BSI Standards Publication

Biological evaluation of medical devices

Part 23: Tests for irritation

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National foreword

This British Standard is the UK implementation of EN ISO 10993-23:2021. It is identical to ISO 10993-23:2021.

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 committee manager.

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This publication has been prepared under a mandate given to the European Standards Organizations by the European Commission and the European Free Trade Association and is intended to support essential requirements of the EU legislation detailed in the European foreword. Annex ZA/ZZ describes how the publication relates to the legislation.

For the Great Britain market (England, Scotland and Wales), if the UK Government has designated this publication for conformity with UKCA marking legislation and has not amended the essential requirements of that legislation, Annex ZA/ZZ and any references to EU law in the publication should be read in accordance with the designation as applying to UK legislation in the same way as to EU law. Further information on designated standards can be found at www.bsigroup.com/standardsandregulation.

For the Northern Ireland market, UK law will continue to implement relevant EU law subject to periodic confirmation. References to EU legislation are therefore still valid.

More information on legislation can be found at www.gov.uk.

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Biological evaluation of medical devices - Part 23: Tests for irritation (ISO 10993-23:2021)

Évaluation biologique des dispositifs médicaux - Partie 23: Essais d'irritation (ISO 10993-23:2021, Version corrigée inclus 2021-02)

Biologische Beurteilung von Medizinprodukten - Teil 23: Prüfungen auf Irritation (ISO 10993-23:2021)

This European Standard was approved by CEN on 1 October 2020.

CEN members are bound to comply with the CEN/CENELEC Internal Regulations which stipulate the conditions for giving this European Standard the status of a national standard without any alteration. Up-to-date lists and bibliographical references concerning such national standards may be obtained on application to the CEN-CENELEC Management Centre or to any CEN member.

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-CENELEC Management Centre has the same status as the official versions.

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EUROPÄISCHES KOMITEE FÜR NORMUNG

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Ref. No. EN ISO 10993-23:2021: E

European foreword

This document (EN ISO 10993-23:2021) has been prepared by Technical Committee ISO/TC 194 "Biological and clinical evaluation of medical devices" in collaboration with 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 September 2021, and conflicting national standards shall be withdrawn at the latest by September 2021.

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 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 the relationship with EU Directive(s) see informative Annex ZA, ZB and ZC, which are integral parts 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 10993-1:2021 [a]	ISO 10993-1:2018
ISO 10993-2	EN ISO 10993-2:2006	ISO 10993-2:2006
ISO 10993-9	EN ISO 10993-9:2021 [a]	ISO 10993-9:2019
ISO 10993-12	EN ISO 10993-12:2021 [a]	ISO 10993-12:2020
ISO 10993-13	EN ISO 10993-13:2010	ISO 10993-13:2010
ISO 10993-14	EN ISO 10993-14:2001	ISO 10993-14:2009
ISO 10993-15	EN ISO 10993-15:2021 [a]	ISO 10993-15:2019
ISO 10993-18	EN ISO 10993-18:2021 [a]	ISO 10993-18:2020
ISO 14155	EN ISO 14155:2020	ISO 14155:2020

[a] Under preparation at European level.

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, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Republic of North Macedonia, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and the United Kingdom.

Endorsement notice

The text of ISO 10993-23:2021 has been approved by CEN as EN ISO 10993-23:2021 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)/sub-clause(s) of this EN	Remarks/Notes
7.1 (First and second indent)	4, 5, 6, 7, 8 and Annex A, D and E	ER 7.1 is only partly covered by this standard, since the standard does not provide requirements on design and manufacture. However, this standard provides a means to assess potential irritancy induced by chemical and/or physical properties of substances used in the manufacture of medical devices. Other forms of toxicity and flammability are not covered.
7.2	4, 5, 6, 7, 8 and Annex A, D and E	ER 7.2 is only partly covered by this standard, since the standard does not provide requirements on design, manufacture and packaging and does not oblige to minimize risk. However, this standard provides a means to assess irritancy to contaminants and residues in medical devices.

