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Biološko ovrednotenje medicinskih pripomočkov - 4. del: Izbira preskusov za ugotavljanje interakcij s krvjo (ISO/DIS 10993-4:2026)

Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood (ISO/DIS 10993-4:2026)

Biologische Beurteilung von Medizinprodukten - Teil 4: Auswahl von Prüfungen zur Wechselwirkung mit Blut (ISO/DIS 10993-4:2026)

Évaluation biologique des dispositifs médicaux - Partie 4: Choix des essais pour les interactions avec le sang (ISO/DIS 10993-4:2026)

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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 pour les interactions avec le sang

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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).

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For an explanation on 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 the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 194, *Biological and clinical evaluation of medical devices,* in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 206, *Biocompatibility of medical and dental materials and devices,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This fourth edition cancels and replaces the third edition (ISO 10993-4:2017), which has been technically revised.

The following changes were made:

— Reference to ISO/TR 10993-20 was replaced by ISO/TS 10993-20;

— Definitions to “indirect blood contact” and “legally-marketed comparator device” were updated;

— Table 1 in 6.1.6 was updated;

— Figure 2 was updated;

— Bibliography was updated;

— Annex ZA was added to reflect the relationship between this European Standard the General Safety and Performance Requirements of Regulation (EU) 2017/745 aimed to be covered

The changes in this document do not indicate that testing conducted according to prior versions of this document is invalid. For marketed devices with a history of safe clinical use, additional testing according to this revision is not recommended.

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 document was the publication, *Guidelines for blood/material interactions*, Report of the National Heart, Lung, and Blood Institute[17] chapters 9 and 10. This publication was subsequently revised[18].

Biological evaluation of medical devices —

Part 4: Selection of tests for interactions with blood

1 Scope

This document 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 evaluating interactions of devices with blood. This document 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 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 10993-1, *Biological evaluation of medical devices — Part 1: Requirements and general principles for the evaluation of biological safety within a risk management process*

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

3 Terms and definitions

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

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— IEC Electropedia: available at https://www.electropedia.org/

— ISO Online browsing platform: available at https://www.iso.org/obp

3.1
anticoagulant
agent which prevents or delays blood coagulation

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

3.2
blood/device interaction
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 document. (See ISO/TS 10993-20.)

Note 2 to entry: The focus in this document 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
haemolysis
liberation of haemoglobin from erythrocytes, either by destruction or through a partially damaged but intact cell membrane

3.11
haemocompatible
<device or device material> able to come into contact with blood without any appreciable clinically-significant adverse reactions such as thrombosis, *haemolysis* (3.10), platelet, leukocyte, and complement activation, and/or other blood-associated adverse event occurring

3.12
indirect blood contact
nature of devices that contact the patient's blood path at one point and serve as a conduit for entry into the vascular system or devices that contact cerebrospinal fluid (CSF) as CSF is reabsorbed into the venous system

EXAMPLE Drug and parenteral nutrition solution delivery devices.

3.13
legally-marketed comparator device
LMCD
approved, or cleared currently marketed medical device that is recognized to be safe based on the history of safe clinical use, 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

Note 1 to entry: It may be necessary that the LMCD be legally marketed in the same region as the regulatory submission for the test device.

3.14
non-blood-contact
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 that are present in blood and contribute to the process of thrombosis by adhering to surfaces, releasing factors, and/or aggregating to form a haemostatic plug

3.17
platelet adherent
<material or device> having the tendency to allow or promote *platelets* (3.16) to attach to its surface

Note 1 to entry: This is often characterized relative to a negative control, positive control, and/or LMCD upon blood contact due to its surface properties.

Note 2 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
<material or device> due to its surface properties, having the tendency to promote or show increased thrombin formation

Note 1 to entry: This is often characterized relative to a negative control, positive control, and/or LMCD upon blood contact.

3.19
thrombogenic
<material or device> due to its surface properties, having the tendency to form or promote thrombus formation

Note 1 to entry: This is often characterized relative to a negative control, positive control, and/or LMCD upon blood contact.

3.20
thromboembolization
process where a dislodged *thrombus* (3.21) is carried downstream, where it may cause subsequent vascular blockage or occlusion

3.21
thrombus
coagulated mixture of red blood cells, aggregated *platelets* (3.16), fibrin and other cellular elements

3.22
thrombosis
formation of a *thrombus* (3.21) under *in vivo*, *ex vivo*, or *in vitro* simulated conditions, caused by activation of the coagulation system and *platelets* (3.16) 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 human donor or test animal

Note 1 to entry: 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 an RBC suspension
D-Dimer	specific fibrin degradation products (F XIII cross-linked fibrin) consisting of D-fragment dimer
ELISA	enzyme-linked immunosorbent assay
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
LMCD	legally marketed comparator device
MSC	mechanical circulatory support
MRI	magnetic resonance imaging
PET	positron emission tomography
PF-4	platelet factor 4
PFH	plasma free hemoglobin
PRP	platelet-rich plasma
PT	prothrombin time

PTT	partial thromboplastin time
SC5b-9	product of terminal pathway complement activation
SEM	scanning electron microscopy
TAT	thrombin-antithrombin complexe
TCC	terminal complement complex; also called membrane attack complex (MAC); estimated by measuring SC5b-9
TT	thrombin time
TxB2	thromboxane B2

5 Types of devices in contact with blood (as categorized in ISO 10993-1)

5.1 Non-blood-contact devices

Non-blood-contact devices are devices that do not have direct or indirect contact with either blood or blood constituents that reside in the body or that are returned to the body. An *in vitro* diagnostic device and a blood-collection tube are examples of non-blood-contact devices. Some devices, such as introducer systems for implants, may contain both blood-contacting and non-blood-contacting components.

