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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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ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Fax: +41 22 749 09 47
Email: copyright@iso.org
Website: www.iso.org

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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).

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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.

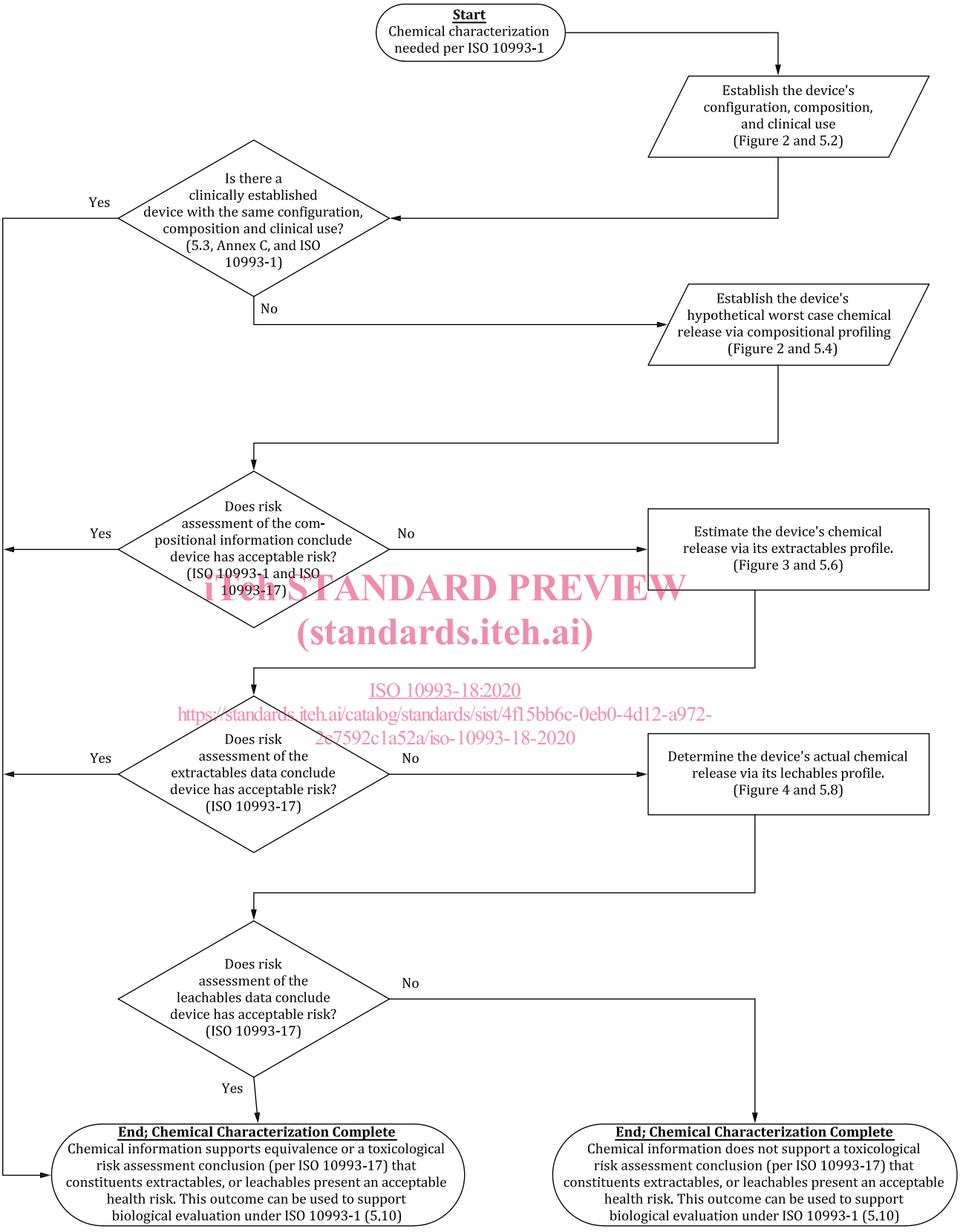
At each step of the characterization procedure, the adequacy of the available data as the basis for performing the risk assessment shall be established. The available data can be considered adequate if it reflects or exceeds the conditions of clinical use and a risk assessment based on the available 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