BRITISH STANDARD

BS EN ISO
10993-9:2009

Biological evaluation of medical devices

Part 9: Framework for identification and quantification of potential degradation products (ISO 10993-9:1999)

ICS 11.100.20

BSI
British Standards

National foreword

This British Standard is the UK implementation of EN ISO 10993-9:2009. It is identical to ISO 10993-9:1999. It supersedes BS EN ISO 10993-9:1999 which is withdrawn.

The UK participation in its preparation was entrusted to Technical Committee CH/194, Biological evaluation of medical devices.

A list of organizations represented on this committee can be obtained on request to its secretary.

This publication does not purport to include all the necessary provisions of a contract. Users are responsible for its correct application.

Compliance with a British Standard cannot confer immunity from legal obligations.

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English Version

Biological evaluation of medical devices - Part 9: Framework for identification and quantification of potential degradation products (ISO 10993-9:1999)

Évaluation biologique des dispositifs médicaux - Partie 9: Cadre pour l'identification et la quantification des produits potentiels de dégradation (ISO 10993-9:1999)

Biologische Beurteilung von Medizinprodukten - Teil 9: Rahmen zur Identifizierung und Quantifizierung von möglichen Abbauprodukten (ISO 10993-9:1999)

This European Standard was approved by CEN on 28 April 2009.

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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 CEN Management Centre has the same status as the official versions.

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Management Centre: Avenue Marnix 17, B-1000 Brussels

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Foreword

The text of ISO 10993-9:1999 has been prepared by Technical Committee ISO/TC 194 “Biological evaluation of medical devices” of the International Organization for Standardization (ISO) and has been taken over as EN ISO 10993-9:2009 by Technical Committee CEN/TC 206 “Biological evaluation of medical devices” the secretariat of which is held by NEN.

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 November 2009, and conflicting national standards shall be withdrawn at the latest by March 2010.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. CEN [and/or CENELEC] shall not be held responsible for identifying any or all such patent rights.

This document supersedes EN ISO 10993-9:1999.

This document has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of EU Directives 93/42/EEC on Medical Devices and 90/385/EEC on Active Implantable Medical Devices.

For relationship with EU Directives, see informative Annex ZA and ZB, which is an integral part of this document.

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

Endorsement notice

The text of ISO 10993-9:1999 has been approved by CEN as a EN ISO 10993-9:2009 without any modification.

Annex ZA
(informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 93/42/EEC on Medical Devices

This European Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association to provide a means of conforming to Essential Requirements of the New Approach Directive 93/42/EEC on medical devices.

Once this standard is cited in the Official Journal of the European Communities under that Directive and has been implemented as a national standard in at least one Member State, compliance with the clauses of this standard given in table ZA confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA regulations.

Table ZA — Correspondence between this European Standard and Directive 93/42/EEC on medical devices

Clause(s)/sub-clause(s) of this EN	Essential Requirements (ERs) of Directive 93/42/EEC	Qualifying remarks/Notes
4, 5, & Annex A	Annex I: 7.1, 7.2, 7.5	

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this standard.

Annex ZB
(informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 90/385/EEC on Active Implantable Medical Devices

This European Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association to provide a means of conforming to Essential Requirements of the New Approach Directive 90/385/EEC on active implantable medical devices.

Once this standard is cited in the Official Journal of the European Communities under that Directive and has been implemented as a national standard in at least one Member State, compliance with the clauses of this standard given in table ZB confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA regulations.

Table ZB — Correspondence between this European Standard and Directive 90/385/EEC on active implantable medical devices

Clause(s)/sub-clause(s) of this EN	Essential Requirements (ERs) of Directive 90/385/EEC	Qualifying remarks/Notes
4, 5, Annex A	Annex I : 9	The test methods do not include pass/fail criteria

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this standard.

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.

International Standard ISO 10993-9 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

This first edition cancels and replaces the first edition of ISO/TR 10993-9:1994, 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*

— *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 sensitization*

— *Part 11: Tests for systemic toxicity*

— *Part 12: Sample preparation and reference materials*

— *Part 13: Identification and quantification of degradation products from polymers*

— *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 18: Chemical characterization.*

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

Annex A forms a normative part of this part of ISO 10993. Annex B is for information only.

Introduction

This part of 10993 is intended to present the general principles on which the specific material investigations to identify and quantify degradation products described in ISO 10993-13 (polymers), ISO 10993-14 (ceramics) and ISO 10993-15 (metals and alloys) are based.

Information obtained from these studies is intended to be used in the biological evaluations described in the remaining parts of ISO 10993.

