SLOVENSKI STANDARD
oSIST prEN ISO 10993-4:2016

01-februar-2016

Biološko ovrednotenje medicinskih pripomočkov - 4. del: Izbira preskusov za ugotavljanje interakcij s krvjo (ISO/DIS 10993-4:2015)

Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood (ISO/DIS 10993-4:2015)

Biologische Beurteilung von Medizinprodukten - Teil 4: Auswahl von Prüfungen zur Wechselwirkung mit Blut (ISO 10993-4:2002, einschließlich ¿nderung 1:2006)

Évaluation biologique des dispositifs médicaux - Partie 4: Choix des essais pour les interactions avec le sang (ISO/DIS 10993-4:2015)

Ta slovenski standard je istoveten z: **prEN ISO 10993-4**

ICS:

11.100.20	Biološko ovrednotenje medicinskih pripomočkov	Biological evaluation of medical devices

oSIST prEN ISO 10993-4:2016 **en**

DRAFT INTERNATIONAL STANDARD

ISO/DIS 10993-4

ISO/TC **194**

Secretariat: **DIN**

Voting begins on:
2015-11-26

Voting terminates on:
2016-02-26

Biological evaluation of medical devices —

Part 4:
Selection of tests for interactions with blood

Évaluation biologique des dispositifs médicaux —

Partie 4: Choix des essais pour les interactions avec le sang

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.

Reference number
ISO/DIS 10993-4:2015(E)

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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 WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

The committee responsible for this document is ISO/TC 194, *Biological and clinical evaluation of medical devices.*

This third edition cancels and replaces the second edition (ISO 10993-4:2007, ISO 10993-4: A1:2009), which has been technically revised.

The major technical changes are the following:

a) some definitions have been revised and new definitions have been added;

b) Original Tables 1 and 2 have been consolidated into a single new Table 1 with test categories and headers reorganized to emphasize and include (1) material and mechanical-induced haemolysis testing and (2) in vitro and *in vivo* testing for assessment of risk for thrombosis;

c) Original Tables 3 and 4 have been consolidated into a single new Table 2 with a simplified list of suggested and most common tests;

d) Annex B has been updated to cover only the most common practiced tests for assessing blood interactions;

e) A new Annex C has been added to cover the topic of *in vivo* thrombosis and methods for testing;

f) Annex D, previously Annex C Evaluation of the haemolytic properties of medical devices and their components, has been updated and now includes added information on mechanically-induced haemolysis;

g) New Annex E has been added to cover the topic of Complement testing and best test method practices;

h) New Annexes F and Annex G are added to present the less common tests used to assess interactions with blood, and, tests not used in preclinical assessment of medical device blood interaction, respectively. Many of these methods were previously included in Annex B;

i) Subtle language refinements can be found throughout the revised document;

j) The Bibliography has been reorganized by common subjects of interest and updated with additional and more current references.

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: *Method for the 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]*

Introduction

The selection and design of test methods for the interactions of medical devices with blood should take into consideration device design, materials, clinical utility, usage environment and risk benefit. This level of specificity can only be covered in vertical standards.

The initial source for developing this part of ISO 10993 was the publication, *Guidelines for blood/material interactions,* Report of the National Heart, Lung, and Blood Institute [16]; chapters 9 and 10. This publication has since been revised [17].

Biological evaluation of medical devices — Part 4: Selection of tests for interactions with blood

1 Scope

This part of ISO 10993 specifies general requirements for evaluating the interactions of medical devices with blood.

It describes

a) a classification of medical devices that are intended for use in contact with blood, based on the intended use and duration of contact as defined in ISO 10993-1,

b) the fundamental principles governing the evaluation of the interaction of devices with blood,

c) the rationale for structured selection of tests according to specific categories, together with the principles and scientific basis of these tests.

Detailed requirements for testing cannot be specified because of limitations in the knowledge and precision of tests for interactions of devices with blood. This part of ISO 10993 describes biological evaluation in general terms and may not necessarily provide sufficient guidance for test methods for a specific device.

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 system*

ISO 10993-2:2006, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

3 Terms and definitions

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

3.1
anticoagulant
agent which prevents or delays blood coagulation

EXAMPLES Heparin, ethylenediaminetetraacetic acid (EDTA), sodium citrate.

3.2
blood/device interaction
any interaction between blood or a blood component and a device

3.3
coagulation
phenomenon that results from activation of the clotting (coagulation) factor cascade

Note 1 to entry: Factors of the coagulation cascade and fibrinolytic systems can be measured following exposure to devices either *in vitro* or *in vivo*.

