor) or via appropriate compositional testing.

The medical device shall be described and its configuration, its intended purpose, and its clinical use shall be documented. This shall include its individual materials of construction, the proportion of those materials (e.g. by surface area or weight) in the device, and its physical structure (including surface properties such as topography and chemistry, where applicable). Providing the geometric distribution of the materials within the medical device (medical device configuration) is relevant as such a structural description establishes the nature of contact, if any, between individual materials of construction and the potentially affected individual.

Once the medical device configuration has been established, each material of construction in direct or indirect contact should be compositionally described and its intended interaction with body tissues and fluids established. A documented, qualitative description of the known composition of each material of construction and known additives and processing residues from manufacturing activities is required. Additional guidance on preparing a qualitative description can be found in ISO 10993-1 and Annex B. The amount of detail in the qualitative and/or quantitative compositional data provided/required (e.g. the levels of additives and residuals in the material) shall reflect the potential safety risk associated with the medical device and its materials (see ISO 10993-1:2018, 6.1). For example, long-term contact devices need more detail than limited contact devices and implanted devices need more detail than surface devices. The amount of and detail in the provided compositional data shall be justified. The effect of processing (including sterilization) of the materials and the medical device shall be considered.

The qualitative description of each material shall include details of trade name or specification number, supplier name and material specification (e.g. formulation disclosure, certificate of analysis, technical data sheet, safety data sheet) to the extent that such information can be secured and is relevant. The use of a standardised material, e.g. ISO 5832 series, in its intended use is considered to meet this requirement.

5.2.2 Information gathering

Medical device manufacturers should preferably obtain qualitative and quantitative compositional information about materials from the supplier of the starting material. Qualitative information about any additional processing additives, for example, mould release agents, should also be obtained from appropriate members of the manufacturing chain, including convertors and component suppliers. In the absence of sufficient supplier information, such information should be obtained by chemical testing (e.g. compositional, extractables, or leachables testing). The information obtained can be sufficient to identify all biological hazards arising from the chemical constituents of the material for inclusion in the toxicological risk assessment (see ISO 10993-1). Information on whether any constituents from the cohort of concern (see E.6) are likely to be present is important if extractables testing with a TTC approach may be planned (see ISO/TS 21726).

The biological evaluation considers data from several datasets alongside those derived from chemical characterization. Thus, the inability to obtain such information from suppliers does not necessarily prevent the biological evaluation. However, when a toxicological hazard has been identified, information gaps that would prevent a toxicological risk assessment shall either be filled or otherwise addressed.

The composition of materials used in medical devices shall either be documented in accordance with applicable materials standards or shall be specified by the medical device manufacturer.

NOTE The supplier can be a useful source of appropriate material composition information. In the absence of any initial compositional data, a literature study to establish the likely nature of the starting material and any additives is recommended.

5.2.3 Information generation

Compositional testing of the medical device and/or its materials of construction can be needed to supplement any information gaps and to provide the necessary quantitative information on materials and chemical constituents.

NOTE As stated in ISO 10993-1:2018, 6.1, "The extent of physical and/or chemical characterization required 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. At a minimum, the characterization shall address the constituent chemicals of the medical device and possible residual process aids or additives used in its manufacture."

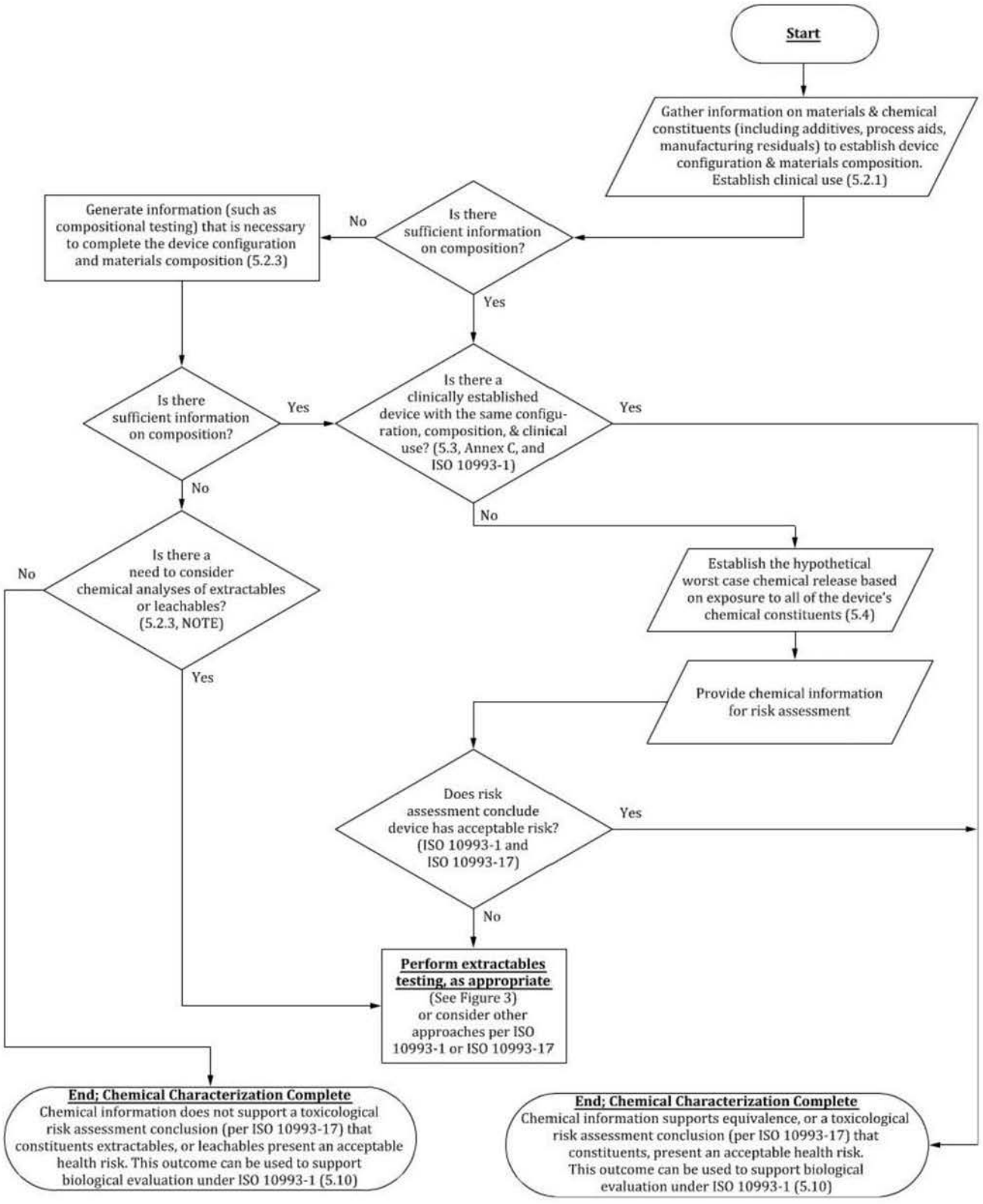


Figure 2 — Compositional profiling process

5.3 Assess material/chemical equivalence to a clinically established material or medical device

When specified in the flowcharts, the information compiled in 5.2 shall be used to compare the medical device under consideration to another device that has been clinically established. Specifically, the

information is used to determine whether the medical device under consideration is equivalent, in configuration, composition, manufacturing, processing and intended use, to a clinically established medical device. Annex C and ISO 10993-1 present principles for judging equivalence.

In some cases (e.g. change in the material supplier for a component), demonstration of material equivalence can be sufficient. Enough qualitative and quantitative information shall be obtained to determine whether a material under consideration is equivalent, in composition (including impurities), physical and chemical properties, processing and use, to a clinically established material. If a device or material is determined to be equivalent to a clinically established device or material, then that determination shall be justified and documented.

When an equivalent clinically established medical device can be identified and justified for the device under consideration, then the chemical characterization process shall be deemed to have been completed. When a clinically established equivalent medical device cannot be established and justified, then other elements of a biological evaluation in accordance with ISO 10993-1 should be considered, including additional chemical characterization, as established by the additional steps in the flowchart system.

Material equivalence can be based on either material composition or extractable profile data compared to a clinically established material, provided that the analytical methods used to generate the data are justified.

Physical, chemical, morphological and topographical characteristics (see ISO/TS 10993-19 and ISO/TR 10993-22 as applicable) should be considered as appropriate when determining material equivalence.

5.4 Assess the hypothetical worst-case chemical release based on total exposure to the medical device's chemical constituents

5.4.1 Establish the hypothetical worst-case chemical release

The greatest potential chemical impact of a medical device would be achieved if the device's entire composition were to transfer to the potentially affected individual during clinical use. This would be accomplished, for example, if an implantable medical device were to dissolve during clinical use or if an externally communicating device were to be completely leached during clinical use. Accordingly, the qualitative and quantitative data collected in 5.2 regarding the material or medical device configuration, materials of construction, process residuals and supplier information can be used to establish the hypothetical worst-case chemical release, even if it is unlikely that this worst-case would happen under the clinical conditions of use. Additional factors shall be considered when establishing hypothetical worst-case chemical release, such as the medical device size and the possible clinical use of multiple devices.

5.4.2 Assess the hypothetical worst-case chemical release

The health impact of the medical device's individual chemical constituents is assessed by providing the hypothetical worst-case chemical release, established in 5.4.1 to a risk assessor to establish the potential adverse impact that the chemical constituents could have on the health of a potentially affected individual according to ISO 10993-1 and ISO 10993-17.

When exposure to a medical device's entire composition can be established as being acceptable (e.g. by comparing the exposure to a safety threshold established in 5.5), then the chemical characterization process shall be deemed to have been completed. The biological evaluation can then be completed according to ISO 10993-1. When exposure to a medical device's entire composition is established to be potentially unacceptable, then the chemical characterization process can be continued by moving to the next step (see 5.5, 5.6 and Figure 3). Alternatively, it can be appropriate to return to ISO 10993-1:2018 to continue forward with biological endpoint evaluation, if characterization information is not likely to provide further benefit.

