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Biological evaluation of medical devices —

Part 19: Physico-chemical, morphological and topographical characterization of materials

Évaluation biologique des dispositifs médicaux —

Partie 19: Caractérisations physicochimique, morphologique et topographique des matériaux

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Contents

Page

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.

In other circumstances, particularly when there is an urgent market requirement for such documents, a technical committee may decide to publish other types of normative document:

— an ISO Publicly Available Specification (ISO/PAS) represents an agreement between technical experts in an ISO working group and is accepted for publication if it is approved by more than 50 % of the members of the parent committee casting a vote;

— an ISO Technical Specification (ISO/TS) represents an agreement between the members of a technical committee and is accepted for publication if it is approved by 2/3 of the members of the committee casting a vote.

An ISO/PAS or ISO/TS is reviewed after three years in order to decide whether it will be confirmed for a further three years, revised to become an International Standard, or withdrawn. If the ISO/PAS or ISO/TS is confirmed, it is reviewed again after a further three years, at which time it must either be transformed into an International Standard or be withdrawn.

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/TS 10993-19 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*

— *Part 19: Physico-chemical, morphological and topographical characterization of materials*

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

Introduction

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

ISO 10993-1 provides a framework for a structured programme of assessment for the evaluation of biological safety. ISO 10993-1:2003, Clause 3, 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. ISO 10993-1:2003, 7.2 notes that the continuing acceptability of a biological evaluation is an aspect of a quality management system.

The identification and evaluation of the physico-chemical, morphological and topographical properties of materials used in a finished medical device are important in determining the biological evaluation of that device and its materials. Such information can be used in:

a) assessing the overall biological evaluation of a medical device (ISO 10993);

b) screening of potential new materials and/or processes for suitability in a medical device for a proposed clinical application.

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 production processes used by the medical device manufacturer.

Biological evaluation of medical devices —

Part 19: Physico-chemical, morphological and topographical characterization of materials

1 Scope

This Technical Specification provides a compilation of parameters and test methods that can be useful for the identification and evaluation of the physico-chemical, morphological and topographical (PMT) properties of materials in finished medical devices. Such an assessment is limited to those properties that are relevant to biological evaluation and the medical device's intended use (clinical application and duration of use) even if such properties overlap with clinical effectiveness.

This part of ISO 10993 does not address the identification or quantification of degradation products, which are covered in ISO 10993-9, ISO 10993-13, ISO 10993-14 and ISO 10993-15. Chemical characterization of materials is covered by ISO 10993-18.

The ISO 10993 series of International Standards is not applicable when the material or device does not contact the body directly or indirectly (see ISO 10993-1:2003, 4.2).

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 10993-18, *Biological evaluation of medical devices — Part 18: Chemical characterization of materials*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 10993-1, ISO 10993-18 and the following apply.

3.1
physico-chemical
relating to the physical chemistry (of materials)

3.2
morphological
relating to the shape, contours and microstructural organization (of materials)

3.3
topographical
relating to the features of the surface (of materials)

4 Symbols and abbreviated terms

The following abbreviations are used throughout the document.

- NP: nanoparticle
- PMT: physico-chemical, morphological and topographical

The abbreviations listed in Table 1 are used in Clause 7.

Table 1 — Methodology abbreviations

Abbreviation	Analytical method
AES	Auger Electron Spectroscopy including scanning tunneling auger
AFM/SPM	Atomic Force Microscopy/Scanning Probe Microscopy including topographical roughness and phase contrast
BET	Brunauer-Emmett-Teller, a porosity measurement methodology
CLSM	Confocal Laser Scanning Microscopy
DMTA	Dynamic Mechanical Thermal Analysis
DSC	Differential Scanning Calorimetry
EPMA	Electron Probe Microanalyser
ESC	Equilibrium Solvent Content
EWC	Equilibrium Water Content
EDX-SEM	Energy Dispersive X-ray Analysis — Scanning Electron Microscopy
FTIR	Fourier Transform Infra Red (spectroscopy) including microscopy, imaging and diffuse reflectance
FTIR-ATR	Fourier Transform Infra Red (spectroscopy) — Attenuated Total Reflectance (multiple internal reflectance)
IR	Infra Red (spectroscopy)
OM	Optical Microscopy including polarized light and phase contrast microscopy
QCM	Quartz Crystal Microbalance (or other microbalance techniques)
SEM/TEM	Scanning Electron Microscopy/Transmission Electron Microscopy
SPR	Surface Plasmon Resonance
TOF/SIMS	Time of Flight — Secondary Ionization Mass Spectroscopy
TMA	Thermal Mechanical Analyser
XPS/ESCA	X-ray Photoelectron Spectroscopy/ Electron Spectroscopy for Chemical Analysis