Essential Requirements of Directive 93/42/EEC	Clause(s)/sub-clause(s) of this EN	Remarks/Notes
7.5 (First paragraph)	4, 5, 6, 7, 8 and Annex A, D and E	ER 7.5 is only partly covered by this standard, since the standard does not provide requirements on design and manufacture. However, this standard provides a means to assess irritancy to substances leaking from medical devices. 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 the relevant parts of the ISO 10993 series.

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)/sub-clause(s) of this EN	Remarks/Notes
9 (only first and second indent)	4, 5, 6, 7, 8 and Annex A, D and E	ER 9 is only partly covered by this standard, since the standard does not provide requirements on design and manufacture. However, this standard provides a means to assess potential irritancy induced by chemical and/or physical properties of substances used in the manufacture of medical devices. Other forms of toxicity and flammability are not covered.

GENERAL NOTE Presumption of conformity depends on also complying with the relevant parts of the ISO 10993 series.

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 ZC
(informative)

Relationship between this European standard and the General Safety and Performance Requirements of Regulation (EU) 2017/745 aimed to be covered

This European standard has been prepared under a Commission's standardisation request to provide one voluntary means of conforming to the General Safety and Performance Requirements of Regulation (EU) 2017/745 of 5 April 2017 concerning medical devices [OJ L 117].

Once this standard is cited in the Official Journal of the European Union under that Regulation, compliance with the normative clauses of this standard given in Table ZC.1 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding General Safety and Performance Requirements of that Regulation, 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 Regulation (EU) 2017/745. This means that risks have to be 'reduced as far as possible', 'reduced to the lowest possible level', 'reduced as far as possible and appropriate', 'removed or reduced as far as possible', 'eliminated or reduced as far as possible', 'removed or minimized as far as possible', or 'minimized', according to the wording of the corresponding General Safety and Performance Requirement.

NOTE 2 The manufacturer's policy for determining acceptable risk must be in compliance with General Safety and Performance Requirements 1, 2, 3, 4, 5, 8, 9, 10, 11, 14, 16, 17, 18, 19, 20, 21 and 22 of the Regulation.

NOTE 3 This Annex ZC 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 a General Safety and Performance Requirement does not appear in Table ZC.1, it means that it is not addressed by this European Standard.

Table ZC.1 — Correspondence between this European Standard and Annex I of Regulation (EU) 2017/745 [OJ L 117]

General Safety and Performance Requirements of Regulation (EU) 2017/745	Clause(s)/sub-clause(s) of this EN	Remarks/Notes
10.1 a), b), g) and h)	4, 5, 6, 7, 8 and Annex A, D and E	10.1 is only partly covered by EN ISO 10993-23, since the standard does not provide requirements on design and manufacture. However, this standard provides a means to assess potential irritancy induced by chemical and/or physical properties of substances used in the manufacture of medical devices. Other forms of toxicity and flammability (10.1 a) and b) are not covered.

General Safety and Performance Requirements of Regulation (EU) 2017/745	Clause(s)/sub-clause(s) of this EN	Remarks/Notes
10.2	4, 5, 6, 7, 8 and Annex A, D and E	10.2 is only partly covered by this standard, since the standard does not provide requirements on design, manufacture and packaging and does not oblige to minimize risk. However, this standard provides a means to assess irritancy to contaminants and residues in medical devices.
10.4.1 (First paragraph, first sentence)	4, 5, 6, 7, 8 and Annex A, D and E	10.4.1 is only partly covered by this standard, since the standard does not provide requirements on design and manufacture. However, this standard provides a means to assess irritancy to substances leaking from medical devices. 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 the relevant parts of the ISO 10993 series.

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 product(s) falling within the scope of this standard.

Contents

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 of 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 www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 194, *Biological and clinical evaluation of medical devices,* in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 206, *Biological and clinical evaluation of medical devices,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

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

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

This document assesses possible contact hazards from medical devices, which can produce irritation.

