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Biological evaluation of medical devices —

Part 18: Chemical characterization of materials

Évaluation biologique des dispositifs médicaux —

Partie 18: Caractérisation chimique des matériaux

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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.

ISO 10993-18 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

ISO 10993 consists of the following parts, under the general title *Biological evaluation of medical devices*:

— *Part 1: Evaluation and testing*

— *Part 2: Animal welfare requirements*

— *Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity*

— *Part 4: Selection of tests for interactions with blood*

— *Part 5: Tests for in vitro cytotoxicity*

— *Part 6: Tests for local effects after implantation*

— *Part 7: Ethylene oxide sterilization residuals*

— *Part 9: Framework for identification and quantification of potential degradation products*

— *Part 10: Tests for irritation and delayed-type hypersensitivity*

— *Part 11: Tests for systemic toxicity*

— *Part 12: Sample preparation and reference materials*

— *Part 13: Identification and quantification of degradation products from polymeric medical devices*

— *Part 14: Identification and quantification of degradation products from ceramics*

— *Part 15: Identification and quantification of degradation products from metals and alloys*

— *Part 16: Toxicokinetic study design for degradation products and leachables*

— *Part 17: Establishment of allowable limits for leachable substances*

— *Part 18: Chemical characterization of materials*

The following parts are under preparation:

— *Part 19: Physico-chemical, mechanical and morphological characterization*

— *Part 20: Principles and methods for immunotoxicology testing of medical devices*

Future parts will deal with other relevant aspects of biological testing.

For the purposes of this part of ISO 10993, the CEN annex regarding fulfilment of European Council Directives has been removed.

Introduction

ISO 10993-1 provides a framework for a structured programme of assessment for the evaluation of biological safety. Clause 3 of ISO 10993-1:2003 states that in the selection of materials to be used for device manufacture the first consideration should be fitness for purpose. This should have regard to the characteristics and properties of the material, which include chemical, toxicological, physical, electrical, morphological and mechanical properties. This information is necessary prior to any biological evaluation. Subclause 7.2 of ISO 10993-1:2003 notes that the continuing acceptability of a biological evaluation is an aspect of a quality management system.

Also ISO 14971 points out that a toxicological risk analysis should take account of the chemical nature of the materials.

The requirements specified in this document are intended to yield the following information, which will be of value in predicting the biological response of the materials:

— The chemical composition of the materials used in the manufacturing process including processing additives and residues e.g. trace chemicals, cleaning, disinfection and testing agents, acids and caustic substances.

— The characterization of materials to be used in the production of medical devices, as well as in devices in their final form.

— Identification of the materials of construction of the medical device.

— The potential of medical device materials to release substances or breakdown products due to the manufacturing process.

— Changes in the materials of construction, which result from changes in the manufacturing process or insufficient control of the manufacturing process.

The compositional characteristics of the materials of manufacture are mainly under the control of the suppliers of these materials. However other characteristics are chiefly influenced by the requirements to be met by the finished medical device as well as the processes used by the medical device manufacturer.

Biological evaluation of medical devices —

Part 18:
Chemical characterization of materials

1 Scope

This part of ISO 10993 describes a framework for the identification of a material and the identification and quantification of its chemical constituents. The chemical characterization information generated can be used for a range of important applications, for example:

— As part of an assessment of the overall biological safety of a medical device (ISO 10993-1 and 14971).

— Measurement of the level of a leachable substance in a medical device in order to allow the assessment of compliance with the allowable limit derived for that substance from health based risk assessment (ISO 10993-17).

— Judging equivalence of a proposed material to a clinically established material.

— Judging equivalence of a final device to a prototype device to check the relevance of data on the latter to be used to support the assessment of the former.

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

This part of ISO 10993 does not address the identification or quantification of degradation products, which is covered in ISO 10993-9, ISO 10993-13, ISO 10993-14 and ISO 10993-15.

The ISO 10993 series of standards is applicable when the material or device comes into contact with the body directly or indirectly (see 4.2.1 of ISO 10993-1:2003).

This part of ISO 10993 is intended for suppliers of materials and manufacturers of medical devices, when carrying out a biological safety assessment.

