SLOVENSKI STANDARD
SIST EN 30993-4:2000

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Biološko ovrednotenje medicinskih pripomočkov - 4. del: Izbira preskusov za ugotavljanje interakcij s krvjo (ISO 10993-4:1992)

Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood (ISO 10993-4:1992)

Biologische Beurteilung von Medizinprodukten - Teil 4: Auswahl von Prüfungen zur Wechselwirkung von Blut mit Fremdoberflächen (ISO 10993-4:1992)

Evaluation biologique des dispositifs médicaux - Partie 4: Choix des essais concernant les actions avec le sang (ISO 10993-4:1992)

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Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood (ISO 10993-4:1992)

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This European Standard was approved by CEN on 1993-12-06. CEN members are bound to comply with the CEN/CENELEC Internal Regulations which stipulate the conditions for giving this European Standard the status of a national standard without any alteration.

Up-to-date lists and bibliographical references concerning such national standards may be obtained on application to the Central Secretariat or to any CEN member.

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CEN

European Committee for Standardization
Comité Européen de Normalisation
Europäisches Komitee für Normung

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FOREWORD

This European Standard is the endorsement of ISO 10 993-4:1992. Endorsement of ISO 10 993-4 was recommended by CEN/TC 206 "Biocompatibility of medical and dental materials and devices" under whose competence this European Standard will henceforth fall.

ISO 10 993 consists of the following parts, under the general title "*Biological evaluation of medical devices*":

Part 1:	Guidance on selection of tests
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 cytotoxicity: *in vitro* methods
Part 6:	Tests for local effects after implantation
Part 7:	Ethylene oxide sterilization residuals
Part 8:	Clinical investigation
Part 9:	Degradation of materials related to biological testing
Part 10:	Tests for irritation and sensitization
Part 11:	Tests for systemic toxicity
Part 12:	Sample preparation and reference materials

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

Annex A, B and C of this part of ISO 10 993 are for information only.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by 1994-06, and conflicting national standards shall be withdrawn at the latest by 1994-06.

The Standard was approved and in accordance with the CEN/CENELEC Internal Regulations, the following countries are bound to implement this European Standard:

Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom.

Endorsement notice

The text of the International Standard ISO 10 993-4:1992 was approved by CEN as a European Standard without any modification.

INTERNATIONAL STANDARD

ISO 10993-4

First edition
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Biological evaluation of medical devices —

Part 4:
Selection of tests for interactions with blood

Évaluation biologique des dispositifs médicaux —

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

Reference number
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Contents

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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.

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.

International Standard ISO 10993-4 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: Guidance on selection of tests*

— *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 cytotoxicity: in vitro methods*

— *Part 6: Tests for local effects after implantation*

— *Part 7: Ethylene oxide sterilization residuals*

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— *Part 9: Degradation of materials related to biological testing*

— *Part 10: Tests for irritation and sensitization*

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— *Part 12: Sample preparation and reference 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.

Introduction

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 working group* [26]; chapters 9 and 10. This publication is being revised [29].

Biological evaluation of medical devices —

Part 4:
Selection of tests for interactions with blood

1 Scope

This part of ISO 10993 gives guidance to agencies, manufacturers, research laboratories and others for evaluating the interactions of medical devices with blood.

It describes:

a) a classification of medical and dental 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, together with the principles and scientific basis of these tests.

Detailed requirements for testing cannot be specified because of the limitations in knowledge and precision of tests for interactions of devices with blood.

2 Normative reference

The following standard contains provisions which, through reference in this text, constitute provisions of this part of ISO 10993. At the time of publication, the edition indicated was valid. All standards are subject to revision, and parties to agreements based on this part of ISO 10993 are encouraged to investigate the possibility of applying the most recent edition of the standard indicated below. Members of IEC and ISO maintain registers of currently valid International Standards.

ISO 10993-1:1992, *Biological evaluation of medical devices — Part 1: Guidance on selection of tests.*

3 Definitions

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

3.1 blood/device interaction: Any interaction between blood or any component of blood and a device resulting in effects on the blood, or on any organ or tissue or on the device. Such effects may or may not have clinically significant or undesirable consequences.

3.2 *ex vivo*: Term applied to test systems that shunt blood directly from a human subject or test animal into a test chamber. If using an animal model, the blood may be shunted directly back into the animal (recirculating) or collected into test tubes for evaluation (single pass). In either case, the test chamber is located outside the body.

4 Abbreviations

Table 1 provides a list of abbreviations used in the context of this part of ISO 10993.

