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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

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

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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 document 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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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, *Biological and clinical evaluation of medical 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 are as follows:

— this document has been completely reorganised and the title has been aligned with the risk management framework described in ISO 14971;

— content has been added to provide guidance and clarification of calculation of exposure duration;

— content has been added to provide guidance on characterization of the device and identification of biological hazards;

— the identification of biological effects (previously referred to as biological end points) has been modified;

— the term “externally communicating” has been replaced 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 most of the content to the main text and the remaining text in Annex A is now confined to the provision of guidance on materials characterization;

— Annex B has been added to explain the rationale for the changes to biological effects listed in Table 1 to Table 4.

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

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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.

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Introduction

The aim of this document is to provide guidance and requirements for the biological evaluation of a medical device within a risk management process to protect humans from biological risks arising from the use of medical devices and the materials from which they are made. Biological risk 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 can also generate information on device performance. For example, functional implant models can be used 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. 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 the 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 conducted in the context of the intended use of a particular medical device. Materials can be safe in one medical device and not in another. It is impossible to make generalized 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, are not necessarily regarded as adverse in a different situation.

Physical and chemical information supports the overall biological evaluation and can be used to inform testing needs, if any. When biological testing is required, 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 to the evaluation of candidate materials or prototype devices during a medical device development process, biological evaluation allows the informed and timely consideration of risk control measures such as use of alternative materials, manufacturing processes or designs.

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

This document is supported by a wide range of test methods and guidance published in other documents in the ISO 10993 series, as well as other standards. Those who use this document can also consider more specific guidance contained in device-specific standards, where available. For some complex or novel 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 alternative procedures where scientifically justified.

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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.

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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

1 Scope

This document specifies the requirements and general principles governing the biological evaluation of medical devices within a risk management process according to ISO 14971.

This document applies to the biological 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, surgical 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 in this document can address the biological safety of the medical device, considering the life cycle from design and development through initial use of the finished medical device to final decommissioning or withdrawal from use. The biological 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 document 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 conducting a clinical trial. This means that principles outlined in this document can be applied to the evaluation of prototype or development stage devices, as well as to finished medical devices.

Other parts of the ISO 10993 series cover specific aspects of biological evaluation, such as chemical characterization, biological testing, sample preparation, 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 a justification for the approach taken if there are differences between the requirements of the ISO 10993 series and those provided in other standards. For example, the ISO 18562 series 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.

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NOTE 2 The evaluation of risks related to viruses, TSE agents and other pathogens originating from materials of animal origin is addressed by the ISO 22442 series.

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

ISO 10993-9:2019, *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 10993-17:2023, *Biological evaluation of medical devices — Part 17: Toxicological risk assessment of medical device constituents*

ISO 10993-18:2020, *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 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

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

3.1
biocompatibility
ability of a *medical device* (3.28) or *material* (3.27) to perform with an appropriate host response in a specific application

3.2
biological effect
observable or measurable response of cells or a living organism to the physical characteristics or chemical *constituents* (3.15) of a *medical device* (3.28) including a physical [e.g. *nanomaterial* (3.30)] or biological agent (e.g. animal *tissue* (3.40) derivative)

3.3
biological equivalence
circumstance where the chemical and physical characteristics and manufacturing process of a *medical device* (3.28) or *material* (3.27) under evaluation can be shown to be sufficiently similar to a comparator medical device or material for which there are existing data demonstrating *biological safety* (3.11) in a relevant type and duration of body contact and that no new or increased *biological risks* (3.8) are identified for the medical device or material under evaluation

3.4
biological evaluation
biocompatibility evaluation
risk management (3.37) process associated with *biological risks* (3.8) of a *medical device* (3.28) or *material* (3.27)

3.5
biological risk evaluation
process of comparing the *biological risk* (3.8) of a *medical device* (3.28) or *material* (3.27) against defined criteria to determine the acceptability of the biological risk

Note 1 to entry: Biological risk evaluation is a subset of the overall *biological evaluation* (3.4).

[SOURCE: ISO 14971:2019, 3.23, modified — "biological" has been added before "risk" in the term and in the definition, and "biological risk of a medical device or material" has replaced "estimated risk" and "defined criteria" has replaced "given risk criteria" in the definition.]

3.6
biological harm
injury to humans from one or more adverse *biological effects* (3.2) associated with a *medical device* (3.28) or *material* (3.27)

3.7
biological hazard
potential source of *biological harm* (3.6)

Note 1 to entry: Biological hazards relevant to the *intended use* (3.23) can arise from either exposure to a *constituent* (3.15) of a *medical device* (3.28) or the physical characteristics [e.g. texture, stiffness, *configuration* (3.14)] of the medical device.

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

3.8
biological risk
combination of the probability of occurrence of *biological harm* (3.6) and the severity of that biological harm

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

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3.9
biological risk analysis
systematic use of available information to identify *biological hazards* (3.7) and to estimate *biological risks* (3.8)

[SOURCE: ISO 14971:2019, 3.19, modified — "biological" has been added before "risk" in the term, and before "hazards" and "risks" in the definition.]