2 Normative references

The following referenced documents are indispensable for the application 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 10993-1:2003, *Biological evaluation of medical devices — Part 1: Evaluation and testing*

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

ISO 14971:2000, *Medical devices — Application of risk management to medical devices*

3 Terms and definitions

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

3.1
supplier
person or company who manufactures and/or supplies the basic starting materials to be used in the manufacture of a medical device

3.2
manufacturer
natural or legal person with responsibility for the design, manufacture, packaging and labelling of a device before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third party

3.3
component
item which is manufactured from a basic starting material but is not itself a medical device, since it forms only one part of a medical device

3.4
convertor
person or company who converts or fabricates a basic raw material into a semi-finished product (e.g. lengths of rod, tubing or lay-flat film)

3.5
chemical characterization
identification of a material and the identification and quantification of the chemicals present in materials or finished medical devices

3.6
exhaustive extraction
extraction until the amount of residues in a subsequent extraction is less than 10 % of that detected in the first extraction

NOTE Extraction is a complex process influenced by time, temperature, surface-area-to-volume-ratio, extraction medium and the phase equilibrium of the material. The phase equilibrium of a material controls the relative amounts of amorphous and crystalline phases present. For the amorphous phase, the glass transition temperature, T_g, dictates the polymer chain mobility and the diffusion rate in the phase. Usually the diffusion rate is considerably higher above the T_g compared with that below. The diffusion rate is lowest in the crystalline phase.

The extraction conditions should not alter the phase equilibrium of the material. Phase alteration may affect the amount and type of extractables. The effects of higher temperatures or other conditions on extraction kinetics and the identity of the extractant(s) should be considered carefully if exhaustive extraction is used. For example, there are a few concerns in using elevated temperatures:

a) the energy of the increased temperature may cause increased cross-linking of a polymer and therefore decrease the amount of free monomer that is available to migrate from the polymer;

b) the increased temperature could cause degradant materials to form that are not typically found in the finished device under use conditions;

c) the increased temperature could cause the disappearance of a leachable material typically found in the finished device.

3.7
simulated extraction
extraction for evaluating potential risk to the patient or user during routine use of a device, using an extraction method with an appropriate medium that simulates product use

NOTE See NOTE to 3.6.

4 Symbols and abbreviated terms

The following abbreviated terms are used in Clause 7.

Table 1 — Methodology abbreviations

Abbreviated term	Analytical method
DMTA	Dynamic mechanical thermal analysis
DSC	Differential scanning calorimetry
EDX-SEM	Electron dispersal X-ray analysis – scanning electron microscopy
FTIR	Fourier transform infra red (spectroscopy)
GC	Gas chromatography
MS	Mass spectroscopy [a]
GPC	Gel permeation chromatography
HPLC	High performance liquid chromatography
ICP	Inductively coupled plasma
IR	Infrared (spectroscopy)
NMR	Nuclear magnetic resonance (spectroscopy)
UV	Ultraviolet (spectroscopy)
XPS	X-ray photoelectron spectroscopy
XRF	X-ray fluorescence
2D PAGE	Two-dimensional polyacrylamide gel electrophoresis

[a] Mass spectroscopy is frequently combined with chromatographic techniques such as GC-MS, LC-MS and MS-MS.

5 General principles

Consideration of the chemical characterization of the materials from which a medical device is made is a necessary first step in assessing the biological safety of the device. It is also important in judging equivalence of

a) a proposed material to a clinically established material, and

b) a prototype device to a final device.

An overview of the chemical characterization procedure outlined in this document and its relationship to risk assessment is given in Annex A.

Qualitative data shall be obtained to describe the chemical composition of a material. When relevant to biological safety, quantitative data shall also be obtained. For some materials compositional information may be readily available as part of the material specification. Materials such as polymers may possess more complex formulations and compositional details should be obtained from the supplier of the material. In the absence of such details appropriate analytical techniques should be applied to a material to yield compositional data.

Identification of the constituents of a material intended for use in the manufacture of a medical device enables the intrinsic toxicity of each constituent to be investigated. The data obtained are intended for use by the medical device manufacturer as part of the overall biological safety evaluation of the medical device. It is therefore important that controls should 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 the consequences of any notified changes on the biological safety of the product.

