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Biological evaluation of medical devices —

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

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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.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

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 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 10993-19:2006), which has been technically revised. The main changes compared to the previous edition are as follows:

— errors identified in the revision and commenting processes have been corrected;

— Table 1 (on methodology abbreviations) has been updated and moved to Annex A;

— Table 2 (on examples of relevant methodologies and parameters) has been updated, moved to Annex A and split into two tables: one listing typical methods, and one listing other methods (i.e. those that are rarely used);

— pointers to ISO 10993-18:2020, Annex C have been added to 5.3 and Annex A, where material equivalence is discussed.

— pointers to ISO/TR 10993-22 for information on nanomaterials have been added to 5.3 and Table A.3.

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 14971 highlights the importance of taking into account the nature of the materials within a biological risk analysis.

ISO 10993-1 is to serve as a framework in which to plan a biological evaluation which, as scientific knowledge advances human understanding of the basic mechanisms of tissue responses, minimizes the number and exposure of test animals by giving preference to chemical constituent testing and *in vitro* models. In situations where these methods yield equally relevant information to that obtained from *in vivo* models, ISO 10993-1 states that, when selecting the materials to be used for device manufacture, fitness for purpose with regards to characteristics and properties of the material, which include chemical, toxicological, physical, electrical, morphological and mechanical properties, will be the first consideration. 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:

— assessing the overall biological evaluation of a medical device according to ISO 10993;

— 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 document provides a compilation of parameters and test methods that can be useful for the identification and evaluation of the physical, i.e. 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 document does neither address the identification or quantification of degradation products nor the evaluation of the physico-chemical properties of the degraded materials, 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 is not applicable when the material or device is not in contact with the body directly or indirectly.

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 10993-18, *Biological evaluation of medical devices — Part 18: Chemical characterization of medical device materials within a risk management process*

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.

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

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

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

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 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,

b) a prototype device to a final device,

c) a material or device after a process or manufacturing change, or

d) a real-time and/or accelerated device and the non-aged device.

The relationship between PMT characteristics of medical device materials and 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.

— 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.

— 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 (see Reference [49]).

— 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.

— Alterations to the micro-topography of surfaces, for example, 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 (see References [42] and [45]).

— For certain medical devices, for example, orthopaedic implants and vascular prostheses, mechanical properties can influence biological responses such as tissue re-modelling.

— To characterize the PMT principally surface topography/morphology following a process change.

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

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

Medical device manufacturers should select relevant PMT 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 can 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), for example, solid, liquid, gel, composite or biologically-sourced material. Characterization generally requires the close collaboration of material scientists, analytical scientists and risk assessors.

5 Characterization procedure

5.1 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 can 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 6 and 7. 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. To verify the validity of the PMT method or instrument, the use of surrogate materials/surfaces and/or system suitability on analysis system may be used for PMT method used to ensure reliability of the data obtained.

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 can 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 being evaluated.

5.2 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 physico-chemical characteristics of each material used in the device (see ISO 10993-1:2018, Clause 4). 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 include details of the batch or lot, the supplier and the material specification for each material.

Medical device manufacturers should obtain qualitative material characterization information, relevant to the final product. Such information can 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. Importantly, it should be assumed that PMT characteristics will change during manufacture. Therefore, PMT characterization should be performed on or otherwise represent the final product.

5.3 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 or prototype 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.

NOTE Discussion on nanomaterials is presented in ISO/TR 10993-22. See also ISO 10993-18:2020, Annex C for more on material equivalence.

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.

5.4 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 can 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 document and combines information gained from many other parts of the ISO 10993 series and utilizes ISO 14971.

6 Characterization parameters and methods

Clause 5 indicates the generation of qualitative and quantitative PMT characterization data for use in the suitability/risk assessment. Table 1 lists properties that are typically assessed for the characterization of materials, components, or devices. Depending on the material composition, it can be useful to evaluate for additional properties which are described in Table 2. Additional information on example methods and references used to characterize the properties are referenced in Table A.2 and Table A.3.

The characterization parameters used should be selected based on 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 ISO 10993-1:2018, 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 1 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 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.

NOTE 2 Pharmacopoeia monographs exist for many of these materials and the ASTM F04 committee on medical and surgical materials and devices has also published relevant standards (see the Bibliography).