Some materials that are included in medical devices have been tested, and their skin or mucosal irritation potential has been demonstrated. Other materials and their chemical components have not been tested and can induce adverse effects when in contact with human tissue. The manufacturer is thus obliged to evaluate each device for potential adverse effects prior to marketing.

The irritation potential of a medical device or its components can be predicted either by an *in vivo* animal irritation test or by an *in vitro* irritation test if qualified for use with medical devices.

ISO 10993-2 describes animal welfare aspects for performing animal studies for the biological evaluation of medical devices thereby also emphasizing the 3R's for replacement, reduction, and refinement of animal studies. This document describes tests to determine the irritancy of medical devices, materials or their extracts either by *in vitro* tests or *in vivo* tests. *In vitro* tests have preference over *in vivo* tests when appropriately validated and providing equally relevant information to that obtained from *in vivo* tests (see ISO 10993-1 and ISO 10993-2).

Traditionally, tests in small animals have been performed prior to testing on humans to help predict human responses. More recently, *in vitro* tests as well as human tests have been added as adjuncts or alternatives. For skin irritation testing of neat chemicals *in vitro* tests were developed using reconstructed human epidermis (RhE) models[31]. The method was adapted for detection of irritant chemicals in medical device extracts. The results of a large round robin study that tested two types of RhE models showed that these models can also be used to detect the presence of irritant chemicals extracted from polymeric materials [polyvinylchloride (PVC) and silicone] commonly used in the manufacture of medical devices[6]. This method was found to be equally sensitive in the detection of low concentrations of some strong irritant compounds when compared to the human patch testing and intracutaneous rabbit test[14]. Therefore, a stepwise approach for irritant testing can start with the *in vitro* RhE model.

The developed and validated RhE models are appropriate to predict skin tissue irritation response. It is recommended to explore the use of other alternative *in vitro* models to assess the irritation potential for mucosal or eye epithelial applications.

It is intended that, for regulatory submission, these studies be conducted using GLP or ISO/IEC 17025 as applicable to the respective country and comply with regulations related to animal welfare. Statistical analysis of data is recommended and can be used whenever appropriate.

This document is intended for use by professionals, appropriately qualified by training and experience, who are able to interpret its requirements and judge the outcomes 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.

The tests included in this document are important tools for the development of safe products, provided that they are executed and interpreted by trained personnel.

This document is based on numerous standards and guidelines, including OECD Test Guidelines (TG), U.S. Pharmacopoeia[40] and the European Pharmacopoeia[39]. It is intended to be the basic document for the selection and conduct of tests enabling evaluation of irritation responses relevant to the safety of medical materials and devices.

Instructions are given in normative Annex A for the preparation of materials specifically in relation to the above tests. In normative Annex D several special *in vivo* irritation tests are described for application of medical devices in areas other than skin. In addition, normative Annex E provides information for conducting human skin irritation testing.

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INTERNATIONAL STANDARD ISO 10993-23:2021

Biological evaluation of medical devices —

Part 23: Tests for irritation

1 Scope

This document specifies the procedure for the assessment of medical devices and their constituent materials with regard to their potential to produce irritation. The tests are designed to predict and classify the irritation potential of medical devices, materials or their extracts according to ISO 10993-1 and ISO 10993-2.

This document includes:

— pre-test considerations for irritation, including *in silico* and *in vitro* methods for dermal exposure;

— details of *in vitro* and *in vivo* irritation test procedures;

— key factors for the interpretation of the results.

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*

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

ISO 10993-9, *Biological evaluation of medical devices — Part 9: Framework for identification and quantification of potential degradation products*

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 10993-18, *Biological evaluation of medical devices — Part 18: Chemical characterization of medical device materials within a risk management process*

ISO 14155, *Clinical investigation of medical devices for human subjects — Good clinical practice*

OECD 404, *Acute Dermal Irritation/Corrosion*

OECD 439, *In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method*