NOTE 1 In some cases, theoretical compositional profiling might not be sufficient (e.g. if degradation products and unintended contaminants during manufacture are likely).

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.

The primary objective of the extraction is to produce an extractables profile that is at least as comprehensive as a device's leachables' profile, meaning that the extractables profile includes all leachables as extractables and that the concentration of the extractables is at least as great as the concentrations of leachables. An extractables' profile that overestimates the leachables' profile, specifically by overestimating the extractables' concentrations versus leachables' concentrations, provides an added margin for uncertainty in the toxicological risk assessment, and can be appropriate in many circumstances. However, care must be taken to limit the extent of overestimation, as overly aggressive extractions conditions can lead to an altered extractables' profile.

The recommended extraction conditions in Table 2 will, in many circumstances, provide such an appropriate overestimation. However, in certain circumstances, the overestimation provided by the recommended exhaustive extraction conditions will be excessive and thus the recommended extraction circumstances are not appropriate. For all device classifications, alternative credible extraction conditions can be considered and used if deemed appropriate. The use of alternative extraction conditions shall be documented and justified. Extractions done for specific purposes other than identification and quantification of extractables (e.g. determining release kinetics) can be conducted using other extraction conditions.

Considering replication of extractions, a single extraction replicate for each vehicle shall be sufficient in those circumstances where it can be established that the variation in the test article's composition and/or the variation in the extraction process is low, establishing that the single extraction is properly representative of the test article and the extraction process. In cases where other information (e.g. engineering testing) indicates higher variability either within or across test article units or lots or inherent to the extraction process, multiple (e.g. duplicate or triplicate) extractions can be necessary. Multiple extractions should also be performed in those circumstances where the test article and/or extraction variability is unknown. Regardless of the number of replicate extractions performed, the number of extracts generated should be justified.

NOTE Multiple (e.g. triplicate) extraction replicates per solvent could be important for:

— Absorbable devices, *in situ* polymerizing devices, and combination products which are physically and chemically combined. For these types of devices, there can be a higher potential for variability between devices, and for small changes in chemistry at manufacture, over shelf life, or while in use.

— Devices with existing vertical standards or device-specific guidance which call for multiple extractions.

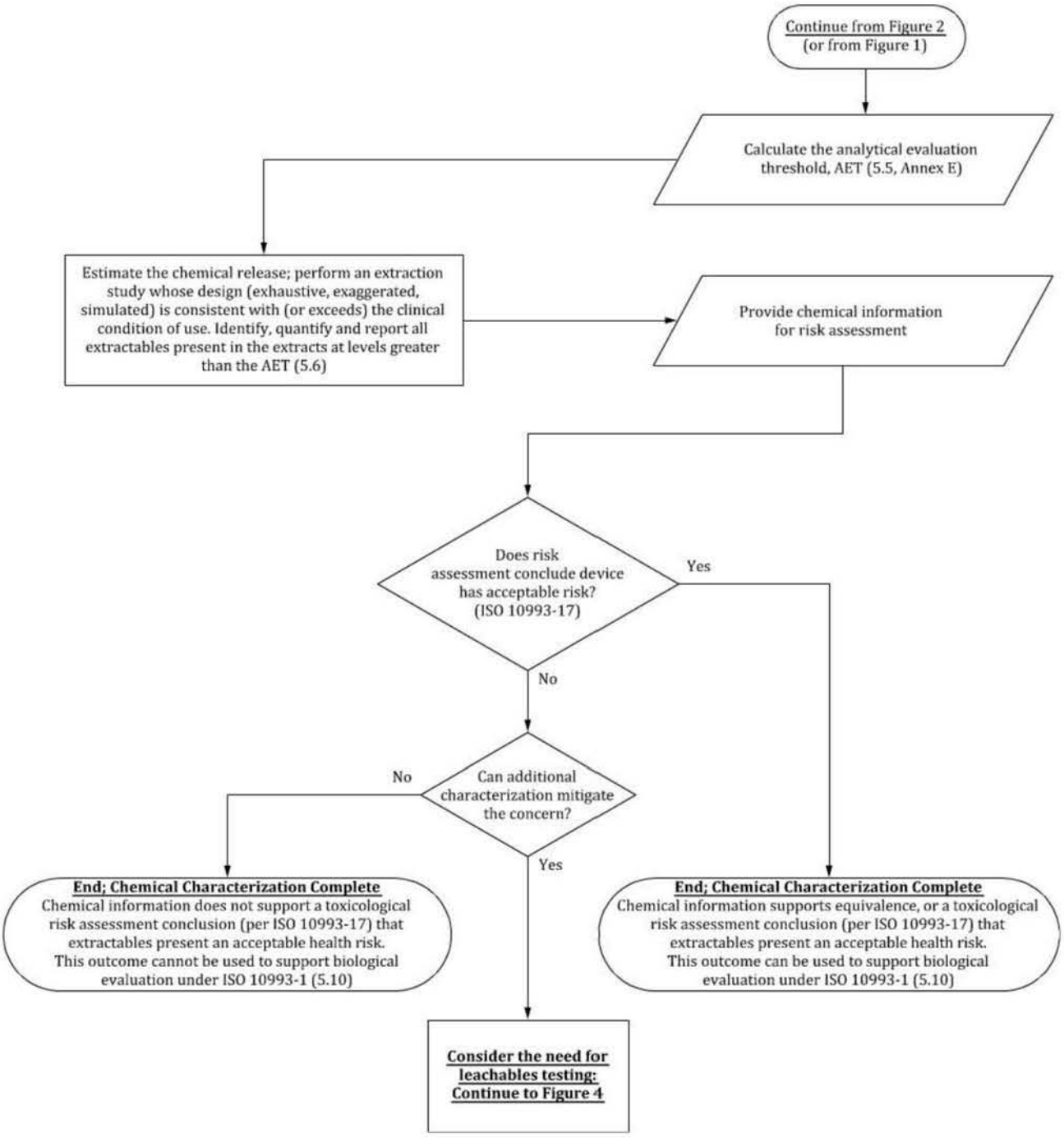


Figure 3 — Extractables profiling process

The extracts shall be analysed using sensitive and selective methods to screen the extracts for extractables, and the detected extractables above the analytical evaluation threshold, AET (5.5 and Annex E), should be identified and quantified. Adequate chromatographic resolution is an example of how adequate selectivity can be demonstrated. The analytical methods shall be selected and the analytical results reported consistent with the AET. Table 3 establishes those analytical methods that are generally applicable to extractables studies.

The analytical process should be replicated by testing multiple aliquots of the extract, to account for analytical variation. Although triplicates are recommended, a smaller number of replicates can be more practical, if justified.

The information from this study will be used to determine the risk associated with the estimated chemical release. If a toxicological risk assessment determines that a chemical or chemicals could be a risk to the potentially affected individual using the extractables data, a more clinically relevant extraction can be done to more precisely estimate the amount of the chemical or chemicals released from the medical device in clinical use (see 5.8). When a more clinically relevant extraction cannot be justified, other risk mitigation strategies can include targeted analysis, biological testing, reduction of the chemical in the device, and in some cases, labelling as described in ISO 14971, ISO 10993-1 and ISO 10993-17.

5.7 Assess the estimated chemical release (extractables profile)

The results of the extraction study shall be reported so that the risks attributable to each identified extractable can be assessed according to ISO 10993-17, ISO 10993-1 and ISO 14971.

5.8 Determine the actual chemical release; perform leachables study

When the quantity of any extractable released from the medical device presents a potential safety hazard in the light of its estimated clinical release, a more accurate estimate of actual exposure to, and actual case chemical release of, that chemical can be established by performing a leachables assessment of the device using actual or accelerated extraction conditions (e.g. using elevated temperature) as presented in Figure 4. If a leachables study is performed because substances of concern were identified in an extractables study, the new study should target those substances of concern. Extractables which do not present a potential toxicological concern in light of estimated clinical release have already been established to be safe and their further characterization is unnecessary. When it is anticipated that additional leachables that were not revealed as extractables can be present, the leachables study should include screening for the additional leachables.

