INTERNATIONAL STANDARD

ISO 10993-1

Fourth edition
2009-10-15

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 10993-1:2009(E)

ISO copyright office
Case postale 56 • CH-1211 Geneva 20
Tel. + 41 22 749 01 11
Fax + 41 22 749 09 47
E-mail copyright@iso.org
Web www.iso.org

Published in Switzerland

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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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*.

This fourth edition cancels and replaces the third edition (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 process*

— *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 identification and quantification of potential degradation products*

— *Part 10: Tests for irritation and skin sensitization*

— *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: Establishment of allowable limits for leachable substances*

— *Part 18: Chemical characterization of materials*

— *Part 19: Physico-chemical, morphological and topographical characterization of materials* (Technical Specification)

— *Part 20: Principles and methods for immunotoxicology testing of medical devices* (Technical Specification)

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

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 a 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, at one extreme, consists 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.

ISO 10993 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 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 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 ISO 10993 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 outcome 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 that 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 process

1 Scope

This part of ISO 10993 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 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 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 10993-18:2005, *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 document, 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).

[ISO 13485:2003, definition 3.7]

NOTE 2 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 (see Note 4);

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.

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 ISO 10993.

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

NOTE 5 Medical devices can include dental devices.

3.2
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

3.3
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 characterize the biological response of a device

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 set out in Figure 1. Annex B provides guidance on this process. The biological evaluation shall be planned, carried out, and documented by knowledgeable and experienced professionals. See Annex C for how to perform a literature review of existing data.

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 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;

NOTE Where this information is already documented within the risk management for the device it can be included by reference.

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 ISO 10993-9, for general principles and 10993-13, 10993-14 and 10993-15 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 of material chemical constituents and consideration of chemical characterization (see ISO 10993-18) shall precede any biological testing (see Figure 1).

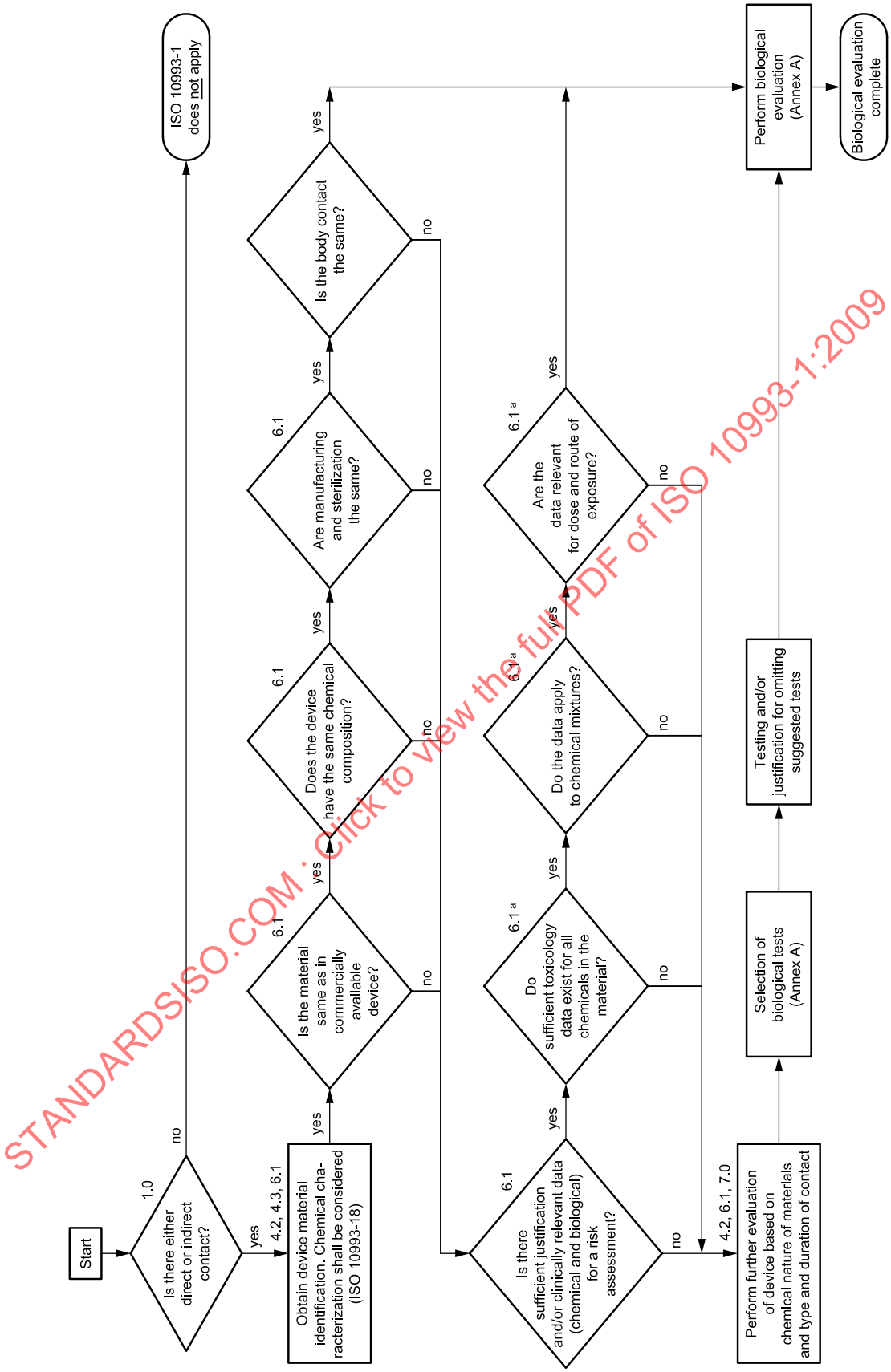
Physical effects of the device shall be considered if they impact the biocompatibility (see ISO/TS 10993-19).

