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Biological evaluation of medical devices —

Part 1: Evaluation and testing within a risk management process

Évaluation biologique des dispositifs médicaux —

Partie 1: Évaluation et essais au sein d'un processus de gestion du risque

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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).

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For an explanation on the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 194, *Biological and clinical evaluation of medical devices.*

This fifth edition cancels and replaces the fourth edition (ISO 10993-1:2009), which has been technically revised. It also incorporates the Technical Corrigendum ISO 10993-1:2009/Cor.1:2010.

The main changes compared to the previous edition are as follows:

a) revised Annex A "Endpoints to be addressed in a biological risk assessment" with new columns for "physical and/or chemical information" and "material mediated pyrogenicity" as well as columns for "chronic toxicity," "carcinogenicity," "reproductive/developmental toxicity," and "degradation" which now indicates "endpoints" to be considered with "E" (instead of "tests" to be conducted with an "X");

b) replaced Annex B "Guidance on the risk management process" with "Guidance on the conduct of biological evaluation within a risk management process" (formerly ISO TR 15499);

c) additional definitions for terms used throughout the ISO 10993 series of standards;

d) additional information on the evaluation of "Non-contacting medical devices" and new information on the evaluation of "Transitory-contacting medical devices";

e) additional information on the evaluation of nanomaterials, and absorbable materials;

f) additional reference to ISO 18562 (all parts) for "Biocompatibility evaluation of breathing gas pathways in healthcare applications";

g) significant editing changes throughout the document;

A list of all parts in the ISO 10993 series can be found on the ISO website.

This corrected version of ISO 10993-1:2018 incorporates the following correction.

—In Table A.1, 6th column, “Sensitization” has been added as a table heading.

Introduction

The primary aim of this document is the protection of humans from potential biological risks arising from the use of medical devices. It is compiled from numerous International and national standards and guidelines concerning the biological evaluation of medical devices. It is intended to describe the biological evaluation of medical devices within a risk management process, as part of the overall evaluation and development of each medical device. This approach combines the review and evaluation of existing data from all sources with, where necessary, the selection and application of additional tests, thus enabling a full evaluation to be made of the biological responses to each medical device, relevant to its safety in use. The term "medical device" is wide-ranging and, at one extreme, consists of a single material, which can exist in more than one physical form, and at the other extreme, of a medical device consisting of numerous components made of more than one material.

This document addresses the determination of the biological response to medical devices, mostly in a general way, rather than in a specific device-type situation. Thus, for a complete biological evaluation, it classifies medical devices according to the nature and duration of their anticipated contact with human tissues when in use and indicates, in a matrix, the biological endpoints that are thought to be relevant in the consideration of each medical device category. See also 3.14, Note 1 to entry.

The range of biological hazards is wide and complex. The biological response to a constituent material alone cannot be considered in isolation from the overall medical device design. Thus, in designing a medical device, the choice of the best material with respect to its biocompatibility might result in a less functional medical device, biocompatibility being only one of a number of characteristics to be considered in making that choice. Where a material is intended to interact with tissue in order to perform its function, the biological evaluation needs to address this.

Biological responses that are regarded as adverse, caused by a material in one application, might not be regarded as such in a different situation. Biological testing is based upon, among other things, *in vitro* and *ex vivo* test methods and upon animal models, so that the anticipated behaviour when a medical device is used in humans can be judged only with caution, as it cannot be unequivocally concluded that the same biological response will also occur in this species. In addition, differences in the manner of response to the same material among individuals indicate that some patients can have adverse reactions, even to well-established materials.

The primary role of this document is to serve as a framework in which to plan a biological evaluation. A secondary role is to utilize scientific advances in our understanding of basic mechanisms, to minimize the number and exposure of test animals by giving preference to *in vitro* models and to chemical, physical, morphological, and topographical characterization testing, in situations where these methods yield equally relevant information to that obtained from *in vivo* models.

It is not intended that this document provide a rigid set of test methods, including pass/fail criteria, as this might result in either an unnecessary constraint on the development and use of novel medical devices, or a false sense of security in the general use of medical devices. Where a particular application warrants it, experts in the product or in the area of application concerned can choose to establish specific tests and criteria, described in a product-specific vertical standard.

ISO 10993 series is intended for use by professionals, appropriately qualified by training and experience, who are able to interpret its requirements and judge the outcome of the evaluation for each medical device, taking into consideration all the factors relevant to the medical device, its intended use and the current knowledge of the medical device provided by review of the scientific literature and previous clinical experience.

