SLOVENSKI STANDARD
oSIST prEN ISO 10993-6:2015

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Biološko ovrednotenje medicinskih pripomočkov - 6. del: Preskusi, povezani z lokalnimi učinki po implantaciji (ISO/DIS 10993-6:2014)

Biological evaluation of medical devices - Part 6: Tests for local effects after implantation (ISO/DIS 10993-6:2014)

Biologische Beurteilung von Medizinprodukten - Teil 6: Prüfungen auf lokale Effekte nach Implantationen (ISO/DIS 10993-6:2014)

Évaluation biologique des dispositifs médicaux - Partie 6: Essais concernant les effets locaux après implantation (ISO/DIS 10993-6:2014)

Ta slovenski standard je istoveten z: **prEN ISO 10993-6**

ICS:

11.100.20	Biološko ovrednotenje medicinskih pripomočkov	Biological evaluation of medical devices

oSIST prEN ISO 10993-6:2015 **en**

DRAFT INTERNATIONAL STANDARD

ISO/DIS 10993-6

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Biological evaluation of medical devices —

Part 6:
Tests for local effects after implantation

Évaluation biologique des dispositifs médicaux —

Partie 6: Essais concernant les effets locaux après implantation

ICS: 11.100.20

ISO/CEN PARALLEL PROCESSING

This draft has been developed within the International Organization for Standardization (ISO), and processed under the **ISO lead** mode of collaboration as defined in the Vienna Agreement.

This draft is hereby submitted to the ISO member bodies and to the CEN member bodies for a parallel five month enquiry.

Should this draft be accepted, a final draft, established on the basis of comments received, will be submitted to a parallel two-month approval vote in ISO and formal vote in CEN.

To expedite distribution, this document is circulated as received from the committee secretariat. ISO Central Secretariat work of editing and text composition will be undertaken at publication stage.

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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.

The committee responsible for this document is ISO/TC 194.

The major technical changes are the following:

a)

b)

c)

d)

e)

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

Part 1: Evaluation and testing within a risk management system

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 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

Part 18: Chemical characterization of materials

Part 19: Physico-chemical, morphological and topographical characterization of materials (Technical specification)

Part 20: Principles and methods for immunotoxicology testing of medical devices (Technical specification)

Part 33: Supplement to ISO 10993-3:— *Guidance on tests to evaluate genotoxicity [Technical Report]*

The following definitions apply in understanding how to implement an ISO International Standard and other normative ISO deliverables (TS, PAS, IWA).

— "shall" indicates a requirement

— "should" indicates a recommendation

— "may" is used to indicate that something is permitted

— "can" is used to indicate that something is possible, for example, that an organization or individual is able to do something

In 3.3.1 of the ISO/IEC Directives, Part 2 (sixth edition, 2011) defines a **requirement** as an "expression in the content of a document conveying criteria to be fulfilled if compliance with the document is to be claimed and from which no deviation is permitted."

In 3.3.2 of the ISO/IEC Directives, Part 2 (sixth edition, 2011) defines a **recommendation** as an "expression in the content of a document conveying that among several possibilities one is recommended as particularly suitable, without mentioning or excluding others, or that a certain course of action is preferred but not necessarily required, or that (in the negative form) a certain possibility or course of action is deprecated but not prohibited."

Biological evaluation of medical devices —

Part 6:
Tests for local effects after implantation

1 Scope

This part of ISO 10993 specifies test methods for the assessment of the local effects after implantation of biomaterials intended for use in medical devices.

This part of ISO 10993 applies to materials that are:

— solid and non- absorbable;

— degradable and/or absorbable;

— non-solid, such as porous materials, liquids, gels, pastes and particulates.

The test sample is implanted into a site and animal species appropriate for the evaluation of the biological safety of the material. These implantation tests are not intended to evaluate or determine the performance of the test sample in terms of mechanical or functional loading. This part of ISO 10993 may also be applied to medical devices that are intended to be used topically in clinical indications where the surface or lining may have been breached, in order to evaluate local tissue responses.

The local effects are evaluated by a comparison of the tissue response caused by a test sample to that caused by control materials used in medical devices of which the clinical acceptability and biocompatibility characteristics have been established. The objective of the test methods is to characterize the history and evolution of the tissue response after implantation of a medical device/biomaterial including final integration or absorption/degradation of the material. In particular for degradable/absorbable materials the degradation characteristics of the material and the resulting tissue response should be determined.

This part of ISO 10993 does not deal with systemic toxicity, carcinogenicity, teratogenicity or mutagenicity. However, the long-term implantation studies intended for evaluation of local biological effects may provide insight into some of these properties. Systemic toxicity studies conducted by implantation may satisfy the requirements of this part of ISO 10993. When conducting combined studies for evaluating local effects and systemic effects, the requirements of both standards shall be fulfilled.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 10993-1:2009, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-2, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

ISO 10993-11, *Biological evaluation of medical devices — Part 11: Tests for systemic toxicity*

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

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 10993-1, ISO 10993-2, ISO 10993-12, ISO 10993-16 and the following apply.