For implanted devices, in addition to systemic effects, local effects should also be considered for risk evaluation.

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 hazards, 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 subchronic and chronic toxic effects, sensitization, allergy, genotoxicity, carcinogenicity (tumorigenicity) and effects on reproduction including teratogenicity.



[a] This process only applies to those medical devices that contact the patient's body directly or indirectly.

Figure 1 — Summary of the systematic approach to a biological evaluation of medical devices as part of a risk management process

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 recognised current/valid best laboratory/quality practices, for example Good Laboratory Practice (GLP) or ISO/IEC 17025, where applicable, and the data shall be evaluated by competent, informed professionals.

In vitro test methods, which are appropriately validated, reasonably and practically available, reliable and reproducible shall be considered for use in preference to *in vivo* tests. Whenever possible, *in vitro* screening shall be carried out before *in vivo* tests are commenced. Test data, complete to the extent that an independent analysis could be made, shall be retained.

4.7 The materials or final product shall be re-evaluated if any of the following occurs:

a) any change in the source or in the specification of the materials used in the manufacture of the product;

b) any change in the formulation, processing, primary packaging or sterilization of the product;

c) any change in the manufacturer's instructions or expectations concerning storage, e.g. changes in shelf life and/or transport;

d) any change in the intended use of the product;

e) any evidence that the product may produce adverse effects when used in humans.

4.8 The biological evaluation shall take into account the nature and mobility of the chemical constituents in the materials used to manufacture the device and other information, other non-clinical tests, clinical studies, and post-market experience for an overall assessment.

5 Categorization of medical devices

5.1 General

Medical devices shall be categorized according to the nature and duration of body contact as described in 5.2 and 5.3. The categorization of medical devices facilitates identification of appropriate data sets (see Annex A).

The evaluation of any device that does not fall into one of the categories described shall follow the general principles contained in this part of ISO 10993. Certain devices might fall into more than one category, in which case evaluation appropriate to each category shall be carried out.

5.2 Categorization by nature of body contact

5.2.1 Surface-contacting devices

These include medical devices in contact with the following.

a) Skin

— devices that contact intact skin surfaces only.

EXAMPLES Electrodes, external prostheses, fixation tapes, compression bandages and monitors of various types.

b) Mucosal membranes

— devices that contact intact mucosal membranes.

