

First edition
2000-12-01

Corrected and reprinted
2001-04-01

**Biological evaluation of medical devices —
Part 15:
Identification and quantification of
degradation products from metals and
alloys**

iTeh STANDARD PREVIEW

Évaluation biologique des dispositifs médicaux —

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

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Reference number
ISO 10993-15:2000(E)

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Printed 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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 3.

Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this part of ISO 10993 may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

International Standard ISO 10993-15 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

ISO 10993 consists of the following parts, under the general title *Biological evaluation of medical devices*:

- *Part 1: Evaluation and testing*
- *Part 2: Animal welfare requirements*
- *Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity*
- *Part 4: Selection of tests for interactions with blood*
- *Part 5: Tests for in vitro cytotoxicity*
- *Part 6: Tests for local effects after implantation*
- *Part 7: Ethylene oxide sterilization residuals*
- *Part 8: Selection and qualification of reference materials for biological tests*
- *Part 9: Framework for identification and quantification of potential degradation products*
- *Part 10: Tests for irritation and delayed-type hypersensitivity*
- *Part 11: Tests for systemic toxicity*
- *Part 12: Sample preparation and reference materials*
- *Part 13: Identification and quantification of degradation products from polymeric medical devices*
- *Part 14: Identification and quantification of degradation products from ceramics*
- *Part 15: Identification and quantification of degradation products from metals and alloys*
- *Part 16: Toxicokinetic study design for degradation products and leachables*

- *Part 17: Establishment of allowable limits for leachable substances using health-based risk assessment*
- *Part 18: Chemical characterization of materials*

Future parts will deal with other relevant aspects of biological testing.

Annexes A, B and C of this part of ISO 10993 are for information only.

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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 2×10^{-3} mol and 150×10^{-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.

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Biological evaluation of medical devices —

Part 15:

Identification and quantification of degradation products from metals and alloys

1 Scope

This part of ISO 10993 provides guidance on general requirements for the design of tests for identifying and quantifying degradation products from finished metallic medical devices or corresponding material samples finished as ready for clinical use. It is applicable only to those degradation products generated by chemical alteration of the finished 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 part of ISO 10993 is not applicable to degradation products induced by applied mechanical stress.

NOTE Mechanically induced degradation, such as wear, may 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 ($< 10^{-6}$) 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 part of ISO 10993 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 normative documents contain provisions which, through reference in this text, constitute provisions of this International Standard. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this International Standard are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

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.*

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

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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 part of ISO 10993, the terms and definitions given in ISO 8044, ISO 10993-1, ISO 10993-9, ISO 10993-12 and the following apply.

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

See Figure 1.

3.5 breakdown potential

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

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 analysed.

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.

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.

NOTE Fulfilment 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 isotonic aqueous solution of 0,9 % sodium chloride. Other electrolytes may be used, such as artificial saliva or artificial plasma. Examples of alternative compositions are given in annex C.

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. The samples shall be representative of the finished devices.

5.3.2 Sampling

For each chemical test, at least two test samples shall be prepared as specified in ISO 10993-12. If substantial deviations in the test results are found, the reasons for the deviation shall be determined, and more samples shall be tested.

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, either circular- or rectangular-section bars or flat coupons, or one single free surface may be used for degradation testing if they are prepared in a manner comparable to the representative 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 an accuracy of better than 10 % of the total geometrical area to assure an accurate and repeatable determination of the degradation rates.

5.3.4 Sample surface condition

Since the surface condition of a material may affect its electrochemical behaviour, the surface condition of the test sample shall be identical to the finished medical device and shall be described in the test report. For comparing test results of different materials, the surface condition of the test samples shall be the same.

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 $\pm 1\%$ 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.

6.1.8 pH-meter with a sensitivity of $\pm 0,1$.

A schematic diagram of the electrochemical measurement circuit which may be used as a system with variable potential is given in annex A.

A schematic drawing of an electrolytic cell is given in annex B.

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 the formation of a crevice between the mounting and the sample. Before testing, clean the specimen ultrasonically for 10 min to 15 min in ethanol, carefully rinse with water of grade 2 in accordance with ISO 3696 and immediately transfer into the test cell.

6.3 Test conditions

Fill the test cell with the test solution (electrolyte). If the electrochemical behaviour 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 $100 \text{ cm}^3 \text{ min}^{-1}$ 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.

Magnetic stirrers often interfere with electrochemical test cells. If they are used, their effect on the test cell shall be determined as part of the validation of test equipment, see 4.2.

6.4 Potentiodynamic measurements

Measure the open-circuit potential not less than 2 h after the immersion of the working electrode. This potential shall be the starting potential for potentiodynamic measurements. The sweep rate shall be $1,0 \text{ mV} \cdot \text{s}^{-1}$, except in tests where the sweep rate has little effect, where the test may be accelerated by increasing the sweep rate to $10 \text{ mV} \cdot \text{s}^{-1}$. Record the potential/current density curve up to a maximum of 2000 mV or a maximum current density of $1,0 \text{ mA} \cdot \text{cm}^{-2}$, whichever comes first, to evaluate the transpassive range of the sample (see Figure 1). To ensure consistency, reverse the scan and continue back at least to the open-circuit potential. Then repeat the test back to 2000 mV or $1,0 \text{ mA} \cdot \text{cm}^{-2}$. If the curves are not reproducible, then continue cycling 5 to 10 times. If consistent potential/current density curves are not achieved after 5 to 10 cycles, investigate possible causes such as test set-up, electrode function, innate material properties, etc. The log current density/potential curves should also be recorded (see Figure 2). Record the breakdown potential (E_p) from the last cycle taken (see Figure 1).

Noble metals may behave differently from passivating metals during an electrochemical test. Therefore, take care in determining the breakdown potential (E_p) for different metal systems.

6.5 Potentiostatic measurements

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This method permits qualitative and quantitative determination of degradation products which might be dissolved in the electrolyte.

Hold a new test sample at a constant electrode potential during the test time, and record the current density/time curve. The potential used to determine the degradation products shall be the breakdown potential (E_p) + 50 mV. Depending upon the material studied, the polarization duration shall be either 1 h or 5 h and shall be reported. Measure and record the volume of the electrolyte for use in future calculations.

7 Immersion test

7.1 Apparatus

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

7.1.2 pH-meter with a sensitivity of $\pm 0,1$.