3.4
complement system
part of the innate immune system consisting of over 30 distinct plasma proteins, including enzymes, cofactors, and cellular receptors which may be involved in the promotion of thrombosis

Note 1 to entry: Effector molecules produced from complement components are possible components in the phenomena of inflammation, phagocytosis and cell lysis. Complement activation related to immunotoxicity, hypersensitivity and generation of anaphylatoxins is not covered in this part of ISO 10993. (See ISO/TR 10993-20) The focus here in this part of ISO 10993 is complement activation as it can promote and accelerate haemolysis, platelet and leukocyte activation, and thrombosis on device material surfaces. (See also Annex E on complement activation).

3.5
direct blood contact
term used when the device or device material comes into physical contact with blood or blood constituents

3.6
embolization
process whereby a blood thrombus, or foreign object, is carried in the bloodstream and which may become lodged and cause obstructed blood flow downstream

3.7
***ex vivo* test system**
term applied to a test system that shunts blood directly from a human subject or test animal into a test chamber located outside the body

Note 1 to entry: If using an animal model, the blood may be shunted directly back into the animal (recirculating) or collected in test tubes for evaluation (single pass). In either case, the test chamber is located outside the body.

3.8
haematology
study of blood that includes quantification of cellular and plasma components of the blood

3.9
haematocrit
ratio of the volume of erythrocytes to that of whole blood in a given sample

3.10
hemolysis
liberation of haemoglobin from erythrocytes, either by destruction or through a partially damaged but intact cell membrane

3.11
hemocompatible
term applied to a device or device material wherein contact with blood does not cause any appreciable clinically-significant adverse reactions such as thrombosis, haemolysis, platelet, leukocyte, and complement activation, and/or other blood-associated adverse event

3.12
indirect blood contact
term used in reference to devices that contact the patient's blood path at one point and serve as conduit for entry into the vascular system; e.g., drug and parenteral nutrition solution delivery devices.

3.13
legally-marketed comparator device (LMCD)
an approved, long-established, and recognized-to-be-safe medical device used as a reference control in an in vitro or *in vivo* safety evaluation of a test device of similar design, material(s), and clinical use

3.14
non-blood-contact
term used in reference to the nature of the device or material contact with the patient's body where the device or potentially extracted material does not have direct or indirect contact with blood

3.15
colloidal osmotic pressure
total influence of the proteins or other large molecular mass substances on the osmotic activity of plasma

3.16
platelets
anuclear, cellular bodies which include platelets and platelet-derived microparticles that are present in blood and contribute to the blood coagulation process by adhering to surfaces, releasing factors, and/or aggregating to form a haemostatic plug

3.17
platelet adherent
adjective describing a material or device that tends to allow or promote platelets to attach to its surface relative to a negative control, positive control, and/or LMCD upon blood contact due to its surface properties

Note 1 to entry: Platelet adherent does not necessarily mean platelet activating i.e., platelets on a surface may or may not be activated)

3.18
thrombin generating
adjective describing a material or device that due to its surface properties tends to promote or show increased *thrombin* formation relative to a negative control, positive control, and/or LMCD upon blood contact

3.19
thrombogenic
adjective describing a material or device that due to its surface properties tends to form or promote *thrombus* formation relative to a negative control, positive control, and/or LMCD upon blood contact

3.20
thromboembolisation
process where a dislodged thrombus is carried downstream, where it adheres and may cause subsequent vascular blockage or occlusion

3.21
thrombus
coagulated mixture of red cells, aggregated platelets, fibrin and other cellular elements

3.22
thrombosis
formation of a thrombus under *in vivo*, *ex vivo*, or in vitro simulated conditions, caused by activation of the coagulation system and platelets in flowing whole blood

Note 1 to entry: Thrombosis can also occur in regions of a blood vessel or device where there is stasis.

3.23
whole blood
unfractionated blood drawn from a selected donor; the blood may be non-anticoagulated or anticoagulated e.g., contain sodium citrate or heparin as an anticoagulant

4 Abbreviated terms

Bb	enzymatically active fragment of Factor B produced by cleavage (by Factor D) in the activation of the Alternative Pathway
β-TG	beta-thromboglobulin
C4d	degradation product of C4 by classical pathway complement activation
C3a, C5a	complement split products from C3 and C5
CH-50	amount of complement required to lyse 50% of a RBC suspension.
D-Dimer	specific fibrin degradation products (F XIII cross-linked fibrin) consisting of D-fragment dimer
ELISA	enzyme/linked immunosorbent assay
SEM	scanning electron microscopy
FDP	fibrin/fibrinogen degradation products
FPA	fibrinopeptide A
F1.2	the non-catalytic fragment split off from prothrombin in its conversion to thrombin (also referred to as F1+2)
iC3b	inactive form of C3b, a sub-fragment of C3
IFU	Instruction for use
IVC	inferior vena cava