The materials used to construct medical devices may form degradation products when exposed to the biological environment, and these products may behave differently than the bulk material in the body.

Degradation products can be generated in different ways, either mechanically (by relative motion between two or more different components), by fatigue loading, as a result of fracture and/or by release from the medical device due to interactions with the environment, or combinations thereof.

Mechanical wear causes mostly particulate debris, whereas the release of substances from surfaces due to leaching, chemical breakdown of structures or corrosion can lead to free ions or to different kinds of reaction products in the form of organic or inorganic compounds.

The degradation products may be either reactive, or stable and without biochemical reaction with their environment. Accumulations of substantial quantities of stable degradation products may, however, have physical effects on the surrounding tissues. Degradation products may remain at the location of their generation or may be transported within the biological environment by various mechanisms.

The level of biological tolerability of degradation products depends on their nature and concentration, and should be primarily assessed through clinical experience and focused studies. For theoretically possible, new and/or unknown degradation products, relevant testing is necessary. For well-described and clinically accepted degradation products, no further investigation may be necessary.

INTERNATIONAL STANDARD © ISO **ISO 10993-9:1999(E)**

Biological evaluation of medical devices —

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

1 Scope

This part of ISO 10993 provides general principles for the systematic evaluation of the potential and observed biodegradation of medical devices and for the design and performance of biodegradation studies.

This part of ISO 10993 is not applicable to:

a) viable-tissue engineered products;

b) methodologies for the generation of degradation products by mechanical processes. Methodologies for the production of this type of degradation product are described in specific product standards, where available;

c) leachable components which are not degradation products.

Where product standards provide applicable product-specific methodologies for the identification and quantification of degradation products, those standards shall be considered as alternatives.

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 10993-1:1997, *Biological evaluation of medical devices — Part 1: Evaluation and testing*.

ISO 10993-2:1992, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*.

3 Terms and definitions

For the purposes of this part of ISO 10993, the terms and definitions given in ISO 10993-1 and the following apply.

3.1
degradation
decomposition of a material

3.2
biodegradation
degradation due to the biological environment

NOTE Biodegradation may be modelled by *in vitro* tests.

3.3
bioresorbable medical device
medical device intended for degradation and resorption in the biological environment of the body

3.4
leachable
extractable component from a material that is not a product of chemical degradation

3.5
corrosion
attack on metallic materials by chemical or electrochemical reactions

NOTE The term is sometimes used in a general sense for the deterioration of other materials, but is in this part of ISO 10993 reserved for metallic materials.

3.6
substance
single chemical element or compound, or a complex structure of compounds

3.7
device component
one of the different parts of which a device is composed

3.8
degradation product
any particle or chemical compound that is derived from the chemical breakdown of the original material

4 Principles for design of degradation studies

4.1 General

The approach to the assessment of degradation varies with the nature of the material under investigation, the medical device, the local environment and the anatomic location of the specific device. When a specific device is to be evaluated, and where the details of the chemistry of the service environment for that device are known, the evaluation should be carried out in an environment appropriate to these conditions.

When available, materials-specific degradation standards that address identification and quantification of degradation products, such as ISO 10993-13 for polymers, ISO 10993-14 for ceramics and ISO 10993-15 for metals and alloys, shall be used in the design of degradation studies. Devices composed of more than two material types shall consider all relevant degradation standards.

4.2 Preliminary considerations

Careful consideration of the potential for intended or unintended degradation of a material is essential to the evaluation of the biological safety of a device. Part of this consideration is an assessment of the chemical characteristics and known degradation mechanisms, followed by an assessment of the need for, and design of, experimental biodegradation studies. Based upon a review of the literature and previous clinical experience with equivalent materials, further biological evaluation of the degradation products may be considered necessary.

It is neither necessary nor practical to conduct degradation studies for all medical devices. Consideration of the need for degradation studies is provided in annex A. The assessment of the need for experimental degradation studies shall include a review of the literature and/or documented clinical experience. Such a study can result in the

conclusion that no further testing is needed if the product under consideration has a demonstrated history of acceptable clinical experience, new data, published data and analogies with known devices, materials and degradation products.

Guidance on the biological evaluation of degradation products is given in ISO 10993-1.

4.3 Study design

A study protocol complete with the purpose of the study shall be designed and documented to address the issues identified in 4.1. The protocol shall define the analytical methods by which the following characteristics of degradation products are to be investigated:

a) chemical and physicochemical properties;

b) surface morphology; and

c) biochemical properties.

