SLOVENSKI STANDARD
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Biološko ovrednotenje medicinskih pripomočkov - 1. del: Ocena in preskušanje znotraj procesa obvladovanja tveganja (ISO/DIS 10993-1:2017)

Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process (ISO/DIS 10993-1:2017)

Biologische Beurteilung von Medizinprodukten - Teil 1: Beurteilung und Prüfungen im Rahmen eines Risikomanagementsystems (ISO/DIS 10993-1:2017)

Évaluation biologique des dispositifs médicaux - Partie 1: Évaluation et essais au sein d'un processus de gestion du risque (ISO/DIS 10993-1:2017)

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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).

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 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.

The committee responsible for this document is 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 Corrigendum ISO 10993-1:2009/Cor.1.

The following technical were changes:

a) revised Annex A "Endpoints to be addressed in a biological risk assessment";

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

c) editing changes in the genotoxicity section and other sections of the normative document;

d) additional definitions for terms used throughout the 10993 series of standards added;

e) additional "Non-contacting devices" and "Transient-contacting devices" categories.

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

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 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. It must be appreciated that 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 device category.

NOTE Products which might be considered to be medical devices in some jurisdictions but for which there is not yet a harmonized approach, are:

1) aids for disabled/handicapped people;

2) devices for the treatment/diagnosis of diseases and injuries in animals;

3) accessories for medical devices;

4) disinfection substances;

5) devices incorporating animal and human tissues, which might meet the requirements of the above definition but are subject to different controls.

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 device design. Thus, in designing a device, the choice of the best material with respect to its biocompatibility might result in a less functional 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 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 role of this document is to serve as a framework in which to plan a biological evaluation which, as scientific knowledge advances our understanding of the basic mechanisms of host responses, minimizes the number and exposure of test animals by giving preference to chemical, physical, morphological, and topographical characterization testing and *in vitro* models, 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.

The ISO 10993- series of standards are 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, taking into consideration all the factors relevant to the 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 part document describes:

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

— the general categorization of 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 part document applies to evaluation of materials and devices that are expected to have direct or indirect contact with the patient's body during intended use. In addition, this document applies to medical devices that are expected to have direct or indirect contact with the clinician's body, if the device is intended to protect the clinician (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.

Biological hazards arising from other risks, such as mechanical failures or changes to the device over time, should be considered as a part of the overall biological safety assessment, and can be addressed by relevant biocompatibility, mechanical or other in vivo animal testing or other information. Other parts of ISO 10993 cover specific aspects of biological assessments and related tests.

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, *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 interaction 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, *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 10993-19, *Biological evaluation of medical devices — Part 19: Physico-chemical, morphological and topographical characterization of materials*

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

ISO/TR 10993-22, *Biological evaluation of medical devices — Part 22: Guidance on nanomaterials*

ISO 14971, *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 http://www.iso.org/obp

3.1
biocompatibility
ability of a medical device or material to perform with an appropriate host response in a specific application

Note 1 to entry: This can be demonstrated by biological testing, as well as assessment of effects of leachable chemicals and/or morphological properties (e.g., bound chemicals, topological features) of the medical device or materials, and device performance (e.g., maintenance of mechanical integrity) potentially impacting the biological response.

3.2
biological risk
probability of harm to health occurring as a result of medical device or material interactions

3.3
biological safety
freedom from unacceptable risk 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 and/or medical devices, 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 of a device

3.6
direct contact
term used for a device or device component that comes into physical contact with body tissue

3.7
externally communicating
term used for a device or device component that is placed within the body during a medical procedure, with a portion of the device residing within the body, and another portion of the device outside of the body

3.8
final product
medical device or device component that includes all manufacturing processes for the "to be marketed" device including packaging and sterilization, if applicable

3.9
implant
term used for a device or device component that that is placed entirely within the body during a medical procedure

3.10
indirect contact
term used for a device or 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 device or device component itself does not physically contact body tissue)

3.11
material
any synthetic or natural polymer, metal, alloy, ceramic or other non-viable substance, including tissue rendered non-viable, used as a medical device or any part thereof

3.12
material characterization
the broad and general process by which a material's chemistry, structure and properties are evaluated and measured, to include assessment of compositional, structural, and mechanical properties, if appropriate

3.13
medical device
any instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material 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 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 for medical purposes by means of *in vitro* examination of specimens derived from the human body,

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

Note 1 to entry: This definition has been developed by the Global Harmonization Task Force (GHTF).

Accessories intended specifically by manufacturers to be used together with a "parent" medical device to enable that medical device to achieve its intended purpose, should be assessed according to the ISO 10993- series of standards.

[SOURCE: ISO 14971:2007, definition 2.9, modified to refer to ISO 10993]

Medical devices are different from drugs/biologics, and their biological evaluation requires a different approach.

Medical devices can include dental devices.

3.14
non-contact
term used to indicate that the device or device component has neither direct nor indirect contact with body tissues

3.15
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

3.16
risk analysis
systematic use of available information to identify hazards and to estimate the risk

[SOURCE: ISO 14971:2007, definition 2.17]

3.17
risk assessment
overall process comprising a risk analysis and a risk evaluation

[SOURCE: ISO 14971:2007, definition 2.18]

3.18
risk evaluation
process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk

[SOURCE: ISO 14971:2007, definition 2.21]

3.19
risk management
systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk

[SOURCE: ISO 14971:2007, definition 2.22]

3.20
toxic
capable of causing an adverse biological response

3.21
toxicological hazard
potential for a chemical substance or material to cause an adverse biological reaction, taking into account the nature of the reaction and the dose required to elicit it

3.22
toxicological risk
probability of a specified degree of an adverse reaction occurring in response to a specified level of exposure

3.23
toxicological threshold
a 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

3.24
transient contact
term used for a device or device component that has a very brief duration of contact with body tissue (e.g., for less than one minute)

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 programme within a risk management process in accordance with ISO 14971, as given in Figure 1. 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 programme shall include documented, informed consideration of advantages/disadvantages and relevance of:

a) device configuration and a listing of a device's materials of construction (qualitative) and where necessary, the proportion and amount (mass) of each material in the device (quantitative);

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

NOTE Where this information is already documented within the risk management for the 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 study of relevant preclinical and clinical experience 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 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).