Table 1 — Typical properties assessed for PMT characterization of materials including polymers, metals, alloys, ceramics and natural macromolecules

Property to be assessed	Evaluate for
shape and form	size and shape of relevant material, component, or device
morphology	phase (crystalline, amorphous, multiple phases), micro/macro structure, hardness/softness of surfaces
topography	roughness/smoothness, including pits, grooves, irregular terrain (hills, valleys)
surface chemistry	surface chemistry, its homogeneity/heterogeneity laterally and how it compares to bulk chemical composition
surface energy	hydrophilicity/ hydrophobicity, temperature, surface potential

Table 2 — Other properties to consider assessing for PMT characterization, depending on material composition

Property to be assessed	Evaluate for
porosity	mean pore diameter, pore diameter range/distribution, total porous volume, interconnectivity
swelling	water or solvent absorption, dimensional and shape changes, isotropy or anisotropy of swelling, surface crazing, weight gain
abrasion resistance	stability of treated surface, surface friction
particles	chemical identification/nature, size, size distribution, 3D shape
biointeractions	protein adsorption and repulsion, cell attachment and repulsion

7 Reporting of data obtained

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

a) description and details of material or finished medical device;

b) characterization methods;

c) qualitative data generated;

d) quantitative data generated.

For areas for which no standards exist, the qualitative and quantitative PMT data generated will be collected and documented for information purposes. These data are needed to be able to trace unanticipated adverse events back to seemingly minor material, manufacturing or PMT changes. These data may be used to assist in the development of appropriate future standards.

Annex A
(informative)

Principles for judging material equivalence

In 5.3 characterization data is used in risk assessment to judge equivalence of a proposed material to an existing clinically established material or finished medical device for the same type of clinical exposure. The key principle applied in making this judgement is that the proposed material or finished medical device has equivalent properties in terms of biological safety and clinical performance to that of the clinically established material or finished medical device. The following list contains examples which can assist the assessment process as outlined in Clauses 4 and 5.

— The proposed material or finished medical device meets an existing standard for its intended use and duration of contact and invasiveness.

— The proposed material or finished medical device is already established in a more invasive comparable exposure than the less invasive proposed application.

— The proposed material or finished medical device has properties very close to a clinically accepted material or finished medical device.

Table A.1 shows the abbreviations used in Table A.2 and Table A.3. Table A.2 and Table A.3 provide examples of characterization techniques useful for the characterization of new materials or devices in addition to equivalency evaluation. The tables give examples and should not be considered as all-encompassing. Some characterization methods (e.g. chemical identification of particles) described in this annex can be relevant to chemical characterization as described in ISO 10993-18 (see also in ISO 10993-18:2020, Annex C for more on material equivalence).

Table A.1 — Methodology abbreviations

Abbreviation	Analytical method
BET	Brunauer-Emmett-Teller (porosity and surface area measurement methodology)
CLSM	confocal laser Scanning microscopy
DMTA	dynamic mechanical thermal analysis
DSC	differential scanning calorimetry
EPMA	electron probe microanalyser
ESC	equilibrium solvent content (porosity measurement)
ESCA	electron spectroscopy for chemical analysis
EWC	equilibrium water content (porosity measurement)
EDX-SEM	energy dispersive X-ray analysis — scanning electron microscopy
IR	infrared (spectroscopy)
OM	optical microscopy, including polarized light and phase contrast microscopy
QCM	quartz crystal microbalance (or other microbalance techniques)
SEM	scanning electron microscopy
SPM	scanning probe microscopy (including topographical roughness and phase contrast)
SPR	surface plasmon resonance
TEM	transmission electron microscopy
TMA	thermal mechanical analyser
TOF-SIMS	time-of-flight secondary ion mass spectrometry
XPS	X-ray photoelectron spectroscopy

Table A.2 — Typical properties assessed for PMT characterization and potential methods and references

