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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

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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 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

3.8
potentiostatic test
test in which the electrode potential is maintained constant and the current is recorded as a function of time

4 Degradation test methods

4.1 General

To identify and quantify degradation products from metals and alloys in medical devices, two procedures are 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 potentiostatic test is used to electrochemically degrade the test material at a constant potential above the breakdown potential to generate degradation products to be analyzed.

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 used 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. If appropriate, toxicokinetic studies in accordance with ISO 10993-16 shall be used.

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/TR 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.

Fulfilment of electrochemical test conditions for stability, warm-up time, etc., can be demonstrated by conformance to Reference [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–related 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.

5.3 Preparation of test samples

5.3.1 Test samples

The sensitivity of chemical degradation testing is related to variation in material composition, to material processing, and to surface-finishing procedures. The sampling procedure, sample shape, and surface preparation are critical. In addition, confined spaces within or around the test article can result in crevice corrosion and defects in coatings can cause pit corrosion, both of which shall be taken into consideration. The samples shall be representative of the final devices.

5.3.2 Sampling

For each chemical test, multiple test samples shall be prepared as specified in ISO 10993-12. If substantial differences in the test results are found, the reasons for the difference shall be determined, and more samples shall be tested. The number of samples shall be justified.

If the metallic sample has anisotropic properties due to manufacturing conditions, tests involving single-surface exposure should include samples cut parallel to both the transverse and longitudinal manufacturing directions.

5.3.3 Sample shape

Standard samples (e.g. circular- or rectangular-section bars, flat coupons, one single free surface) may be used for degradation testing if they are prepared in a manner comparable to the final medical device. Samples of actual device components may be of any shape and condition; however, the testing shall be carried out under well-controlled conditions which shall be reported.

The surface area of the sample exposed to the electrolyte shall be determined to ±10 % of the total geometrical area to assure an accurate and repeatable determination of the degradation rates.

If representative samples are used, consideration shall be made regarding whether the differences between the representative sample and the final medical device or component could affect the results of the test. Testing of representative samples instead of the final medical device shall be supported by a description of any differences between the representative sample and the final device. The report shall contain a detailed rationale for why each difference is not expected to alter the biocompatibility of the final device.

5.3.4 Sample surface condition

Since the surface condition of a material can affect its electrochemical behaviour, the surface condition of the test sample shall be identical to the final medical device and shall be described in the test report.

6 Electrochemical tests

6.1 Apparatus

6.1.1 Test cells of borosilicate glass, in appropriate sizes, in accordance with ISO 3585, with a means of controlling the bath temperature within ±1 °C.

6.1.2 Scanning potentiostat with a potential range ±2 V and a current output range from 10^{-9} A to 10^{-1} A.

6.1.3 Potential-measuring instrument with a high input impedance (>10^{11} Ω) and a sensitivity and accuracy to detect a change of 1 mV over a potential range between ±2 V.

6.1.4 Current-measuring instrument capable of measuring a current to ±1 % of the absolute value over a current range between 10^{-9} A and 10^{-1} A.

6.1.5 Working electrode (test sample).

6.1.6 Counter-electrode(s) such as platinum (grid, plate, or wire) or vitreous carbon with an area at least 10 times that of the working electrode.

6.1.7 Reference electrode which has a known electrode potential and is stable.

6.1.8 pH-meter with a sensitivity of ±0,1.

A schematic diagram of the electrochemical measurement circuit which can be used as a system with variable potential is given in Annex B, Figure B.1.

A schematic drawing of an electrolytic cell is given in Annex C.

6.2 Sample preparation

Mount the test sample in a watertight electrode holder so that only the test surface is in contact with the electrolyte. Take care to avoid the creation of conditions where crevice corrosion can occur due to the formation of a crevice between the mounting and the sample. Before testing, clean the sample ultrasonically for 10 min to 15 min in ethanol, carefully rinse the sample with water of grade 2 in accordance with ISO 3696, and immediately transfer the sample into the test cell.

6.3 Test conditions

Fill the test cell with the test solution (electrolyte). If the electrochemical behavior is temperature sensitive in the range of 10 °C to 50 °C, maintain the electrolyte cell at (37 ± 1) °C. Reduce the oxygen level in the electrolyte by bubbling oxygen-free nitrogen or argon at a rate of approximately 100 cm^3/min for not less than 30 min prior to the start of the test. The electrolyte shall be agitated either by the bubbling gas or mechanical means to avoid concentration gradients. If gas agitation is used, take care not to have any gas bubbles adhering to the active test surface.