Any of the constituents of a material or additives used in the process of manufacture of a medical device are potentially bio-available. However it is necessary to obtain information demonstrating the extent to which the constituents will be available under the actual conditions of use of the finished product to estimate the risk arising from them. This can be estimated from extraction tests on the material. Appropriate extraction conditions (simulated extraction) are used to ensure that any constituent which is likely to be released during finished product use will be released into the extraction media. The extract obtained can be analysed qualitatively and/or quantitatively to generate data that can then be used in the biological safety evaluation of the medical device.

The extent of chemical characterization required should reflect the nature and duration of the clinical exposure and shall be determined by the toxicological risk assessor based on the data necessary to evaluate the biological safety of the device. It will also reflect the physical form of the materials used, e.g. liquids, gels, polymers, metals, ceramics, composites or biologically sourced material.

The successful completion of the chemical characterization outlined in this document requires the close collaboration of material scientists, analytical chemists and toxicological risk assessors. In this partnership, the material scientist and analytical chemist provide the necessary qualitative and quantitative data that a risk assessor may use to determine device safety.

6 Characterization procedure

6.1 General

The generation of chemical characterization data is a step-wise process linked to risk assessment and a flowchart composed of 5 steps is given in Annex A. The chemical characterization requirements and guidance at each step are specified in 6.2 to 6.6. The analytical methods shall be selected to give the required information for the toxicological evaluation. If suitable methods cannot be identified, appropriate new methods shall be developed. 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 may need to be adapted and validated before use.

The analytical methods used shall be validated, justified and reported (see Clause 8). The validation of an analytical method is the process by which it is established that the performance characteristics of the method meet the requirements for the intended analytical applications. Analytical methods shall be validated as appropriate with respect to the following justified analytical characteristics:

— accuracy;

— precision;

— specificity;

— limit of detection;

— limit of quantification;

— linearity;

— range;

— ruggedness;

— robustness;

— system suitability.

At each step of the characterization procedure, a decision shall be made on the adequacy of the data obtained as a basis for the risk analysis. This procedure should consider each of the materials used in a medical device in addition to the requirement for chemical characterization of the finished device.

NOTE 1 Steps 2 and 4, 6.3 and 6.5 respectively, are part of the risk assessment process and are outside the scope of this part of ISO 10993. They are given for information to indicate the important interaction between chemical characterization and risk assessment.

NOTE 2 The supplier can be a useful source of appropriate analytical methods. 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 to assist in the selection of the most appropriate methods of analysis for the material concerned.

If the material or device contacts the body directly or indirectly then this part of ISO 10993 is applicable (see 4.2.1 of ISO 10993-1:2003).

6.2 Step 1 — Qualitative information

Describe the material/device and its intended purpose. A documented, qualitative description is required of the composition of the finished device, including additives and processing residues for each material used in the device (see 3.3 and Clause 4 of ISO 10993-1:2003 and Annex B). The level of qualitative data provided/required shall reflect the category of medical device in terms of degree of invasiveness and clinical exposure duration as well as the nature of the materials and shall be justified.

The qualitative description shall, where applicable, include details of batch or lot, supplier and material specification for each material. The use of a standardised material, e.g. ISO 5832-1, in its intended use is considered to meet this requirement.

Medical device manufacturers should preferably obtain qualitative and quantitative compositional information 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 manufacturers. The composition of materials shall either be in accordance with applicable materials standards or shall be specified by the manufacturer. Sufficient information shall be obtained at this stage to identify all toxic hazards arising from the chemical components of the material and sent for risk assessment (see 4.3 of ISO 14971:2000).

6.3 Step 2 — Material equivalence

Sufficient qualitative information shall be obtained to allow a comparison to determine whether the material is equivalent to that utilized in a device with the same clinical exposure/use and having had the same manufacturing and sterilization processes applied, e.g. established safe use of materials in a product to be used on intact skin.

NOTE See Annex C for examples of toxicological equivalence.

6.4 Step 3 — Quantitative information

Where qualitative analysis alone has not provided sufficient data for a toxicological risk analysis to be completed, quantitative chemical composition shall be established, documented (see B.6) and sent for risk assessment. Specifically, quantitative chemical composition denotes the total amount of identified chemicals present in the material.