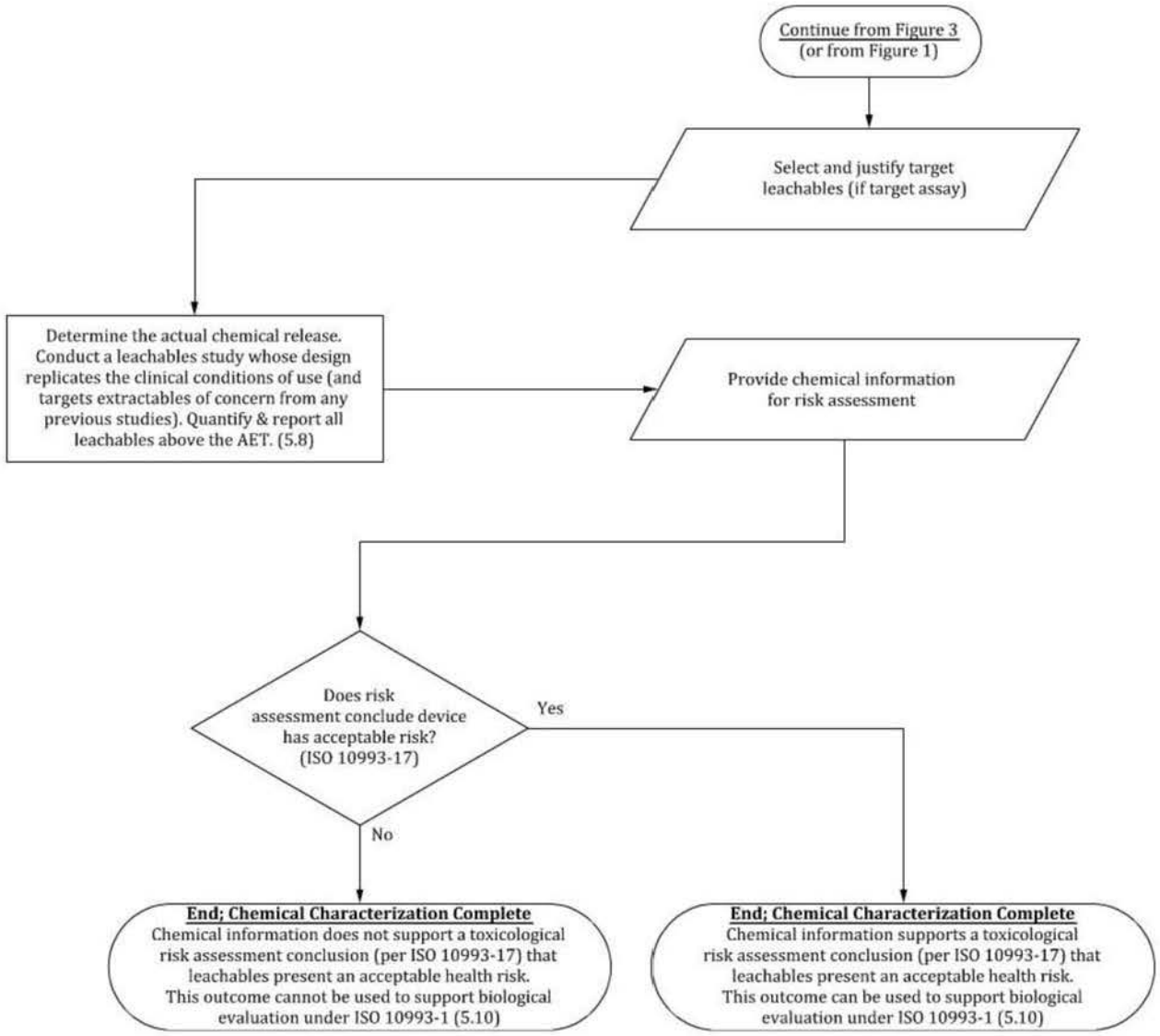


Figure 4 — Leachables profiling process

Alternatively, a sponsor may decide to perform a leachables study without having previously performed other chemical characterizations processes (e.g. extractables profiling). For example, it can be possible to readily perform a leaching study with an analytically expedient contacting vehicle under the exact or accelerated clinical conditions of use (e.g. for a medical device that serves to deliver fluids). In such a circumstance, the leaching vehicle shall be screened for leachables in a manner similar to, and with the same requirements for, extractables screening as discussed in 5.6.

Leachables studies include two actions; generation of the leachate and testing of the leachate. At this stage in the chemical assessment process, the leaching conditions should be either accelerated or actual clinical use. In either circumstance, the leaching conditions used to generate the leachate shall be documented and justified.

The leachate shall be analysed using sensitive and selective methods, and the levels of target or screened leachables quantified. Table 4 lists those analytical methods that are generally applicable to leachables quantification.

Analytical methods used to quantify leachables shall be qualified for that purpose (see 6.5 and Annex F for further information related to method qualification). Targeting leachables and use of qualified analytical methods for their quantification will produce a more accurate assessment of a potentially affected individual's exposure than that obtained using extractables screening data.

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.

Considering analytical methods appropriate for relevant data, 6.2 and 6.3 provide examples of qualitative and quantitative parameters that can be relevant for assessing structural and composition of medical device materials, and also provide examples of specific methods which can be used.

6.2 Material composition

As the material composition of a medical device is relevant to its biocompatibility, it is necessary to determine and consider device characteristics that establish the device's composition. Table 3 lists some of the characteristics which could be relevant, along with examples of appropriate analytical approaches.

Table 3 — Test methods for establishing the material composition of medical device materials

Material type	Characteristic	Example methods[a]	Qualitative	Quantitative
Synthetic Polymers	Residual monomer	GC, LC (*)	X	X
	Surface composition	FTIR	X	X[f]
		XPS	X	X
	Residual catalyst, initiators	Atomic spectroscopy[e] (*)	X	X
		LC (*)	X	X
	Additives, process residues, trace	GC, LC, IC (*)	X	X
	Impurities[b]	X-ray diffraction	X	—
		Residue on ignition	X	X[g]
		X-ray fluorescence	X	X
		GC, LC, IC (*)	X	X
	Chemical structure	FTIR	X	X[f]
		^{13}C and ^{1}H NMR (*)	X	X
Metals and alloys	Material composition[c]	X-ray fluorescence	X	X[f]
		EDX/SEM, XPS	X	X[f]
		Combustion analysis (C, S)	X	X
		Atomic spectroscopy[e] (*)	X	X
		Gas fusion (N, O, H)	X	X
		Titrimetric	X	X
		Gravimetric		X
		Electrolytic	X	X
		Colourimetric	X	—
	Elemental distribution between phases	EDX/SEM, XPS	X	X[f]
		Electron microscopy	X	X
	Phase or surface composition	EDX/SEM, XPS	X	X
Ceramics	Trace substances, including additives[d]	X-ray fluorescence	X	X[f]
		Atomic spectroscopy[e] (*)	X	X
		LC, GC (*)	X	X
	Anions	Ion chromatography (IC)	X	X
	Material composition	X-ray diffraction	X	—

[a] Not comprehensive or exclusive. Methods denoted with a (*) are methods that are most commonly employed for the indicated purpose. In certain situations, the other methods listed in this table can be used.

[b] Examples can include lubricants, crosslinking agents, mould release and blowing agents, and catalysts.

[c] Metals and alloys are frequently supplied with documented composition. When such information is already available, it is generally not necessary to repeat the analysis.

[d] Examples of additives that should be considered include metal deactivators, light/heat stabilizers, plasticizers, lubricants, viscosity modifiers, impact modifiers, antistatic agents, antimicrobials, antioxidants, flame retardants, whitening agents, fillers, sintering agents, mould release agents, binders, pigments, and coatings.

[e] Atomic spectroscopy includes AA and inductively coupled plasma spectroscopy with either optical emission detection (ICP-AES) or mass spectrometric (ICP-MS) detection.

[f] The nature of these analyses is such that their quantitative measurements are characterized by either limited sensitivity or a relatively high degree of imprecision.

[g] This method quantifies total impurities but not individual impurities.

Table 3 *(continued)*

Material type	Characteristic	Example methods[a]	Qualitative	Quantitative
Natural macro-molecules	Identity	Colourimetric	X	—
		2D PAGE (*)	X	X
		GPC/SEC	X	X
	Chemical structure	Amino acid sequencing	X	X
		FTIR	X	X[f]
		^{13}C and ^{1}H NMR (*)	X	X

[a] Not comprehensive or exclusive. Methods denoted with a (*) are methods that are most commonly employed for the indicated purpose. In certain situations, the other methods listed in this table can be used.

[b] Examples can include lubricants, crosslinking agents, mould release and blowing agents, and catalysts.

[c] Metals and alloys are frequently supplied with documented composition. When such information is already available, it is generally not necessary to repeat the analysis.

[d] Examples of additives that should be considered include metal deactivators, light/heat stabilizers, plasticizers, lubricants, viscosity modifiers, impact modifiers, antistatic agents, antimicrobials, antioxidants, flame retardants, whitening agents, fillers, sintering agents, mould release agents, binders, pigments, and coatings.

[e] Atomic spectroscopy includes AA and inductively coupled plasma spectroscopy with either optical emission detection (ICP-AES) or mass spectrometric (ICP-MS) detection.

[f] The nature of these analyses is such that their quantitative measurements are characterized by either limited sensitivity or a relatively high degree of imprecision.

[g] This method quantifies total impurities but not individual impurities.

6.3 Extractables and leachables

Test methodologies that can be used in extractables screening and leachables studies are listed in Table 4.

Analysis of extracted (or leached) substances should consider both organic and inorganic entities.

Organic extractables can be qualitatively placed into three classes based on their volatility; VOC, SVOC and NVOC. The analytical techniques used to screen for these classes of organic extractables are different, though one chemical can often be detected using a variety of techniques; for example, gas chromatography with headspace sampling (HS-GC) is typically used to analyse VOCs, gas chromatography (GC) is typically used to analyse SVOCs and LC is used to analyse NVOCs. The chromatographic techniques used for screening are coupled with appropriate sensitive, broadly applicable, and information-rich detection methods to ascertain the extractables' identity and concentration. As extracts usually contain mixtures of chemicals, chromatographic methods are typically coupled to multiple detectors. Thus, for example, GC separations may be coupled to flame ionization (FID) and MS detectors and LC separations may be coupled to ultraviolet radiation absorption (UV) and MS detectors.

Table 4 — Test methodologies for extractables and leachables

Material type	Characteristic	Example methods[a]	Qualitative	Quantitative
All	Organic extractables, VOC	HS–GC or GC with FID and/or MS*	X	X
		Total organic carbon (TOC)[b]	—	X
	Organic extractables, SVOC	HS-GC and GC, with FID and/or MS*	X	X
		HPLC, with UV, CAD, ELSD and/or MS*		
		Total organic carbon (TOC)[b]	—	X
		NMR	X	X
	Organic extractables, NVOC	HPLC, with UV, CAD, ELSD and/or MS*	X	X
		NMR	X	X
		Total organic carbon (TOC)[b]	—	X
		Non-volatile residue*	—	X
	Elemental extractables	ICP-AES, ICP-MS*[b]	X	X
	Anions and cations	Ion chromatography[b]	X	X

[a] Not comprehensive or exclusive. Methods denoted with a (*) are the most typically and commonly employed for the indicated purpose and are generally considered sufficient. The selection of the appropriate methods should be carried out by qualified personnel, in accordance with the composition of materials of construction and their manufacturing.

[b] Generally employed for aqueous extracting solvents (e.g. water, saline).

As an extract can contain compounds from all three classes (VOC, SVOC and NVOC), an appropriate strategy for comprehensively screening an extract for organic extractables could involve application of all three chromatographic techniques and the various detection strategies. The exact combination of separation and detection strategies used to accomplish the screening depends on the nature of the organic extractable, as no single chromatographic method is applicable to the wide range of potential organic extractables.

