Irish Standard
I.S. EN ISO 10993-16:2017

Biological evaluation of medical devices - Part 16: Toxicokinetic study design for degradation products and leachables (ISO 10993-16:2017)

I.S. EN ISO 10993-16:2017

Incorporating amendments/corrigenda/National Annexes issued since publication:

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National Foreword

I.S. EN ISO 10993-16:2017 is the adopted Irish version of the European Document EN ISO 10993-16:2017, Biological evaluation of medical devices - Part 16: Toxicokinetic study design for degradation products and leachables (ISO 10993-16:2017)

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EUROPEAN STANDARD

NORME EUROPÉENNE

EUROPÄISCHE NORM

EN ISO 10993-16

December 2017

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Supersedes EN ISO 10993-16:2010

English Version

Biological evaluation of medical devices - Part 16: Toxicokinetic study design for degradation products and leachables (ISO 10993-16:2017)

Évaluation biologique des dispositifs médicaux - Partie 16: Conception des études toxicocinétiques des produits de dégradation et des substances relargables (ISO 10993-16:2017)

Biologische Beurteilung von Medizinprodukten - Teil 16: Entwurf und Auslegung toxikokinetischer Untersuchungen hinsichtlich Abbauprodukten und herauslösbaren Substanzen (ISO 10993-16:2017)

This European Standard was approved by CEN on 9 August 2017.

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EUROPEAN COMMITTEE FOR STANDARDIZATION
COMITÉ EUROPÉEN DE NORMALISATION
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European foreword

The text of ISO 10993-16:2017 has been prepared by Technical Committee ISO/TC 194 "Biological and clinical evaluation of medical devices" of the International Organization for Standardization (ISO) and has been taken over as EN ISO 110993-16:2017 by Technical Committee CEN/TC 206 “Biological and clinical evaluation of medical devices” the secretariat of which is held by DIN.

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of an identical text or by endorsement, at the latest by June 2018, and conflicting national standards shall be withdrawn at the latest by June 2018.

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

This document supersedes EN ISO 10993-16:2010.

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 Directive(s).

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

The following referenced documents are indispensable for the application of this document. For undated references, the latest edition of the referenced document (including any amendments) applies. For dated references, only the edition cited applies. However, for any use of this standard ‘within the meaning of Annex ZA’, the user should always check that any referenced document has not been superseded and that its relevant contents can still be considered the generally acknowledged state-of-art.

When an IEC or ISO standard is referred to in the ISO standard text, this shall be understood as a normative reference to the corresponding EN standard, if available, and otherwise to the dated version of the ISO or IEC standard, as listed below.

NOTE The way in which these referenced documents are cited in normative requirements determines the extent (in whole or in part) to which they apply.

Table — Correlations between undated normative references and dated EN and ISO standards

Normative references as listed in Clause 2 of the ISO standard	**Equivalent dated standard**	
	EN	ISO or IEC
ISO 10993-1	EN ISO 10993-1:2009	ISO 10993-1:2009

NOTE This part of EN ISO 10993 refers to ISO 10993-1 which itself refers to ISO 14971. In Europe, it should be assumed that the reference to ISO 14971 is to EN ISO 14971:2012.

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, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Former Yugoslav Republic of Macedonia, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and the United Kingdom.

Endorsement notice

The text of ISO 10993-16:2017 has been approved by CEN as EN ISO 10993-16:2017 without any modification.

Annex ZA
(informative)

Relationship between this European Standard and the essential requirements of Directive 93/42/EEC [OJ L 169] aimed to be covered

This European Standard has been prepared under a Commission's joint standardization request M/BC/CEN/89/9 concerning harmonized standards relating to horizontal aspects in the field of medical devices to provide one voluntary means of conforming to essential requirements of Council Directive 93/42/EEC of 14 June 1993 concerning medical devices [OJ L 169].

Once this standard is cited in the Official Journal of the European Union under that Directive, compliance with the normative clauses of this standard given in Table ZA.1 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.

