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Biological evaluation of medical devices —

Part 1:
Evaluation and testing within a risk management system

Évaluation biologique des dispositifs médicaux —

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

[Revision of third edition (ISO 10993-1:2003)]

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Contents

Page

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.

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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.

ISO 10993-1 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*, and by Technical Committee CEN/TC 206, *Biological evaluation of medical devices* in collaboration.

This third edition cancels and replaces the second edition (EN ISO 10993-1:2003), which has been technically revised.

ISO 10993 consists of the following parts, under the general title *Biological evaluation of medical devices*:

— *Part 1: Evaluation and testing within a risk management system*

— *Part 2: Animal welfare requirements*

— *Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity*

— *Part 4: Selection of tests for interactions with blood*

— *Part 5: Tests for in vitro cytotoxicity*

— *Part 6: Tests for local effects after implantation*

— *Part 7: Ethylene oxide sterilization residuals*

— *Part 9: Framework for the identification and quantification of potential degradation products*

— *Part 10: Tests for irritation and delayed-type hypersensitivity*

— *Part 11: Tests for systemic toxicity*

— *Part 12: Sample preparation and reference materials*

— *Part 13: Identification and quantification of degradation products from polymeric medical devices*

— *Part 14: Identification and quantification of degradation products from ceramics*

— *Part 15: Identification and quantification of degradation products from metals and alloys*

— *Part 16: Toxicokinetic study design for degradation products and leachables*

— *Part 17: Method for the establishment of allowable limits for leachable substances*

— *Part 18: Chemical characterization of materials*

— *Part 19: Physico-chemical, morphological and topographical characterization of materials*

— *Part 20: Principles and methods for immunotoxicology testing of medical devices*

Future parts will deal with other relevant aspects of biological testing.

Annexes A and B are for information only.

Introduction

The primary aim of this part of ISO 10993 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 be the guidance document for 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 does, at one extreme, consist of a single material, which may exist in more than one physical form, and at the other extreme, of a complex instrument or piece of apparatus, consisting of numerous components made of more than one material.

This international standard addresses the determination of the effects of medical devices on tissues, mostly in a general way, rather than in a specific device-type situation. Thus, for a complete biological safety evaluation, it classifies medical devices according to the nature and duration of their anticipated contact with human tissues when in use and indicates, in matrices, the biological data sets that are thought to be relevant in the consideration of each device category.

The range of biological hazards is wide and complex. The tissue interaction with 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 tissue interaction might result in a less functional device, tissue interaction 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.

Tissue interactions that are regarded as adverse caused by a material in one application might not be regarded so 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 adjudged only with caution, as it cannot be unequivocally concluded that the same tissue reactions 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 part of ISO 10993 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 tissue responses, minimizes the number and exposure of test animals by giving preference to chemical constituent 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 international standard will 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.

This part of ISO 10993 is intended for use by professionals, appropriately qualified by training and experience, who are able to interpret its requirements and judge the outcomes of the evaluation for each medical device, 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.

Annex A contains an informative table which is generally helpful in identifying biological data sets recommended in the evaluation of medical devices, according to their category of body contact and duration of clinical exposure. 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 system

1 Scope

This part of ISO 10993 describes:

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

— 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 analyze the biological safety of the medical device;

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

This part of ISO 10993 does not cover testing of materials and devices that do not come into direct or indirect contact with the patient's body, nor does it cover biological hazards arising from any mechanical failure. Other parts of ISO 10993 cover specific tests as indicated in the foreword.

2 Normative references

The following documents are indispensable for the application 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 delayed–type hypersensitivity*

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 device*

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 14971, *Medical Devices — Application of risk management to medical devices*

3 Terms and definitions

For the purposes of this part of ISO 10993, the following terms and definitions apply.

3.1
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 This definition has been developed by the Global Harmonization Task Force (GHTF). See bibliographic reference [5]. [ISO 13485:2003, definition 3.7]

NOTE 2 Products, which may 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 (see Note 4),

4) disinfection substances,

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

NOTE 3 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 subject to this international standard.

NOTE 4 Medical devices are different from drugs/biologics, and their biological evaluation requires a different approach.

NOTE 5 Medical devices may include dental devices.

3.2
material
any synthetic or natural polymer, metal, alloy, ceramic, or other nonviable substance, including tissue rendered nonviable, used as a medical device or any part thereof

3.3
final product
medical device in its "as-used" state, as defined by the manufacturer's specification or labelling

3.4
chemical constituent
any synthetic or natural substance that is used in a process for manufacturing materials and/or medical devices, such as additives (antioxidants, UV stabilizers, dyestuff, etc.), processing aids (solvents, lubricants, antifoaming agents, etc.)

3.5
data set
information from a variety of sources necessary to characterise the biological response of a device.

4 General principles applying to biological evaluation of medical devices

4.1 The selection and evaluation of any material or medical device intended for use in humans shall form part of a structured biological evaluation programme, as set out in Figure 1, within a risk management process. Annex B, which is based on ISO 14971, provides guidance on this process. The biological evaluation shall be planned, carried out, and documented by knowledgeable and experienced individuals.

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

The evaluation programme shall include documented informed decisions that assess the advantages/disadvantages and relevance of:

a) the physical and chemical characteristics of the various candidate materials;

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

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

d) test procedures.

Evaluation may 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.

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

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

a) the material(s) of manufacture;

b) intended additives, process contaminants and residues (see ISO 10993-7 for ethylene oxide residues);

c) leachable substances (see ISO 10993-17);

d) degradation products (see ISO10993-9, -13, -14 and -15 for degradation products from polymers, ceramics, and metals, respectively);

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

f) the performance and characteristics of the final product;

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

Identification and quantification of extractable chemical constituents shall precede any biological testing as specified in ISO 10993-18.

4.4 The choice of tests and the data required in a biological evaluation, and their interpretation, shall take into account the chemical composition of the materials, including the conditions of exposure as well as the nature, degree, frequency and duration of exposure of the medical device or its constituents to the body, enabling the categorization of devices to facilitate the selection of appropriate tests (see clause 5). The rigour necessary in the biological evaluation is principally determined by the nature, degree, duration and frequency of the exposure and the hazards identified for the material.

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

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

4.6 Selection of any in vitro or in vivo tests shall be based on end-use applications. All tests shall be conducted according to recognized current/valid best laboratory/quality practices, for example GLP or ISO 17025, where applicable, and the data shall be evaluated by competent, informed persons.