SLOVENSKI STANDARD

oSIST prEN ISO 10993-15:2018

01-junij-2018

Biološko ovrednotenje medicinskih pripomočkov - 15. del: Identifikacija in ugotavljanje količine razgradnih produktov iz kovin in zlitin (ISO/DIS 10993-15:2018)

Biological evaluation of medical devices - Part 15: Identification and quantification of degradation products from metals and alloys (ISO/DIS 10993-15:2018)

Biologische Beurteilung von Medizinprodukten - Teil 15: Qualitativer und quantitativer Nachweis von Abbauprodukten aus Metallen und Legierungen (ISO/DIS 10993-15:2018)

Évaluation biologique des dispositifs médicaux - Partie 15: Identification et quantification des produits de dégradation issus des métaux et alliages (ISO/DIS 10993-15:2018)

Ta slovenski standard je istoveten z: prEN ISO 10993-15

ICS:

11.100.20	Biološko ovrednotenje medicinskih pripomočkov	Biological evaluation of medical devices

oSIST prEN ISO 10993-15:2018 en,fr,de

DRAFT INTERNATIONAL STANDARD

ISO/DIS 10993-15

ISO/TC **194**

Secretariat: **DIN**

Voting begins on:
2018-04-24

Voting terminates on:
2018-07-17

Biological evaluation of medical devices —

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

Évaluation biologique des dispositifs médicaux —

Partie 15: Identification et quantification des produits de dégradation issus des métaux et alliages

ICS: 11.100.20

This document is circulated as received from the committee secretariat.

ISO/CEN PARALLEL PROCESSING

Reference number
ISO/DIS 10993-15:2018(E)

ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Fax: +41 22 749 09 47
Email: copyright@iso.org
Website: www.iso.org

Published in Switzerland

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

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

c) test solution (electrolyte) more specified;

d) sample shape more specified;

e) immersion test procedure expanded;

f) Annex C changed to normative and now Annex A.

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

Introduction

One of the potential health hazards resulting from medical devices may 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 behavior 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 x 10 –3 mol and 150 x 10 –3 mol. A range of organic molecules such as proteins, enzymes, and lipoproteins is also present, but their concentrations may 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–protein 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 may 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 provides guidance on 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 accelerated degradation test. Because of the accelerated nature of these tests, the test results may not reflect the implant or material behavior in the body. The described chemical methodologies are a means to generate degradation products for further assessments.

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

This document is not applicable to degradation products induced by applied mechanical stress.

Mechanically induced degradation, such as wear, can be covered in the appropriate product-specific standard. Where product-group standards provide applicable product-specific methodologies for the identification and quantification of degradation products, those standards should be considered.

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 part of ISO 10993, nor are specific requirements for acceptable levels of degradation products provided in this part of ISO 10993.

This document does not address 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:

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

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

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
solution containing ions with the capacity to conduct electric current

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.

4 Degradation test methods

4.1 General

To identify and quantify degradation products from metals and alloys in medical devices, a combination of two procedures is described. The choice of test procedure shall be justified according to the function of the medical device.

The first procedure described is a combination of a potentiodynamic test and a potentiostatic test. The second procedure described is an immersion test.

The potentiodynamic test is used to determine the general electrochemical behavior of the material under consideration and to determine certain specific points (E_a and E_p) on the potential/current density curve.

The immersion test is used to chemically degrade the test material to generate degradation products to be analyzed.

If there is the possibility of the loss of a coating from a metallic substrate due to degradation, the potential degradation products from the substrate material shall be considered, as well as the coating itself. In addition, if a metallic substrate coated with a non-metallic material is to be tested, the requirements of ISO 10993-13 and/or ISO 10993-14 shall be considered in order to determine the potential degradation products of the coating.

The identified and quantified degradation products form the basis for evaluation of biological response and, if appropriate, toxicokinetic studies in accordance with ISO 10993-16.

For those medical devices composed of or containing nanoscale materials, and for those instances where metallic degradation products are within the nanoscale size range (approximately 1 nm to 100 nm), the user is referred to ISO 10993-22 when creating their risk assessment documents.

If the medical device is made using a metal or metal alloy designed to be absorbed by the body, the user is directed to relevant material specific standards (see bibliography) for methods and specific considerations (e.g. electrolyte, atmosphere, etc.) appropriate for this class of materials.

4.2 Prerequisites

The rates of electrochemical degradation reactions are sensitive to small variations in test conditions, instrumentation, sample conditions, and preparation. Therefore, electrochemical degradation testing shall be carried out in an appropriately equipped laboratory by experienced and qualified personnel. This includes proper maintenance and calibration of the test equipment. The methods and operating conditions of the equipment shall also be validated.

Fulfillment of electrochemical test conditions for stability, warm-up time, etc., can be demonstrated by conformance to.[1]

5 Reagent and sample preparation

5.1 Sample documentation

The general composition of the material(s) under test shall be documented.

5.2 Test solution (electrolyte)

The test solution (electrolyte) to be used shall be appropriate for the intended use of the medical device. All chemicals shall be of analytical grade and dissolved in water of grade 2 in accordance with ISO 3696.

The first choice for the electrolyte shall be an aqueous solution of 0,9 % sodium chloride.

Dependent on the composition and corrosion mechanism of the metal or alloy being tested, other electrolytes may be used, such as artificial saliva or artificial plasma. Examples of electrolyte compositions are given in Annex A, but other more material and physiologically relevant electrolyte solutions and test conditions may be utilized. Possible effect of implant–protein interactions should be taken into account.

NOTE Formulations for artificial sweat, gastrointestinal fluids, and lung fluids have been used [see Bibliography].

In the test report, the choice of electrolyte shall be justified. If other than an aqueous solution of 0,9 % sodium chloride is used, the pH of the electrolyte shall be specified.