Although GC-MS and LC-MS methods are the primary tools used in screening for organic extractables, additional methods can be applied as necessary and appropriate. For example, NMR can be applied to facilitate the identification of organic extractables.

While the chromatographic methods screen solutions for organic extracted compounds, atomic spectroscopic methods, including atomic absorption (AA), inductively coupled plasma atomic emission spectroscopy (ICP-AES), and inductively coupled plasma mass spectrometry (ICP-MS) screen solutions for extracted elements which may be associated with either organic or inorganic extractables. Note that ICP analysis is not strictly limited to analysis of inorganic extractables, as several of the elements typically included in ICP analysis can exist in both organic and inorganic forms (e.g. S, Si, Zn).

A potential shortcoming in the ICP analysis is that it does not reveal the form in which the element exists. This could complicate the toxicological risk assessment of ICP data in certain (but not all) circumstances. For example, sulphur can be extracted as elemental sulphur, as the sulphate ion or as a part of an organic extractable (such as mercaptobenzothiazole). The chemical form of sulphur detected in an ICP analysis can be necessary to perform the toxicological risk assessment, because the toxicology of sulphur can depend on its form.

IC can be applied to extractables screening to address extracted inorganic anions (e.g. fluoride, chloride, sulphate) and low molecular weight organic acids (e.g. acetic and formic acids).

General methods such as NVR and TOC provide estimates of the total amount of extracted substances but do not provide the identities of the extractables nor the concentrations of individual extractables.

Further discussions around the appropriate analytical strategies and methods for extractables and potentially leachables screening and profiling are found in References [34] and [48].

In many circumstances, leachables profiling involves quantifying known and individually targeted leachables. In this situation, analytical methods suitable for this purpose shall be developed and qualified. In many cases, the same analytical methods used for screening extractables can be optimized for the purpose of targeted leachables analysis.

6.4 Structural composition or configuration

As the structural composition or configuration of a medical device material could be relevant to its biocompatibility, especially in the case of establishing and justifying surrogate devices, it could be appropriate to establish these device characteristics. Table 5 lists some of the characteristics which could be relevant, along with examples of appropriate analytical approaches.

Table 5 — Possible test methodologies for assessing the structural composition of medical device materials

Material type	Characteristic	Example methods[a]	Qualitative	Quantitative
Synthetic Polymer	Constituent structure	FTIR, Raman Spectroscopy	X	X
	Crystallinity	DSC, X-ray diffraction, Raman	X	X
	Configuration, pendant group analysis	Titration	—	X
		Spectroscopy (NMR)	X	X
	Configuration, presence of double bonds	Spectroscopy (IR/UV)	X	X
		Iodine number	—	X
	Configuration, copolymer characterization	Spectroscopy (IR/NMR)	X	X
	Chain configuration, tacticity	Spectroscopy (^{13}C NMR)	X	X
		DSC, TGA	X	—
	Chain configuration, presence of cross links	Sol-gel extraction	X	—
		DMTA	—	X
	Chain branching	Spectroscopy (NMR)	X	X
	Configuration	Rheology	X	—
	Molecular mass and/or molecular mass distribution	GPC	—	X
		End group analysis	—	X
		Osmometry	—	X
		Static light scattering	—	X
		Solution viscometry	—	X
		Sedimentation	—	X
		Mass spectrometry	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.

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.

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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

knowledge of expected substances from material composition, functional group information from MS or similarity in retention time(s).

Alternatively, a method used to analyse a test sample to establish the levels of targeted analytes is generally optimized for this purpose and thus while it might sacrifice broadness in scope (which is critical in screening methods), it does so in a manner that enhances other performance properties such as accuracy and precision. Because the targeting method targets a small and defined list of analytes, the qualification of the method addresses the performance of the method specific to each and every targeted analyte.

The qualification of an analytical method is discussed in Annex F.

7 Reporting of the chemical characterization data

The purpose of a chemical assessment report is to provide information that enables the review of chemical characterization data and supports the toxicological risk assessment of this information. Such reports shall clearly state the purpose and objectives of the chemical assessment that has been performed and shall include description and justification for the following:

a) test article (material or medical device) description and details of sample preparation;

b) analytical methods and extraction conditions (e.g. choice of extraction vehicles, extraction duration and cycles, extraction temperature, extraction/sample ratio, agitation method and speed during extraction);

c) documentation of system suitability testing and its outcome;

d) value for, and justification of, the reporting threshold (e.g. AET);

e) qualitative data generated (e.g. extractables' identities, including a description of the identification procedure);

f) quantitative data generated (e.g. extractables' concentrations, including a description of the quantification procedures and providing the classification of the quantitative data as estimated quantitative analysis, semi-quantitative analysis or quantitative analysis);

g) information necessary to estimate clinical exposure to chemicals (e.g. analyte amounts in µg/device).

As necessary and appropriate, identified substances in the test solutions could be grouped into compound classes, based on structural or functional group similarities, to assist in any toxicological risk assessment.

Chemical or compositional information or data that is obtained without the device's sponsor having to perform testing (e.g. data supplied by a material's vendor, data available from the chemical literature) can be included in reports, as relevant and appropriate. Reporting requirements for data obtained from such additional sources include the same items noted above for sponsor-generated test data but in addition would include a discussion of its relevance to the toxicological risk assessment.

In addition to containing the necessary study design-related details and the relevant and appropriate chemical assessment data, thereby facilitating study review and toxicological risk assessment, a report should contain sufficient information to establish the appropriateness of the analytical processes employed. Such information would be relevant to establishing that the analytical procedures were suitable for their intended use and implemented appropriately at their time of use.

Types of information that can be included in a report to facilitate the toxicological risk assessment and the review of the analytical data and procedures are listed in Annex G.

Annex A
(informative)

General principles of chemical characterization

A.1 The chemical characterization process

Chemical characterization is the process of obtaining chemical information about a medical device, relevant to its biological evaluation and any toxicological risk assessment. Chemical characterization of a medical device, its components, or its materials of construction involves multiple processes, including information gathering and generation, to:

— establish the device's material composition and configuration;

— identify and quantify extractables and/or leachables associated with the device.

Chemically characterizing a medical device and/or its components and materials of construction is a necessary aspect in assessing the biological safety of that medical device.

A.2 The uses of chemical characterization

Chemical characterization can facilitate the biological safety assessment process in one of three ways by providing

— the chemical information that enables a comparison between the medical device in question and clinically established medical devices (establish equivalence),

— the chemical basis for comparing the medical device in question to a relevant material standard (confirm conformance), and

— the chemical information that serves as the basis for a toxicological risk assessment (enable assessment).

In certain circumstances, the toxicological implications associated with use of a medical device can be assessed by comparing the device in question to a clinically established device. In such circumstances, chemical characterization is important in establishing chemical equivalence between, for example,

— a proposed item (materials, component or device) and a clinically established item (see Annex C),

— a finished and marketable medical device and a prototype device, and

— a material, component, or medical device after a process, material, application or manufacturing change.

Standards that include requirements for material composition exist for some medical device materials (e.g. the ISO 5832 series). It is possible that a material complying with such a standard would not require further chemical characterization to support toxicological or biological evaluation. However, the conversion of the material into the final form of the medical device can introduce contaminants or process residues. These can leach from the medical device and be of toxicological concern. Evaluation of the finished medical device should consider and address such leachables. In addition, physical, chemical, morphological, and topographical characteristics of a component manufactured with the material may need to be assessed to determine the overall safety.

Lastly, and in other circumstances, most notably at its inception and in the absence of a relevant clinically established medical device, the toxicological implications associated with the use of a device, including its components or materials of construction, can be assessed using a chemical characterization

approach. Such an approach can include data gathering, data generation (e.g. extractables or leachables profiles), and data interpretation.

An overview of the chemical characterization procedure outlined in this document and its relationship to risk assessment is given in Clause 5. The procedure is based on the following considerations.

a) The first step in chemical characterization is establishing contact according to ISO 10993-1.

b) The extent of chemical characterization (e.g. whether information gathering can be sufficient; design of extraction studies, if performed) should reflect:

   1) the nature and duration of the clinical exposure;

   2) the physical form of the materials used (e.g. liquids, gels, pastes, solids, or biologically sourced material);

   3) the history of use of the materials.

   Further, it should be sufficient to produce the data necessary to establish the biological safety of the medical device.

c) Establishing the configuration of a medical device, by delineating its materials of construction, is the necessary first step in establishing the device's biocompatibility as (a) use of appropriate materials of construction increases the likelihood a device will be biocompatible and (b) knowledge of the materials of construction could provide the starting point for establishing chemical equivalence to a clinically established device.

   For some medical devices, configuration and material composition information could be readily available to the device manufacturer as part of the device specification, or it could be obtained through inquiry. In other circumstances, such information can be obtained by appropriate testing of the device. In any case, processing aids and additives (see Table 3, footnotes b and d) should be included as part of this compositional information.

d) Establishing the composition of a medical device's materials of construction is a necessary step in establishing a device's biocompatibility, as (a) the composition of the individual materials of construction can serve as the basis for establishing chemical equivalence to a clinically established device, and (b) the chemical entities contained in a material of construction can be sources of extractables and leachables.

   1) Compositional data include qualitative data, which describe the composition of a material and establish which chemicals are present in the material, and quantitative data which establish the concentrations of the material's chemical constituents. Quantitative information can be necessary to assess biological safety, as the identity and amounts of the constituents of a medical device's materials of construction enables the investigation of the intrinsic toxicity of each constituent. The data obtained are intended for use by the medical device manufacturer to support the biological evaluation of the medical device.

