194

INTERNATIONAL STANDARD

ISO 10993-1

First edition
1992-04-15

Biological evaluation of medical devices —

Part 1:
Guidance on selection of tests

Essais biologiques des dispositifs médicaux —
Partie 1: Lignes directrices pour le choix des essais

Reference number
ISO 10993-1:1992(E)

Contents

International Organization for Standardization
Case Postale 56 • CH-1211 Genève 20 • Switzerland

Printed in Switzerland

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.

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.

International Standard ISO 10993-1 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices* .

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

— *Part 1: Guidance on selection of tests*

— *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 cytotoxicity: in vitro methods*

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

— *Part 7: Ethylene oxide sterilization residuals*

— *Part 8: Clinical investigation*

— *Part 9: Degradation of materials related to biological testing*

— *Part 10: Tests for irritation and sensitization*

— *Part 11: Tests for systemic toxicity*

— *Part 12: Sample preparation and reference materials*

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

This part of ISO 10993 is a combination/harmonization of numerous International and national Standards and guidelines. It is intended to be

the overall guidance document for the selection of tests enabling evaluation of biological responses relevant to material and device safety.

Annexes A and B of this part of ISO 10993 are for information only.

Introduction

The selection and evaluation of any material or device intended for use in humans requires a structured programme of assessment. In the design process, an informed decision should be made that weighs the advantages/disadvantages of the various material and test procedure choices. To give assurance that the final product will perform as intended and be safe for human use, the programme should include a biological evaluation.

The role of this part of ISO 10993 is to serve as a framework in which to plan such a biological evaluation which minimizes the number and exposure of animals. The biological evaluation should be planned and carried out by knowledgeable and experienced individuals capable of making informed decisions based on the advantages and disadvantages of the various materials and test procedures available.

The protection of humans is the primary goal of ISO 10993.

The appropriate selection and interpretation of biological evaluation tests requires an understanding of the rationale behind such testing. An informative rationale for the use of this part of ISO 10993 is provided in annex A. Annex B contains an informative bibliography.

Biological evaluation of medical devices —

Part 1:
Guidance on selection of tests

1 Scope

This part of ISO 10993 gives guidance on

a) the fundamental principles governing the biological evaluation of medical devices;

b) the definition of categories of devices based on the nature and duration of contact with the body;

c) the selection of appropriate tests.

ISO 10993 does not cover testing of materials and devices that do not come into contact with the patient's body directly or indirectly. Nor does it cover biological hazards arising from any mechanical failure. Other parts of ISO 10993 cover specific tests as indicated in the foreword. (See A.2, clause 1 Scope.)

2 Normative references

The following standards contain provisions which, through reference in this text, constitute provisions of this part of ISO 10993. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this part of ISO 10993 are encouraged to investigate the possibility of applying the most recent editions of the standards indicated below. Members of IEC and ISO maintain registers of currently valid International Standards.

ISO 9001:1987, *Quality systems — Model for quality assurance in design/development, production, installation and servicing.*

ISO 9004:1987, *Quality management and quality system elements — Guidelines.*

3 Definitions

For the purposes of ISO 10993, the following definitions apply.

3.1 medical device: Any instrument, apparatus, appliance, material or other article, including software, whether used alone or in combination, intended by the manufacturer to be used for human beings solely or principally for the purpose of:

— diagnosis, prevention, monitoring, treatment or alleviation of disease, injury or handicap;

— investigation, replacement or modification of the anatomy or of a physiological process;

— control of conception;

and which does not achieve its principal 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.

NOTES

1 Devices are different from drugs and their biological evaluation requires a different approach.

2 Use of the term "medical device" includes dental devices.

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

3.3 final product: Medical device in its "as used" state.

4 General principles applying to biological evaluation of materials and devices

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

4.2 The following should be considered for their relevance to the overall biological evaluation of the device:

a) the material(s) of manufacture;

b) intended additives, process contaminants and residues;

c) leachable substances;

d) degradation products;

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

f) the properties and characteristics of the final product.

NOTE 3 If appropriate, identification and quantification of extractable chemical entities of the final product should precede biological evaluation.

4.3 Tests and their interpretation to be used in the biological evaluation should take into account the chemical composition of the materials including the conditions of exposure as well as the nature, degree, frequency and duration of the device or its constituents to the body. By following these principles devices can be categorized to facilitate the selection of appropriate tests. This guide is concerned with the tests to be carried out on materials and/or the final product.

The range of potential hazards is wide and may include:

a) short-term effects (e.g., acute toxicity, irritation to the skin, eye and mucosal surfaces, sensitization, haemolysis and thrombogenicity);

b) long-term or specific toxic effects (e.g., subchronic and chronic toxic effects, sensitization, genotoxicity, carcinogenicity (tumorigenicity) and effects on reproduction including teratogenicity).