Informative Annex A contains a table that is generally helpful in identifying endpoints recommended in the biocompatibility evaluation of medical devices, according to their category of body contact and duration of clinical exposure. Informative Annex B contains guidance for the application of the risk management process to medical devices which encompasses biological evaluation.

Biological evaluation of medical devices —

Part 1:
Evaluation and testing within a risk management process

1 Scope

This document specifies:

— the general principles governing the biological evaluation of medical devices within a risk management process;

— the general categorization of medical devices based on the nature and duration of their contact with the body;

— the evaluation of existing relevant data from all sources;

— the identification of gaps in the available data set on the basis of a risk analysis;

— the identification of additional data sets necessary to analyse the biological safety of the medical device;

— the assessment of the biological safety of the medical device.

This document applies to evaluation of materials and medical devices that are expected to have direct or indirect contact with:

— the patient's body during intended use;

— the user’s body, if the medical device is intended for protection (e.g., surgical gloves, masks and others).

This document is applicable to biological evaluation of all types of medical devices including active, non-active, implantable and non-implantable medical devices.

This document also gives guidelines for the assessment of biological hazards arising from:

— risks, such as changes to the medical device over time, as a part of the overall biological safety assessment;

— breakage of a medical device or medical device component which exposes body tissue to new or novel materials.

Other parts of ISO 10993 cover specific aspects of biological assessments and related tests. Device-specific or product standards address mechanical testing.

This document excludes hazards related to bacteria, moulds, yeasts, viruses, transmissible spongiform encephalopathy (TSE) agents and other pathogens.

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 10993-2:2006, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

ISO 10993-3, *Biological evaluation of medical devices — Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity*

ISO 10993-4, *Biological evaluation of medical devices — Part 4: Selection of tests for interactions with blood*

ISO 10993-5, *Biological evaluation of medical devices — Part 5: Tests for in vitro cytotoxicity*

ISO 10993-6, *Biological evaluation of medical devices — Part 6: Tests for local effects after implantation*

ISO 10993-7, *Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals*

ISO 10993-9, *Biological evaluation of medical devices — Part 9: Framework for identification and quantification of potential degradation products*

ISO 10993-10, *Biological evaluation of medical devices — Part 10: Tests for irritation and skin sensitization*

ISO 10993-11:2017, *Biological evaluation of medical devices — Part 11: Tests for systemic toxicity*

ISO 10993-12, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials*

ISO 10993-13, *Biological evaluation of medical devices — Part 13: Identification and quantification of degradation products from polymeric medical devices*

ISO 10993-14, *Biological evaluation of medical devices — Part 14: Identification and quantification of degradation products from ceramics*

ISO 10993-15, *Biological evaluation of medical devices — Part 15: Identification and quantification of degradation products from metals and alloys*

ISO 10993-16, *Biological evaluation of medical devices — Part 16: Toxicokinetic study design for degradation products and leachables*

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

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

ISO/TS 10993-20, *Biological evaluation of medical devices — Part 20: Principles and methods for immunotoxicology testing of medical devices*

ISO 14971:2007, *Medical devices — Application of risk management to medical devices*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

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

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

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

3.1
biocompatibility
ability of a *medical device* (3.14) or *material* (3.12) to perform with an appropriate host response in a specific application

3.2
biological risk
combination of the probability of harm to health occurring as a result of adverse reactions associated with *medical device* (3.14) or *material* (3.12) interactions, and the severity of that harm

3.3
biological safety
freedom from unacceptable *biological risk* (3.2) in the context of the intended use

3.4
chemical constituent
any synthetic or natural substance that is used in a process for manufacturing *materials* (3.12) and/or *medical devices* (3.14), including the base material(s), additives (antioxidants, UV stabilizers, color additives, dyes, etc.), and processing aids (solvents, lubricants, antifoaming agents, etc.)

3.5
data set
information, such as physical and/or chemical characterization, toxicity data, etc. from a variety of sources necessary to characterize the biological response to a *medical device*

3.6
direct contact
medical device (3.14) or medical device component that comes into physical contact with body tissue

3.7
externally communicating medical device
medical device (3.14) or medical device component that is partially or wholly located outside the body but has either direct or indirect contact with the internal body fluids and/or tissues

3.8
final product
medical device (3.14) or medical device component that has been subjected to all manufacturing processes for the "to be marketed" medical device including packaging and if applicable, sterilization

3.9
geometry
device configuration
shape and relative arrangement of the parts of the *medical device* (3.14)

3.10
implant
medical device (3.14) which is intended to be totally introduced into the human body or to replace an epithelial surface or the surface of the eye by means of clinical intervention and which is intended to remain in place after the procedure

