SLOVENSKI STANDARD
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Biološko ovrednotenje medicinskih pripomočkov - 1. del: Zahteve in splošna načela za oceno biološke varnosti znotraj procesa obvladovanja tveganja (ISO/DIS 10993-1:2024)

Biological evaluation of medical devices - Part 1: Requirements and general principles for the evaluation of biological safety within a risk management process (ISO/DIS 10993-1:2024)

Biologische Beurteilung von Medizinprodukten - Teil 1: Anforderungen und allgemeine Grundsätze für die Beurteilung der biologischen Sicherheit im Rahmen eines Risikomanagementsystems (ISO/DIS 10993-1:2024)

Évaluation biologique des dispositifs médicaux - Partie 1: Exigences et principes généraux pour l'évaluation de la sécurité biologique au sein d'un processus de gestion des risques (ISO/DIS 10993-1:2024)

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Biological evaluation of medical devices —

Part 1: Requirements and general principles for the evaluation of biological safety within a risk management process

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Foreword

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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).

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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,* in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 206, *Biocompatibility of medical and dental materials and devices,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This sixth edition cancels and replaces the fifth edition (ISO 10993-1:2018), which has been technically revised.

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

— The standard has been completely reorganised and the title was changed to align with the *risk management* framework described in ISO 14971.

— Additional content has been added to provide more detailed guidance and clarification of calculation of exposure duration.

— Additional content has been added to provide more detailed guidance on characterisation of the device and identification of *biological hazards*.

— The identification of *biological effects* (previously referred to as biological endpoints) has been modified.

— The term “externally communicating” has been replaced in the normative text by language which reflects the specific tissue contact of device components.

— The term “effects after implantation” has been changed to “local effects after tissue contact” as some non-implanted devices also will need this type of assessment.

— Annex A has been revised to move much of the content to the normative text. The remaining text in Annex A is now confined to provision of guidance on *materials* characterisation.

— New Annex B explains the rationale for the changes to *biological effects* listed in Table 1-Table 4.

— New Annex C provides guidance on possible approaches to *biological risk estimation*.

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

The primary aim of this document is to provide guidance and requirements for the *biological evaluation* of a *finished medical device* within a *risk management* process in order to protect humans from *biological risks* arising from the use of *medical devices*. *Biological evaluation* compares the estimated *biological risk* against given risk criteria to determine the acceptability of the *biological risk* as part of the overall *risk management*.

Biological evaluation is primarily concerned with *medical device biological safety*, through consideration of risks associated with *biological hazards*. Nonetheless, some activities undertaken in the course of *biological evaluation* in addition to assessments of long-term safety may also generate information on device performance, for example use of functional *implant* models to assess long-term responses such as tissue ingrowth. *Biological evaluation*, as described in this document, is synonymous with *biocompatibility evaluation*.

Biological evaluation is conducted on the *finished medical device* as it is intended to be used. The principles and methods described can also be useful in the evaluation of candidate *materials* or prototype devices during a *medical device* development process, and data obtained from such evaluations can be of value in assessment of the *finished medical device*.

Medical device design is wide-ranging, and, at one extreme, a *medical device* consists only of a single *material*, which can exist in more than one physical form, while at the other extreme, is a complex article consisting of numerous components made from multiple *materials*. *Biological safety* cannot be considered in isolation from the overall *medical device* design and can require the balancing of conflicting requirements. For example, the choice of the best *material* with respect to its *biological safety* can result in a less functional *medical device*.

The evaluation of *biological safety* is also conducted in the context of the specific *intended use* of a particular *medical device*. *Materials* can be safe in one *medical device* and not in another. It is impossible to make generalised conclusions about the safety of a particular *material* for all medical applications. Biological responses that are regarded as adverse, caused by a *material* in one application, may not be regarded as adverse in a different situation.

When biological testing is required to support an overall *biological evaluation*, such testing is based upon in vitro, ex vivo, or in vivo models. The interpretation of the results of biological tests requires caution because the inherent variability in biological responses between species and individuals means that the biological response observed in animal or cell culture models can differ from those observed in clinical use. Differences in response to the same *material* among individuals means that some individuals can have adverse reactions, even to well-established *materials*. Thus, *biological evaluation* is an exercise in *risk management*. When applied in the evaluation of candidate *materials* or prototype devices during a *medical device* development process, it also allows the informed and timely consideration of risk control measures like using alternative *materials*, manufacturing processes or designs.