EXAMPLES Contact lenses, urinary catheters, intravaginal and intra-intestinal devices (stomach tubes, sigmoidoscopes, colonoscopes, gastroscopes), endotracheal tubes, bronchoscopes, some dental prostheses and orthodontic devices.

c) Breached or compromised surfaces

— devices that contact breached or otherwise compromised body surfaces.

EXAMPLES Dressings or healing devices and occlusive patches, for ulcers, burns and granulation tissue.

5.2.2 External communicating devices

External communicating devices shall be categorized according to their contact with the following application sites:

a) Blood path, indirect

— devices that contact the blood path at one point and serve as a conduit for entry into the vascular system.

EXAMPLES Solution administration sets, extension sets, transfer sets and blood administration sets.

b) Tissue/bone/dentin

— devices that contact tissue, bone or pulp/dentin systems.

EXAMPLES Laparoscopes, arthroscopes, draining systems, dental cements, dental filling materials and skin staples.

c) Circulating blood

— devices that contact circulating blood.

EXAMPLES Intravascular catheters, temporary pacemaker electrodes, oxygenators, extracorporal oxygenator tubing and accessories, dialysers, dialysis tubing and accessories, haemoadsorbents and immunoadsorbents.

5.2.3 Implant devices

Implant devices shall be categorized according to their contact with the following application sites:

a) Tissue/bone

— devices principally contacting bone.

EXAMPLES Orthopaedic pins, plates, replacement joints, bone prostheses, bone cements and intra-osseous devices.

— devices principally contacting tissue and tissue fluid.

EXAMPLES Pacemakers, drug supply devices, neuromuscular sensors and simulators, replacement tendons, breast implants, artificial larynxes, subperiosteal implants, ligation clips and intra-uterine devices.

b) Blood

— devices principally contacting blood.

EXAMPLES Pacemaker electrodes, artificial arteriovenous fistulae, heart valves, vascular grafts, internal drug-delivery catheters and ventricular assist devices.

5.3 Categorization by duration of contact

Medical devices shall be categorized according to the anticipated duration of contact as follows.

a) Limited exposure (A) – devices whose cumulative single, multiple or repeated use or contact is up to 24 h.

b) Prolonged exposure (B) – devices whose cumulative single, multiple or repeated long-term use or contact is likely to exceed 24 h but not 30 d.

c) Permanent contact (C) – devices whose cumulative single, multiple or repeated long-term use or contact exceeds 30 d.

If a material or device can be placed in more than one duration category, the more rigorous testing and/or evaluation considerations shall apply. With multiple exposures to the device, the decision into which category a device is placed shall take into account the potential cumulative effect, bearing in mind the period of time over which these exposures occur. If a device is intended to change during its lifetime, as those that are polymerized and/or biodegraded *in situ*, separate evaluations shall be conducted for the different device states. For example, for a biodegradable glue intended to polymerize *in situ*, the different device states would include starting components, intermediate reaction products, the fully polymerized material and degradation products.

6 Biological evaluation process

6.1 Material characterization

Material characterization is a crucial first step in the biological evaluation process. The extent of chemical characterization required depends on what pre-clinical and clinical safety and toxicological data exist, and on the nature and duration of body contact with the medical device; but, as a minimum, the characterization shall address the constituent chemicals of the device and possible residual process aids or additives used in its manufacture. Material characterization is described in ISO 10993-18 and ISO/TS 10993-19.

Figure 1 indicates how the different steps in the chemical characterization process link to the overall biological evaluation decision points.

If the combination of all materials, chemicals and processes has an established history of safe use in the intended application, then further characterization and biological evaluation might not be necessary.

The identity and quantity of novel materials and chemicals present should be established or measured.

For device extractables and leachables that have known toxicological data relevant to the intended dose and for which route and frequency of exposure that indicate adequate safety margins exist, the need for further testing is likely to be minimal or non-existent. For devices that have known leachable chemical mixtures, potential synergies of the leachable chemicals should be considered.

The results of the risk assessment can lead to the conclusion that additional material characterization is necessary, for example, where the margin of safety is not considered adequate if the entire amount of a particular chemical were to leach out. In such cases, appropriate extraction testing, simulating clinical exposure, can be used to estimate the degree of clinical exposure to the chemical constituent. The acceptability of the level of leachables shall be established in accordance with ISO 10993-17.

