MEDITSIINISEADMETE BIOLOOGILINE HINDAMINE. OSA 15: METALLIDE JA SULAMITE DEGRADATSIOONISAADUSTE TUVASTAMINE JA KOGUSELINE KINDLAKSMÄÄRAMINE

Biological evaluation of medical devices - Part 15: Identification and quantification of degradation products from metals and alloys (ISO 10993-15:2019)

EESTI STANDARDI EESSÕNA

NATIONAL FOREWORD

See Eesti standard EVS-EN ISO 10993-15:2023 sisaldab Euroopa standardi EN ISO 10993-15:2023 ingliskeelset teksti.	This Estonian standard EVS-EN ISO 10993-15:2023 consists of the English text of the European standard EN ISO 10993-15:2023.
Standard on jõustunud sellekohase teate avaldamisega EVS Teatajas.	This standard has been endorsed with a notification published in the official bulletin of the Estonian Centre for Standardisation and Accreditation.
Euroopa standardimisorganisatsioonid on teinud Euroopa standardi rahvuslikele liikmetele kättesaadavaks 24.05.2023.	Date of Availability of the European standard is 24.05.2023.
Standard on kättesaadav Eesti Standardimis-ja Akrediteerimiskeskusest.	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.

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EUROPEAN STANDARD

NORME EUROPÉENNE

EUROPÄISCHE NORM

EN ISO 10993-15

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English Version

Biological evaluation of medical devices - Part 15: Identification and quantification of degradation products from metals and alloys (ISO 10993-15:2019)

Évaluation biologique des dispositifs médicaux - Partie 15: Identification et quantification des produits de dégradation issus des métaux et alliages (ISO 10993-15:2019)

Biologische Beurteilung von Medizinprodukten - Teil 15: Qualitativer und quantitativer Nachweis von Abbauprodukten aus Metallen und Legierungen (ISO 10993-15:2019)

This European Standard was approved by CEN on 19 April 2023.

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 10993-15:2023 E

European foreword

This document (EN ISO 10993-15:2023) 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 November 2023, and conflicting national standards shall be withdrawn at the latest by November 2023.

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 10993-15:2009.

This document has been prepared under a Standardization Request given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of EU Directive(s) / Regulation(s).

For the relationship with EU Directive(s) / Regulation(s), 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 10993-15:2019 has been approved by CEN as EN ISO 10993-15:2023 without any modification.

Contents

Page

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.*

This second edition cancels and replaces the first edition (ISO 10993-15:2000), which has been technically revised.

The main changes compared to the previous edition are as follows:

a) the document now considers materials designed to degrade in the body as well as materials that are not intended to degrade;

b) the information on test methods has been amended to consider nanomaterials and relevant material specific standards;

c) the test solution (electrolyte) has been specified more;

d) the sample shape has been specified more;

e) the immersion test procedure has been expanded;

f) the status of Annex C in the previous edition has been changed and now included as Annex A.

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

One of the potential health hazards resulting from medical devices can be due to the interactions of their electrochemically induced degradation products with the biological system. Therefore, the evaluation of potential degradation products from metallic materials by methods suitable for testing the electrochemical behaviour of these materials is a necessary step in the biological performance testing of materials.

The body environment typically contains cations of sodium, potassium, calcium, and magnesium, and anions of chloride, bicarbonate, phosphate, and organic acids generally in concentrations between 2×10^{-3} mol/l and 150×10^{-3} mol/l. A range of organic molecules such as proteins, enzymes, and lipoproteins are also present, but their concentrations can vary to a great extent. Earlier studies assumed that organic molecules did not exert a significant influence on the degradation of metallic implants, but newer investigations indicate that implant–tissue interactions should be taken into account. Depending on a particular product or application, altering the pH of the testing environment may also need to be considered.

In such biological environments, metallic materials may undergo a certain degradation, and the different degradation products can interact with the biological system in different ways. Therefore, the identification and quantification of these degradation products is an important step in evaluating the biological performance of medical devices.

Biological evaluation of medical devices —

Part 15: Identification and quantification of degradation products from metals and alloys

1 Scope

This document specifies general requirements for the design of tests for identifying and quantifying degradation products from final metallic medical devices or corresponding material samples finished as ready for clinical use.

This document is applicable only to those degradation products generated by chemical alteration of the final metallic device in an *in vitro* degradation test. Because of the nature of *in vitro* tests, the test results approximate the *in vivo* behaviour of the implant or material. The described chemical methodologies are a means to generate degradation products for further assessments.

This document is applicable to both materials designed to degrade in the body as well as materials that are not intended to degrade.

This document is not applicable to evaluation of degradation which occurs by purely mechanical processes; methodologies for the production of this type of degradation product are described in specific product standards, where available.

NOTE Purely mechanical degradation causes mostly particulate matter. Although this is excluded from the scope of this document, such degradation products can evoke a biological response and can undergo biological evaluation as described in other parts of ISO 10993.

Because of the wide range of metallic materials used in medical devices, no specific analytical techniques are identified for quantifying the degradation products. The identification of trace elements ($<10^{-6}$ w/w) contained in the specific metal or alloy is not addressed in this document, nor are specific requirements for acceptable levels of degradation products provided in this document.

This document excludes the biological activity of the degradation products. (See instead the applicable clauses of ISO 10993-1 and ISO 10993-17).

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 3585, *Borosilicate glass 3.3 — Properties*

ISO 3696, *Water for analytical laboratory use — Specification and test methods*

ISO 8044, *Corrosion of metals and alloys — Basic terms and definitions*

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

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 10993-16, *Biological evaluation of medical devices — Part 16: Toxicokinetic study design for degradation products and leachables*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 8044, ISO 10993-1, ISO 10993-9, ISO 10993-12 and the following apply.

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

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

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

3.1
alloy
material composed of a metallic element with one or more addition(s) of other metallic and/or non-metallic elements

3.2
electrolyte
medium in which electric current is transported by ions

3.3
open-circuit potential
potential of an electrode measured with respect to a reference electrode or another electrode when no current flows to or from it

3.4
passive limit potential
E_a
electrode potential of the positive limit of the passive range

Note 1 to entry: See Figure 1.

3.5
breakdown potential
E_p
critical electrode potential above which localized or transpassive corrosion is found to occur

Note 1 to entry: See Figure 1.

3.6
absorb
action of a non-endogenous (foreign) material or substance passing through or being assimilated by cells and/or tissue over time

3.7
potentiodynamic test
test in which the electrode potential is varied at a preprogrammed rate and the relationship between current density and electrode potential is recorded