3.10
biological risk assessment
overall process comprising a *biological risk analysis* (3.9) and a *biological risk evaluation* (3.5)

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

3.11
biological safety
freedom from unacceptable *biological risk* (3.8) in the context of the *intended use* (3.23) or *reasonably foreseeable misuse* (3.34)

[SOURCE: ISO 14971:2019, 3.26, modified — "biological" has been added before "safety" in the term and before "risk" in the definition, and "in the context of the *intended use* (3.23) or *reasonably foreseeable misuse*" has been added to the definition.]

3.12
biologically hazardous situation
circumstances which result in exposure to one or more *biological hazards* (3.7)

3.13
chemical characterization
process of obtaining chemical information, accomplished either by information gathering or by information generation, for example, by literature review or chemical testing

[SOURCE: ISO 10993-18:2020, 3.6]

3.14
configuration
geometry, shape, size and relative arrangement of the parts of the *medical device* (3.28)

3.15
constituent
chemical that is present in or on the *finished medical device* (3.20) or its *materials* (3.27) of construction

Note 1 to entry: Constituents 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* (3.17) products, reaction products, or impurities or contaminants.

[SOURCE: ISO 10993-17:2023, 3.4, modified — "reaction products" has been added to and "(e.g. byproducts or side products)" has been removed from Note 1 to entry.]

3.16
contact day
day in which a *medical device* (3.28) or component thereof comes into contact with *tissue* (3.40) including circulating blood, irrespective of the length of time of that contact within the day

3.17
degradation
breakdown of a *material* (3.27) by physical or chemical means

3.18
direct contact
physical contact of a *medical device* (3.28) or component thereof, with *tissue* (3.40) including circulating blood

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3.19
extractable
substance (3.39) that is released from a *medical device* (3.28) or *material* (3.27) when the medical device or material is extracted using laboratory extraction conditions and vehicles

[SOURCE: ISO 10993-18:2020, 3.16, modified — 'of construction' has been removed from the definition.]

3.20
finished medical device
medical device (3.28) that is in the state in which it is intended to be used, following all manufacturing processes such as packaging, storage and sterilisation

3.21
implant
medical device (3.28) or component thereof, that is intended to be introduced into the human body or to replace an epithelial surface or the surface of the eye, by means of surgical intervention and that is intended to remain in place after the procedure

Note 1 to entry: The duration of an implant remaining in the body is dependent on the clinical need.

3.22
indirect contact
medical device (3.28) or component thereof, having no physical contact with *tissue* (3.40), through which a fluid (liquid or gas), semi-solid or solid passes prior to contacting tissue

3.23
intended use
intended purpose
use for which a *medical device* (3.28) is intended according to the specifications, instructions and information provided by the *manufacturer* (3.26)

Note 1 to entry: The intended medical indication, patient population, part of the body or type of *tissue* (3.40) interacted with, *user* (3.43) profile, use environment, and operating principle are typical elements of the intended use.

[SOURCE: ISO 14971:2019, 3.6, modified — "product, process or service" has been replaced with "*medical device*" in the definition.]

3.24
leachable
substance (3.39) that is released from a *medical device* (3.28) or *material* (3.27) during its clinical use

[SOURCE: ISO 10993-18:2020, 3.22, modified — Note 1 to entry has been deleted.]

3.25
life cycle
series of all phases in the life of a *medical device* (3.28), from the initial conception to final decommissioning and disposal

Note 1 to entry: Terms for phases within the life cycle can include shelf life, service life, use life, lifetime or similar terms.

[SOURCE: ISO 14971:2019, 3.8, modified — Note 1 to entry has been added.]

3.26
manufacturer
natural or legal person with responsibility for the design or manufacture of a *medical device* (3.28) with the intention of making the medical device available for use, under their name, whether or not such a medical device is designed or manufactured by that person themselves or on their behalf by another person(s)

[SOURCE: ISO 14971:2019, 3.9, modified — "his" has been changed to "their" and "himself" has been changed to "themselves" in the definition, and Notes 1, 2, 3, 4, 5, 6 and 7 to entry have been deleted.]

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3.27
material
synthetic or natural *substance* (3.39), including polymer, metal or alloy, ceramic, composite, *tissue* (3.40), used as a *medical device* (3.28) or any part thereof

3.28
medical device
instrument, apparatus, implement, machine, appliance, *implant* (3.21), reagent for in vitro use, software, *material* (3.27) or other similar or related article, intended by the *manufacturer* (3.26) 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 a *medical device* (3.28),

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

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

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

— disinfection *substances* (3.39);

— aids for persons with disabilities;

— devices incorporating animal or human *tissues* (3.40);

— devices for in vitro fertilization or assisted reproduction technologies.

[SOURCE: ISO/IEC Guide 63:2019, 3.7, modified — “and/or” has been replace with ""or” in Note 1 to entry.]