Where the potential for degradation exists under the conditions of manufacture, sterilization, transport, storage, and use of the device, the presence and nature of degradation products shall be characterized in accordance with ISO 10993-9, ISO 10993-13, ISO 10993-14, and ISO 10993-15.

6.2 Biological evaluation tests

6.2.1 General

Assess all reasonably and practicably available information and compare to the data set(s) needed to assess the biological safety of the device (see Annex A and Clause 4). Identify any additional data or testing needed to complete the data sets required to perform the risk assessment.

ISO 10993-2 applies to any *in vivo* testing being considered. Additional *in vivo* testing shall not be carried out where:

1) results are available from relevant studies that have been carried out previously

or

2) the existing pre-clinical and clinical data, including history of safe use, meet the requirements of biological evaluation and therefore further animal testing would be unethical. In assessing the relevance of data, on prior use of a material, to the biological evaluation, the level of confidence in the historical data should be taken into account. ISO 10993-18:2005, Annex C, gives some informative principles for judging toxicological equivalence.

In addition to the general principles given in Clause 4, the following shall apply when biological testing of medical devices is considered necessary as part of the overall risk management process.

a) Testing shall be performed on the sterile final product, or representative samples from the final product or materials processed in the same manner as the final product (including sterilization).

b) The choice of test procedures shall take into account:

1) the nature, degree, duration, frequency and conditions of exposure to or contact of humans with the device in the normal intended use;

2) the chemical and physical nature of the final product;

3) the toxicological activity of the chemicals in the formulation of the final product;

4) that certain tests (e.g. those designed to assess systemic effects) might not be applicable where the presence of leachable chemicals has been excluded, or where chemicals have a known and acceptable toxicity profile, allowing the safe use by evaluation in accordance with ISO 10993-17 and risk assessment in accordance with ISO 14971;

5) the relationship of device surface area to recipient body size;

6) the existing information based on the literature, previous experience and non-clinical tests;

7) the sensitivity and specificity of the test being considered in relation to the relevant biological evaluation data set;

8) that the protection of humans is the primary goal of this part of ISO 10993; a secondary goal is to ensure animal welfare and to minimize the number and exposure of the test animals.

c) If extracts of the devices are prepared, the solvents and conditions of extraction used should be appropriate to the nature and use of the final product, as well as to the predictability (such as test purpose, rationale, sensitivity, specificity, etc.) of the test method (see ISO 10993-12).

d) Positive and negative controls should be used where appropriate.

The test methods used in the biological evaluation tests shall be sensitive, precise and accurate. All tests shall be conducted in compliance with current/valid best laboratory/quality practices, for example GLP or ISO/IEC 17025, where applicable.

The test results should be reproducible (intralaboratory) as well as repeatable (interlaboratory) and robust.

6.2.2 Test descriptions

6.2.2.1 General

The evaluation tests described in 6.2.2.2 to 6.2.2.15 shall be considered and carried out where necessary to complete the data sets needed for the biological evaluation of the particular medical device. Where the existing data are adequate, additional testing is not required (see Annex A).

Due to the diversity of medical devices, it is recognised that not all tests identified in a category will be necessary or practicable (see ISO 14971) for a given device. It is indispensable for testing that each device be considered on its own merits.

Additional tests not indicated in the table may be necessary (e.g. bio-degradation and toxicokinetics).

6.2.2.2 Cytotoxicity

Cytotoxicity tests employing cell culture techniques shall be used to determine the lysis of cells (cell death), the inhibition of cell growth, colony formation, and other effects on cells caused by medical devices, materials and/or their extracts (see ISO 10993-5).

6.2.2.3 Delayed-type hypersensitivity

Hypersensitivity tests shall be used to estimate the potential for contact sensitization by medical devices, materials and/or their extracts, using an appropriate animal model (see ISO 10993-10).

These tests are important because exposure or contact to even minute amounts of potential leachables can result in allergic or sensitization reactions.

6.2.2.4 Irritation (including intracutaneous reactivity)

Irritation tests shall be used to estimate the irritation potential of medical devices, materials and/or their extracts, using an appropriate site for application such as skin, eye and mucous membrane in a suitable model. The test(s) performed shall be appropriate for the route (skin, eye, mucosa) and duration of exposure or contact (see ISO 10993-10).

