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MEDITSIINISEADMETE BIOLOOGILINE HINDAMINE. OSA 4: VASTASMÕJUDE HINDAMISEKS LÄBIVIIDAVAD VALIKKATSED VEREGA

Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood (ISO 10993-4:2017 + ISO 10993-4:2017/Amd 1:2025, Corrected version 2025-04)

EVS • EESTI STANDARDIMIS- JA AKREDITEERIMISKESKUS
ESTONIAN CENTRE FOR STANDARDISATION AND ACCREDITATION

EESTI STANDARDI EESSÕNA

NATIONAL FOREWORD

See Eesti standard EVS-EN ISO 10993-4 V2:2017 +A1:2025 sisaldab Euroopa standardi EN ISO 10993-4:2017 ja selle muudatuse A1:2025 ingliskeelset teksti.	This Estonian standard EVS-EN ISO 10993-4 V2:2017+A1:2025 consists of the English text of the European standard EN ISO 10993-4:2017 and its amendment A1:2025.
Standard on jõustunud sellekohase teate avaldamisega EVS Teatajas. Euroopa standardimisorganisatsioonid on teinud Euroopa standardi rahvuslikele liikmetele kättesaadavaks 18.10.2017, muudatus A1 26.02.2025.	This standard has been endorsed with a notification published in the official bulletin of the Estonian Centre for Standardisation and Accreditation. Date of Availability of the European standard is 18.10.2017, for A1 26.02.2025.
Muudatusega A1 lisatud või muudetud teksti algus ja lõpp on tekstis tähistatud sümbolitega ⟨A1⟩ ⟨A1⟩. Standard on kättesaadav Eesti Standardimis-ja Akrediteerimiskeskusest.	The start and finish of text introduced or altered by amendment A1 is indicated in the text by tags ⟨A1⟩ ⟨A1⟩. The standard is available from the Estonian Centre for Standardisation and Accreditation.

Tagasisidet standardi sisu kohta on võimalik edastada, kasutades EVS-i veebilehel asuvat tagasiside vormi või saates e-kirja meiliaadressile standardiosakond@evs.ee.

ICS 11.100.20

EUROPEAN STANDARD

NORME EUROPÉENNE

EUROPÄISCHE NORM

EN ISO 10993-4 + A1

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Supersedes EN ISO 10993-4:2009, EN ISO 10993-4:2017

English Version

Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood (ISO 10993-4:2017 + ISO 10993-4:2017/Amd 1:2025, Corrected version 2025-04)

Évaluation biologique des dispositifs médicaux - Partie 4: Choix des essais pour les interactions avec le sang (ISO 10993-4:2017 + ISO 10993-4:2017/Amd 1:2025, Version corrigée 2025-04)

Biologische Beurteilung von Medizinprodukten - Teil 4: Auswahl von Prüfungen zur Wechselwirkung mit Blut (ISO 10993-4:2017 + ISO 10993-4:2017/Amd 1:2025, korrigierte Fassung 2025-04)

This European Standard was approved by CEN on 4 October 2017. Amendment A1 was approved by CEN on 1 July 2024.

The Amendment A1 was corrected and reissued by the CEN-CENELEC Management Centre on 16 April 2025.

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

CEN-CENELEC Management Centre: Rue de la Science 23, B-1040 Brussels

Ref. No. EN ISO 10993-4:2017 E
+ EN ISO 10993-4:2017/A1:2025 E

European foreword

The text of ISO 10993-4:2017 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 10993-4:2017 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 April 2018, and conflicting national standards shall be withdrawn at the latest by April 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 10993-4:2009 and EN ISO 10993-4:2017.

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.

For relationship with EU Directives, 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 1 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
ISO 10993-12	EN ISO 10993-12:2012	ISO 10993-12:2012

NOTE 2 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 10993-4:2017 has been approved by CEN as EN ISO 10993-4:2017 without any modification.

