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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).