4.4 All potential biological hazards should be considered for every material and final product but this does not imply that testing for all potential hazards will be necessary or practical (see clause 7).

4.5 Any *in vitro* or *in vivo* tests shall be based on end-use applications and appropriate good laboratory practice followed by evaluation by competent informed persons. Whenever possible, *in vitro* screening should be carried out before *in vivo* tests are commenced. Test data, complete to the extent that an independent analysis conclusion could be made, should be retained.

4.6 The materials or final product shall be considered (see A.2, subclause 4.6) for biological re-evaluation 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 final product during storage;

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

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

4.7 The biological evaluation performed in accordance with this part of ISO 10993 should be considered in conjunction with the nature and mobility of the ingredients in the materials used to manufacture the device and other information, other non-clinical tests, clinical studies, and post-market experiences for an overall assessment (see A.2, subclause 4.7).

5 Categorization of medical devices

The testing of any device that does not fall into one of the following categories should follow the general principles contained in this part of ISO 10993. Certain devices may fall into more than one category, in which case testing appropriate to each category should be considered.

5.1 Categorization by nature of contact

5.1.1 Non-contact devices

These are devices that do not contact the patient's body directly or indirectly and are not included in ISO 10993.

5.1.2 Surface-contacting devices

These include devices in contact with the following:

a) **skin:** devices that contact intact skin surfaces only; examples include electrodes, external

prostheses, fixation tapes, compression bandages and monitors of various types;

b) **mucosal membranes:** devices communicating with intact mucosal membranes; examples include contact lenses, urinary catheters, intravaginal and intraintestinal devices (stomach tubes, sigmoidoscopes, colonoscopes, gastroscopes), endotracheal tubes, bronchoscopes, dental prostheses, orthodontic devices and IUDs;

c) **breached or compromised surfaces:** devices that contact breached or otherwise compromised body surfaces; examples include ulcer, burn, and granulation tissue dressings or healing devices and occlusive patches.

5.1.3 External communicating devices

These include devices communicating with the following:

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 include solution administration sets, extension sets, transfer sets and blood administration sets;

b) **tissue/bone/dentin communicating:** devices and materials communicating with tissue, bone and pulp/dentin system; examples include laparoscopes, arthroscopes, draining systems, dental cements, dental filling materials and skin staples;

c) **circulating blood:** devices that contact circulating blood; examples include intravascular catheters, temporary pacemaker electrodes, oxygenators, extracorporeal oxygenator tubing and accessories, dialyzers, dialysis tubing and accessories, haemoadsorbents and immunoadsorbents.

5.1.4 Implant devices

These include devices in contact with the following:

a) **tissue/bone:** devices principally contacting bone; examples include orthopaedic pins, plates, replacement joints, bone prostheses, cements and intraosseous devices. Devices principally contacting tissue and tissue fluid; examples include pacemakers, drug supply devices, neuromuscular sensors and stimulators, replacement tendons, breast implants, artificial larynxes, subperiosteal implants and ligation clips;

b) **blood:** devices principally contacting blood; examples include pacemaker electrodes, artificial arteriovenous fistulae, heart valves, vascular grafts, internal drug delivery catheters and ventricular assist devices.

5.2 Categorization by duration of contact

Contact duration may be categorized as follows:

a) **limited exposure (A):** devices whose single or multiple use or contact is likely to be up to 24 h;

b) **prolonged exposure (B):** devices whose single, multiple ~~(cumulative)~~ or long-term use or contact is likely to exceed 24 h but not 30 days;

c) **permanent contact (C):** devices whose single, multiple ~~(cumulative)~~ or long-term use or contact exceeds 30 days.

If a material or device may be placed in more than one duration category, the more rigorous testing requirements should apply. With multiple exposures, the decision into which category a device is placed should take into account the potential cumulative effect, bearing in mind the period of time over which these exposures occur.

6 Testing

6.1 General

In addition to the general principles laid down in clause 4, the following should be applied to biological testing of medical devices.

a) Testing should be performed on the final product, or representative samples from the final product or materials.

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 to 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) may not be applicable where the presence of leachable materials has been excluded, or where leachables have a known and acceptable toxicity profile;

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

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

7) the protection of humans is the primary goal of this document: a secondary goal is to ensure animal welfare and to minimize the number and exposure of 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.

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

e) Test results cannot ensure freedom from potential biological hazard, thus biological investigations should be followed by careful observations for unexpected adverse reactions or events in humans during clinical use of the device.

Annex B provides a Bibliography of International Standards and Guidelines on biological response test methods.

6.2 Initial evaluation tests

The initial biological response tests that should be considered are as given in 6.2.1 to 6.2.9.