The intracutaneous reactivity test shall be used to assess the localized reaction of tissue to medical device extracts. This test is applicable where the determination of irritation by dermal or mucosal tests is inappropriate (e.g. where medical devices are implanted or have blood contact).

This test might also be useful where extractables are hydrophobic (see ISO 10993-10).

6.2.2.5 Systemic toxicity (acute)

Acute systemic toxicity tests shall be used where contact allows potential absorption of toxic leachables and degradation products, to estimate the potential harmful effects of either single or multiple exposures, during a period of less than 24 h, to medical devices, materials and/or their extracts in an animal model (see ISO 10993-11).

Pyrogenicity tests are included to detect material-mediated pyrogenic reactions of extracts of medical devices or materials. No single test can differentiate pyrogenic reactions that are material-mediated from those due to endotoxin contamination.

If feasible, acute systemic toxicity tests may be combined with subacute and subchronic toxicity and implantation test protocols.

6.2.2.6 Subacute and subchronic toxicity

Subacute and subchronic toxicity tests shall be carried out to determine the effects of either single or multiple exposures or contact to medical devices, materials and/or their extracts for a period not less than 24 h to a period not greater than 10 % of the total life-span of the test animal (e.g. up to 13 weeks in rats).

These tests shall be waived if available data for the chronic toxicity of the relevant materials are sufficient to allow the subacute and subchronic toxicity to be evaluated. The reason for waiving of the tests shall be included in the overall biological evaluation report. These tests shall be appropriate for the route and duration of contact.

Subacute and subchronic toxicity tests are given in ISO 10993-11.

If feasible, subacute and subchronic systemic toxicity test protocols may be expanded to include implantation test protocols to evaluate subacute and subchronic systemic and local effects.

6.2.2.7 Genotoxicity

A battery of *in vitro* genotoxicity tests employing mammalian or non-mammalian cell culture or other techniques shall be used to determine gene mutations, changes in chromosome structure and number, and other DNA or gene toxicities caused by medical devices, materials and/or their extracts.

If any of the *in vitro* tests are positive, either *in vivo* mutagenicity tests shall be performed or the presumption shall be made that the material is mutagenic (see ISO 10993-3).

6.2.2.8 Implantation

Implantation tests shall be used to assess the local pathological effects on living tissue, at both the gross level and microscopic level, of a sample of a material or final product that is surgically implanted or placed in an implant site or tissue appropriate to the intended application (e.g. special dental usage tests). These tests shall be appropriate for the route and duration of contact.

If feasible, implantation test protocols may be expanded to evaluate both local and systemic effects to meet acute, subacute, subchronic, and chronic toxicity testing requirements (see ISO 10993-6).

6.2.2.9 Haemocompatibility

Haemocompatibility tests shall be used to evaluate, using an appropriate model or system, the effects of blood-contacting medical devices or materials on blood or blood components.

One haemocompatibility test, haemolysis, determines the degree of red cell lysis and the release of haemoglobin caused by medical devices, materials, and/or their extracts *in vitro*.

Other specific haemocompatibility tests may also be designed to simulate the geometry, contact conditions and flow dynamics of the device or material during clinical applications and determine blood/material/device interactions (see ISO 10993-4).

6.2.2.10 Chronic toxicity

Chronic toxicity tests shall be used to determine the effects of either single or multiple exposures to medical devices, materials and/or their extracts during a major period of the life-span of the test animal (e.g. usually 6 months in rats). These tests shall be appropriate for the route and duration of exposure or contact (see ISO 10993-11).

If feasible, chronic systemic toxicity test protocol may be expanded to include an implantation test protocol to evaluate both chronic systemic and local effects.

6.2.2.11 Carcinogenicity

If there is no information from other sources, testing the potential carcinogenicity of the material/device shall be considered. However, it is rare for carcinogenicity tests to be considered appropriate for medical devices (see ISO 10993-3). Carcinogenicity tests shall be used to determine the tumorigenic potential of medical devices, materials and/or their extracts from either single or multiple exposures or contacts over a period of the major portion of life-span of the test animal. Carcinogenicity tests should be appropriate for the route and duration of exposure or contact; lifetime studies or transgenic models may be appropriate. These tests may be designed to examine both chronic toxicity and tumorigenicity in a single experimental study.