Table 1 — Abbreviations

Abbreviation	Meaning
Bb	Product of alternate pathway complement activation
β-TG	Beta-thromboglobulin
C4d	Product of classical pathway complement activation
C3a, C5a	(active) complement split products from C3 and C5
D-Dimer	Specific fibrin degradation products (F XIII cross-linked fibrin)
ECMO	Extracorporeal membrane oxygenator
E.M.	Electron microscopy
FDP	Fibrin/fibrinogen degradation products
FPA	Fibrinopeptide A
F_{1+2}	Prothrombin activation fragment 1 + 2
iC3b	Product of central C complement activation
IL-1	Interleukin-1
IVC	Inferior vena cava
MRI	Magnetic resonance imaging
PAC-1	Monoclonal antibody which recognizes the activated form of platelet surface glycoprotein IIb/IIIa
PET	Positron emission tomography
PF-4	Platelet factor 4
PT	Prothrombin time
PTT	Partial thromboplastin time
RIA	Radioimmunoassay
S-12	Monoclonal antibody which recognizes the alpha granule membrane component GMP140 exposed during the platelet release reaction
SC5b-9	Product of terminal pathway complement activation
TAT	Thrombin-antithrombin complex
TCC	Terminal complement complex
TT	Thrombin time
VWF	von Willebrand factor

5 Devices contacting blood

Devices contacting blood are categorized in ISO 10993-1:1992, clause 5.

5.1 Non-contact devices

(See subclause 5.1.1 of ISO 10993-1:1992.)

An example is *in vitro* diagnostic devices.

5.2 External communicating devices

(See subclause 5.1.3 of ISO 10993-1:1992.)

These are devices that contact the circulating blood and serve as a conduit into the vascular system. Examples include but are not limited to those in 5.2.1 and 5.2.2.

5.2.1 External communicating devices that serve as an indirect blood path [see subclause 5.1.3 a) of ISO 10993-1:1992] include but are not limited to

cannulae,

extension sets,

devices for the collection of blood,

devices for the storage and administration of blood and blood products (e.g. tubing, needles and bags).

5.2.2 External communicating devices in contact with circulating blood [see 5.1.3 c) of ISO 10993-1:1992] include but are not limited to

cardiopulmonary bypass,

extracorporeal membrane oxygenators,

haemodialysis equipment,

donor and therapeutic apheresis equipment,

devices for absorption of specific substances from blood,

interventional cardiology and vascular devices,

percutaneous circulatory support systems,

temporary pacemaker electrodes.

5.3 Implant devices

These are devices (see 5.1.4 of ISO 10993-1:1992) that are placed largely or entirely within the vascular system. Examples include but are not limited to

mechanical or tissue heart valves,

prosthetic or tissue vascular grafts,

circulatory support devices (ventricular-assist devices, artificial hearts, intra-aortic balloon pumps),

inferior vena cava filters,

stents,

arteriovenous shunts,

blood monitors,

internal drug delivery catheters,

pacemaker electrodes,

intravascular membrane oxygenators (artificial lungs).

6 Tests

6.1 General recommendations

6.1.1 Where possible, tests should use an appropriate model or system which simulates the geometry and conditions of contact of the device with blood during clinical applications, including duration of contact, temperature, sterile condition and flow conditions. For devices of defined geometry such as vascular grafts of varying lengths, the relation of surface area (length) to test results should be evaluated.

The selected methods and parameters should be in accordance with the current state of the art.

NOTE 1 Only blood-contacting parts should be tested.

6.1.2 Controls shall be used unless their omission can be justified. Where possible, testing should include a device already in clinical use or well-characterized reference materials. Several materials and configurations are available (see ISO 10993-12 [7]).

Reference materials used should include negative and positive controls. All materials tested should meet all quality control and quality assurance procedures of the manufacturer and test laboratory and should be identified as to source, manufacturer, grade and type.

6.1.3 Testing of materials which are candidates to be components of a device should be conducted for screening purposes. However, such tests do not serve as a substitute for the requirement that the complete device be tested under conditions which simulate clinical application.

6.1.4 Tests which do not simulate the conditions of a device during use may not predict accurately the nature of the blood/device interactions which may occur during clinical applications. For example, some short-term *in vitro* or *ex vivo* tests are poor predictors of long-term *in vivo* blood/device interactions [22], [23].

6.1.5 It follows from the above that devices whose intended use is *ex vivo* (external communicating) should be tested *ex vivo* and devices whose intended use is *in vivo* (implants) should be tested *in vivo* in an animal model under conditions simulating where possible clinical use.

6.1.6 *In vitro* tests are regarded as useful in screening external communicating devices or implants but may not be accurate predictors of blood/device interactions occurring upon prolonged or repeated exposure or permanent contact (see 6.3.2). Devices intended for non-contact use only do not require evaluation of blood/device interactions. Devices which come into very brief contact with circulating blood (e.g. lancets, hypodermic needles, capillary tubes) generally do not require blood/device interaction testing.

6.1.7 The two recommendations in 6.1.5 and 6.1.6, together with clause 5, serve as a guide for the selection of tests listed in 6.2.1.

6.1.8 Disposable laboratory equipment used for the collection of blood and performance of *in vitro* tests on blood should be validated to ascertain that there is no significant interference with the test being performed. This can be conducted by performing tests on reference standards and comparing results with those obtained by a clinically approved technique.

6.1.9 If tests are selected in the manner described and testing is conducted under conditions which simulate clinical applications, the results of such testing have the greatest probability of predicting clinical performance of devices. However, species differences and other factors may limit the predictability of any test.

6.1.10 Because of species differences in blood reactivity, human blood should be used where possible. When animal models are necessary, for example for evaluation of devices used for prolonged or repeated exposure or permanent contact, species differences in blood reactivity should be considered. Blood values and reactivity between humans and non-human primates are very similar [23].