The protocol shall also describe the methods used to generate degradation products.

The protocol for multicomponent devices shall take into account each individual component/material and shall consider synergistic effects on the degradation of the different components.

4.4 Characterization of degradation products from medical devices

The degradation products produced in the study may be particulate or soluble compounds or ions. Appropriate analytical methods to characterize these products shall be used, validated and reported in the study report.

If biological evaluation of the degradation products is required, then care shall be taken in the design of the degradation study to ensure that it does not interfere with the biological assay.

Considerations for the biodegradation study are provided in annex B. The protocol shall include:

a) identification and characterization of device and/or material and intended use;

b) identification and characterization of possible mechanism of degradation;

c) identification and characterization of known, probable and potential degradation products;

d) test methodologies.

NOTE 1 The extent and rate of release of degradation products depends on variables such as manufacturing processes which alter surface composition and structures, migration to the surface from within the material, solubility in and chemical composition of the physiological milieu, etc.

NOTE 2 The study may lead to the conclusion that enough data are available, so that further investigation is not necessary.

5 Study report

The study report shall include the following information, where relevant:

a) description of material and/or device (see B.1 in annex B), including intended use and nature of body contact;

b) assessment of degradation and rationale for the assessment of degradation;

c) identification and quantification of degradation products (e.g. form and condition of degradation products, their stability and controls used);

d) description of degradation test methods, test conditions, test materials and procedures, including controls;

e) description of analytical methods, including quantification limits and controls;

f) statement of compliance to appropriate good laboratory practices, to quality management systems for test laboratories and/or ISO Guide 25;

g) summary of results; and

h) interpretation and discussion of results.

Annex A
(normative)

Consideration of the need for degradation studies

Degradation studies shall be considered if:

a) the device is designed to be bioresorbable; or

b) the device is intended to be implanted for longer than thirty days; or

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

Degradation studies may not be necessary if:

a) 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

b) 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

c) sufficient degradation data relevant to the substances and degradation products in the intended use already exist.

The need for *in vivo* studies shall be considered in light of results from *in vitro* studies.

Where appropriate, *in vitro* experiments shall be considered to investigate theoretically possible degradation processes. *In vivo* studies shall take into consideration animal welfare (see ISO 10993-2). *In vivo* and *in vitro* studies shall also be considered to determine the probability of occurrence of degradation and the identification of probable degradation products and degradation rate.

Annex B
(informative)

Biodegradation study considerations

B.1 General

This annex contains aspects to be considered in the evaluation of possible biodegradation.

Appropriate practical studies shall be considered in the case where essential information is missing on the degradation of devices or materials and the biological effects of potential biodegradation products.

B.2 Description of medical device and/or material

a) Name of medical device and/or material;

b) function of medical device;

c) intended use;

d) intended biological environment;

e) composition of the material;

f) conditioning of the material (processing, sterilization);

g) surface condition;

h) dimensions;

i) single component;

j) single component to be used with others;

k) multicomponent device – assessment carried out for each component material;

l) contact duration;

m) other characterizations.

B.3 Assessment of potential and known degradation products

B.3.1 Bulk material changes

Intended or unintended changes in the bulk material can lead to particulate degradation products and can influence the stability of the surface. For example, bulk material changes can occur:

— during fabrication;

— during sterilization;

— during implantation and while implanted;

— by intended bioresorption;

— during storage and due to instability;

— during changes in the physical state (swelling, phase transitions, etc.).

B.3.2 Release of substances from the surface

Release of substances from the surface can be induced by processes such as:

— chemical reactions;

— leaching;

— migration;

— depolymerization;

— peeling, scaling off.

B.3.3 Multicomponent device or device used with other components

In addition to the considerations for single-component systems, items such as the following need to be addressed:

— breakdown of structures;

— delamination;

— migration of substances from one component to another.

Bibliography

[1] ISO 10993-13, *Biological evaluation of medical devices — Part 13: Identification and quantification of degradation products from polymers*.

[2] ISO 10993-14, *Biological evaluation of medical devices — Part 14: Identification and quantification of degradation products from ceramics*.

[3] ISO 10993-15, *Biological evaluation of medical devices — Part 14: Identification and quantification of degradation products from metals and alloys*.

[4] ISO Guide 25:1990, *General requirements for competence of calibration and testing laboratories*.

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BSI Group
Headquarters 389
Chiswick High Road,
London, W4 4AL, UK
Tel +44 (0)20 8996 9001
Fax +44 (0)20 8996 7001
www.bsigroup.com/
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