NOTE 1 Where a reference from a clause of this standard to the risk management process is made, the risk management process needs to be in compliance with Directive 93/42/EEC as amended by 2007/47/EC. This means that risks have to be reduced 'as far as possible', 'to a minimum', 'to the lowest possible level', 'minimized' or 'removed', according to the wording of the corresponding essential requirement.

NOTE 2 The manufacturer's policy for determining acceptable risk must be in compliance with Essential Requirements 1, 2, 5, 6, 7, 8, 9, 11 and 12 of the Directive.

NOTE 3 This Annex ZA is based on normative references according to the table of references in the European foreword, replacing the references in the core text.

NOTE 4 When an Essential Requirement does not appear in Table ZA.1, it means that it is not addressed by this European Standard.

Table ZA.1 — Correspondence between this European Standard and Annex I of Directive 93/42/EEC [OJ L 169]

Essential Requirements of Directive 93/42/EEC	Clause(s)/subclause(s) of this EN	Remarks/Notes
7.1 (First and second indent)	4, 5, and Annex A	ER 7.1 is only partly covered by EN ISO 10993-16, since the standard does not provide requirements on design and manufacture, and the compatibility between the materials used and biological tissues, cells and body fluids. However, this standard provides a means to evaluate the absorption, distribution, metabolism and excretion, with time, of degradation products and leachables from materials which are used in the device and circumstances in which such studies shall be considered. Other forms of toxicity and flammability are not dealt with in this standard.

7.2	4, 5, and Annex A	ER 7.2 is not covered by EN ISO 10993-16, since the standard does not provide requirements on design and manufacture and does not oblige to minimize risk. However, this standard provides a means to evaluate the absorption, distribution, metabolism and excretion, with time, of residuals in exposed persons and circumstances in which such studies shall be considered. This evaluation can be a preliminary step for risk minimization. Other forms of toxicity are not dealt with in this standard.
7.5 (First paragraph)	4, 5, and Annex A	ER 7.5 is not covered by EN ISO 10993-16, since the standard does not provide requirements on design and manufacture and does not oblige to minimize risk. However, this standard provides a means to evaluate the absorption, distribution, metabolism and excretion, with time, of substances leaking from the device and circumstances in which such studies shall be considered. This evaluation can be a preliminary step for risk minimization. Other forms of toxicity are not dealt with in this standard.

General Note: Presumption of conformity depends on also complying with all relevant clauses/subclauses of ISO 10993-1.

WARNING 1 — Presumption of conformity stays valid only as long as a reference to this European Standard is maintained in the list published in the Official Journal of the European Union. Users of this standard should consult frequently the latest list published in the Official Journal of the European Union.

WARNING 2 — Other Union legislation may be applicable to the products falling within the scope of this standard.

Annex ZB
(informative)

Relationship between this European Standard and the essential requirements of Directive 90/385/EEC [OJ L 189] aimed to be covered

This European Standard has been prepared under a Commission's joint standardization request M/BC/CEN/89/9 concerning harmonized standards relating to horizontal aspects in the field of medical devices to provide one voluntary means of conforming to essential requirements of Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices [OJ L 189].

Once this standard is cited in the Official Journal of the European Union under that Directive, compliance with the normative clauses of this standard given in Table ZB.1 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.

NOTE 1 Where a reference from a clause of this standard to the risk management process is made, the risk management process needs to be in compliance with Directive 90/385/EEC as amended by 2007/47/EC. This means that risks have to be reduced 'as far as possible', 'to a minimum', 'to the lowest possible level', 'minimized' or 'removed', according to the wording of the corresponding essential requirement.

NOTE 2 The manufacturer's policy for determining acceptable risk must be in compliance with Essential Requirements 1, 4, 5, 8, 9 and 10 of the Directive.

NOTE 3 This Annex ZB is based on normative references according to the table of references in the European foreword, replacing the references in the core text.

NOTE 4 When an Essential Requirement does not appear in Table ZB.1, it means that it is not addressed by this European Standard.