6.2.2.12 Reproductive and developmental toxicity

Reproductive and developmental toxicity tests shall be used to evaluate the potential effects of medical devices, materials and/or their extracts on reproductive function, embryonic development (teratogenicity), and prenatal and early postnatal development. Reproductive/developmental toxicity tests or bio-assays shall only be conducted when the device has potential impact on the reproductive potential of the subject. In addition, such tests should be considered for devices/materials used during pregnancy. The application site of the device is the primary criterion when considering carrying out the tests. Reproductive and developmental toxicity tests are described in ISO 10993-3.

6.2.2.13 Biodegradation

Biodegradation tests shall be considered if

a) the device is designed to be biodegradable

or

b) the device is intended to be implanted for longer than 30 d

or

c) an informed consideration of the material(s) system indicates that toxic substances might be released during body contact.

Parameters that affect the rate of degradation shall be described and documented.

The mechanisms of biodegradation should be described. These mechanisms should be simulated *in vitro* to determine the rates of degradation and release of potentially toxic chemicals to estimate the exposure. *In vivo* tests may be required to assess biodegradation of a material.

Biodegradation tests might not be necessary if the probable products of degradation are in the predicted quantities, and produced at a rate similar to those that have a history of safe clinical use; and/or if particulate, they are present in a physical state, i.e. size distribution and shape, similar to those with a history of safe clinical use or sufficient degradation data relevant to the substances and degradation products in the intended use already exists.

A general framework for biodegradation tests is given in ISO 10993-9.

Specific *in vitro* biodegradation tests for polymers, ceramics and metals are described in ISO 10993-13, ISO 10993-14 and ISO 10993-15 respectively.

6.2.2.14 Toxicokinetic studies

The purpose of conducting toxicokinetic studies is to evaluate the absorption, distribution, metabolism and excretion (ADME) of a chemical that is known to be toxic or whose toxicity is unknown. These studies will also serve to determine the delivered dose to the target organ(s) in order to assess any health hazards using the physiologically based pharmacokinetic (PBPK) modelling. The extrapolation of test results across gender, age, species and doses/exposure may be possible, but requires critical expert judgement to be exercised and explained.

The need for *in vivo* toxicokinetic studies, to determine the processes of absorption, distribution, metabolism and elimination of leachables and degradation products of medical devices, materials and/or their extracts (see 6.2.2.13 and ISO 10993-16), shall be considered in the light of results from the *in vitro* biodegradation studies.

When deciding whether or not to conduct toxicokinetic studies as part of the biological evaluation of a medical device, the final product and its chemical constituents, including potential and designed degradation products and leachables in combination with the intended use of the device, shall all be taken into account (see 6.2.2.13).

Where appropriate, theoretical degradation processes shall be investigated prior to toxicokinetic studies by means of *in vitro* experiments (e.g. tissue, homogenates or cells), not only for animal welfare reasons as given in ISO 10993-2, but also to determine probable rather than possible degradation products.

Toxicokinetic studies shall be considered if

a) the device is designed to be bioresorbable

or

b) the device is a permanent contact implant, and biodegradation or significant corrosion is known or likely, and/or migration of leachables from the device occurs

or

c) substantial quantities of potentially toxic or reactive degradation products and leachables are likely or known to be released from a medical device into the body during clinical use.

Toxicokinetic studies are not required if the achieved or expected rates of release of degradation products and leachables from a particular device or material have been judged to provide safe levels of clinical exposure following reference to significant historical experience, or if sufficient toxicological data or toxicokinetic data relevant to the degradation products and leachables already exist.

The release of leachables and degradation products from metals, alloys and ceramics is usually too low to justify toxicokinetic studies, unless the material is designed to biodegrade.

Toxicokinetic study design for degradation products and leachables is given in ISO 10993-16.