   2) For some materials, compositional information could be readily available as part of the material specification. As materials such as polymers can have complex formulations, compositional details should be requested from the supplier of the material. Furthermore, some relevant information can be available in the published chemical literature (e.g. typical variability in composition or guidance on possible analytes of interest). In the absence of such details, appropriate analytical techniques can be applied to a material to obtain compositional data.

e) Determining the medical device's potential to release chemical substances under clinical use conditions can provide the basis for understanding and assessing the device's potential safety impact. Although any of the substances in a material or additives used in the process of manufacturing a medical device could be leached from the device and thereby become bio-available, it could potentially be necessary to obtain information demonstrating the extent to which the substances will be leached under the clinical use conditions of the finished product to estimate the risk arising from them. This can be estimated by conducting extraction studies of the medical

device. Appropriate extraction conditions should be established, justified and then used to ensure that any substance which is likely to be released during finished product use will be released into the extraction media (see also Annex D). Extractions can be used to determine the total amount of extractable materials that is present in the medical device/material (exhaustive extraction) or the total available amount of extractable material (exaggerated or simulated use extraction) in order to complete the toxicological risk assessment. Exhaustive extractions are generally necessary to produce sufficient data for medical devices with prolonged or long-term contact; exaggerated extractions should only be used for long term contact devices if appropriately justified.

Regardless of the means by which the extract is obtained, the extract is quantitatively analysed to generate the data for use in the toxicological risk assessment of the medical device (see ISO 10993-17).

Depending on the nature and sources of the chemical information to be assembled, the successful completion of the chemical characterization outlined in this document can require expertise in material science or analytical chemistry to provide the necessary qualitative and quantitative data that a risk assessor can use to assess medical device safety. Toxicology expertise is valuable in understanding the types of compounds that might be of toxicological concern so that the materials and chemistry experts can design appropriate experiments.

The chemical characterization outlined in this document is performed as part of the initial biocompatibility assessment of the medical device. It is noted that the biological safety of the medical device is inferred over the medical device's time in market only so long as the device's materials of construction and manufacturing process remain unchanged. It is important that controls be introduced to prevent a material supplier from changing the composition of a material supplied under a specific commercial trade name or supply agreement without prior notification to the medical device manufacturer. The manufacturer should assess and document the consequences of any notified changes on the biological safety of the product.

A.3 The analytical evaluation threshold

An important aspect of extractables/leachables analysis is the testing of a liquid sample (e.g. extract, digest) to detect, identify, and quantify solubilized (extracted or leached) substances. For the purposes of toxicological assessment, the analytical test methods will be capable of detecting, identifying, and quantifying solubilized substances in the extract at the levels which could potentially have an effect on the health of potentially affected individuals in contact with a medical device. However, in certain circumstances some essential chemical characterization activities, such as identification, cannot be performed. In the absence of reliable identification or sufficient toxicological information for identified compounds, the probable risk can often be inferred via the application of toxicological threshold concepts. Accordingly, substances lower than such a threshold do not require further chemical characterization, including identification and quantification. It is noted that these thresholds make exceptions for special case compounds of known high toxicity.

If a threshold is expressed in terms of dose, then it is not directly applicable to analytical characterization of a liquid test sample. However, these thresholds can be converted to a concentration via the appropriate mathematical conversion, which takes into account the clinical use of the medical device and the experimental conditions used to derive the liquid sample. Such a concentration-based threshold, termed the AET, becomes that threshold above which an analytical chemist should produce that information (concentration and identity) which is necessary for toxicological risk assessment (e.g. application of ISO 10993-17). A substance that is present in a liquid sample at a concentration below the AET is established as having an acceptable toxicological risk without further assessment, meaning that the substance does not have to be accurately quantified or identified.

The AET is not applicable to analytical targeting methods in which the specified analytes are compounds with sufficient toxicological safety data to address using ISO 10993-17.

The calculation and application of the AET is discussed in greater detail in Annex E.

A.4 The role of chemical characterization in biological analysis

The primary objective of ISO 10993 is the protection of humans from potential biological risks arising from the use of medical devices. This objective is achieved via the biological evaluation of medical devices, which includes the means (testing procedures) for producing the biological data and the means of interpreting the biological data in the context of a risk assessment.

Generally, biocompatibility information can be obtained from two types of assessments: (1) chemical characterization coupled with relevant toxicology data, and (2) biological testing. Generally, risk assessment should include the proper mix of chemical and biological data, which can vary depending upon the circumstances. If information from both types of assessments address the same biological endpoint in a comparable manner, information from either type of assessment could be used to address that endpoint. However, *in vitro* tests should be favoured as far as possible (see ISO 10993-2). In the event conflicting data is obtained, the biological test (given it has acceptable sensitivity) should be given greater weight due to its being directly applicable to biological systems.

The general category of biological evaluation can be further subdivided into two sub-categories: those types of testing that evaluate a systemic effect (i.e. one that depends on systemic distribution of extracts or leachates), and those that evaluate local effects (i.e. those that occur in the vicinity of the medical device). Tests that evaluate systemic effects, or endpoints (e.g. systemic toxicity) are more likely to be suitably addressed by chemical characterization than are those tests for local effects (e.g. irritation and implantation effects). Endpoints that have both local and systemic effects (e.g. sensitization) may be addressed through chemical characterization, if sufficient toxicology data exist.

The use of chemical characterization in place of biological testing should be documented and justified.

Annex B
(informative)

Information sources for chemical characterization

B.1 General

Knowledge of a medical device's material composition is an essential input into a device's biological evaluation and toxicological risk assessment (see ISO 10993-1 and ISO 10993-17). As described in 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. Gathering of chemical characterization data could require the use of multiple sources of information as described in B.2 to B.4 and could include a review of the available published chemical literature.

B.2 Information from the material supplier

The following information, where available, is useful to specify the material used (e.g. raw and basic starting materials, processing aids), and the compositional information is particularly useful to aid quantitative risk assessment:

a) name of material manufacturer or supplier;

b) generic material trade name;

EXAMPLE Silastic®, Dacron®, Tetoron®, Pellethane®, Nylon, Teflon®[1)].

c) chemical identifier (e.g. CAS number) or systematic name (IUPAC/USAN) (see B.5);

d) product code and number;

EXAMPLE Pellethane 2393-80AE, methylvinylpolysiloxane 0215.

e) material manufacturer's specification, including, for example, purity, impurity identities and levels, quality, molecular weight, molecular weight distribution, thermal properties, tensile strength, Rockwell hardness, bending modulus, conduction of electricity, and others in addition to the general parameters described in 5.2;

f) details of material composition and formulation (see 5.2) such as Chemical Abstracts Service (CAS) numbers (see B.5.2), mass fraction in percent (%) of each chemical in the formulation, function of each chemical constituent, and structure and formula of each chemical;

NOTE For medical grade components often used in medical devices, a detailed description can be found in material standards [e.g. ASTM F136-13 Standard Specification for Wrought Titanium-6Aluminum-4Vanadium ELI (Extra Low Interstitial) Alloy for Surgical Implant Applications], and sometimes in pharmacopoeias.

g) certificates of compliance with regional compendia and relevant global regulations (e.g. REACH, indirect food additives).

1) Silastic®, Dacron®, Tetoron®, Pellethane®, Nylon, Teflon® are examples of suitable products available commercially. This information is given for the convenience of users of this document and does not constitute an endorsement by ISO of these products.

B.3 Chemical analyses

B.3.1 General

Further to Clause 6, several modes of chemical analyses are described in B.3.2 to B.3.5.

B.3.2 Non-specific chemical analysis relevant to exposure assessment

Non-specific chemical analyses have been included in some international standards and national guidelines or standards intended to ensure safety. These methods are generally usable for an imprecise, first pass estimation of the chemical hazards of medical devices, though their direct relationship to safety is limited. Some examples are given below:

EXAMPLE 1 OECD Guidelines; Test No. 120[17].

This test protocol[17] describes the procedure for determining the solution/extraction behaviour of polymers in water at 20 °C at pH 2 and pH 9 and at 37 °C at pH 7. Total organic carbon content (TOC) analysis is recommended for determining total polymeric species in aqueous phase. Other more specific methods are also described.

EXAMPLE 2 JP XVII[21], USP 41[22] or Ph. Eur. Ed. 9[20].

The JP and Ph. Eur methods (see References [21] and [20]) include test methods and specifications for residue on ignition, heavy metals, extractable substances such as potassium permanganate-reducing substances and residue of evaporation. The USP methods (Reference [22]) include test methods and specifications for acidity/alkalinity, UV absorbance, total organic carbon (TOC), extractable metals, polymer additives and biocompatibility.

B.3.3 Qualitative analysis

If material composition and/or formulation is required but the available qualitative information is judged to be incomplete or not available, further chemical testing can be necessary. Depending on the information needs, qualitative or quantitative information might be required.

Many of the analytical methods employed for chemical characterization are capable of both qualitative and quantitative analyses. However, the purpose of the qualitative analysis is to provide a list of identified chemical constituents in a sample. Conversely, the aim of quantitative analysis is to establish the level or amount of each individual chemical constituent in a sample, whether the constituent is identified or not. Since a toxicological risk assessment is typically based on both identity (which establishes the constituent's toxic potential) and concentration (which establishes exposure), both qualitative and quantitative analyses are important and relevant.

NOTE Semi-quantitative methods can be sufficient for an initial risk assessment, and quantitative methods might be needed when a specific risk has been identified (i.e. an inadequate margin of safety found after semi-quantitative analysis).

B.3.4 Quantitative analysis of specific toxic chemicals for exposure assessment

If qualitative analyses identify chemicals of toxicological concern, then quantitative and specific analysis should be performed. The specificity, level of sensitivity and limit of quantification of the analytical method should be sufficient for the required level of risk assessment.

B.3.5 Qualitative and quantitative analytical methods

NMR, attenuated total reflectance/Fourier transform infrared spectroscopy (ATR/FT-IR) and pyrolysis gas chromatography/mass spectrometry are useful methods for compositional and formulation analyses. Medical device or material extracts can be analysed by chromatographic methods combined with appropriate detection techniques (e.g. GC and LC each combined with MS) to identify and quantify, as appropriate, extracted substances. Inductively coupled plasma (ICP) analysis is useful for establishing the levels of elements present in extracts or digests of medical devices or materials,

although this method does not establish the chemical form of the element. Such analytical methods can be employed so that gaps in material composition and/or formulation are adequately and appropriately addressed.