6.5 Step 4 — Quantitative risk assessment

Sufficient quantitative information shall be obtained to permit a risk assessment, when combined with existing toxicological information (see ISO 10993-17 and 4.1 of ISO 14971:2000).

6.6 Step 5 — Estimated clinical exposure to chemicals present

If the quantity of any chemical present remains of toxicological concern in the light of anticipated clinical exposure, the rate of exposure to that chemical shall be measured and the total dose estimated. The extraction conditions used shall be documented and justified.

NOTE 1 The degree of extraction necessary varies with the nature of the body contact and the extent of exposure. As the duration and invasiveness of contact increases, an analysis that provides information on the kinetics of extraction might be necessary.

The extract shall be analysed using sensitive and selective methods and the levels of chemicals of concern quantified.

NOTE 2 Leachables can, in some cases, be determined by mathematical models as well as tests.

7 Chemical characterization parameters and methods

7.1 General

Clause 6 and Annex A of this part of ISO 10993 indicate the stepwise generation of qualitative and quantitative chemical characterization data for use in the toxicological risk assessment. Subclauses 7.2 to 7.5 indicate, for each of the main medical device material classes, examples of qualitative and quantitative parameters that may be relevant to be determined and examples of methods which can be used.

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 device uses. As noted in 6.2 the extent of characterization required is determined by the invasiveness and duration of clinical exposure in the intended use.

At steps 1) and 3) of Clause 6, (6.2 and 6.4 respectively), the material scientist and analyst in consultation with the toxicological risk assessor shall determine which parameters are relevant to the assessment of a material or medical device. The reasons for the inclusion or exclusion of a parameter shall be documented. Characterization data is required for all of the relevant parameters.

7.2 Polymers

Table 2 — Parameters and test methodologies for analysis of polymers

Examples of parameters to be analysed	Example methods (not comprehensive or exclusive)	Qualitative	Quantitative
Chemical structure	*MS, NMR, FTIR*	X	X
Chemical chain configuration:	Titration	—	X
— Pendant group analysis	Spectroscopy (NMR)	X	X
— Presence of double bonds	Spectroscopy (*IR/UV*)	X	X
	Iodine number	—	X
— Copolymer characterization	Spectroscopy (*IR/NMR*)	X	X
Physical chain configuration:	Spectroscopy (^{13}C *NMR*)	X	X
— Tacticity	*DSC*	X	—
— Presence of crosslinks	Sol-gel extraction	X	—
	DMTA	—	X
— Branching	Spectroscopy (NMR)	X	X
Additives, process residues, trace substances or impurities such as: — Metal deactivators, light/heat stabilizers, plasticizers, lubricants, viscosity improvers, impact modifiers, antistatic agents, antimicrobial agents, crosslinking agents, mould release agents	*HPLC, GC*	X	X
— Antioxidants, blowing agents	*GC*	—	X
	HPLC	X	X
— Flame retardants and whitening agents	*HPLC*	X	X
	X-ray diffraction	X	—
— Fillers	Residue on ignition	X	—
	XRF dissolution	X	X
Surface composition	*FTIR*	X	X
	XPS	X	X
Residual monomer	*GC, HPLC*	X	X
Residual catalyst, initiators	*ICP*	X	X
	HPLC	X	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

7.3 Metals and alloys

Table 3 — Parameters and test methodologies for analysis of metals and alloys

Examples of parameters to be analysed	Example methods [a] (not comprehensive or exclusive)	Qualitative	Quantitative
Chemical composition [b]	X-ray fluorescence Vacuum emission spectroscopy Combustion analysis (C, S) Atomic absorption Gas fusion (N, O, H) *ICP* Titrimetric Gravimetric Electrolytic Colorimetric	X	X
Crystallographic phases	X-ray diffraction, selected area electron diffraction	X	—
Elemental distribution between phases	*EDX*/*SEM, XPS* Electron microscopy probe	X X	— X
Phase specific or surface composition	*EDX*/*SEM, XPS*	X	X
Micro/macro structure	Metallography	X	X

[a] The choice of analysis should be made with the advice of experts in the field since the optimum method can be dependent on specific combinations of alloying elements within the alloy.

