

English version

Biological evaluation of medical devices - Part 8: Selection and qualification of reference materials for biological tests (ISO 10993-8:2000)

Evaluation biologique des dispositifs médicaux - Partie 8:
Sélection et qualification des matériaux de référence
utilisés pour les essais biologiques (ISO 10993-8:2000)

Biologische Beurteilung von Medizinprodukten - Teil 8:
Auswahl und Eignung von Referenzmaterialien für
biologische Prüfungen (ISO 10993-8:2000)

This European Standard was approved by CEN on 1 September 2000.

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This European Standard exists in three official versions (English, French, German). A version in any other language made by translation under the responsibility of a CEN member into its own language and notified to the Central Secretariat has the same status as the official versions.

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EUROPEAN COMMITTEE FOR STANDARDIZATION
COMITÉ EUROPÉEN DE NORMALISATION
EUROPÄISCHES KOMITEE FÜR NORMUNG

Central Secretariat: rue de Stassart, 36 B-1050 Brussels

Foreword

The text of the International Standard ISO 10993-8:2000 has been prepared by Technical Committee ISO/TC 194 "Biological evaluation of medical devices" in collaboration with Technical Committee CEN/TC 206 "Biocompatibility of medical and dental materials and devices", the secretariat of which is held by BSI.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by March 2001, and conflicting national standards shall be withdrawn at the latest by March 2001.

According to the CEN/CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom.

Endorsement notice

The text of the International Standard ISO 10993-8:2000 was approved by CEN as a European Standard without any modification.

NOTE: Normative references to International Standards are listed in annex ZA (normative).

INTERNATIONAL STANDARD

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Biological evaluation of medical devices — Part 8: Selection and qualification of reference materials for biological tests

Évaluation biologique des dispositifs médicaux —

*Partie 8: Sélection et qualification des matériaux de référence utilisés pour
les essais biologiques*



Reference number
ISO 10993-8:2000(E)

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 3.

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 part of ISO 10993 may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

International Standard ISO 10993-8 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: Evaluation and testing*
- *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 8: Selection and qualification of reference materials for biological tests*
- *Part 9: Framework for identification and quantification of potential degradation products*
- *Part 10: Tests for irritation and 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 using health-based risk assessment*
- *Part 18: Chemical characterization of materials*

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

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Introduction

The information given in this part of ISO 10993 should be considered as a supplement to ISO 10993-12 which specifies requirements and gives guidance on procedures to be followed in the preparation of samples of medical devices for testing in biological systems in accordance with one or more parts of the ISO 10993 series. In clause 4 of ISO 10993-12:1996, there is a discussion of the use of reference materials as experimental controls. Annex A of ISO 10993-12:1996 provides specific information regarding current sources of commercially available reference materials.

Biological evaluation of medical devices —

Part 8: Selection and qualification of reference materials for biological tests

1 Scope

This part of ISO 10993 specifies requirements on the use of reference materials or certified reference materials used to determine the biological response of a material. It specifies the selection and qualification of reference materials for biological tests and the characteristics of reference materials for the use of reference materials as experimental controls.

2 Normative references

The following normative documents contain provisions which, through reference in this text, constitute provisions of this part of ISO 10993. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this part of ISO 10993 are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

ISO 10993-12, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials*.

ISO Guide 30:1992, *Terms and definitions used in connection with reference materials*.

3 Terms and definitions

For the purposes of this part of ISO 10993, the terms and definitions given in ISO 10993-12, ISO Guide 30 and the following apply.

3.1

certified reference material

CRM

reference material, accompanied by a certificate, one or more of whose property values are certified by a procedure which establishes its traceability to an accurate realization of the unit in which the property values are expressed, and for which each certified value is accompanied by an uncertainty at a stated level of confidence

[ISO Guide 30:1992, 2.2]

NOTE Standard reference material (SRM) is a trademark-protected certification supplied by the National Institutes for Standards and Technology, Gaithersburg, MD, USA.

3.2

reference material

RM

material or substance one or more of whose property values are sufficiently homogeneous and well established to be used for the calibration of an apparatus, the assessment of a measurement method, or for assigning values to materials

[ISO Guide 30:1992, 2.1]

3.3

homogeneous

condition of being of uniform structure or composition with respect to the biological endpoint under study

NOTE 1 The RM is said to be homogeneous if the biological response to a specific test is found to lie within the specified uncertainty limits of the test, irrespective of the site in the batch or lot of material from where the test sample is taken.

