

INTERNATIONAL STANDARD

ISO 10993-1

Fifth edition
2018-08

Corrected version
2018-10

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*



Reference number
ISO 10993-1:2018(E)

© ISO 2018

ISO 10993-1:2018(E)



COPYRIGHT PROTECTED DOCUMENT

© ISO 2018

All rights reserved. Unless otherwise specified, or required in the context of its implementation, no part of this publication may be reproduced or utilized otherwise in any form or by any means, electronic or mechanical, including photocopying, or posting on the internet or an intranet, without prior written permission. Permission can be requested from either ISO at the address below or ISO's member body in the country of the requester.

ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Fax: +41 22 749 09 47
Email: copyright@iso.org
Website: www.iso.org

Published in Switzerland

Contents

Page

Foreword	iv
Introduction	vi
1 Scope	1
2 Normative references	1
3 Terms and definitions	2
4 General principles applying to biological evaluation of medical devices	5
5 Categorization of medical devices	9
5.1 General.....	9
5.2 Categorization by nature of body contact.....	9
5.2.1 Non-contacting medical devices.....	9
5.2.2 Surface-contacting medical devices.....	10
5.2.3 Externally communicating medical devices.....	10
5.2.4 Implant medical devices.....	11
5.3 Categorization by duration of contact.....	11
5.3.1 Contact duration categories.....	11
5.3.2 Transitory-contacting medical devices.....	11
5.3.3 Medical devices with multiple contact duration categories.....	11
6 Biological evaluation process	12
6.1 Physical and chemical information for biological risk analysis.....	12
6.2 Gap analysis and selection of biological endpoints for assessment.....	12
6.3 Biological testing.....	13
6.3.1 General.....	13
6.3.2 Testing for evaluation.....	14
7 Interpretation of biological evaluation data and overall biological risk assessment	18
Annex A (informative) Endpoints to be addressed in a biological risk assessment	20
Annex B (informative) Guidance on the conduct of biological evaluation within a risk management process	25
Annex C (informative) Suggested procedure for literature review	38
Bibliography	40

ISO 10993-1:2018(E)

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 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.

ISO 10993-1:2018(E)

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 10993-1:2018(E)

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:

ISO 10993-1:2018(E)

- 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;