6.2.1 Cytotoxicity

With the use of cell culture techniques, these tests determine the lysis of cells (cell death), the inhibition of cell growth, and other effects on cells caused by devices, materials and/or their extracts.

6.2.2 Sensitization

These tests estimate the potential for contact sensitization of devices, materials and/or their extracts, using an appropriate model. These tests are appropriate because exposure or contact to even minute amounts of potential leachables can result in allergic or sensitization reactions.

6.2.3 Irritation

These tests estimate the irritation potential of devices, materials and/or their extracts, using appropriate site or implant tissue such as skin, eye and mucous membrane in a suitable model. The test(s) performed should be appropriate for the route (skin, eye, mucosa) and duration of exposure or contact to determine irritant effects of devices, materials and potential leachables.

6.2.4 Intracutaneous reactivity

These tests assess the localized reaction of tissue to device extracts. These tests are applicable where determination of irritation by dermal or mucosal tests are inappropriate (e.g., devices having access to the blood path). These tests may also be useful where extractables are hydrophobic.

6.2.5 Systemic toxicity (acute)

These tests estimate the potential harmful effects of either single or multiple exposures, during a period of less than 24 h, to devices, materials and/or their extracts in an animal model. These tests are appropriate where contact allows potential absorption of toxic leachables and degradation products.

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

6.2.6 Sub-chronic toxicity (sub-acute toxicity)

These tests determine the effects of either single or multiple exposures or contact to devices, materials and/or their extracts during a period of 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 90 days in rats). These tests may be waived for materials with chronic toxicity data. The reason for waiving of the tests should be included in the final report. These tests should be appropriate for the route and duration of contact.

6.2.7 Genotoxicity

These tests apply mammalian or non-mammalian cell culture or other techniques to determine gene mutations, changes in chromosome structure and number, and other DNA or gene toxicities caused by devices, materials and/or their extracts.

6.2.8 Implantation

These tests 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 into an implant site or tissue appropriate to the intended application (e.g., special dental usage tests have been described). These tests should be appropriate for the route and duration of contact. For a material, these tests are equivalent to sub-chronic toxicity tests if systemic effects are also investigated.

6.2.9 Haemocompatibility

These tests evaluate effects on blood or blood components by blood-contacting devices, materials or using an appropriate model or system. Specific haemocompatibility tests may also be designed to simulate the geometry, contact conditions and flow dynamics of the device or material during clinical applications.

Haemolysis tests determine the degree of red blood cell lysis and the release of haemoglobin caused by devices, materials and/or their extracts *in vitro*.

6.3 Supplementary evaluation tests

The supplementary biological evaluation tests that should be considered are as given in 6.3.1 to 6.3.4.

6.3.1 Chronic toxicity

These tests determine the effects of either single or multiple exposures to devices, materials and/or their extracts during a period of at least 10 % of the life-span of the test animal (e.g., over 90 days in rats). These tests should be appropriate for the route and duration of exposure or contact.

6.3.2 Carcinogenicity

These tests determine the tumorigenic potential of devices, materials and/or their extracts from either a single or multiple exposures or contacts over a period of the total life-span of the test animal. These tests may be designed in order to examine both chronic toxicity and tumorigenicity in a single experimental study. Carcinogenicity tests should be conducted only if there are suggestive data from other sources. These tests should be appropriate for the route and duration of exposure or contact.

6.3.3 Reproductive and developmental toxicity

These tests evaluate the potential effects of devices, materials and/or their extracts on reproductive function, embryonic development (teratogenicity), and prenatal and early postnatal development. Reproductive/developmental toxicity tests or bioassays should only be conducted when the device has potential impact on the reproductive potential of the subject. The application site of the device should be considered.

6.3.4 Biodegradation

Where the potential for resorption and/or degradation exists, such tests may determine the processes of absorption, distribution, biotransformation, and elimination of leachables and degradation products of devices, materials and/or their extracts.

7 Guidance on selection of biological evaluation tests

Table 1 identifies the initial evaluation tests that shall be considered for each device and duration category. Table 2 identifies the supplementary evaluation tests that shall be considered for each device and duration category.

Due to the diversity of medical devices, it is recognized 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 shall be considered on its own merits: additional tests not indicated in the table may be necessary.

It is strongly recommended that the rationale for selection and/or waiving of tests be recorded.

8 Assurance of test methods

8.1 Test method assurance

The test methods used in the biological evaluation shall be sensitive, precise, and accurate. The test results should be reproducible (interlaboratory) as well as repeatable (intralaboratory).

8.2 Continued assurance

The assurance that a material is initially acceptable for its intended use in a product, and its continued acceptability in the long term, is an aspect of a quality system. (See A.2, subclause 8.2.)

ISO 9001:1987, clause 4 specifies the requirements for such quality assurance systems. ISO 9004 provides more detailed guidance for designing and manufacturing products.