6.2.2.15 Immunotoxicology

ISO/TS 10993-20 provides an overview of immunotoxicology with particular reference to the potential immunotoxicity of medical devices. Immunotoxicity testing shall be considered based on the chemical nature of the materials of manufacture and data from sources that are suggestive of immunotoxicological effects or if the immunogenic potential of any of the chemicals is unknown.

7 Interpretation of biological evaluation data and overall biological safety assessment

Expert assessors who have the necessary knowledge and experience shall determine and document:

a) the strategy and programme content for the biological evaluation of the medical device;

b) the criteria for determining the acceptability of the material for the intended purpose, in line with the risk management plan;

c) the adequacy of the material characterization;

d) the rationale for selection and/or waiving of tests;

e) the interpretation of existing data and results of testing;

f) the need for any additional data to complete the biological evaluation;

g) overall biological safety conclusions for the medical device.

Annex A gives the general evaluation tests that should be considered for each device and duration category.

Due to the diversity of medical devices, it is recognised that not all tests identified in a category will be necessary or practical for any given device. It is indispensable for testing that each device be considered on its own merits.

Annex A
(informative)

Biological evaluation tests

Table A.1 is a framework for the development of an assessment programme and is not a checklist (see Clause 6). For particular medical devices, different sets of tests may be necessary, including either more or less testing than is indicated in the Table A.1. In addition to the framework set out in Table A.1, the following should be considered based on a risk assessment, which considers the specific nature and duration of exposure: chronic toxicity, carcinogenicity, biodegradation, toxicokinetics, immunotoxicity, reproductive/developmental toxicity or other organ-specific toxicities.

Table A.1 — Evaluation tests for consideration

Medical device categorization by			**Biological effect**							
nature of body contact (see 5.2) **Category**	**Contact**	**contact duration** (see 5.3) **A – limited** (⩽ 24 h) **B – prolonged** (> 24 h to 30 d) **C – permanent** (> 30 d)	**Cytotoxicity**	**Sensitization**	**Irritation or intracutaneous reactivity**	**Systemic toxicity** (acute)	**Subchronic toxicity** (subacute toxicity)	**Genotoxicity**	**Implantation**	**Haemocompatibility**
Surface device	Skin	A	X [a]	X	X					
		B	X	X	X					
		C	X	X	X					
	Mucosal membrane	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
	Breached or compromised surface	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
External communicating device	Blood path, indirect	A	X	X	X	X				X
		B	X	X	X	X				X
		C	X	X		X	X	X		X
	Tissue/bone/dentin	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Circulating blood	A	X	X	X	X				X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X
Implant device	Tissue/bone	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Blood	A	X	X	X	X	X		X	X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X

[a] The crosses indicate data endpoints that can be necessary for a biological safety evaluation, based on a risk analysis. Where existing data are adequate, additional testing is not required.

Annex B
(informative)

Guidance on the risk management process

B.1 General

This annex describes a continuous process by which a manufacturer can identify the biological hazards associated with medical devices, estimate and evaluate the risks, control these risks, and monitor the effectiveness of the control.

B.2 Risk management process

B.2.1 General

Table A.1 should be used in the performance of a biological risk assessment to identify areas of concern to be addressed by literature review, clinical experience and testing. The risks posed by the identified biological hazards should be evaluated. The evaluation of the biological safety of a medical device should be a strategy planned on a case-by-case basis to identify the hazards and better estimate the risks of known hazards. Testing strategy should include a rationale for the selection and/or the waiving of tests. The rationale should be a clear, concise, logical and scientifically reasoned plan for evaluating biological safety that demonstrates that all biological hazards have been considered and relevant risks assessed and controlled.

Based on the risk management process described in ISO 14971, the biological evaluation of medical devices and their materials comprises the following elements.

B.2.2 Risk analysis

B.2.2.1 Intended use/device characteristics

a) Define each material/device and its use, and its reasonably foreseeable misuse.

b) Physically and chemically characterize each material/device.

B.2.2.2 Biological hazard identification

a) Identify hazards in the materials, additives, processing aids, and other potential leachables.

b) Characterization of chemically-mediated hazards:

- toxicology data on component materials;
- dose-response relationship;
- nature of toxicity.

c) Characterization of non-chemically-mediated hazards.