NOTE 2 Adapted from ISO Guide 30:1992, 2.6.

3.4

reference method

thoroughly investigated test method that clearly and exactly describes the necessary conditions and procedures for the evaluation of a specific biological endpoint, has been shown to have accuracy and precision commensurate with its intended use and can, therefore, be used to characterize a RM

NOTE Adapted from ISO Guide 30:1992, 3.10.

3.5

stability of property values

ability of a material, when stored under specified conditions, to maintain the stated biological response, within specified limits, for a specific period of time

NOTE Adapted from ISO Guide 30:1992, 2.7.

4 Use of certified reference materials or reference materials

Reference materials (RM) or certified reference materials (CRM) shall be used in biological tests as control materials to qualify in-house tests and control materials. They demonstrate the suitability of the procedure to yield a reproducible, predictable response, e.g. positive or negative. Use of a reference material in this way will ensure the comparability of the response between laboratories.

The property values of any material used in this way shall be characterized with each biological test procedure for which the use of the material is desired. A material characterized and then certified for one reference test method or response, e.g. sensitization [6], shall not be used as a reference material for another, e.g. cytotoxicity [5], without additional characterization.

5 Characteristics of reference materials

5.1 One or more property values

RMs or CRMs used to determine the biological response of a material shall be evaluated with each biological test procedure for which the use of the material is desired. It is not sufficient to qualify a material for one type of reference test method or response, e.g. sensitization [6], and declare it a reference material for another, e.g. cytotoxicity [5], without additional qualification testing.

5.2 Long-term availability of the reference material

To ensure the long-term availability of a reference material for determination of biological response, the user of the material should obtain a commitment as long as possible, preferably not less than five years, from the supplier of the RMs or CRMs.

A second, but less desirable, option is the publication by the reference material supplier of an "open formulation" for the material, i.e. publication of the source materials and details of the processing needed to ensure uniform batches of RM.

5.3 Certification of reference materials for biological safety testing

The biological response of the certified reference material under specific test conditions shall be established through interlaboratory studies.

6 Use of reference materials as experimental controls

6.1 Material screening versus biocompatibility of medical devices

The use of the reference materials described in ISO 10993-12 and elsewhere in this part of ISO 10993 are limited to biological screening of the materials intended for use in the manufacture of medical devices. However, while not intended for the purpose, they are often used in the performance assessment of the finished medical device. The vertical standard for the device, when available, shall address the biological testing of the product in the performance environment of the device. Biological testing described in the vertical product standard takes precedence over testing performed to screen the materials for suitability.

6.2 Misuse of CRMs

The attention of the users of this part of ISO 10993 is directed to the discussion of "proper use" and "misuse" of CRMs in the introduction to ISO Guide 33. This discussion points out areas of potential under- and over-utilization of RMs and CRMs.

Users of this part of ISO 10993 shall note that the use of calibration materials to evaluate the biological response of materials under investigation within a single laboratory is acceptable.

Bibliography

The ISO Guides listed below provide material which will enable the reader to place the discussion in this International Standard into context.

- [1] ISO Guide 31:1981, *Contents of certificates of reference materials*.
- [2] ISO Guide 33:1989, *Uses of certified reference materials*.
- [3] ISO Guide 35:1989, *Certification of reference materials — General and statistical principles*.
- [4] ISO/IEC Directives, Part 2:1992, *Methodology for the development of International Standards*¹⁾.

The following International Standards contain additional information on biological evaluation procedures for specific biological endpoints.

- [5] ISO 10993-5:1999, *Biological evaluation of medical devices — Part 5: Tests for in vitro cytotoxicity*.
- [6] ISO 10993-10:1995, *Biological evaluation of medical devices — Part 10: Tests for irritation and sensitization*.

1) At present under revision. It is anticipated that the contents will be divided between the revision of Part 1 and a new Part 2 comprising mainly the revision of present Part 3.

Annex ZA (normative)
**Normative references to international publications
with their relevant European publications**

This European Standard incorporates by dated or undated reference, provisions from other publications. These normative references are cited at the appropriate places in the text and the publications are listed hereafter. For dated references, subsequent amendments to or revisions of any of these publications apply to this European Standard only when incorporated in it by amendment or revision. For undated references the latest edition of the publication referred to applies.

Publication	Year	Title	EN	Year
ISO 10993-12	1996	Biological evaluation of medical devices – Part 12: Sample preparation and reference materials	EN ISO 10993-12	1996