3.1
absorb
in biomaterials, action of a non-endogenous (foreign) material or substance passing through or being assimilated by cells and/or tissue over time

3.2
degradation
decomposition of a material

[SOURCE: ISO 10993-9:1999, definition 3.1]

3.3
degradation product
<byproduct> any intermediate or final result from the physical, metabolic, and/or chemical decomposition of a material or substance

[SOURCE: ISO/TR 37137:2014, definition 2.2]

3.4
degrade
to physically, metabolically, and/or chemically decompose a material or substance

[SOURCE: ISO/TR 37137:2014, definition 2.3]

3.5
biomaterial
material intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body

[SOURCE: European Society Biomaterials Conference II]

4 Common provisions for implantation test methods

4.1 General

It is important that the study be planned in sufficient detail such that all relevant information can be extracted from the use of each animal and each study (see ISO 10993-2, ISO 10993-11 and ISO 10993-16).

All animal studies shall be performed in a facility approved by a nationally recognized organization and in accordance with all appropriate regulations dealing with laboratory animal welfare. These studies shall be performed under good laboratory practices or other recognized quality assurance systems, and comply with the requirements of ISO 10993-2.

The provisions of this clause shall apply to the test methods specified in Annex A, Annex B, Annex C, and Annex D.

4.2 Preparation of samples for implantation

Test sample and reference or control material preparation shall be in compliance with ISO 10993-12. The implant size and shape shall be documented and justified. Test samples for various implant sites are described in Annex A, Annex B, Annex C, and Annex D. Physical characteristics (such as form, density, hardness, surface) can influence the character of the tissue response to the test material and shall be recorded and taken into account when the response is characterized.

Each implant shall be manufactured, processed, cleaned of contaminants and sterilized by the method intended for the final product and this shall be confirmed in the study documentation. After final preparation and sterilization, the implant specimens shall be handled aseptically and in such a way as to ensure that they are not damaged or contaminated in any way prior to or during implantation.

For materials used as scaffolds for tissue-engineered medical products, it may be appropriate not to use the final preparation pre-populated with cells, as the immune reaction of the animal to the cellular components of such products and the reaction of the cells to the animal, may interfere with the resulting local tissue response.

For composite materials (e.g. bone cements, dental materials) the components may be mixed before use and allowed to set before implantation. However, materials that are designed for use in devices with *in situ* polymerization shall be introduced in a manner such that *in situ* polymerization occurs. The procedure used shall be documented and justified.

Non-solid materials (including powders) may be contained in open-ended cylindrical tubes for the purpose of testing for local effects after implantation (see ISO 10993-12 for the selection of materials for tubes). Prepare the test material according to the manufacturer's instructions and insert the material into the tube until level with the end, taking care not to contaminate the outer surface of the tube with the test material; if contamination occurs the sample shall not be implanted. Avoid entrapment of air in the tube and ensure that the end surfaces of the inserted material in the tube and the tube ends are smooth.

NOTE 1 Polyethylene (PE), polypropylene (PP) or polytetrafluoroethylene (PTFE) tubes are commonly used for this purpose. PE tubes can be deformed by autoclaving. PTFE tubes are difficult to section in the microtome, and substitution by PE or PP tubes of the same dimensions can be preferable when the tubes are to remain in the tissue blocks during sectioning.

Evaluation shall be performed by comparing to the tissue reaction to that of a similar sample/material of which the clinical acceptability and biocompatibility characteristics have been established.

NOTE 2 For further guidance, see ISO 10993-12.

The physical characteristics such as shape, and especially the surface condition of the control(s), shall be as similar to that of the implant test samples as is practically possible, with any deviations being explained and justified. When the test material is contained in a tube, the control shall be of the same material as the tube and have the same diameter as the outer diameter of the tube. The choice of the control rod or tube shall be documented and justified.

For implantation studies the amount or size of the test and control article shall be documented.

4.3 Study design

For devices comprised of 2 or more different materials, the test articles should be of similar composition or multiple implants may be needed e.g. if a device is made of HDPE and titanium then the test article should be made of HDPE and titanium or separate HDPE and titanium coupons should be implanted

5 Test methods, general aspects

5.1 Tissue and implantation site

The test sample shall be implanted into the tissues most relevant to the intended clinical use of the material. The justification for the choice of sample numbers, tissue and implantation sites shall be documented. Test methods for various implantation sites are given in Annex A, Annex B, Annex C, and Annex D. If other implantation sites are chosen, the general scientific principles behind the test methods