3.11
indirect contact
medical device (3.14) or medical device component through which a fluid or gas passes, prior to the fluid or gas coming into physical contact with body tissue (in this case the medical device or medical device component itself does not physically contact body tissue)

3.12
material
synthetic or natural polymer, metal or alloy, ceramic, or composite, including tissue rendered non-viable, used as a *medical device* (3.14) or any part thereof

3.13
material characterization
broad and general process of collecting existing information about a material's chemistry, structure and other properties, and if appropriate, new data, to facilitate the evaluation of these properties

3.14
medical device
any instrument, apparatus, implement, machine, appliance, implant, reagent for *in vitro* use, software, *material* (3.12) or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of:

— diagnosis, prevention, monitoring, treatment or alleviation of disease;

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury;

— investigation, replacement, modification, or support of the anatomy or of a physiological process;

— supporting or sustaining life;

— control of conception;

— disinfection of medical devices;

— providing information by means of *in vitro* examination of specimens derived from the human body;

and does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means. Medical devices include dental devices.

Note 1 to entry: Products which may be considered to be medical devices in some jurisdictions but not in others include:

— disinfection substances;

— aids for persons with disabilities;

— devices incorporating animal and/or human tissues;

— devices for *in vitro* fertilization or assisted reproduction technologies;

[SOURCE: GHTF/SG1/N071:2012, 5.1 modified to clarify that dental devices are included]

3.15
nanomaterial
material (3.12) with any external dimension in the nanoscale or having internal structure or surface structure in the nanoscale

[SOURCE: ISO/TR 10993-22:2017, 3. 7, modified — Notes to entry have been deleted.]

3.16
non-contacting
indicates that the *medical device* (3.14) or medical device component has neither direct nor indirect contact with body tissues

3.17
physical and chemical information
knowledge regarding formulation, manufacturing processes, geometric and physical properties and type of body contact and clinical use that is used to determine whether any additional biological or material characterization testing is needed

3.18
risk analysis
systematic use of available information to identify hazards and to estimate the risk

[SOURCE: ISO 14971:2007, 2.17, modified— The Note has been deleted.]

3.19
risk assessment
overall process comprising a *risk analysis* (3.18) and a *risk evaluation* (3.20)

[SOURCE: ISO 14971:2007, 2.18]

3.20
risk evaluation
process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk

[SOURCE: ISO 14971:2007, 2.21]

3.21
risk management
systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk

[SOURCE: ISO 14971:2007, 2.22]

3.22
toxic
capable of causing an adverse biological response

3.23
toxicological hazard
potential for a chemical substance or *material* (3.12) to cause an adverse biological reaction, taking into account the nature of the reaction and the dose required to elicit it

3.24
toxicological risk
probability of a specified degree of an adverse reaction occurring in response to a specified level of exposure

3.25
toxicological threshold
limit, such as a tolerable intake (TI), tolerable exposure (TE), allowable limit (AL) value, or Threshold of Toxicological Concern (TTC) below which adverse effects are not expected for relevant biological endpoints

3.26
transitory contact
medical device (3.14) or medical device component that has a very brief duration of contact with body tissue

4 General principles applying to biological evaluation of medical devices

4.1 The biological evaluation of any material or medical device intended for use in humans shall form part of a structured biological evaluation plan within a risk management process in accordance with ISO 14971:2007, Annex I, as given in Figure 1 of this document. This risk management process involves identification of biological hazards, estimation of the associated biological risks, and determination of their acceptability. Annex B provides guidance on this process. The biological evaluation shall be planned, carried out, and documented by knowledgeable and experienced professionals.

The risk management plan should identify aspects of the biological evaluation requiring specific technical competencies and shall identify the person(s) responsible for the biological evaluation.

The evaluation shall include documented, informed consideration of advantages/disadvantages and relevance of:

a) medical device configuration (e.g. size, geometry, surface properties) and a listing of a medical device's materials of construction (qualitative) and where necessary, the proportion and amount (mass) of each material in the medical device (quantitative);

b) the physical and chemical characteristics of the various materials of construction and their composition;

NOTE Where this information is already documented within the risk management for the medical device, it can be included by reference.

c) any history of clinical use or human exposure data;

NOTE Previous regulatory approval history can be relevant.

d) any existing toxicology and other biological safety data on product and component materials, breakdown products and metabolites;

e) test procedures.