B.4 National and international material and/or product standards

Most material and/or product standards specify a quality of material in the standard in relation to the purpose of use. When the material used in the medical device meets such a standard and when the category and duration of contact of the device are comparable to those in the standard, giving the title and number of the standard can be sufficient for characterization of the material. Applicability of these standards for chemical characterization depends on the following factors.

— Does the standard specify the medical device and its contact and duration?

— Does the standard specify the material (e.g. specific material, category of material)? If so, to what extent?

— Does the standard set any limits on the level of certain chemicals? Are such limits comprehensive, specific, general, or total?

— Does the medical device or material standardized have a history of safe clinical use?

The extent to which these factors are addressed in the standard determines the extent to which their use can fulfil chemical characterization needs.

NOTE Use of material standards might not be sufficient to address the effects that manufacturing and processing can have on materials when incorporated into the final device. For example, the manufacturing process for medical devices manufactured out of metallic materials described in national and international material or product standards can have a negative influence upon the overall biocompatibility, as residues of cutting oils used during the CNC cutting process can be insufficiently removed.

B.5 Reporting chemical descriptions of materials

B.5.1 Generic name of material

The generic name should be supplied with references to the specific chemical name.

NOTE Generic names can be misunderstood. For instance, "polyester" refers to a class of polymers comprised of ester linkages, but is commonly used to refer specifically to poly(ethylene terephthalate).

B.5.2 Other nomenclatures and chemical descriptions of materials

B.5.2.1 General

There are several nomenclature systems that specify the materials more exactly.

B.5.2.2 IUPAC nomenclature and structure formulae of polymeric chemicals

The International Union of Pure and Applied Chemistry (IUPAC) Macromolecular Nomenclature Commission has published rules for naming polymers[37]. Naming and describing polymers according to the rules present some exact features of polymeric chemicals as defined. It does not give any information however about the commercially available polymers that often contain some additives.

B.5.2.3 CAS Registry number, USAN, REACH and other registry name and/or number

Chemical Abstract Service (CAS) and United States Adopted Names (USAN) give a specific number and name respectively to newly developed polymeric chemicals such as contact lens materials. When the material used has its given CAS No. and/or USAN name, it is easy to discriminate it from similar but not

identical materials. Concise information on the chemical constituents/ingredients is possibly available from USAN.

Though the REACH registration number is primarily to demonstrate REACH registration, it provides a link to the ECHA database which can contain helpful information such as substance identification, purity, identity and levels of impurities.

B.6 Reporting general information concerning chemical nature of materials

Several parameters are generally usable to specify the chemical nature of the material used. These parameters differ by category of materials. For synthetic polymers, examples of such parameters are molecular mass and its distribution, glass transition temperature, melting point, specific gravity, solubility and swelling nature.

NOTE The OECD Guidelines, Section 1, Test No. 118:1996 can be useful for synthetic polymers[16].

B.7 Material master file

When it can be secured, a master file may be used in the review of a pending application for marketing authorization of a specific medical device. It often contains detailed information about a specific material formulation, or its processing, which is used in a medical device. It is a reference source that allows a third party to submit information to a regulatory agency. A master file is useful for supporting equivalence of a material or suitability of a material for a specific category of use. Its contents are considered to be trade secret or commercially confidential information.

Annex C
(informative)

Principles for establishing biological equivalence

C.1 General

As noted in 5.3, it can be appropriate to compare a new or modified medical device (or material) with an existing clinically established medical device (material). When the term medical device is used in this annex, it is understood that the same concepts are applicable to materials as well. The purpose of such a comparison would be to establish whether the new or modified medical device is biologically equivalent to the existing medical device since if biological equivalence can be established then the existing medical device's biocompatibility can be extended to the new or modified medical device.

C.2 Principles of biological equivalence

The concept of biological equivalence consists of the following elements (Figure C.1):

— Chemical equivalence: situation where the chemical characteristics of two materials or medical devices are sufficiently similar, such that the composition and processing do not result in additional or different toxicological concerns.

— Physical equivalence: situation where the physical characteristics of two materials or medical devices are sufficiently similar, such that the configuration, morphology, topography (per ISO/TS 10993-19) and tribology do not result in additional or different biocompatibility concerns.

— Material equivalence: situation where two materials or medical devices demonstrate chemical and physical equivalence.

— Contact equivalence: situation where the intended clinical use of two materials or medical devices is sufficiently similar that the endpoints of biological evaluation identified in ISO 10993-1:2018, A.1 are identical.

— Biological equivalence: situation where two materials or medical devices demonstrate material and contact equivalence.

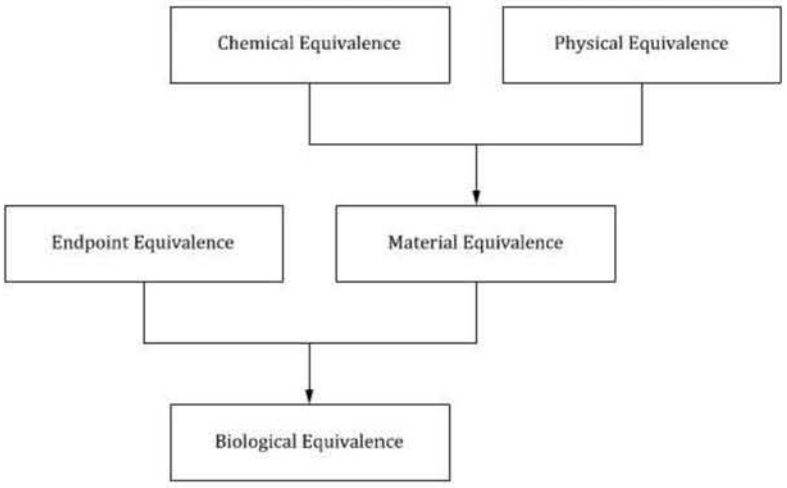

Figure C.1 — Biological equivalence relationship map

C.3 Process for determining biological equivalence

Figure C.2 describes the process for determining biological equivalence between two medical devices.

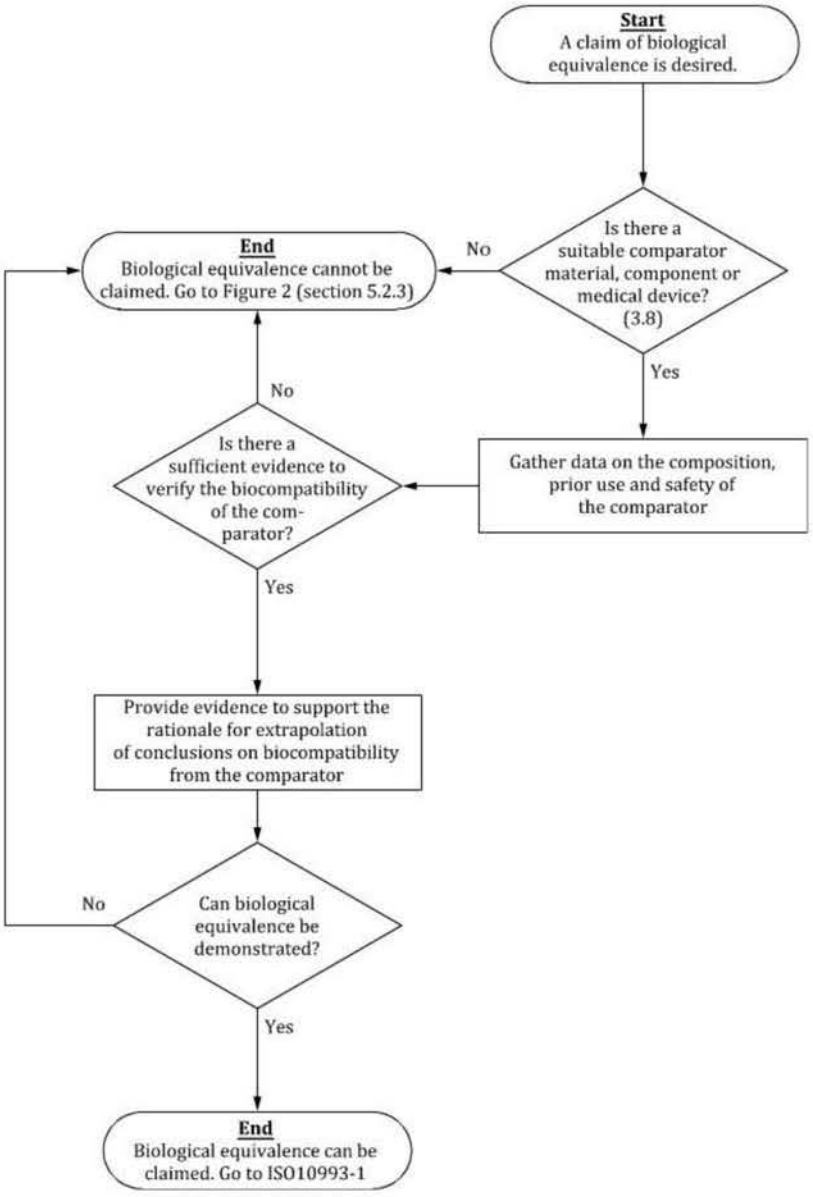

Figure C.2 — Biological equivalence process map

If biological equivalence is established, this satisfactorily completes the biological risk assessment of a new or modified medical device.

If biological equivalence cannot be established, the biocompatibility of a new or modified medical device can only be established based on the medical device's own contact, chemical, physical, toxicological and biological characteristics.

C.4 Examples of chemical equivalence

The following list of examples is provided to assist with establishing chemical equivalence (according to 5.3), where the requirements of chemical equivalence are met.

a) The composition or extractables profile of the proposed material is equivalent (i.e. same chemicals at the same or lower level and no new chemicals) to that of a clinically established material, and

there are no significant differences in physical, chemical, morphological and topographical characteristics which could impact the biological safety of the medical device.