[b] Metals and alloys are frequently supplied with documented chemical composition. When product analysis is already available, it is generally not necessary to repeat the analysis of those elements already reported.

7.4 Ceramics

Table 4 — Parameters and test methodologies for analysis of ceramics

Examples of parameters to be analysed [a]	Example methods (not comprehensive or exclusive)	Qualitative	Quantitative
Chemical composition, trace substances	X-ray fluorescence, *ICP*	X	X
Anions	Ion chromatography	X	X
Valency	Colorimetric analysis	X	—
Phases	X-ray diffraction	X	—
Microstructure	Microscopy	—	X
Extractable characterization of leachates	*ICP*	X	X

[a] Typical types of additives that should be considered in any analysis include, but are not limited to, sintering aids, mould release agents, binders, pigments and coatings.

7.5 Natural macromolecules

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

NOTE 1 The EN 12442 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.

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, heparin, chitosan, processed bone, coral and natural rubber. These materials may have been processed, purified and modified to different extents.

NOTE 2 Pharmacopoeia monographs (Ph.Eur./USP/JP) exist for many of these materials and several ASTM F04 standards also cover the characterization of these materials (see Bibliography).

Table 5 — Parameters and test methodologies for analysis of natural macromolecules

Examples of parameters to be analysed	Example methods (not comprehensive or exclusive)	Qualitative	Quantitative
Identity	Colorimetric	X	—
	2D PAGE	X	X
	GPC	X	—
Chemical structure	Amino acid analysis and sequencing	X	X
	FTIR	X	—
	^{13}C ^{1}H and ^{13}C *NMR*	X	—
Chemical chain configuration:	Titration	—	X
— Pendant group analysis	Spectroscopy	X	X
Physical chain configuration:			
1 Tacticity	Spectroscopy (^{13}C NMR)	X	X
	DSC	X	—
2 Presence of crosslinks	Sol-gel extraction,	X	—
	Di-sulphide link analysis	X	X
3 Branching	*DMTA*	—	X
	Spectroscopy	X	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
Impurities	*HPLC*	X	X
	GC	X	X
	2D PAGE	X	X
	Dialysis	X	X

8 Reporting of data obtained

The data shall be reported in a format which enables data entry to a materials database. Any quantitative data shall be presented in a way that permits estimation of human exposure.

Test reports shall clearly state the purpose of the chemical characterization that has been performed and where appropriate shall include the following:

a) material description and details;

b) analytical methods and extraction conditions;

c) qualitative data generated;

d) quantitative data generated;

e) estimated clinical exposure to chemicals.

Annex A
(normative)

Flowchart summarizing the stepwise generation of chemical characterization data for use in toxicological risk assessment

A.1 General

This procedure is only applicable to materials/devices in direct or indirect body contact (see 4.2.1 of ISO 10993-1:2003).

A.2 Procedure

The procedure consists of the following steps which are given in the flowchart in Figure A.1:

a) Step 1: qualitative information;

b) Step 2: material equivalence;

c) Step 3: quantitative information;

d) Step 4: quantitative risk assessment;

e) Step 5: estimated clinical exposure to chemicals present.

NOTE Steps 2) and 4) are part of the risk assessment process and are outside of the scope of this part of ISO 10993. They are shown here for information to indicate the important interaction between chemical characterization and risk assessment.