Evaluation can include both a review of relevant existing preclinical and clinical data and actual testing. Such an evaluation might result in the conclusion that no testing is needed if the material has a demonstrable safe history of use in a specified role and physical form that is equivalent to that of the medical device under design. The type of information that can be useful to demonstrate equivalence is included in Annex B. Testing is usually not necessary when sufficient information is already available to perform a risk assessment of the material and/or the medical device (see Annex C).

4.2 In the selection of materials to be used in the medical device manufacture, the first consideration shall be fitness for purpose with regard to characteristics and properties of the material, which include chemical, toxicological, physical, electrical, morphological and mechanical properties.

4.3 The following shall be taken into account for their relevance to the overall biological evaluation of the medical device:

a) the material(s) of construction (i.e. all direct and indirect tissue contacting materials);

b) intended additives, process contaminants and residues (for example, testing for ethylene oxide sterilization residuals shall be conducted in accordance with ISO 10993-7);

c) packaging materials that directly or indirectly contact the medical device can transfer chemicals to the medical device and then indirectly to the patient or clinician;

d) leachable substances (see ISO 10993-17 and ISO 10993-18);

e) degradation products (see ISO 10993-9, for general principles and 10993-13, 10993-14 and 10993-15 for degradation products from polymers, ceramics and metals, respectively);

f) other components and their interactions in the final product;

g) the performance and characteristics of the final product;

h) physical characteristics of the final product, including but not limited to, porosity, particle size, shape and surface morphology.

Description of medical device chemical constituents and consideration of material characterization including chemical characterization (see ISO 10993-18) shall precede any biological testing (see Figure 1). Chemical characterization with an appropriate toxicological threshold can be used to determine if further testing is needed (see Annex B, ISO 10993-17 and ISO 10993-18).

Physical effects of the medical device shall be considered if they impact the biocompatibility.

NOTE See ISO/TR 10993-19 for information.

Medical devices that contain, generate, or are composed of nanomaterials can pose specific challenges to the biological evaluation due to their potentially unique properties (see ISO/TR 10993-22).

Both local and systemic effects shall be considered for risk evaluation.

4.4 The biological evaluation shall commence with categorization of medical devices (see Clause 6). Assessment of the information already available then enables a gap analysis to facilitate the selection

of appropriate tests. The rigour necessary in the biological evaluation is principally determined by the nature, degree, frequency and duration of the exposure and the hazards identified for the medical device or material. Testing is usually not necessary when sufficient information is already available to perform a risk assessment of the material and/or the medical device (see Annex C). For example, biological testing is usually not necessary, if material characterization (e.g. physical and chemical) demonstrates equivalence to a previously assessed medical device or material with established safety (see ISO 10993-18 and ISO/TR 10993-19).

The interpretation of the data shall take into account the chemical composition of the materials, including the conditions of exposure as well as the nature, degree, frequency and duration of exposure of the body to the medical device or its constituents.

4.5 All known possible biological hazards shall be taken into account for every material and final product, but this does not imply that testing for all possible hazards will be necessary or practical (see Clauses 5 and 6). Test results cannot guarantee freedom from potential biological hazards, thus biological investigations shall be followed by careful observations for unexpected adverse reactions or events in humans during clinical use of the medical device.

The range of possible biological hazards is wide and can include short-term effects such as acute toxicity, irritation to the skin, eye and mucosal surfaces, haemolysis and thrombogenicity, as well as long-term or specific toxic effects such as subchronic and chronic toxic effects, sensitization resulting in allergy, genotoxicity, carcinogenicity (tumorigenicity) and effects on reproduction or development, including teratogenicity.

4.6 If testing is needed, selection of any *in vitro* or *in vivo* tests (see Annex A) shall be based on intended use.

In vitro test methods, which are appropriately validated, reasonably and practically available, reliable and reproducible, shall be considered for use in preference to *in vivo* tests (see ISO 10993-2). Whenever *in vivo* tests are indicated by findings of the initial risk assessment, use of appropriate *in vitro* screening, if available, shall be considered before *in vivo* tests are commenced. A rationale for the testing strategy, as well as for test selection, shall be provided. Test data, complete to the extent that an independent analysis could be made, shall be evaluated by competent, informed professionals, and shall be retained.

In certain circumstances, such as for specific medical devices, or biological endpoint assessments, if a non-standardized, non-validated test is necessary, additional information regarding the rationale for the study design and data interpretation should be provided.

4.7 The biological safety of a medical device shall be evaluated by the manufacturer over the whole life-cycle of a medical device.

4.8 For re-usable medical devices, biological safety shall be evaluated for the maximum number of validated processing cycles by the manufacturer.