NOTE If there are slight increases in any chemicals, it can be reasonable to justify chemical equivalence within the statistical variability of the semi-quantitative methods being used. Use of calibration standards across a range of chemistries and concentrations can be helpful to this approach.

b) A material that is already clinically established in a more invasive exposure is proposed to be used in a comparable but less invasive application, where less invasive is understood in the context of ISO 10993-1 as having a shorter duration of contact or a contact category calling for fewer endpoints to be addressed.

c) A chemical constituent or residue in a clinically established material is replaced in the proposed material with a chemical constituent or residue whose toxicological safety profile is no worse than that of the constituent or residue that it is replacing, assuming similar exposure.

d) The only difference between a proposed material and a clinically established material is that the proposed material has eliminated or reduced the level of an additive/contaminant/residue present in the clinically established material.

e) The only difference between a proposed material and a clinically established material is that the proposed material is produced using processing conditions that either maintain or reduce the number and/or levels of extractables in the clinically established material.

f) A material in a clinically established medical device is moved to a location in a proposed medical device where contact between a potentially affected individual and the material is lessened.

g) Both the proposed material and the clinically established material meet relevant and rigorous compositional specifications.

Annex D
(informative)

Principles of sample extraction

D.1 General

Information generation in the chemical characterization of a medical device and/or its materials of construction is typically a two-step process in which the medical device or material is extracted and the extract is subsequently chemically analysed to establish the extracted substances. The goal of the extraction is to produce an extractables profile that equals or exceeds the leachables generated in clinical use but does not cause deleterious effects to the materials (such as degradation) or the extractables profile (such as chemical alteration of the extractables). Doing so may provide an extractables profile that is at least as extensive as the medical device's leachables profile, meaning that the extractables profile minimally accounts for the leachables and their levels. Under certain circumstances (e.g. exhaustive extractions), the extractables profile can greatly exaggerate the actual chemical release, meaning that the extractables represent all possible leachables at their highest possible concentration. However, it should be noted that all leachables might not necessarily be present in the extractables profile. Extractables studies which differ significantly from simulated use conditions in terms of solvent properties and extraction method might not fully represent every leachable compound which would be observed under simulated use conditions. This should be taken into account in design of extractables studies and determination of when chemical characterization is complete (according to Figure 1).

As chemical characterization is a general term that describes several individual activities with varying objectives (e.g. compositional analysis, extractables profiling), it is clear that there are numerous means of performing an extraction, where the means of performing an extraction is closely linked to the objective of the characterization. Thus, an extraction to support establishment of the composition of a medical device is necessarily and appropriately performed differently from an extraction done to support establishment of the medical device's extractables profile under the device's typical clinical use conditions.

In general, there can be four objectives of extractions for a chemical characterization:

— to establish the compositional aspects of the configuration of a medical device or the composition of a material of construction (digestion, dissolution or exhaustive extraction);

— to establish the worst-case extractables profile of a medical device or material as either the total pool of extractables in the medical device (exhaustive extraction) or the maximum amount that can be extracted under defined experimental conditions that exaggerate a device's clinical conditions of use (exaggerated or accelerated extraction);

— to establish the extractables profile of a medical device or material under its clinical conditions of use (simulated extraction);

— to correlate chemical data to the results of biological testing performed as described elsewhere in ISO 10993.

Each of these cases will be considered in greater detail in subsequent clauses with respect to establishing appropriate extraction conditions that are consistent with the objectives of the case.

Regardless of the type of extraction performed, extraction is a complex process influenced by aspects including time, temperature, surface area-to-volume ratio, extraction vehicle and the partitioning behaviour of the substances in the test article relative to the extraction vehicle. In general, the extraction conditions should not alter the test article, unless justified, as alteration of the test article could change the amount and/or type of extractables released from the test article. Thus, the material's

chemical properties might also need to be considered when selecting extraction vehicles, for example, to avoid or enhance (e.g. in dissolution studies) solubilisation of the base material.

As stated in ISO 10993-12:2012, 3.8, extraction conditions are expected to be at least as aggressive as the conditions of clinical use. However, for extractables and leachables studies, avoid using extraction solvents that can cause significant swelling and/or compromise the integrity of the test article. Significant swelling can cause reduction of free extraction solvent, which could impact the concentration of extractables and lead to inaccurate analytical calculations. Regarding evaporative loss that might occur during extraction, it is not recommended to compensate for solvent loss by adding additional solvent after extraction is complete; rather, steps should be taken to reduce evaporative loss (e.g. by covering sample containers), or the final extract volume should be measured for later calculations on extractables device. Measurement of solvent volumes in order to compensate for solvent loss due to swelling should be done cautiously, given that the amount of solvent that swells a test article might be unknown and difficult to measure. In either case, the final extract volume should be measured and reported for later calculations on extractables per device. Furthermore, destructive swelling can induce material/medical device disintegration and result in particulate debris, and extractables and leachables that would not otherwise be present; this could potentially interfere with analysis.

Although choice of extraction vehicles will depend on the specific extraction objectives, it is generally appropriate for long-term implants that a minimum of two extraction solvents of differing polarity be employed; for example, polar and non-polar vehicles consistent with ISO 10993-12. For medical devices with indirect contact, it can be appropriate to use a single extraction solvent that replicates the expected contacting fluid. In any case, the choice of extraction vehicle(s) shall be justified.

NOTE For some regulatory regions, such as the U.S., three solvents (e.g. polar, non-polar, and semi-polar) are recommended for long term implants, unless justified.

Examples of possible extraction vehicles are presented in Table D.1. Inclusion of these solvents in Table D.1 serves only as a starting point for solvent vehicles selection and does not constitute a complete justification for their use.

SAFETY PRECAUTIONS — If hazardous solvents are used, occupational health requirements should be observed.

Table D.1 — Parameters of solvents commonly used for extraction of polymeric medical devices/materials

	Solvent[a]	Polarity index[50]	Boiling point (°C)[b]
Polar	Water[c]	10,2	100
Semi Polar	Dimethyl sulfoxide	7,2	189
	Acetonitrile	5,8	82
	Methanol	5,1	65
	Acetone	5,1	56
	Ethanol[d]	4,3	78
	Tetrahydrofuran	4,0	65
	n-Propyl alcohol	4,0	97

[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].

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):

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

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.

To establish the elemental composition of a ceramic, metallic or polymeric test articles, digestion using an appropriate chemical (e.g. strong acid, base or enzyme) is recommended. In digesting the test article, the chemical form of its constituents is largely disrupted and the constituents are typically converted to their elemental form. Although the use of digestion is generally not appropriate for assessment of extractables, it can facilitate the procurement of otherwise unavailable information on material composition and it establishes the absolute and maximum total pool of elemental entities present in a test article.

To establish chemical formulation, dissolution is typically applied to polymeric or natural macromolecule test articles via the use of an appropriate organic solvent and is typically performed to establish the intact organic and/or inorganic constituents in a test article. Once the test article is dissolved with an appropriate vehicle, analysis of the dissolution solution is performed. In many cases, the analysis is facilitated after the polymer itself has been re-precipitated with an antivehicle and filtered out. Although the use of dissolution is not appropriate for assessment of clinical exposure, unless the medical device or material being assessed dissolves in clinical use, it can facilitate the procurement of otherwise unavailable information on material composition and it establishes the absolute total and maximum pool of constituents in a test article. If this step is undertaken, the possibility of co-precipitation of constituents other than the base polymer should be considered.

Possible solvent/anti-solvent combinations for common polymers are listed in Table D.2 and can be found in the literature[28][29][30][31][33][43].

Table D.2 — Possible solvent/anti-solvent combinations for common polymers

Polymer	Solvents[a]	Anti-solvents[a]
Polyethylene (high density)	Xylene[b], Decaline[b], TCB[b]	Acetone, MeOH, ether
Polyethylene (low density)	Toluene	MeOH, ACN
Polypropylene (general)	Toluene	MeOH, ACN
Polypropylene (atactic)	General hydrocarbons	EA, iPrOH
Polypropylene (isotactic)	Xylene[b], Decaline[b], TCB[b]	Acetone, MeOH, ether
Polybutadiene	Hydrocarbons, benzene	Gasoline, alcohols, esters, ketones
Polyisoprene	Benzene	Gasoline, alcohols, esters, ketones
Polyamides	HFIP, Formic acid, DMF, m-cresol	MeOH, ACN
Polyurethanes	DMF	MeOH, ether
Polyesters (except PET)	Toluene, chloroform, benzene	MeOH, EtOH, iPrOH, ether
PET	THF, m-Cresol, o-Chlorophenol	MeOH, acetone
Polycarbonate	THF, DCM	MEOH, EtOH, ACN
Poly(methyl methacrylate)	Toluene, chloroform, acetone, THF	MeOH, EtOH, ACN, petroleum ether
Poly(vinyl chloride)	Toluene, THF, DMF	MeOH, EtOH, hexane, ACN
Poly(vinylidene chloride)	THF, dioxane, ketones, butylacetate	Hydrocarbons, alcohols, phenols
Poly(vinyl alcohol)	Water, formamide	Gasoline, aromatic hydrocarbons, alcohols
Polystyrene	Toluene, chloroform, cyclohexanone, DCM	MeOH, EtOH, can
Styrenics (ABS)	Toluene, acetone	MeOH, EtOH, can
Polysulphone	THF	THF-water gradient
Rubbers	Toluene, chlorinated hydrocarbons	MeOH, ACN, ketones, esters
Cellulose esters	Acetone, esters	Aliphatic hydrocarbons

[a] ABS = poly(acrylonitrile-butadiene-styrene);
ACN = acetonitrile;
AE = ethyl acetate;
DCM = dichloromethane;
DMF = dimethylformamide;
HFIP = hexafluoroisopropanol;
PET = poly(ethylene terephthalate);
TCB = trichlorobenzene;
THF = tetrahydrofuran;
MeOH = methanol;
EtOH = ethanol;
iPrOH = isopropyl alcohol.

[b] Performed at high temperature (>130 °C).