Property to be assessed	Evaluate for	Example methods (not comprehensive or exclusive)	Qualitative	Quantitative	Standard or Reference
shape and form	size and shape of relevant material,	OM	X	X	ASTM F 754[36]
		SEM	X	X	
morphology	phase (crystalline, amorphous character, multiple phases), hardness/ softness of surfaces	OM	X	X	Hasegawa and Hashimoto[54] Kajiyama et al.[57] Kajiyama et al.[58] Kumaki et al.[62]
		SEM	X	X	
		X-ray diffraction	X	X	
		TEM	X	X	
		SPM	X	X	
		DSC	X	X	
		DMTA	X	X	
		Ultrasound	X	X	
topography	roughness/ smoothness, including pits, grooves, irregular terrain (hills, valleys)	SEM	X	—	ISO 3274 ISO 4287 ISO 4288
		profilometry	X	X	ISO 5436-1 ISO 5436-2 ISO 12179
		SPM	X	X	ISO 13565-1 ISO 13565-2 ISO 13565-3
		tribology	X	—	ISO 16610-21 ISO 18754 ISO 18757 EN 623-4[42]
surface chemistry	surface chemistry, its homogeneity/ heterogeneity laterally and how it compares to bulk chemical composition	IR	X	—	Alaerts et al.[47] Ikada[56] Senshu et al.[65] Senshu et al.[74] Senshu et al.[75]
		EDX-SEM	X	—	
		XPS/ESCA	X	X	
		raman	X	—	
		TOF-SIMS	X	—	
		EPMA	X	X	

Table A.2 *(continued)*

Property to be assessed	Evaluate for	Example methods (not comprehensive or exclusive)	Qualitative	Quantitative	Standard or Reference
surface energy	hydrophilicity/ hydrophobicity, temperature, surface potential	contact angle	X	X	EN 828[44] Jenney and Anderson[56] Kishida et al.[59] MacDonald et al.[64] Niikura et al.[68] Quirk et al.[70] Senshu et al.[71] Senshu et al.[73] Tamada et al.[75] Wagner et al.[76] Weber et al.[78]

Table A.3 — Other properties to consider assessing for PMT characterization and potential methods and references

Property to be assessed	Evaluate for	Example methods (not comprehensive or exclusive)	Qualitative	Quantitative	Standard or reference
porosity	mean pore diameter, pore diameter range/distribution, total porous volume, interconnectivity	OM	X	X	ASTM F 1854[37] ISO 18754 [28] ISO 18757[29]
		SEM	X	X	
		SPM	X	X	
		gas adsorption (BET)	—	X	
		mercury porosimetry	—	X	
		helium pycnometry	X	—	
swelling	water or solvent absorption, dimensional and shape changes, isotropy or anisotoropy of swelling, surface crazing, weight gain	OM	X	X	ISO 17190-5 [26] Moskala and Jones[65]
		SEM	X	X	
		image analysis	X	X	
		EWC	X	X	
		ESC	X	X	
		TMA	X	X	
		microbalance	X	X	
abrasion resistance	stability of treated surface, surface friction	IR	X	—	ASTM D 968[30] ASTM D 1044[31] ASTM D 1894[32] ASTM D 4060[33] ASTM F 732[34] ASTM F 735[35] ASTM F 1978[39] ASTM G 174[41]
		volume loss, strain guage	X	X	
		coefficient of friction	X	X	
		SPM	X	X	

[a] For characterization of nanomaterials, see ISO/TR 10993-22.

Table A.3 *(continued)*

Property to be assessed	Evaluate for	Example methods (not comprehensive or exclusive)	Qualitative	Quantitative	Standard or reference
particles	chemical identification/ nature, size, size distribution, 3D shape[a]	OM	X	X	ASTM F 1877[38]
		EDX-SEM	X	X	ISO 13319
		image analysis	X	X	ISO 13320
		laser diffraction	X	X	ISO 17853
		filters (sieves)	X	—	EN 725-5[45]
		dynamic light scattering	X	X	Brown, et al. [46] Donaldson, et al. [50] Dreher, et al. [51] Everitt and Bermudez[53] Kreuter, et al. [46] Kreyling, et al. [61] Lam, et al. [63] Nemmar, et al. [66] Nemmar, et al. [67] Oberdorster, et al. [69] Stone, et al. [74] Warheit, et al. [77] Wilson, et al. [79]
biointeractions	protein adsorption and repulsion, cell attachment and repulsion	OM	X	X	Collier et al.[47] Dewez et al.[48] Dexter et al.[49] Ebara and Okahata[52] Ikada[55] Jenney and Anderson[56] Kishida et al.[59] MacDonald et al.[64] Niikura et al.[68] Quirk et al.[70] Tamada et al.[75] Wagner et al.[76] Weber et al.[78]
		QCM	X	X	
		SPR	X	X	
		CLSM	X	X	
		biochemical analysis	X	X	
		radioimmunoassay	X	X	
		XPS	X	X	

[a] For characterization of nanomaterials, see ISO/TR 10993-22.

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