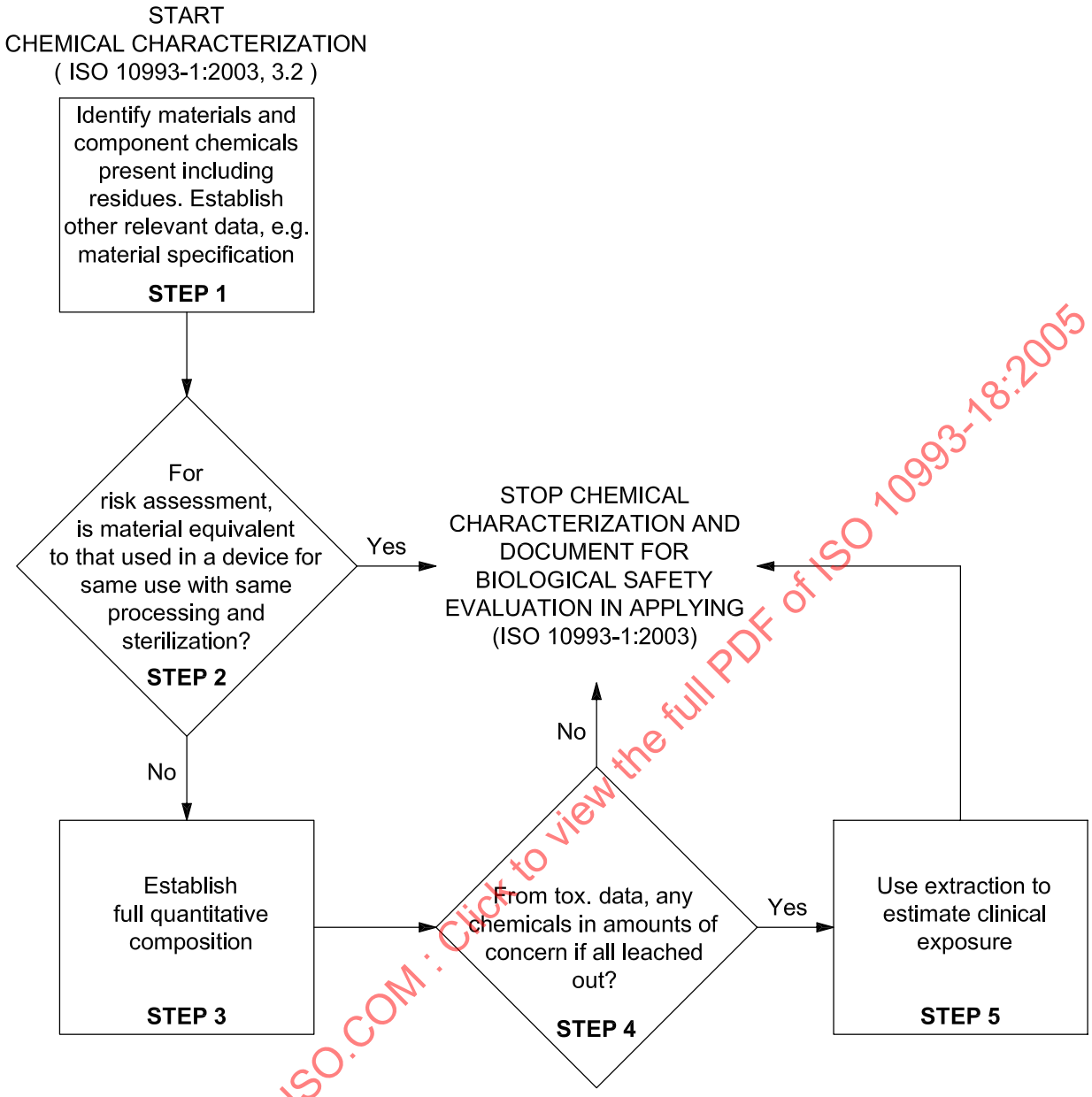

Figure A.1 — Flowchart

Annex B
(informative)

Information sources for chemical characterization

B.1 General

As described in Clause 5, the degree of chemical characterization required is dependant upon the nature and duration of contact of the medical device with the patient's body and its risks in clinical use. Accordingly, the kind and level of detail of the characterization information required depends upon those conditions. This may require the use of multiple sources of information as described in B.2 to B.8.

B.2 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, POLYETHYLENE is sometimes understood to be an ethylene homopolymer, while it has also been defined to be a POLYOLEFIN constituted with ethylene units in more than the given molar percentage.

B.3 Other nomenclatures and chemical descriptions of materials

B.3.1 General

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

B.3.2 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. 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.

NOTE The rules are given in the Bibliography (see Reference [12]).

B.3.3 CAS Registry number, USAN, and other registry name and/or number

Chemical Abstract Service (CAS) and United States Accepted 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 components/ingredients is possibly available from USAN.

B.4 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 differing category of materials (see B.2). 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 118:1996 [15] can be useful for synthetic polymers.