The *biological evaluation* processes described in this document draw on all available sources of information relevant to *biological safety* of the *medical device*, including post-market information. This allows a comprehensive review of the *medical device*, identification of *biological hazards* and the *biological harms* which can arise and estimation of the associated risks. This comprehensive approach allows the identification of any gaps in the existing data set and the consequent need for conduct of supplementary assessments (e.g., chemical analysis and hazard identification, or biological testing to refine the *biological risk* estimates).

This document is supported by a wide range of test methods and other guidance published in other documents in the ISO 10993 series as well as other standards. *User*s should also consider more specific guidance contained in device specific standards where available. For some novel or unusual *materials* or technologies, it can be difficult to use the established methods described in the ISO 10993 series. This document allows for the use of alternate procedures where scientifically justified.

The welfare of animals is very important and the selection of test methods and evolution of testing within the ISO 10993 framework is directed to continue to reduce, refine and, where possible, replace the use of animals for biological testing.

Biological evaluation of medical devices —

Part 1: Requirements and general principles for the evaluation of biological safety within a risk management process

1 Scope

This document specifies requirements and general principles governing the *biological evaluation* of *medical devices* within a *risk management* process per ISO 14971. This document applies to the evaluation of *medical devices* that have *direct contact* or *indirect contact with* either:

— a patient's body during *intended use* or *reasonably foreseeable misuse*; or

— the body of other *users* who are not patients, if the *medical device* is intended for personal protection (e.g., medical gloves, masks).

Biological evaluation assesses the *biological safety* of the *medical device* by considering the *biological risks* associated with:

— *constituents* of a medical device; and

— tissue-device interactions (including physical effects).

The *biological evaluation* specified by this document can address the *biological safety* of the *medical device* throughout its *life cycle* from design and development through initial use of the *finished medical device* to final decommissioning or withdrawal from use. The evaluation considers both the *biological safety* of the finished device in first use, and the significance of any changes to the *medical device* which can occur throughout the *life cycle*. However, the evaluation of risks related to environmental impacts of decommissioning of *medical devices* are not within the scope of this document. This version of the standard does not mandate re-testing of medical devices that are already on the market and have established and acceptable safety profiles (see 6.6.2).

This document can be useful to support clinical or usability evaluations of *medical devices.* For example, a *biological evaluation* is a pre-requisite for conduct of a clinical trial. This means that principles outlined by this standard can be applied to evaluation of prototype or development stage devices as well as to *finished medical devices*.

Other parts of ISO 10993 cover specific aspects of *biological evaluation* such as chemical characterisation, biological testing, sample preparations, animal welfare and toxicological risk assessment.

For some types of *medical devices*, specific requirements from other standards (outside the ISO 10993-series) can be considered with justification for the approach taken in the event of differences between ISO 10993 requirements and those provided in other standards. For example, the ISO 18562 series of standards provides specific requirements for *biological evaluation* of breathing gas pathway *medical devices* and ISO 7405 provides specific requirements for *biological evaluation* of dental devices.

The evaluation of risks related to infectious agents (e.g., bacteria, moulds, yeasts, viruses, transmissible spongiform encephalopathy (TSE) agents) is not within the scope of this document.

NOTE 1 The evaluation of bacterial endotoxins is addressed by ISO 11737-3.

NOTE 2 Evaluation of risks related to viruses, TSE agents and other pathogens is addressed by the ISO 22442 series, which provide requirements for risk assessments for *materials* of animal origin.

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 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 10993-9, *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 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: Toxicological risk assessment of medical device constituents*

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

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 10993-23, *Biological evaluation of medical devices — Part 23: Tests for irritation*

ISO 14971:2019, *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 terminology databases for use in standardization at the following addresses:

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

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

3.1
biocompatibility
ability of a *medical device* (3.25) or *material* (3.24) to perform with an appropriate host response in a specific application

3.2
biological effect
observable or measurable change that occurs in a living organism as a result of exposure to the physical characteristics, or a chemical *constituent* (3.13) of a *medical device* (3.25) as well as to a physical or biological agent