5 General principles

Consideration of the PMT characterization of the materials from which a medical device is made, like chemical characterization of materials (addressed in ISO 10993-18), is a necessary step in assessing the biological safety and clinical effectiveness of the device. Both types of characterization are also important in judging equivalence of:

a) a proposed material to a clinically established material,

or

b) a prototype device to a final device.

The relationship of PMT characteristics of materials used in devices, to their biocompatibility and clinical effectiveness, is still a developing area. However there are several examples of where these relationships are becoming better understood, as listed below.

1) The use of certain PMT characteristics of porous materials as surfaces on orthopaedic implants can encourage tissue in-growth at the surface of the implant and thus result in better integration with the surrounding tissue.

2) The use of material scaffolds and meshes, with certain PMT characteristics, as implants into injured soft or hard tissue can facilitate the beneficial infiltration of certain types of cells which aid the healing process (Dexter et al. [50]).

3) The PMT characteristics of the surfaces of materials used as catheters have a major influence on the adherence of bacteria and proteins to the inner and outer surfaces, which in turn influences the risk of infections and blockages.

4) Alterations to the micro-topography of surfaces, e.g. producing microgrooves or other defined patterns, has been shown to influence the adhesion and direction of movement of certain types of cells on that surface (Alaerts et al. [46]; Dewez et al. [49]).

5) For certain medical devices e.g. orthopaedic implants and vascular prostheses, mechanical properties may influence biological responses such as tissue re-modelling.

NOTE The shape and geometric form of medical devices and their components are known to affect the biological response, e.g. aspect ratio, thickness, form with relation to blood flow. Information on specific devices may be found in the applicable product standards.

This technical specification provides a range of examples of PMT characterization parameters and methods which may be usefully applied in the PMT characterization of materials utilized in medical devices.

Medical device manufacturers should select relevant parameters and methods and justify their selection. Manufacturers should document the level of characterization performed on their medical device and its component materials, appropriate to its clinical application.

The extent of characterization should reflect the nature and duration of the clinical exposure and may be useful for risk assessment of the biological safety of the device. The PMT characterization should also reflect the materials used and their physical form(s), e.g. solid, liquid, gel, polymer, metal, ceramic, composite or biologically sourced material. Characterization generally requires the close collaboration of material scientists, analytical scientists and risk assessors.

6 Characterization procedure

6.1 General

The analytical methods should be selected to give the required information for the evaluation. 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. If suitable methods cannot be identified, appropriate new methods should be developed.

The analytical methods used should be validated, justified and reported in line with Clauses 7 and 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 should 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 and system suitability.

At each step of the characterization procedure, a decision should be made on the adequacy of the data obtained, as a basis for the risk analysis. This procedure should consider each of the materials as they appear in the finished device.

NOTE The supplier may be a useful source of appropriate analytical methods. In the absence of any initial data on material properties, a literature study is recommended to assist in the selection of the most appropriate methods of analysis for the material concerned.

6.2 Qualitative information

Describe the material/device and its intended purpose. A documented, qualitative description of the PMT characteristics of the finished device is recommended, including the characteristics of each material used in the device (see 3.2 and Clause 4 of ISO 10993-1: 2003) (see Annex A). The level of qualitative data provided should reflect the category of medical device in terms of degree of invasiveness and clinical exposure duration, as well as the nature of the materials present.

The qualitative description should, where applicable, include details of batch or lot, supplier and material specification for each material.