Table ZB.1 — Correspondence between this European Standard and Annex I of Directive 90/385/EEC [OJ L 189]

Essential Requirements of Directive 90/385/EEC	Clause(s)/subclause(s) of this EN	Remarks/Notes
9 (only first and second indent)	4, 5, and Annex A	The first and second indents of this relevant Essential Requirement are only partly covered by EN ISO 10993-16, since the standard does not provide requirements on design and manufacture. However, this standard provides a means to evaluate the absorption, distribution, metabolism and excretion, with time, of degradation products and leachables from materials which are used in the device and circumstances in which such studies shall be considered. Other forms of toxicity are not covered.

General Note: Presumption of conformity depends on also complying with all relevant clauses/subclauses of ISO 10993-1.

WARNING 1 — Presumption of conformity stays valid only as long as a reference to this European Standard is maintained in the list published in the Official Journal of the European Union. Users of this standard should consult frequently the latest list published in the Official Journal of the European Union.

WARNING 2 — Other Union legislation may be applicable to the products falling within the scope of this standard.

INTERNATIONAL STANDARD

ISO 10993-16

Third edition
2017-05

Biological evaluation of medical devices —

Part 16: Toxicokinetic study design for degradation products and leachables

Évaluation biologique des dispositifs médicaux —

Partie 16: Conception des études toxicocinétiques des produits de dégradation et des substances relargables

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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.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 194, *Biological and clinical evaluation of medical devices*.

This third edition cancels and replaces the second edition (ISO 10993-16:2010), which has been technically revised with the following changes:

a) definition in 3.1 has been modified for clarification;

b) Clause 4 has been modified for clarification;

c) Clause 5 has been modified for clarification;

d) information regarding toxicokinetic studies on nano-objects have been added;

e) A.4 has been modified for clarification.

A list of all the parts in the ISO 10993 series can be found on the ISO website.

Introduction

Toxicokinetics describe the absorption, distribution, metabolism and excretion, with time, of foreign compounds in the body. Essential to the evaluation of the safety of a medical device is consideration of the stability of the material(s) *in vivo* and the disposition of intended and unintended leachables and degradation products. Toxicokinetic studies can be of value in assessing the safety of materials used in the development of a medical device or in elucidating the mechanism of observed adverse reactions. Toxicokinetic studies can also be applicable to medical devices containing active ingredients, in which case, pharmaceutical legislation are to be considered. The need for and extent of toxicokinetic studies should be carefully considered based on the nature and duration of contact of the device with the body (see A.2). Existing toxicological literature and toxicokinetic data can be sufficient for this consideration.

The potential hazard posed by a medical device can be attributed to the interactions of its components or their metabolites with the biological system. Medical devices can release leachables (e.g. residual catalysts, processing aids, residual monomers, fillers, antioxidants, plasticizers, etc.) and/or degradation products which migrate from the material and have the potential to cause adverse effects in the body.

A considerable body of published literature exists on the use of toxicokinetic methods to study the fate of chemicals in the body (see Bibliography). The methodologies and techniques utilized in such studies form the basis of the guidance in this document. Annex A provides a rationale for the use of this document.

Biological evaluation of medical devices —

Part 16: Toxicokinetic study design for degradation products and leachables

1 Scope

This document provides principles on designing and performing toxicokinetic studies relevant to medical devices. Annex A describes the considerations for inclusion of toxicokinetic studies in the biological evaluation of medical devices.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements 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 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

3 Terms and definitions

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

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— IEC Electropedia: available at http://www.electropedia.org/

— ISO Online browsing platform: available at http://www.iso.org/obp

3.1
absorption
process of uptake of substance into or across tissue, blood and/or lymph system

3.2
bioavailability
extent of systemic *absorption* (3.1) of specified substance

3.3
biodegradation
degradation due to the biological environment

Note 1 to entry: Biodegradation might be modelled by *in vitro* tests.

3.4
bioresorption
process by which a biomaterial is degraded in the physiological environment and the product(s) eliminated and/or absorbed