3.29
medical device family
group of *medical devices* (3.28) manufactured by or for the same organization and having the same basic design, *materials* (3.27), manufacturing process and performance characteristics related to safety, *intended use* (3.23) and function

[SOURCE: ISO 13485:2016, 3.12, modified — “materials and manufacturing process” has been added to the definition.]

3.30
nanomaterial
material (3.27) with any external dimension in the nanoscale or having internal structure or surface structure in the nanoscale, where nanoscale is in the range of approximately 1 nm to 100 nm

[SOURCE: ISO/TR 10993-22:2017, 3.7, modified — “where nanoscale is in the range of approximately 1 nm to 100 nm” has been added to the definition and Notes 1, 2 and 3 to entry have been deleted.]

3.31
non-contacting
indicates that a *medical device* (3.28) or component thereof, has neither *direct contact* (3.18) nor *indirect contact* (3.22) with *tissue* (3.40)

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3.32
novel material
material (3.27) that has not previously been used in a *medical device* (3.28) for which *biological safety* (3.11) has been established relevant to the *intended use* (3.23)

3.33
physical and chemical information
knowledge regarding a *finished medical device* (3.20) or *material* (3.27) including the geometric, chemical and physical properties and the identity of the supplier of a material or component

3.34
reasonably foreseeable misuse
use of a *medical device* (3.28) in a way not intended by the *manufacturer* (3.26), but which can result from readily predictable human behaviour

Note 1 to entry: Readily predictable human behaviour includes the behaviour of all types of *users* (3.43), e.g. lay and professional users.

Note 2 to entry: Reasonably foreseeable misuse can be intentional or unintentional.

[SOURCE: ISO 14971:2019, 3.15, modified — "product or system" has been replaced with "medical device in the definition".]

3.35
residual biological risk
biological risk (3.8) remaining after risk control measures have been implemented

[SOURCE: ISO 14971:2019, 3.17, modified — "biological" has been added before "risk" in the term and in the definition.]

3.36
risk estimation
process used to assign values to the probability of occurrence of harm and the severity of that harm

[SOURCE: ISO 14971:2019, 3.22]

3.37
risk management
systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring *biological risk* (3.8)

[SOURCE: ISO 14971:2019, 3.24, modified — "biological" has been added before "risk" in the definition.]

3.38
sensitive population
persons who are more susceptible to *biological harm* (3.6) due to exposure to hazardous *substances* (3.39) than the average, healthy person

Note 1 to entry: These populations can include persons who are: young infants, very elderly, chronically ill, immunocompromised, pregnant women or women of childbearing age.

3.39
substance
single chemical element or compound, or a complex structure of compounds

[SOURCE: ISO 10993-9:2019, 3.5]

3.40
tissue
organization of cells or extra-cellular components

Note 1 to entry: This can include epithelial tissue, muscle tissue, nervous tissue and connective tissue (including adipose, blood, bone, cartilage, and lymphatic tissue).

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[SOURCE: ISO 22442-1:2020, 3.9, modified — "and/or" has been changed to "or", "constituents" has been changed to "components" in the definition and Note 1 to entry has been added.]

3.41
total exposure period
number of *contact days* (3.16) from the first to the last use of a *medical device* (3.28)

3.42
toxicity
capability of a *constituent* (3.15) to cause a *biological harm* (3.6) under specified conditions of exposure or dose

3.43
user
person who comes into contact [including *indirect contact* (3.22)] with a *medical device* (3.28) during its use, including patients or persons who are required to operate or handle the medical device during its use

4 General principles

4.1 Biological evaluation within the ISO 14971 risk management framework

The biological evaluation (biocompatibility evaluation) of a medical device shall be conducted within a risk management process in accordance with ISO 14971 (see Figure 1), which involves the identification of biological hazards, the estimation of the associated biological risks and the determination of their acceptability (see Clause 6 and Clause 7).

The biological evaluation shall be planned (see Clause 5), conducted and reported by competent personnel, capable of making informed decisions based upon scientific data and a knowledge of relevant medical devices. Competence shall be demonstrated and documented on the basis of education, training, skills and experience (see Clause 9).

NOTE 1 Biological evaluation tasks can be performed by representatives of several functions or organizations, each contributing their specialist knowledge and competence.

To understand the relationship between ISO 14971 and the ISO 10993 series, it is useful to apply the risk management terminology of ISO 14971 as follows:

— Biological hazards can arise from the presence of constituents which are in or on the medical device, or from physical characteristics of the medical device.

— A biologically hazardous situation arises when direct contact or indirect contact with a medical device causes exposure to a hazardous constituent or physical characteristic.

— The biologically hazardous situation can lead to a biological harm.

— The biological risk is the combination of the probability of occurrence and severity of the adverse biological effect resulting from exposure to the hazardous constituent or physical characteristic.

The following summarizes the application of the ISO 14971 risk management principles to the evaluation of biological safety.

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