5.2 External communicating devices

5.2.1 General

These are devices that contact the circulating blood and serve as a conduit into the vascular system. Some devices may have components or portions with different types of contact (direct and indirect). Examples include but are not limited to the following.

5.2.2 External communicating devices that indirectly contacting blood

— blood monitors with indirect blood contact.

— devices for the storage and administration of saline and/or therapeutics (e.g. tubing and bags);

— extension sets;

5.2.3 External communicating devices directly contacting circulating blood

— atherectomy devices;

— blood collection devices;

— blood monitoring devices with direct blood contact;

— cannulae;

— cardiopulmonary bypass circuitry;

— cell savers;

— devices for adsorption of specific substances from blood;

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

— donor and therapeutic apheresis equipment;

— extracorporeal membrane oxygenators;

— haemodialysis/haemofiltration devices;

— interventional cardiology and vascular devices;

— intravascular catheters (balloon, imaging, laser, ultrasound);

— leukocyte removal filters;

— percutaneous circulatory support devices;

— retrograde coronary perfusion catheters;

— vascular guide wires.

5.3 Implant devices

Implant devices are placed largely or entirely within the vascular system. Examples include but are not limited to the following:

— annuloplasty rings;

— arteriovenous shunts;

— blood monitors (implantable);

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

— embolization devices;

— endovascular synthetic vascular grafts;

— implantable defibrillator and cardioverter leads;

— inferior vena cava filters;

— internal drug delivery catheters;

— intravascular oxygenators (artificial lungs);

— mechanical or tissue heart valves;

— pacemaker leads;

— surgical synthetic or tissue vascular grafts;

— vascular stents.

6 Characterization of blood interactions

6.1 General requirements

IMPORTANT — Since this is a horizontal International Standard, sound rationales can be supplied to justify the choice of test category(ies) based on the device being characterized. For example, for devices with prolonged and long-term blood contact, *in vivo* testing for evidence of thrombosis is typically needed for device characterization in the thrombosis category. For many devices with limited blood contact, in vitro thrombogenicity testing under clinically relevant or well-defined blood flow conditions can generally be used, if the test is appropriately designed. In some cases, with written rationales, a panel of material-mediated tests (e,g., test tube models with defined gentle agitation) from the categories of coagulation, platelets, haematology and complement can be used for thrombogenicity evaluation.

Note on written rationales: In general, the predictive nature of an in vitro test is significantly related to the test's use of blood exposure conditions that mimic intended clinical use. Thus, use of in vitro tests using acute benchtop exposure conditions is generally most applicable to acute blood contact conditions rather than permanent exposure applications. Consequently, written rationales should highlight and contrast important factors of the in vitro vs. clinical use conditions. Such factors include but are not limited to blood exposure duration, type of blood flow, and use of antithrombotic drugs, blood freshness, etc.

6.1.1 Figure 1 illustrates a decision tree that can be used to determine whether testing for interaction with blood is necessary. Blood interactions can be divided into several categories based on the primary process or system being measured. Table 1 lists examples of devices which contact circulating blood and the categories of testing appropriate to each device. The list is not all inclusive and sound judgement shall be applied to devices not listed in the tables.

For medical devices where a specific International Standard (vertical standard) exists, the biological evaluation requirements and test methods set forth in that vertical standard shall take precedence over the general requirements suggested in this document.

6.1.2 Where possible, tests shall use an appropriate model or system which simulates the geometry and conditions of contact of the device with blood during clinical applications. The simulation should include an appropriate duration of contact, temperature, sterile condition, anticoagulant (and level; see 6.1.12) and flow conditions. As stated in ISO 10993-12, clause 7: "Testing shall be performed on the final product, representative samples from the final product, materials processed in the same manner as the final product (see ISO 10993-1), or on appropriate extracts of any of these. The choice of test sample shall be justified."

Only direct or indirect blood-contacting parts should be tested. For direct contact haemocompatibility testing (e.g., direct haemolysis, complement activation, coagulation, platelet activation, haematology, in vitro/ex vivo thrombosis), testing should be conducted using only the direct blood contacting components of the device to minimize interference of non-direct blood contacting components on the results. For extract-based haemocompatibility testing (e.g., indirect haemolysis), testing should be conducted using only the direct and indirect blood-contacting components of the device. The test article shall be described, and a justification shall be provided if the test article includes device components that include different tissue contact than described above. The selected test methods and parameters should be in accordance with the current state of the art.

Appropriate type and level of anticoagulant may be case specific depending on both the device use indication and the type of test conducted. Include information on the specific type and level of anticoagulation used and provide a discussion on the ability to discern positive and negative responses. For further information, see 6.1.6 and C.2 for animal studies, 6.1.12 for in vivo and ex vivo tests, 6.3.1 for *in vitro* tests and A.3 for catheters and guide wires.

As many tests for haemocompatibility are recognized to be generally surface-contact dependent (e.g., direct contact haemolysis, complement activation, coagulation, platelet activation, haematology, and in vitro/ex vivo thrombosis) such tests will not apply to indirect contact applications. For externally communicating medical devices or components that have indirect blood contact, generally only an indirect contact haemolysis test is recommended.

6.1.3 Controls (positive and negative) shall be used unless their omission can be justified. Where possible, testing should include a relevant predicate device already in clinical use (i.e. a LMCD) or a well-characterized material (see ISO 10993-1 for more information) .

Controls should include negative and positive reference materials. All materials and LMCDs tested shall meet all quality control and quality assurance specifications of the manufacturer and test laboratory. All materials and devices tested shall be identified as to source, manufacturer, grade and type.

6.1.4 Testing of materials which are candidates for components of a device may be conducted for screening purposes. However, such preliminary tests do not serve as a substitute for the requirement that the complete sterilized device or device component should be tested under conditions which simulate or exaggerate clinical application.