A1 Amendment A1 European foreword

This document (EN ISO 10993-4:2017/A1:2025) 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 Amendment to the European Standard EN ISO 10993-4:2017 shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by August 2025, and conflicting national standards shall be withdrawn at the latest by August 2025.

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 standardization request addressed to CEN by the European Commission. The Standing Committee of the EFTA States subsequently approves these requests for its Member States.

For the relationship with EU Legislation, see informative Annex ZA, which is an integral part of this document.

Any feedback and questions on this document should be directed to the users’ national standards body/national committee. A complete listing of these bodies can be found on the CEN website.

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, Türkiye and the United Kingdom.

Endorsement notice

The text of ISO 10993-4:2017/Amd 1:2025, Corrected version 2025-04 has been approved by CEN as EN ISO 10993-4:2017/A1:2025 without any modification. A1

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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 10993-4:2002), which has been technically revised.

It also incorporates the Amendment ISO 10993-4:2002/Amd 1:2006.

The following changes were made:

a) some definitions have been revised and new definitions have been added;

b) Tables 1 and 2 have been consolidated into a single new Table 1 with test categories and headers reorganized to emphasize and include material and mechanical-induced haemolysis testing and *in vitro* and *in vivo* testing for assessment of risk for thrombosis;

c) Tables 3 and 4 have been consolidated into a single new Table 2 with a simplified list of suggested and most common tests;

d) Annex B has been updated to cover only the most common practiced tests for assessing blood interactions;

e) Annex C has been added to cover the topic of *in vivo* thrombosis and methods for testing;

f) Annex D, which was Annex C in the previous edition, has been updated and now includes added information on mechanically-induced haemolysis;

g) Annex E has been added to cover the topic of complement testing and best test method practices;

h) Annexes F and G have been added to present the less common tests used to assess interactions with blood and the tests that are not recommended for preclinical assessment of medical device blood interaction, respectively. Many of these methods were previously included in Annex B;

i) subtle language refinements can be found throughout the revised document;

j) the Bibliography has been reorganized by common subjects of interest and updated with additional and more current references.

〈A1〉 Amendment A1 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.

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ISO draws attention to the possibility that the implementation of this document may involve the use of (a) patent(s). ISO takes no position concerning the evidence, validity or applicability of any claimed patent rights in respect thereof. As of the date of publication of this document, ISO had not received notice of (a) patent(s) which may be required to implement this document. However, implementers are cautioned that this may not represent the latest information, which may be obtained from the patent database available at www.iso.org/patents. ISO shall not be held responsible for identifying any or all such patent rights.

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.

This corrected version of ISO 10993-4:2017/Amd.1:2025 incorporates the following correction: the document layout has been corrected so that all the changes are listed from page 1 onwards. 〈A1〉

Introduction

The selection and design of test methods for the interactions of medical devices with blood should take into consideration device design, materials, clinical utility, usage environment and risk benefit. This level of specificity can only be covered in vertical standards.

The initial source for developing this document was the publication, *Guidelines for blood/material interactions*, Report of the National Heart, Lung, and Blood Institute[14] chapters 9 and 10. This publication was subsequently revised[15].

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Biological evaluation of medical devices —

Part 4:
Selection of tests for interactions with blood

1 Scope

This document specifies general requirements for evaluating the interactions of medical devices with blood.

It describes

a) a classification of medical devices that are intended for use in contact with blood, based on the intended use and duration of contact as defined in ISO 10993-1,

b) the fundamental principles governing the evaluation of the interaction of devices with blood,

c) the rationale for structured selection of tests according to specific categories, together with the principles and scientific basis of these tests.

Detailed requirements for testing cannot be specified because of limitations in the knowledge and precision of tests for evaluating interactions of devices with blood. This document describes biological evaluation in general terms and may not necessarily provide sufficient guidance for test methods for a specific device.

The changes in this document do not indicate that testing conducted according to prior versions of this document is invalid. For marketed devices with a history of safe clinical use, additional testing according to this revision is not recommended.

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

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 10993-1, ISO 10993-12 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