Other than this general discussion, this annex provides no additional insights on performing dissolutions and digestions, as the approaches applied to accomplish dissolution or digestion vary significantly on a case by case basis.

The concept of an exhaustive extraction is discussed in ISO 10993-12:2012, Annex D. An exhaustive extraction establishes the maximum amounts of extractables that can be removed (extracted) from the medical device or material and thus defines the upper bound on the amount of leachables that could potentially be released by the device or material during clinical use/lifetime. In many circumstances,

an exhaustive extraction will accomplish the same outcome as digestion or dissolution, but without the solubilisation of the medical device.

For long-term implanted medical devices, an exhaustive extraction is recommended. If an exaggerated extraction is used, then its use should be justified. It should also be recognized that if total extractables from an exhaustive (or justified exaggerated extraction) of a long-term implant medical device exceed a permissible daily exposure, the extraction kinetics (e.g. to determine maximum daily release) might need to be evaluated (e.g. by repeated analysis of a simulated extraction over time), or a leachables study performed, if possible. A toxicologist can be consulted to establish the specific data required to support risk assessment when there is a need to understand the kinetics of release.

As defined in 3.15, exhaustive extraction involves sequential extraction of the test article under relevant extraction conditions and with a relevant extraction vehicle and is achieved when the level of extracted substance by gravimetric (or other analysis) in a subsequent extraction step is less than 10 % of the level of the same extracted substance in the initial extract. Achieving the required 10 % level for each individual extractable can be analytically and practically challenging (e.g. when the 10 % level is below the method's LOQ); thus, it might be necessary to establish that the 10 % level of extraction has been established by alternate means (e.g. total peak area, TOC, non-volatile residue). Such alternate means should be justified. In some cases, the 10 % level cannot be reached in a practical number of sequential extractions. In these cases, the analyst should consider an alternate extraction process (e.g. use of an extraction vehicle with greater extraction power) so that the 10 % level can be achieved in a reasonable number of sequential extractions. It can also be possible to estimate lifetime exposures from the sequential amounts extracted, even if the 10 % level is not achieved.

Additionally, ISO 10993-12:2012, Annex D, describes a set of extraction vehicles [methanol, acetone, isopropanol-hexane (50:50) and hexane] that can be used, as appropriate, in preliminary experiments whose purpose is to optimize the extraction sequence and discusses the need to use extraction conditions and extraction vehicles (including those described above) that do not result in a chemical change of either the test article or the extracted chemical entity. Regardless of the specific extraction parameters selected, each step of exhaustive extractions should use uniform extraction parameters.

The means by which the individual extraction steps in a sequential exhaustive extraction are accomplished are many and varied. Liquid extraction techniques for polymers span a century in terms of development and use and can be divided into two categories "traditional" and "modern". Traditional techniques, including Soxhlet extraction, boiling under reflux, shake flask extraction, and sonication are widely used even today and are more or less simple to implement using basic laboratory apparatus. As the traditional techniques have been used for an extended period of time, their capabilities and performance is well-known and well-documented. Nevertheless, they can have significant practical shortcomings including low extraction efficiencies, long extraction times, and the use of large quantities of environmentally inopportune extraction vehicles. Such shortcomings are addressed, to a certain extent, by the more modern extraction techniques, including microwave-assisted extraction, pressurized fluid extraction, and supercritical fluid extraction, which typically employ instrumental means to increase the heat and/or the pressure at which extraction occurs or the power of the extraction vehicle[26][51]. Nevertheless, the fact that the techniques are more "modern" do not make them superior. The use of any technique, "traditional" or "modern", should carefully and fully consider their technical and practical limitations and relevance to the clinical use of medical devices.

From a practical perspective, sequential extraction is facilitated when the extraction sequence consists of the fewest possible number of extraction steps while not degrading the additives and ingredients.

An exhaustive extraction reveals a test article's constituents and the levels of these constituents. The exhaustive extraction addresses extractables and leachables in the sense of a total leaching, meaning that a profile of exhaustive extractables addresses the clinical use situation of "all constituents (extractables) are leached in their entirety". Although such an exhaustive extractables profile can be relevant to the clinical use of certain medical devices (e.g., long term implants as noted previously), in many cases the clinical leaching of the medical devices is not exhaustive and thus an alternate extraction process, such as exaggerated or simulated extraction, produces a more appropriate extractables profile for the purpose of toxicological risk assessment. Furthermore, clinical use can, in certain circumstances (such as absorbable medical devices) promote the chemical conversion of constituents into related

substances such as degradation products or side products. If this same conversion does not occur during an extraction study (e.g. exhaustive extraction/dissolution), then the exhaustive extraction is not a fully accurate representation of a potentially affected individual's clinical exposure to the chemicals present during the medical device use. In such cases, the knowledge of potential intermediate and final chemical products, including degradation products, in combination with chemical characterization data and implantation data might be needed to evaluate the safety of products. Knowledge of degradation process/products should be incorporated into any related toxicology risk assessment, even if the degradants are not observed in extracts.

D.3 Exaggerated extraction to estimate the worst-case extractables profile of a medical device or material

As stated in 3.16, extractables are defined as the substances that are released from a medical device or material of construction using extraction vehicles and/or laboratory extraction conditions. However, it is clear that the extraction conditions used to establish configuration and composition are generally much more extreme than the medical device's clinical conditions of use, and thus that extractables revealed in compositional studies are less likely to appear as leachables from the device under its clinical conditions of use. Nevertheless, as discussed in Clause 5, the worst-case assessment of the leaching of a medical device considers the situation where all ingredients and additives leach from the medical device in their entirety. Should a toxicological risk assessment of this worst-case establish that the risk related to the total amount of ingredients and additives be acceptable, then the assessment is essentially complete and the medical device is accepted as being suitable for its intended use with no further chemical testing.

However, if the toxicological risk assessment establishes that the worst-case provided by an exhaustive extraction could represent a safety issue, then a less extreme, more practical exaggerated estimate of the medical device's leaching characteristics is necessary and appropriate. Such an estimate is obtained by using justified exaggerated extraction conditions that somewhat more closely reflect the clinical conditions of use. Of course, exaggerated extractions can be useful for other purposes as well, such as addressing limited and prolonged duration medical devices.

The purpose of an exaggerated extraction is to produce an extractables profile which is at least as complete and complex as the worst-case leachables profile. This means that the exaggerated extractables minimally include all leachables, and that the levels of the exaggerated extractables meet or exceed the highest levels reached by leachables. An exaggerated extraction establishes in a single extraction the highest amount of extractables that most likely will be released by the medical device or material as leachables during clinical use. The exaggerated extraction is accomplished by using extraction conditions that are, in one or more dimensions, exaggerated versus the conditions of clinical use. For example, an exaggerated extraction might be performed considering one or more of the conditions below:

— At a temperature that exceeds the clinical use temperature (typically referred to as an accelerated extraction, see D.4);

— With a duration that exceeds the duration of clinical use;

— With a vehicle whose extraction power exceeds that of the solution that mediates the clinical contact between the medical device and potentially affected individual;

— At a surface area/volume ratio that exceed clinical use exposure;

— Via the use of exhaustive (sequential) extraction for limited or prolonged contact medical devices.

Devising and justifying exaggerated extraction conditions can be a technically challenging exercise and great care should be taken to ensure that the scientific basis for the exaggerated conditions is rigorous and sound. Although certain exaggerating conditions can be appropriate and justifiable for certain situations, they might not be universally applicable to all situations.

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.

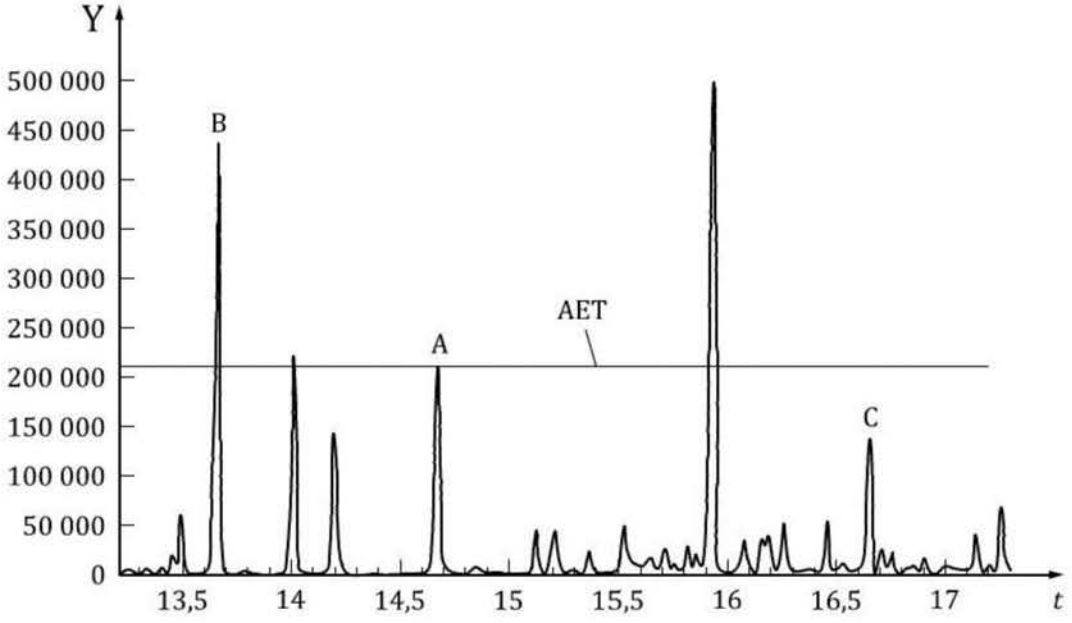

Figure E.1 — Application of the AET in chromatographic analysis

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.

Bibliography

Generally relevant references

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[3] ISO 10993-2, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

[4] ISO 10993-9, *Biological evaluation of medical devices — Part 9: Framework for identification and quantification of potential degradation products*

[5] ISO 10993-12:2012, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials*

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