Medical device manufacturers should obtain qualitative and quantitative material characterization information, relevant to the final product. Such information may be obtained from the supplier of the starting material, the literature or additional testing. The PMT characteristics of materials should either be in accordance with applicable materials standards or should be specified by the manufacturer. It is important to obtain as much information as possible at this early stage to be able to gain a thorough understanding of the hazards (potential risks) and potential benefits arising from the properties of the material, and to develop an initial assessment of the fitness for the intended purpose. This assessment will be further refined as additional information is gained during the product development process.

6.3 Material equivalence

As a part of material suitability assessment, a comparison of these data should be made to determine whether this 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 and effective use of materials in a product to be used on intact skin. Annex A gives further guidance on judging material equivalency and Annex B gives information on the special case of material used as nanoparticles ($\leqslant$ 100 nm in any one dimension).

6.4 Quantitative information

Where qualitative material characterization data alone have not provided sufficient data for a material suitability assessment to be completed, quantitative material characterization data should be established, documented and subjected to assessment of suitability and risk.

6.5 Quantitative assessment

Sufficient quantitative characterization information should be obtained in order to permit an assessment of the fitness of all of the materials in a finished device for their intended purpose as part of the overall biological evaluation of the medical device. This quantitative characterization information can be usefully compared with data for materials and/or finished medical devices clinically established as being safe and effective for the intended use. The characterization information may also be usefully compared to those materials/products found not to have the required characteristics for this use. This overall evaluation is outside the scope of this part of ISO 10993 and will combine information gained from many other parts of the ISO 10993 series of International Standards and will utilize ISO 14971.

7 Characterization parameters and methods

Clause 6 indicates the generation of qualitative and quantitative PMT characterization data for use in the suitability/risk assessment. Table 2 summarizes examples of parameters for material characterization and examples of methods which can be used to provide qualitative and/or quantitative data for these. Relevant standards and/or references are given for the parameter section, e.g. topography. Not all of the parameters or the associated methods may be applicable to all types of material. The characterization parameters used should be selected 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 relevant for all/some device uses. As noted in 6.2 the extent of characterization which should be considered is determined by the invasiveness and duration of clinical exposure in the intended use.

The analyst and material scientist in consultation with the manufacturer's assessor of the material fitness for use (risk assessor) should determine which parameters are relevant to the assessment of a material or medical device. Characterization data should be considered for all of the parameters considered relevant by the manufacturer's risk assessor.

NOTE For natural macromolecules, it is essential that the source organism (species) and breed/strain be clearly identified as a first step. The ISO 22442 series of standards covers the safe utilisation of non-human tissues and their 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 gelatine, 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. Pharmacopoeia monographs exist for many of these materials and several ASTM F04 standards also cover the characterization of these materials.

Table 2 — Examples of parameters and test methodologies for characterization of materials including polymers, metals, alloys, ceramics and natural macromolecules

Examples of parameters to be analysed	Example methods (not comprehensive or exclusive)	Qualitative	Quantitative	Standard or reference
Porosity				ASTM F1854-01 [39] ISO 18754 [22] ISO 18757 [23]
Classical	OM	×	–	
	Gas adsorption (BET)	–	×	
	Mercury porosimetry	–	×	
	Helium pycnometry	×	–	
Connectivity	SEM	–	×	
	AFM	×	–	
Scaffolds	SEM	–	×	
	AFM	×	–	
Morphology				ASTM F665 [35] ASTM F754 [38] ASTM F2081 [42] ASTM F2183 [44] Hasegawa and Hashimoto [55] Kajiyama et al. [58] Kajiyama et al. [59]
Crystallinity	X-Ray Diffraction	×	×	
	OM	×	–	
	DSC	×	×	
	SEM/TEM	×	–	
	AFM	×	–	
Amorphous	DMTA	×	×	
	AFM	×	–	
Multiple phases	OM	×	×	
	AFM	×	–	
	TEM	×	–	
Hard/soft surfaces	OM	×	×	
	AFM/SPM	×	×	
	TEM	×	–	
	Ultrasound	×	–	