3.3
biological equivalence
circumstance where the composition, physical characteristics and manufacturing process of a new *medical device* (3.25) or *material* (3.24) can be shown to be similar to an existing comparator *medical device* (3.25) for which there are existing data demonstrating *biological safety* (3.10) in a relevant type and duration of body contact and that no new or increased *biological risks* (3.7) are identified for the new *medical device* (3.25)

3.4
biological evaluation
biocompatibility evaluation
process of comparing the *biological risk* (3.7) of a *medical device* (3.25) against defined criteria to determine the acceptability of the *biological risk* (3.7)

[SOURCE: ISO 14971:2019, 3.14, modified – "biological" and "*biocompatibility*" were added before "evaluation" in the terms; in the definition, "risk evaluation" removed prior to "process", "biological risk" replaced "estimated risk", "defined criteria" replaced "given risk criteria", and "*biological risk*" replaced "risk evaluation".]

3.5
biological harm
adverse *biological effect* (3.2) associated with a *medical device* (3.25) or *material* (3.24) interactions arising from exposure to a *biological hazard* (3.6)

3.6
biological hazard
potential source of *biological harm* (3.5)

Note 1 to entry: Biological hazards relevant to the *intended use* (3.20) may arise from either exposure to a *constituent* (3.13) of a *medical device* (3.25) or the physical characteristics (e.g. texture, stiffness, *configuration*) of the *medical device* (3.25).

[SOURCE: ISO 14971:2019, 3.4, modified – "biological" has been added before "hazard" in the term and prior to "harm" in the definition, and NOTE 1 to entry has been added.]

3.7
biological risk
combination of the probability of occurrence of *biological harm* (3.5) and the severity of that *biological harm* (3.5)

[SOURCE: ISO 14971:2019, 3.18, modified – "biological" has been added before "risk" in the term.]

3.8
biological risk analysis
systematic use of available information to identify *biological hazards* (3.6) and to estimate *biological risks* (3.7)

[SOURCE: ISO 14971:2019, 3.19, modified – "biological" has been added before "risk analysis" in the term.]

3.9
biological risk assessment
overall process comprising a *biological risk analysis* (3.8) and a *biological risk* (3.7) evaluation

[SOURCE: ISO 14971:2019, 3.20, modified – "biological" has been added before the terms "risk analysis", "risk assessment" and "risk evaluation" in the term.]

3.10
biological safety
freedom from unacceptable *biological risk* (3.7) in the context of the *intended use* (3.20) or *reasonably foreseeable misuse* (3.31)

[SOURCE: ISO 14971:2019, 3.26, modified – "biological" has been added before "safety" and "risk" in the term and in the definition. Concept of "*reasonably foreseeable misuse*" added]

3.11
biologically hazardous situation
circumstances which result in exposure to one or more *biological hazards* (3.6)

[SOURCE: ISO 14971:2019, 3.5, modified – "biological" has been added before "hazardous situation" in the term, "people, property or the environment is/are exposed" was replaced by "cause exposure", and Note 1 to entry was deleted.]

3.12
configuration
geometry
shape, size and relative arrangement of the parts of the *medical device* (3.25)

3.13
constituent
chemical that is present in or on the *finished medical device* (3.25) or its *materials* (3.24) of construction

Note 1 to entry: These can be intentionally or unintentionally added chemicals or compounds, such as: additives (e.g. plasticizers, lubricants, stabilizers, anti-oxidants, colouring agents, fillers), manufacturing process residues (e.g. monomers, catalysts, solvents, sterilant and cleaning agents), degradation products, reaction products, or impurities or contaminants.

[SOURCE: ISO 10993-17:2023, 3.4, modified – Note 1 to entry has been modified to remove "constituents", to add "reaction products", and to remove "(e.g. byproducts or side products)"].

3.14
contact day
any day in which a *medical device* (3.25) or component thereof comes into contact with tissues or circulating blood, irrespective of the length of time of that contact within the day

3.15
direct contact
physical contact of a *medical device* (3.25) or component thereof, with tissues or circulating blood

3.16
extractable
constituent (3.13) that is released from a *medical device* (3.25) or *material* (3.24) when extracted using laboratory extraction conditions and vehicles

[SOURCE: ISO 10993-18:2020, 3.16]

3.17
finished medical device
medical device (3.25) that is in the state in which it is intended to be used, following all manufacturing processes such as packaging, storage and sterilization